Quantitative Analysis of Mitral Annular Geometry and Function in Healthy Volunteers Using Transthoracic Three-Dimensional Echocardiography

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Background: Quantitative assessment of the mitral annulus provides information regarding the pathophysiology of mitral regurgitation and aids in the planning of reparative surgery. Three-dimensional (3D) transthoracic echocardiographic data sets acquired with current scanners have enough spatial and temporal resolution to allow the quantitative analysis of the mitral annulus. Accordingly, the authors performed (1) a validation study to assess the agreement of quantitative analysis of the mitral annulus performed on 3D transthoracic echocardiography (TTE) and 3D transesophageal echocardiography (TEE) and (2) a normative study to obtain the reference values of 3D transthoracic echocardiographic parameters for mitral annular (MA) geometry and dynamics.

Methods: Mitral valve data sets were obtained by 3D TEE and 3D TTE in 30 consecutive patients with clinically indicated TEE (validation study) and 3D TTE in 224 healthy volunteers (aged 18–76 years) (normative study).

Results: In the validation study, MA measurements obtained by 3D TTE were similar to those obtained by 3D TEE (P = NS). In the normative study, MA analysis by 3D TTE was feasible (94.5%) and reproducible (intraclass correlation coefficient = 0.78–0.97). MA diameters, area, and circumference were correlated with body surface area ($r > 0.50$ for all) but not with age. Men had larger MA areas than women (4.9 ± 1.0 vs 4.5 ± 0.7 cm^2/m^2, P = .004). During systole, MA area decreased by $29 \pm 5\%$. This decrease was related mainly to anteroposterior diameter shortening ($20 \pm 7\%$).

Conclusions: MA quantitative analysis by 3D TTE was accurate compared with 3D TEE in unselected patients with mitral valve disease. In healthy subjects, it was highly feasible and reproducible. The availability of reference values for MA geometry and dynamics may foster the implementation of MA quantitative analysis by 3D TTE in clinical settings. (J Am Soc Echocardiogr 2014;27:846-57.)

Keywords: Three-dimensional echocardiography, Transesophageal echocardiography, Transthoracic echocardiography, Mitral annulus, Mitral valve, Reference values, Normal subjects

Transthoracic echocardiography (TTE) is the standard clinical tool for the initial assessment and longitudinal evaluation of patients with mitral regurgitation (MR).[1,2] Changes in the size, shape, and dynamics of the normal mitral annulus are closely related to the development of MR,[3-6] and mitral annuloplasty is the most common surgical procedure to repair a regurgitant mitral valve (MV).[7,8] Therefore, the quantitative assessment of mitral annular (MA) geometry seems to be important for a better understanding of MR pathophysiology and planning of reparative surgery.[9,10] However, MA size is only rarely reported in clinical routine, and according to current recommendations regarding the echocardiographic assessment of patients with MR, the characterization of MA geometry is limited only to the measurement of MA anterior-posterior (A-P) diameter.[1]

Linear or area measurements used to describe MA geometry using tomographic imaging techniques (e.g., two-dimensional [2D] echocardiography or cardiac magnetic resonance [CMR]) depend on the correct alignment of imaging planes and on the recognition of anatomic landmarks.[11] In addition, they are unsuitable to fully characterize the complex nonplanar geometry of the mitral annulus and mitral leaflets.[12] Conversely, three-dimensional (3D) echocardiography has the ability to provide anatomically sound images of the MV

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Abbreviations

ALA = Anterior leaflet area

AL-PM = Anterolateral-posteromedial

Ao-AP angle = Angle between the aortic valve and mitral annulus along the anterior-posterior direction

A-P = Anterior-posterior

BSA = Body surface area

CMR = Cardiac magnetic resonance

LV = Left ventricular

MA = Mitral annular

MR = Mitral regurgitation

MV = Mitral valve

MVC = Mitral valve closure

NPA = Nonplanarity angle

PLA = Posterior leaflet area

TEE = Transesophageal echocardiography

3D = Three-dimensional

TTE = Transthoracic echocardiography

2D = Two-dimensional

apparatus and to analyze the geometry and dynamics of the mitral annulus without geometric assumptions.[3-6,13-15] Indeed, measurements of MV anatomy using 3D transesophageal echocardiography (TEE) have been reported to be accurate compared with surgical measurements and superior to those obtained by 2D TEE.[16]

Until recently, MA quantitative assessment was feasible only with 3D data sets acquired from the transesophageal approach, so it was not practical for the routine assessment and follow-up of patients with MR.[3,17,18] Third-generation 3D scanners have significantly improved the spatial and temporal resolution of 3D data sets acquired by 3D TTE, making feasible both the qualitative and quantitative analysis of the mitral annulus by 3D TTE.[19,20] To the best of our knowledge, there are no data regarding the feasibility and accuracy of MA quantitative analysis performed on 3D transthoracic echocardiographic data sets, and data on reference values of MA parameters assessed using 3D TTE are quite limited.[14]

To address these issues, we designed two consecutive, prospective studies. In a validation study, we compared MA quantitative assessment by 3D TTE against the same measurements obtained by 3D TEE, and in a normative study, (1) we obtained reference values for static and dynamic MA analysis from a large cohort of healthy volunteers, (2) we analyzed the relationships of normal MA geometry with age, gender, and body size, and (3) we assessed the feasibility and reproducibility of quantitative analysis of MA geometry using 3D TTE.

METHODS

Study Population

Between July 2011 and October 2011, we enrolled consecutive patients in sinus rhythm with clinical indications for TEE to conduct the validation study.

To obtain normative values for MA size and geometry, healthy Caucasian volunteers were prospectively recruited among hospital employees, fellows-in-training, their relatives, and individuals who underwent medical assessments for driving or working licenses between October 2011 and February 2013. The inclusion criteria were age > 17 years, no history or symptoms of cardiovascular or lung disease, no cardiovascular risk factors (i.e., systemic arterial hypertension, smoking, diabetes, and hypercholesterolemia), normal results on electrocardiography and physical examination, and no cardio- or vasoactive treatment. Exclusion criteria were athletic training, pregnancy, body mass index > 30 kg/m^2, and a poor apical acoustic window. Blood pressure was measured in all subjects immediately before the echocardiographic examination. The study was approved by the University of Padua Ethics Committee (protocol no. 2380 P), and both patients and volunteers provided informed consent before the study.

Echocardiography

All examinations were performed using standardized protocols and a commercially available Vivid E9 system (GE Vingmed Ultrasound AS, Horten, Norway) equipped with 4V and 6VT probes for 3D TTE and 3D TEE, respectively.

In the validation study, 3D full-volume MV data sets were acquired by 3D TTE from the apical approach in all patients, immediately before TEE. TEE was performed according to the specific clinical indication by the same experienced operator (L.P.B. or D.M.), and at the end, a 3D full-volume MV data set was acquired using the 3D zoom option (Videos 1 and 2; available at www.onlinejase.com).

