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Three-Dimensional Echocardiography is a Feasible and Reproducible Method for the Measurement of Left Atrial Volumes, Regardless of Expertise Level

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ABSTRACT

Aim: *Left atrium (LA) assessment has gained significant interest in recent years because of its diagnostic and prognostic role in cardiovascular diseases. We aimed to assess the feasibility and reproducibility of three-dimensional echocardiography (3DE)* versus *two-dimensional echocardiography (2DE) for LA volumes (LAV) when measurements were performed by users with different levels of expertise in 3DE.*

Method: *We prospectively recruited 35 consecutive patients referred to our echocardiography laboratory. Subjects underwent two separate 2DE and 3DE acquisitions of the LA in the same day by different users. Left atrial volumes were measured by the two users, who had similar levels of training in 2DE but different levels of training in 3DE – one advanced user and one beginner user.*

Results: *Our results showed a good intra-observer reproducibility for 2DE (r=0.98) and an equally good reproducibility for 3DE LAVs when measured by the beginner user (r=0.97). Similarly, there was a good inter-observer reproducibility for the 2DE LAVs when measured by observers with similar levels of expertise in 2DE (r=0.98). However, similarly reproducible results were obtained for the 3DE LAVs when measured by users with significantly different levels of training in 3DE (r=0.98). Furthermore, there was a lower, yet acceptable (r>0.8), reproducibility for the 2DE LAVs when measured on separately acquired datasets by users who acquired the respective datasets, both with advanced level of training in 2DE. However, reproducibility was superior for 3DE LAVs when measured by the beginner and advanced users in 3DE (r=0.97).*

Conclusion: *We conclude that 3DE is a technique that promises to improve patients' overall assessment, showing a good feasibility and better reproducibility than 2DE for the measurement of LAVs, regardless of level of training in the method.*

Keywords: three-dimensional echocardiography, two-dimensional echocardiography, left atrium.

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INTRODUCTION

Assessment of the left atrium (LA) has gained significant interest in recent years because of its diagnostic and prognostic role in cardiovascular diseases.

Left atrium size is a key variable in the diagnosis of diastolic left ventricular (LV) dysfunction (1). Consequently, LA size and function play a role in the diagnosis of heart failure with preserved ejection fraction (HFpEF), whose main underlying mechanism is diastolic LV dysfunction (2). Moreover, LA size has been shown to be a predictor of survival in different cardiovascular pathologies such as ischemic cardiomyopathy (3) and heart failure with reduced ejection fraction (HFrEF) (4). Furthermore, LA size has been used as a determinant of success of mitral valve procedures (5) as well as various techniques for atrial fibrillation (AF) ablation (6).

Transthoracic echocardiography is the main method used to assess LA size due to its availability and cost-efficiency. For the estimation of LA size using two-dimensional echocardiography (2DE), current guidelines recommend the calculation of maximum LA volume (LAV_max) using either the disk summation or area-length biplane algorithms (7). The minimal LA volume (LAV_min), measured with the same technique, has been recently shown to be a predictor of cardiovascular events (8, 9). However, these measurements rely only on geometric assumptions and are potentially biased by foreshortening of the LA cavity. Three-dimensional echocardiography (3DE), which encompasses the true LA volumes, eliminates these biases and has been more accurate than 2DE in measuring LAVs when compared to cardiac magnetic resonance (CMR) (10). Furthermore, 3DE has been shown to be a feasible method, with superior reproducibility for LAVs when compared to 2DE (10, 11). Therefore, the latest guidelines for cardiac chamber quantification published by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) (7) recommend, whenever feasible, the 3D measurement of LAVs. Regardless, 3DE is not routinely used to measure LAVs into routine clinical practice, as the method is considered to have a slow learning curve and uncertain accuracy, feasibility and reproducibility in the hands of inexperienced operators.

The reliability of an imaging method is pivotal in clinicians' daily practice, as it allows one to provide adequate follow-up of patients. Compared to the measurement of left ventricular ejection fraction (LVEF), which can be essential for the indication of device therapy in HF patients, slight variations in the measurement of LAVs might not entail a radically different therapeutic approach, but reproducible serial measurements can highlight the progression of the disease and influence overall management. Moreover, the ability to produce precise measurements at various levels of expertise can add to the value of an imaging method in clinical practice, allowing a wider use.

Study aim

The main objective of our study was to assess the feasibility and reproducibility of 3DE measurements of LAVs, when used by operators with different levels of expertise in 3DE, in comparison to 2DE.

Method

We prospectively recruited 35 consecutive patients, in sinus rhythm, referred to the echocardiography laboratory of the University and Emergency Hospital Bucharest, between April and May 2018. The patients were scheduled to undergo two separate 2DE and 3DE acquisitions of the LA, in the same day, without any medical interventions between acquisitions. Patients with technically inadequate echocardiographic images were excluded.

The investigations were approved by the institutional ethics committee, and all patients gave informed consent.

Study design

The study design included two users with similar levels of expertise in 2DE (over two-year experience with 2DE, over 1000 echocardiographic examinations performed), but different levels of expertise in 3DE. As such, the users were defined, according to their level of expertise in 3DE, as Beginner (six months in practical and theoretical training in 3DE) and Advanced (over four-year experience with 3DE). The two users performed complete 2DE and 3DE acquisitions of the LA during the same clinic visit, with care to encompass the entire LA cavity in the datasets.

Intra-observer variability was determined by repeated measurements on the same datasets by the Beginner user. Measurements for intra-observer variability were performed one week apart, and the order of repeated analysis was randomized beforehand.

Inter-observer variability was determined by using the same set of images, measured by the two users (Advanced and Beginner).

Test-retest variability was determined by measuring different datasets acquired by the Advanced user and the Beginner one. The Advanced and Beginner users performed the measurements of the respective datasets.