In the normative study, all 224 healthy subjects underwent complete TTE to exclude subclinical heart diseases and poor apical acoustic windows. Two 3D full-volume acquisitions (i.e., one for the MV and a separate one for the left ventricle) were recorded by combining six consecutive electrocardiographically triggered subvolumes during a breath-hold (Videos 3 and 4; available at www.onlinejase.com).

Image Analysis

Three-dimensional transthoracic and transesophageal echocardiographic data sets for the MV and the left ventricle were stored digitally in raw-data format for offline analysis. Quantification of 3D left ventricular (LV) volumes and ejection fraction and 3D longitudinal strain was performed using a commercially available software package (4D AutoLVQ, EchoPAC BT 12; GE Vingmed Ultrasound AS) previously described and validated against CMR.[21]

For the validation study, 3D transthoracic and transesophageal echocardiographic MV data sets were converted to Digital Imaging and Communications in Medicine format and analyzed using a dedicated software package for MV quantitative analysis (4D-MV Assessment version 2.3; TomTec Imaging Systems, Unterschleissheim, Germany) by a single observer, who performed the quantitative analysis of transesophageal and transthoracic echocardiographic data sets in random order, in a blinded fashion, with an interval of 1 week.

For the normative study, a single observer (S.M.) analyzed the 3D transthoracic echocardiographic MV data sets of the 224 healthy volunteers to obtain reference values for MA geometry and dynamics, using the same software package. The quality of MV data sets was judged subjectively as excellent, good, fair, or poor, considering the signal-to-noise ratio, the degree of blood-tissue contrast, and the quality of MA tracking. Poor-quality data sets were excluded from the study.

MA analysis on 3D transthoracic echocardiographic data sets started by identifying three time points: early systole (the frame after MV closure [MVC]), end-systole (the frame just before the MV begins to open, and mid-systole (the frame midway between MVC and end-systole). After adding anatomic landmarks for the mitral annulus, aorta, and leaflet coaptation point, the software created a static 3D model of the mitral annulus and leaflets at mid-systole. Afterward, the mitral annulus was tracked in each systolic frame (dynamic

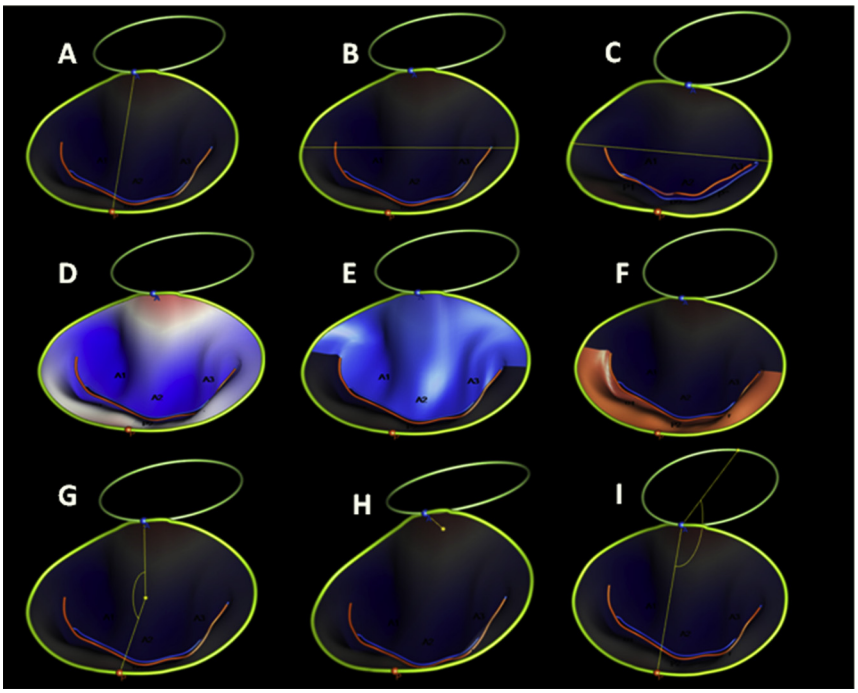

Figure 1 MV parameters automatically analyzed at mid-systolic frame. **(A)** A-P diameter, **(B)** AL-PM diameter, **(C)** commissural diameter, **(D)** MA area, **(E)** MV ALA, **(F)** PLA, **(G)** NPA, **(H)** MA height, **(I)** Ao-AP angle.

analysis) (Video 5; available at www.onlinejase.com). Manual edits of the dynamic models were performed as needed. Quantitative parameters of MV geometry (Figure 1) were 3D and 2D (projected) MA areas; MA circumference; MA A-P diameter, as the shortest distance between the highest anterior and posterior points of the mitral annulus; MA anterolateral-posteromedial (AL-PM) diameter, as the longest diameter of the mitral annulus; MA sphericity index, as the ratio between A-P and AL-PM diameters; MV commissural diameter, measured through the two MV commissures; MV anterior leaflet area (ALA) and length; MV posterior leaflet area (PLA) and length; MA nonplanarity angle (NPA), quantifying the "saddle shape" of the mitral annulus; annular height, as the distance between the lowest and the highest points of the mitral annulus; MV tenting height, area, and volume; and the angle between the aortic valve and mitral annulus along the A-P direction (Ao-AP angle). For all quantitative parameters, the values at MVC, mid-systole, and end-systole, the minimal absolute value, and the time interval from MVC to its minimal value (expressed as a percentage of the total duration of systole) were recorded. MA diameters, area, and circumference were normalized to body surface area (BSA).

The software provided MA displacement, displacement velocity, and MA area fractional change. In addition, the fractional changes (the difference between the maximal and minimal values, divided by the maximal value and expressed as percentages) of MA circumference, A-P diameter, and AL-PM diameter were also calculated (Figure 2).

Statistical Analysis

Normal distribution of variables was checked using the Kolmogorov-Smirnov test. Continuous variables are summarized as mean ± SD, and categorical variables are reported as percentages. Variables were compared between men and women using unpaired *t* tests. In the validation study, 3D transesophageal and transthoracic echocardiographic measurements in the same subjects were compared using paired *t* tests and Bland-Altman analysis.

Comparison of MA measurements obtained at different reference frames during systole was made using analysis of variance for repeated measurements. Pearson's correlation was used to analyze the relationships between age, BSA, and MA parameters, as well as the correlation between 3D transthoracic and transesophageal echocardiographic measurements of the mitral annulus.

Interobserver variability for MA assessment using 3D TTE was performed in 17 random healthy subjects by two independent observers (S.M. and D.M.) by blinded offline analysis of the same 3D data set. Intraobserver variability was assessed by one investigator (S.M.), who repeated the measurements of the same data sets 7 days later. Reproducibility was reported as the coefficient of repeatability (1.9 ± SD of the difference between the two measurements) using Bland-Altman analysis and as intraclass correlation coefficients.

All analyses were carried out using SPSS version 20.0 (SPSS, Inc, Chicago, IL) and MedCalc version 10.0.1.0 (MedCalc Software, Mariakerke, Belgium). Differences among variables were considered significant at $P < .05$.

RESULTS

Validation Study

For the validation study, we enrolled 30 patients with clinical indications for TEE, such as Barlow disease ($n = 4$), MV prolapse ($n = 6$), patent foramen ovale ($n = 3$), rheumatic mitral stenosis ($n = 2$), infective endocarditis ($n = 8$), and other indications ($n = 7$). As expected, 3D transesophageal echocardiographic data sets had superior image quality than 3D transthoracic echocardiographic data sets (good or excellent quality in 81% vs 54%, respectively, $P < .001$).

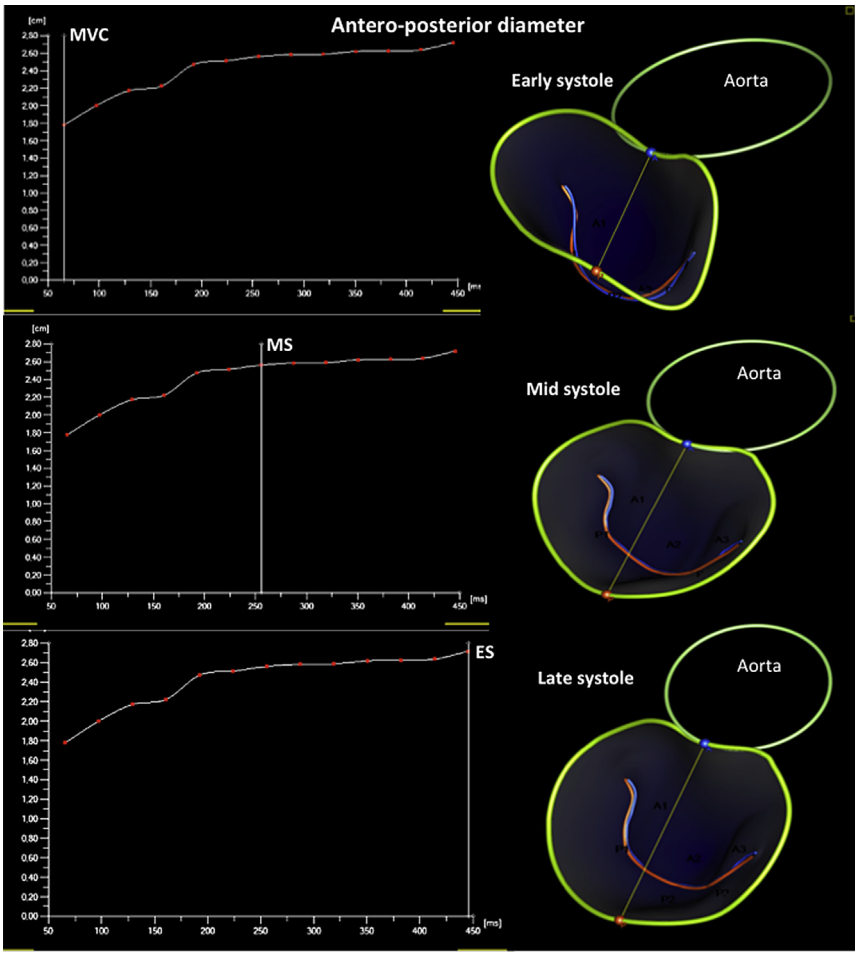

Figure 2 Curves for the dynamic changes in MA A-P diameter during cardiac systole. The minimum value of diameter occurs very early in systole, followed by its enlargement during the rest of the systole. *ES*, End-systole; *MS*, mid-systole; *MVC*, mitral valve closure.

Twenty-eight data sets obtained by 3D TEE (93%) and 22 data sets by 3D TTE (73%) were adequate for MA quantitative analysis ($P = .08$). The mean temporal resolution was 28 ± 13 volumes/sec for 3D TEE and 31 ± 6 volumes/sec for 3D TTE ($P = .408$). Close correlations ($r > 0.89$) (Figure 3) and good agreement (Figure 4) were found when comparing MA parameters measured by 3D TEE and 3D TTE.

Normative Study

The mean temporal resolution of the 3D data sets obtained in the healthy volunteers enrolled in the normative study was 33 ± 4 volumes/sec. The number of systolic frames in each data set ranged from 11 to 19, depending on the subject's heart rate or acquisition settings (volume size, number of consecutive subvolumes, depth, etc). Image quality was excellent in 40%, good in 42%, fair in 13%, and poor in 5% ($n = 13$) of subjects. Therefore, 13 subjects were excluded from the initial cohort of 224 enrolled in the normative study. In healthy subjects, feasibility of MA quantitative analysis by 3D TTE was 94.5%. Characteristics of the final cohort of 211 volunteers (age range, 17–76 years; 54% women) enrolled in the normative study are summarized in Table 1. Age and heart rate were similar between genders. Women had significantly smaller body sizes and lower blood pressure values than men. LV end-diastolic and end-systolic volumes were larger in men, whereas LV ejection fractions were higher in women than in men (Table 2).

The average analysis time for data sets included in the normative study (including manual editing) was 3 ± 1 min for static MA analysis and 8 ± 1 min for dynamic MA analysis.

MA Static Analysis in Healthy Volunteers

At the mid-systolic frame, men had larger MA diameters, areas, and circumferences than women but similar MA sphericity (Table 2). After indexing for BSA, the difference in MA 3D area between genders persisted (4.9 ± 1.0 vs 4.5 ± 0.7 cm^2/m^2, $P = .004$), whereas the difference in MA diameters between genders was no longer significant. MV ALA and PLA were larger in men than in women. However, although MV anterior leaflet length was significantly larger in men ($P < .001$), MV posterior leaflet length was similar between genders ($P = .377$). NPA was similar between genders. Men had higher annular heights, tenting areas, and tenting volumes than women. Conversely, tenting height was similar between genders. Tenting volume showed a closer positive correlation with MA area ($r = 0.586$, $P < .001$) than tenting area ($r = 0.384$, $P < .001$) or tenting height ($r = 0.388$, $P < .001$). The Ao-AP angle was more acute in men than in women (Table 2).

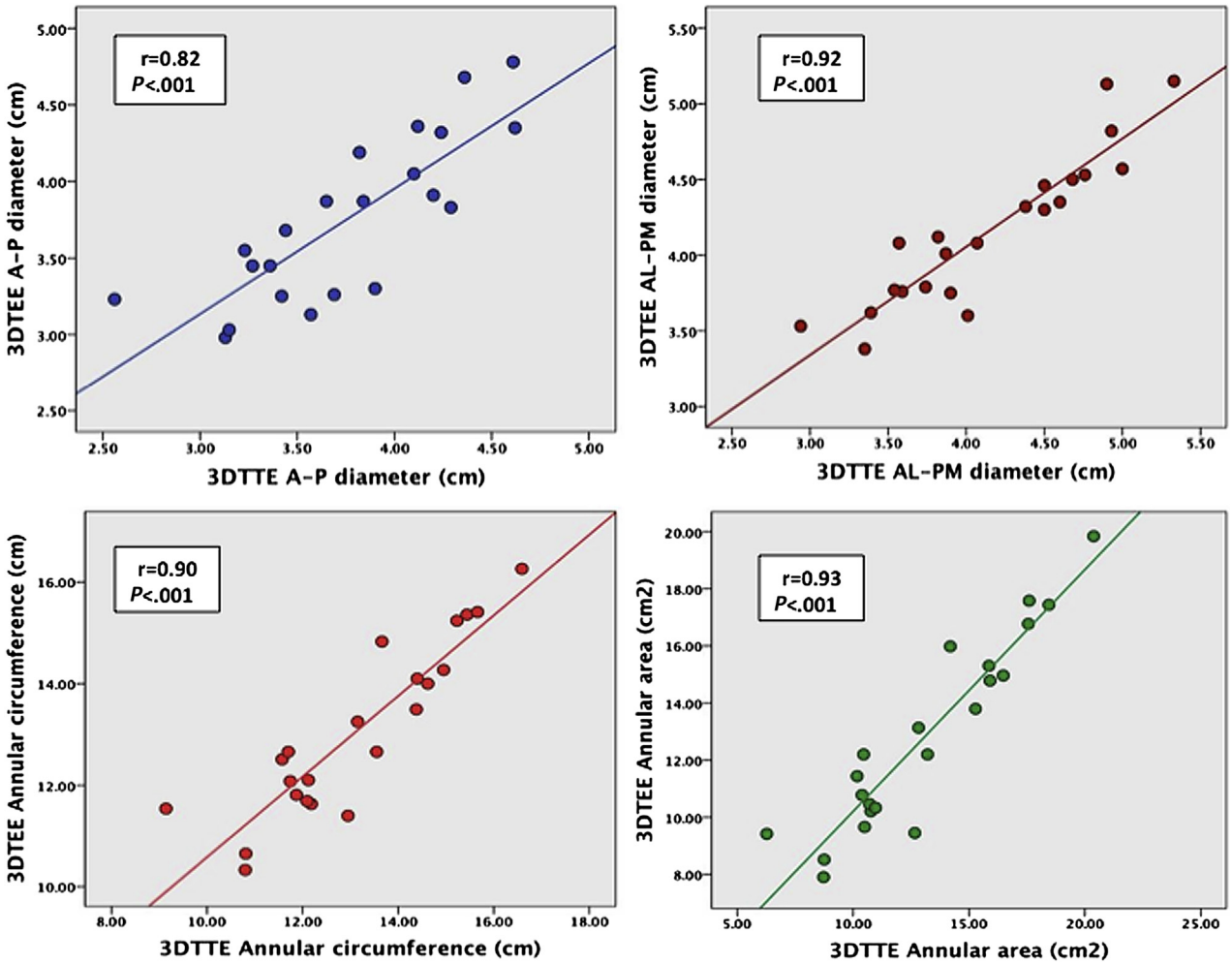

Figure 3 Correlations between MA parameters obtained by 3D TTE and 3D TEE.

A-P and AL-PM diameters and MA area and circumference were positively related to BSA ($r = 0.518$, $r = 0.504$, $r = 0.552$, and $r = 0.546$, respectively, $P < .001$ for all). MV ALA and PLA were also correlated with BSA ($r = 0.554$ and $r = 0.364$, respectively, $P < .001$ for both). MV ALA and anterior leaflet length showed closer correlations with BSA ($r = 0.554$ and $r = 0.425$, respectively, $P < .001$) than PLA and MV posterior leaflet length ($r = 0.364$ and $r = 0.334$, respectively, $P < .001$). Among the various parameters describing MA geometry, only A-P diameter ($r = 0.142$, $P = .04$), MA sphericity ($r = 0.202$, $P = .003$), and Ao-AP angle ($r = -0.40$, $P < .001$) showed modest but significant correlations with age.

MA Dynamic Analysis in Healthy Volunteers

All parameters describing MA geometry changed significantly during ventricular systole ($P < .001$ for all) (Table 3, Figure 5). Minimal MA area occurred at early systole, and average MA area fractional change was 28.5 ± 5.0%. The extent of MA area fractional change was related mainly to A-P diameter shortening ($r = 0.525$, $P < .001$), which also reached its minimum value at early systole and showed a fractional change of 20.0 ± 6.6%. MA area fractional change was also related to AL-PM shortening ($r = 0.461$, $P < .001$). AL-PM diameter reached its minimum at early systole, too, but had a lower fractional change than A-P diameter (only 12.5 ± 4.3%, $P < .001$). MA circumference decreased by 12.2 ± 3.3% during cardiac systole. Fractional changes in MA diameters, circumference, and area were not correlated with age. Minimal MA sphericity occurred at 23 ± 20% of systole duration and increased up to its maximum at end-systole. NPA reached its minimum of 141 ± 1° at 53 ± 29% of systolic duration. MV tenting height, area, and volume were at their maximal values at MVC and decreased progressively to a late-systolic minimum (Table 3).

MA displacement and displacement velocity were 11 ± 2 mm and 54 ± 11 mm/sec, respectively. MA displacement and displacement velocity showed significant inverse correlations with age ($r = -0.481$ and $r = -0.406$, respectively, $P < .001$ for both). MA displacement showed a significant direct correlation with 3D longitudinal strain ($r = 0.410$, $P < .001$).

Reproducibility

MA parameters obtained by 3D TTE from the normative study cohort showed excellent intra- and interobserver reproducibility, with intraclass correlation coefficients ranging from 0.87 to 0.98 for intraobserver reproducibility and from 0.78 to 0.95 for interobserver reproducibility (Table 4, Figure 6).

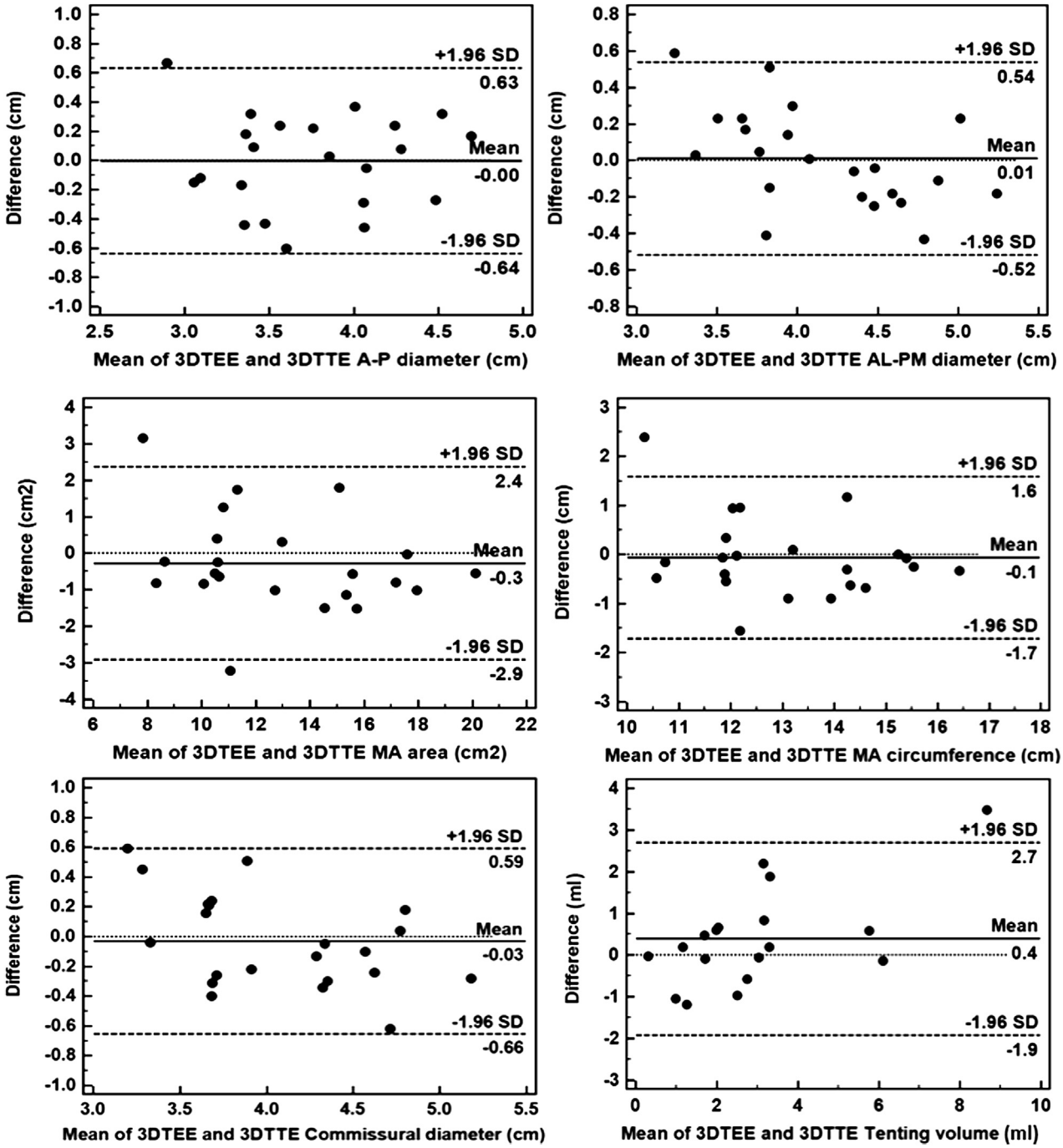

Figure 4 Bland-Altman plots of MA parameters measured from data sets obtained by 3D TTE and 3D TTE.

DISCUSSION

This is the first study specifically designed to assess the feasibility and the accuracy of MA quantitative analysis performed on 3D transthoracic echocardiographic data sets and to obtain normative values for MA geometry static and dynamic parameters from a large number of adult healthy volunteers using 3D TTE. The main results of the study are as follows: (1) In patients, MA size, shape, and complex geometry can be assessed using 3D TTE with similar results to those obtained by 3D TEE, and (2) in normal subjects, the mitral annulus decreases in size at MVC and then progressively increases in size and sphericity during the remainder of systole, men had larger mitral annuli than women but MA shape was similar between genders, MA size is related to BSA but not to age, and MA contraction function is preserved during physiologic aging, whereas MA translational function decreases.

Feasibility of 3D TTE

Alterations of MA geometry and dynamics have been reported in different pathologies causing MR.[3-5,22-24] Therefore, a detailed knowledge of MA geometry in normal subjects may permit correct

Table 1 Characteristics of healthy subjects enrolled for obtaining reference values for MA parameters

Variable	Men (n = 97)	Women (n = 114)	P
Age (y)	43 ± 15	44 ± 15	.356
Height (cm)	178 ± 7	164 ± 6	<.001
Weight (kg)	77 ± 9	61 ± 8	<.001
Body mass index (kg/m^2)	24 ± 3	22 ± 3	<.001
BSA (m^2)	1.93 ± 0.1	1.66 ± 0.1	<.001
Heart rate (beats/min)	68 ± 11	69 ± 10	.37
Systolic blood pressure (mm Hg)	127 ± 13	117 ± 14	<.001
Diastolic blood pressure (mm Hg)	75 ± 8	71 ± 8	<.001
LV end-diastolic volume (mL/m^2)	64 ± 11	56 ± 9	<.001
LV end-systolic volume (mL/m^2)	27 ± 5	20 ± 4	<.001
LV ejection fraction (%)	62 ± 4	65 ± 4	<.001

Data are expressed as mean ± SD.

diagnosis,[25] facilitate understanding of underlying MR mechanisms[22,26] to tailor surgical repair to specific pathophysiology, and enable the design of anatomically sound annular prostheses.[18,27,28] However, most previous clinical studies reported MA geometry and dynamics obtained from 3D transesophageal echocardiographic data sets of the MV. This approach was necessary to obtain data sets of adequate spatial and temporal resolution to perform quantitative analysis of the mitral annulus, but it is not practical for routine assessment and follow-up of patients with MR.

The spatial and temporal resolution of 3D TTE has improved greatly over the years. Using the latest generation 3D systems, we obtained good or excellent quality 3D transthoracic echocardiographic MV data sets in 82% of cases, and the feasibility of MA quantitative analysis was 94.5% in healthy subjects and 73% in patients. Suboptimal apical acoustic window, heavy calcification of the mitral annulus, and irregular cardiac rhythm (frequent ectopic beats) were the most frequent reasons for inadequate quantitative analysis of the mitral annulus from 3D transthoracic echocardiographic data sets. Technical improvements in 3D TTE are needed to allow its use in a larger proportion of patients. However, although data set quality was better and feasibility was higher using 3D TEE, 3D TTE was feasible in three-quarters of patients, it showed good reproducibility, and, in good-quality data sets, MA measurements by 3D TTE were similar to those obtained by 3D TEE. In addition, MA assessment using 3D TTE has previously been compared with CMR assessment, revealing good accuracy.[29] Finally, absolute and indexed MA areas obtained in our normative study were very similar to those obtained in 16 normal individuals using gated cardiac computed tomography.[30]

Three-dimensional transthoracic echocardiographic quantification of the mitral annulus and leaflets has previously been reported in relatively limited cohorts of normal subjects[14,31] or "controls" used for comparison in studies designed to study pathological or bioprosthetic MVs.[3,23,24] MA size parameters obtained by 3D TTE in our healthy cohort were similar to those obtained in smaller cohorts of normal individuals by 3D TTE,[14] 3D TEE,[13] 2D echocardiography,[32] CMR,[33] and multidetector computed tomography[30] (Table 5). In addition, we provide normative values for MA geometry parameters, which are important for normal MV function (i.e., MA nonplanarity)[34] or with prognostic impact in different MV or surrounding structure pathologies (i.e., annular height, tenting volume, Ao-AP angle).[3,5,35] Moreover, no previous study has reported MA dynamics using 3D TTE in a large cohort of healthy adults.

Normal MA Size and Shape

The availability of reference values for MA diameters, sphericity, area, and circumference is a prerequisite for the implementation of MA assessment by 3D TTE in the clinical routine of an echocardiography laboratory.

Anwar *et al.*[29] reported good accuracy for MA area and diameters measured by 3D TTE compared with CMR. MA area and circumference obtained from our adult population were similar to those reported in previous 3D transthoracic echocardiographic studies in smaller numbers of healthy individuals.[14,29] Using 2D echocardiography, Ormiston *et al.*[32] reported an MA area of only 7.1 ± 1.3 cm^2 in 11 normal individuals. This is not an unexpected result, because it has been proved that 2D echocardiography underestimates true MA dimensions compared with 3D echocardiography.[12]

The mean A-P diameter found in our study is similar to that obtained by Anwar *et al.*[29] but smaller than the average values reported by Kovalova and Necas[13] in 28 "normal controls" with a higher prevalence of men (60%) than in our cohort. Indeed, we found significant differences between men and women for all MA size parameters. As previously described, MA dimensions were correlated with body size but not with age.[14]

The analysis of MV leaflets performed in our study did not include the coaptation zone, because the leaflets are closed in systole. In diastole, when the leaflets are wide open, they can be tracked through their entire length. This might explain why our anterior and posterior leaflets' lengths and areas were relatively smaller than those reported by Chaput *et al.*,[36] who measured the same parameters in diastole.

Normal Dynamics of the Mitral Annulus

The mitral annulus changes in shape and size during the cardiac cycle. Its dynamics can be summarized in three types of movements[37]: (1) annular contraction, (2) annular folding, with an increase in nonplanarity; and (3) annular translation, related to atrial and ventricular filling and emptying. Abnormalities of MA dynamics have been described in different MV pathologies,[3,5,6,23] but normal MA dynamics have previously been reported only in small cohorts of individuals.[14] Moreover, the normal pattern of MA dynamics remains to be clarified. Particularly controversial is whether the mitral annulus enlarges or shrinks during ventricular systole.[6,31,32] Our data confirmed the early systolic contraction of the mitral annulus and its subsequent enlargement during the rest of the systole. This finding was previously reported only in small cohorts of "control" subjects from studies designed for the analysis of pathologic mitral annuli.[5,23,38]

The time at which the mitral annulus reaches its minimum size is also controversial, with some reporting mid-systole[4] and others late systole.[6] Our data show that the mitral annulus reaches its minimum size at early systole, and MA contraction occurs mainly along the A-P diameter. Accordingly, MA sphericity was minimal during the first half of systole.

In our subjects, mean MA systolic fractional area change was 28.5 ± 5%. Although Levack *et al.*[38] reported a lower value of MA systolic area change (19.0 ± 5%), a recent 3D echocardiographic study using a software package similar to the one used in our study reported a mean area change of 26.6 ± 8%, but in only 15 healthy volunteers.[6]

Table 2 Reference values for MV parameters in healthy volunteers at mid-systole

Variable	Overall (n = 211)	Men (n = 97)	95% CI	Women (n = 114)	95% CI	P
Mitral annulus						
A-P diameter (cm)	2.6 ± 0.3	2.8 ± 0.3	2.8–2.9	2.5 ± 0.3	2.5–2.6	<.001
Indexed A-P diameter (cm/m^2)	1.5 ± 0.2	1.5 ± 0.4	1.43–1.5	1.5 ± 0.5	1.47–1.53	.07
AL-PM diameter (cm)	3.7 ± 0.4	3.9 ± 0.4	3.9–4.1	3.6 ± 0.3	3.5–3.7	.001
Indexed AL-PM diameter (cm/m^2)	2.1 ± 0.2	2.2 ± 0.2	2.1–2.2	2.1 ± 0.2	2.0–2.1	<.001
Sphericity index	0.7 ± 0.07	0.71 ± 0.07	0.70–0.73	0.69 ± 0.07	0.68–0.71	.05
Commissural diameter (cm)	3.7 ± 0.4	3.9 ± 0.4	3.9–4.0	3.5–3.6	3.5–3.6	<.001
Annular circumference (cm)	10.7 ± 1.1	11.4 ± 1.1	11.1–11.6	10.2 ± 0.8	10.1–10.4	<.001
2D annular area (cm^2)	8.2 ± 1.8	9.2 ± 1.9	8.8–9.6	7.3 ± 1.2	7.1–7.6	<.001
3D annular area (cm^2)	8.4 ± 1.9	9.4 ± 1.9	9.0–9.8	7.5 ± 1.2	7.3–7.8	<.001
3D indexed annular area (cm^2/m^2)	4.7 ± 1.8	4.9 ± 1.0	4.7–5.1	4.5 ± 0.7	4.4–4.6	.004
Mitral leaflets						
MV ALA (cm^2)	5.7 ± 1.2	6.5 ± 1.4	6.2–6.7	5.1 ± 1.0	4.9–5.3	<.001
MV PLA (cm^2)	3.7 ± 1.0	4.1 ± 1.0	3.9–4.4	3.4 ± 0.8	3.3–3.6	<.001
Anterior leaflet length (cm)	2.2 ± 0.5	2.3 ± 0.3	2.2–2.4	2.0 ± 0.3	2.0–2.1	<.001
Posterior leaflet length (cm)	1.0 ± 0.3	1 ± 0.2	1.0–1.1	1 ± 0.4	0.9–1.0	.377
MA shape						
NPA (°)	148 ± 11	148 ± 11	146–150	147 ± 12	144–149	.653
Annular height (mm)	6.1 ± 0.2	6.5 ± 0.2	6.2–7.0	5.6 ± 0.2	5.4–6.1	<.001
Tenting height (cm)	6.2 ± 1.5	6.3 ± 1.4	6.2–6.8	6.1 ± 1.5	5.7–6.3	.155
Tenting area (cm^2)	1.1 ± 0.5	1.25 ± 0.4	1.2–1.4	1.1 ± 0.6	0.9–1.1	.003
Tenting volume (mL)	1.7 ± 0.7	2.0 ± 0.8	1.9–2.2	1.5 ± 0.5	1.3–1.5	<.001
Ao-AP angle (°)	138 ± 13	135 ± 14	133–138	140 ± 11	138–143	.001

CI, Confidence interval.
Data are expressed as mean ± SD.

Table 3 Dynamic analysis of the mitral annulus in the cohort of healthy volunteers

Variable	MVC	Minimum	Time to minimum (% of systole)	Mid-systole	End-systole
MA dimensions					
A-P diameter (cm)	2.3 ± 0.3	2.2 ± 0.3	11 ± 6	2.6 ± 0.3	2.8 ± 0.3
AL-PM diameter (cm)	3.4 ± 0.4	3.3 ± 0.3	13 ± 9	3.7 ± 0.4	3.8 ± 0.4
Commissural diameter (cm)	3.4 ± 0.4	3.3 ± 0.4	13 ± 10	3.7 ± 0.4	3.8 ± 0.4
Annular circumference (cm)	9.8 ± 1.0	9.7 ± 1.0	11 ± 6	10.7 ± 1.1	11.1 ± 1.1
Annular area 3D (cm^2)	6.9 ± 1.5	6.7 ± 1.4	11 ± 5	8.4 ± 1.8	9 ± 1.8
MV ALA (cm^2)	5.8 ± 1.2	5.4 ± 1.2	42 ± 30	5.7 ± 1.4	5.9 ± 1.3
MV PLA (cm^2)	3.7 ± 1.0	3.4 ± 0.9	30 ± 25	3.7 ± 1	4.3 ± 1.2
MA geometry					
Sphericity index	0.66 ± 0.08	0.63 ± 0.06	23 ± 20	0.70 ± 0.07	0.73 ± 0.07
NPA (°)	156 ± 13	141 ± 11	53 ± 29	147 ± 11	148 ± 10
Tenting height (mm)	8.2 ± 1.8	4.3 ± 1.5	82 ± 12	6.2 ± 1.5	5.6 ± 1.9
Tenting area (cm^2)	1.3 ± 0.4	0.9 ± 0.4	70 ± 25	1.1 ± 0.5	1.2 ± 0.5
Tenting volume (mL)	2.4 ± 1.0	1.2 ± 0.7	75 ± 17	1.7 ± 0.7	1.9 ± 0.9
Ao-AP angle (°)	135 ± 12	131 ± 12	21 ± 15	138 ± 12.6	146 ± 14

Data are expressed as mean ± SD.

In our study, NPA, a parameter describing the "saddle-shaped" morphology of the mitral annulus, reached its minimum angle later than previously reported using the ratio between instantaneous annular height and commissural width for an indirect assessment of MA nonplanarity.[5] Because of its conformational changing, the MV reached its maximum tenting height, area, and volume at the beginning of systole, which decreased progressively afterward. Similar MA dynamics were found in other studies in normal "controls."[5]

The average MA displacement measured in our healthy volunteers was identical to the 11 ± 3 mm reported by Little *et al.*[6] in small number of "control" subjects. As expected, MA displacement was correlated with LV myocardium longitudinal deformation determined by

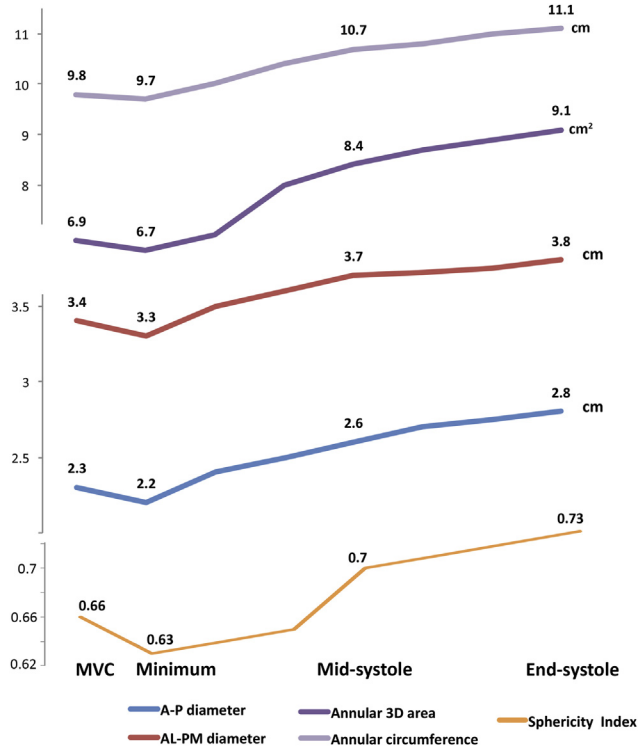

Figure 5 Dynamic changes of MA size and shape during cardiac systole.

3D speckle-tracking echocardiography. Moreover, the extent of MA displacement decreased with age, while MA contraction function was preserved.

MA Parameters in Pathologic Settings

MA size, shape, and function change differently in different heart diseases. MA remodeling in patients with functional MR is characterized by MA enlargement, especially in the A-P diameter,[4] decreased MA height,[22] and saddle shape,[5] with decreased early contraction.[5] In organic MR, the mitral annulus is markedly enlarged,[6] especially in the commissural diameter, and also has reduced dynamicity.[3] MV repair leads to increased NPA, especially when complete MA rings are implanted.[10] MA displacement is reduced in patients with heart failure and aortic stenosis,[39] and it does not recover after transcatheter aortic valve implantation.[40] MV intercommissural diameter and anterior leaflet height are used by cardiac surgeons to size valve prostheses and annuli.[41] Measurements of tenting height and volume are closely related to the severity of functional MR and are used to assess the extent of leaflet tethering, which in turn will allow planning of surgical repair[42] and prediction of the recurrence of MR during follow-up.[43] The Ao-Ap angle becomes more acute in hypertrophic cardiomyopathy[35] and is predictive of the occurrence of systolic anterior motion in patients with LV systolic dysfunction undergoing restrictive mitral annuloplasty for functional MR.[44] The availability of normative data for all these parameters will allow characterization of the pathophysiology of the MR and planning reparative surgery.

Study Limitations

Our study population was composed of Caucasian subjects only, which may limit the applicability of our reference values to other racial groups.

Table 4 Reproducibility of the MA parameters (n = 17)

Parameter	Reproducibility (intraclass correlation coefficient)	
	Intraobserver	Interobserver
A-P diameter	0.97	0.89
AL-PM diameter	0.97	0.92
Commissural diameter	0.95	0.89
Circumference	0.97	0.92
Annular area	0.98	0.95
MV ALA	0.91	0.91
MV PLA	0.90	0.88
Tenting height	0.89	0.91
Tenting volume	0.87	0.78

The need for multibeat acquisition to achieve good spatial and temporal data sets resolution limits the use of 3D TTE to individuals with regular cardiac rhythms.

MV data set acquisitions were performed using a single vendor platform, which may have implications for the applicability of these reference values to data sets acquired with other vendor platforms. However, we used vendor-independent software for 3D echocardiographic MA measurements, which may ensure generalization of our results.

The software performs MA tracking throughout systole only, without providing data about MA dynamics during diastole. Although MA diastolic dynamics were reported to be less accentuated and less important,[31] the fractional shortening of MA parameters provided by our study characterizes only the systolic dynamics of the mitral annulus.

"End-systole" has been variably defined in different MA studies as before aortic valve closure,[5] the frame before the MV starts to open[29] (similar to our study), or between these points.[31] These differences in choosing the "reference frames" may be partially responsible for the variability previously reported for MA dynamics, because MA size and shape have high dynamicity during the cardiac cycle, and a distance of several frames might make a significant difference in measurements.

The absence of a comparison with a reference standard, such as CMR, could be regarded as a limitation of our study. However, even though Anwar *et al.*[29] revealed a good correlation between CMR and 3D transthoracic echocardiographic assessments of the mitral annulus, using similar MV software, there is now evidence that the two techniques are different, so specific references values are needed for each of them.[33] Finally, limited availability and costs of CMR, as well as ethical reasons, prevented its use for studying healthy subjects with no clinical indications for CMR examination.

CONCLUSIONS

New MV-dedicated software and improved quality of 3D transthoracic echocardiographic data sets enable quantitative analysis of MA geometry in the clinical routine of echocardiographic laboratories. The ability to assess MA geometry and function using 3D transthoracic echocardiographic data sets will allow assessment of the pathophysiology of MR and make it possible to follow MA remodeling over

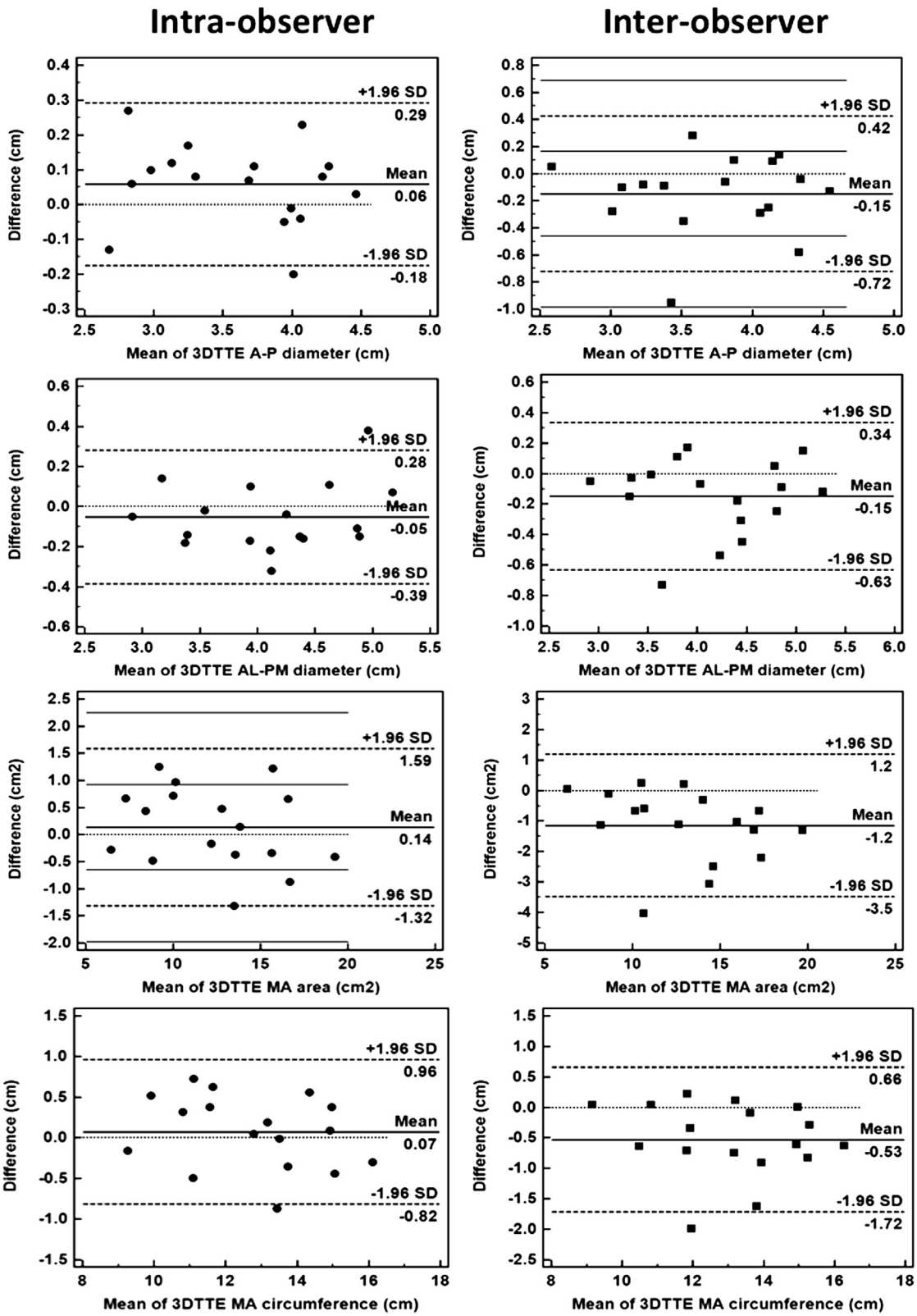

Figure 6 Bland-Altman plots showing intra- and interobserver reproducibility for quantitative analysis of the MV using 3D echocardiography in healthy volunteers.

time without the costs and discomfort of 3D TEE. However, to use it in clinical practice, reference values are needed for the various parameters describing MV geometry and function. To the best of our knowledge, this is the first study specifically designed to obtain normative data on MA geometry in both static and dynamic analyses, on a large number of healthy adults, using 3D TTE. Because both body size

Table 5 Comparison between MA parameters obtained with different imaging methods in healthy individuals

Study	Method	Number of analyzed subjects	A-P diameter (cm)	AL-PM diameter (cm)	MA area (cm^2)	Indexed MA area (cm^2/m^2)	MA circumference (cm)	MA height (mm)	Tenting height (mm)	Tenting area (cm^2)	Tenting volume (mL)	MA fractional area change (%)
This study	3D TTE	211 healthy volunteers, 114 women	2.6 ± 0.3	3.7 ± 0.4	8.4 ± 1.9	4.7 ± 1.8	10.7 ± 1.1	6.1 ± 0.2	6.2 ± 1.5	1.1 ± 0.5	1.7 ± 0.7	29 ± 5
Sonne *et al.*[14]	3D TTE	120 patients without LV dysfunction or VHD, including children and adults, 68 male	3.1 ± 0.4	3.5 ± 0.5	8.6 ± 2.2	5.1 ± 0.8	8.6 ± 2.2	4.3 ± 2.1	5.3 ± 2.4	—	—	—
Kovalova and Necas[13]	3D TEE	28 controls, 17 male, 6 with hypertension	2.8 ± 0.7	3.6 ± 0.8	8.7 ± 3.2	3.8 ± 0.7	11.0 ± 2.1	4.7 ± 1.9	—	—	—	—
Ormiston *et al.*[32]	2DE	11 normal individuals, all male	—	—	7.1 ± 1.3	3.8 ± 0.7	9.3 ± 0.9	—	—		—	26 ± 3
Maffessanti *et al.*[33]	CMR	13 normal individuals, 9 male	3.0 (2.9–3.3)	3.7 (3.4–4.0)	10.0 (8.6–11.4)	—	11.5 (10.6–12.3)	—	—	1.4 ± 0.6	1.5 ± 0.6	—
Beaudoin *et al.*[30]	MDCT	16 normal individuals, 10 female	—	—	8.4 ± 1.7	4.5 ± 0.6	—	—	—	—	—	—

MDCT, Multidetector computed tomography; *2DE*, 2D echocardiography; *VHD*, valvular heart disease.
Data are expressed as mean ± SD or as median (range).

and gender significantly influence MA size, normalized reference values have been provided accordingly.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.echo.2014.04.017.

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