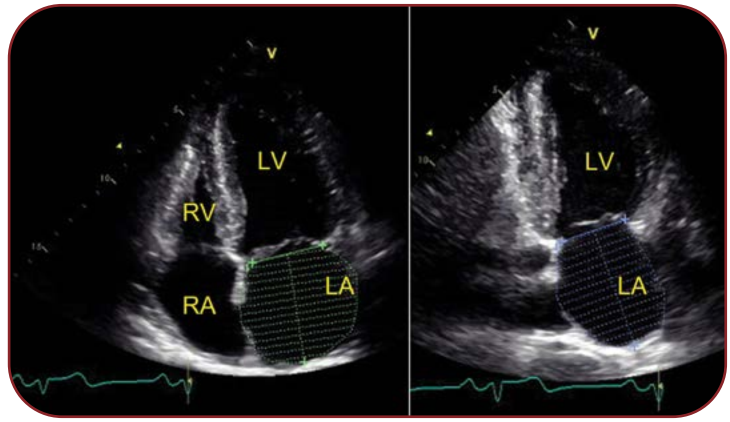

FIGURE 1. Biplane measurements of the LA volume, from dedicated four- and two-chamber views. Acquisitions made to avoid foreshortening of the LA (LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle)

Clinical findings

Clinical information was documented at the time of the echocardiographic study and included age and gender, weight, height, and body surface area (BSA) as well as main diagnosis at the time of presentation.

Echocardiography

The 2DE and 3DE images were acquired during the same echocardiographic study, with a commercially available echo machine (Vivid E9, GE Vingmed, Horten, NO), equipped with both standard 2D (M5S) and 3D (4V) probes. The acquisitions were performed according to the current guideline recommendations (2). Two dimensional acquisitions were obtained using dedicated LA views, assuring that the largest longitudinal and transversal diameters were obtained, from the apical four- and two-chamber views (Figure 1). Three-dimensional datasets of the LA were obtained from the apical four-chamber view, by using multi-beat full-volume acquisition during breath hold (Figure 2). The 3DE acquisitions were optimized to achieve a high temporal resolution and to avoid stitching artifacts. All datasets were stored in a digital archive and exported to be analyzed offline using commercially available software (Echopac BT 12, GE Vingmed, Horten, NO).

The Advanced and the Beginner users measured the LAVs acquired with 2DE in a blinded fashion by using the Echopac software (BT12, GE Healthcare, Horton, Norway). The LAV_max was measured in the frame just prior to the mitral valve opening. The LA tracing was done at

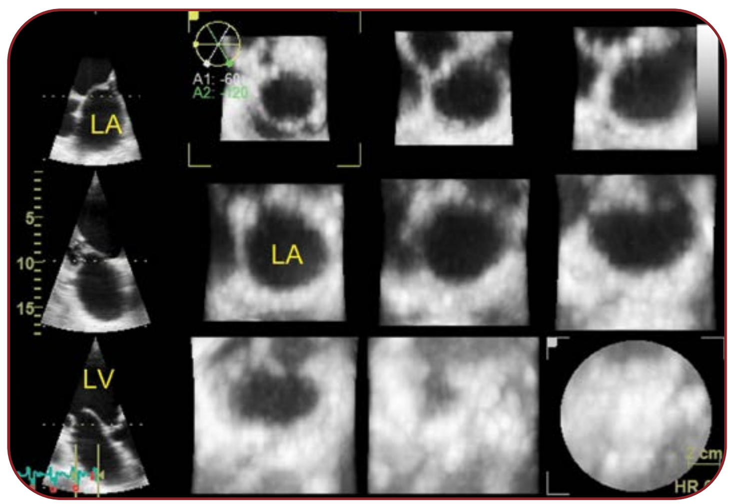

FIGURE 2. Multi-slice ECG-gated acquisition of the LA volume. Care was taken to encompass the entire volume inside the dataset and to avoid stitching artifacts (LA=left atrium; LV=left ventricle)

FIGURE 3. Volume beutel of the LA, on which true volume was determined, after tracing of the LA endocardium (LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle)

the inner border of the cavity, excluding the area under the mitral valve annulus, the inlet of the pulmonary veins and the LA appendage, in both four- and two-chamber dedicated views. The software derived the LAV_max using the biplane method of disks (BP) as well as the area-length method (AL) (2). Careful measurements were performed, ensuring that the length of the long axes measured in four- and two- chamber views were similar (less than 5 mm difference) (2). For the measurement of the LAV_min, the frame just before mitral valve closure was used as well, and measurements were performed in a manner similar to that previously described for LAV_max.

The Advanced and the Beginner users measured the LAVs acquired with 3DE in a blinded fashion by using the dedicated software for LA analysis (GE 4D auto LAQ) (Figure 3). Measurement workflow started with semi-automated detection of the LA endocardial borders, followed by a phase of manual editing, to optimize the endocardial contours. The inlet of the pulmonary veins and the LA appendage were excluded from the contour. Manual check of the automatically selected frames used to measure LAV_max and LAV_min was performed prior to the manual editing of the endocardial borders.

Statistics

Continuous data are expressed as mean±SD and categorical data as frequency or percentages (%). Measurements of the LAV_max and LAV_min were done by the usage of different echocardiographic methods and compared using Student T-test analysis. Intra-observer reproducibility of measurements was assessed using intra-class coefficients (ICCs), while agreements between methods and trainees were expressed using Bland Altman plots. A p value of less than 0.5 was considered significant. Data analysis was performed using statistical software analysis (SPSS 20, SPSS Inc., Chicago, Illinois) and MedCalc (MedCalc Software). ❑

RESULTS

Thirty five patients were enrolled in the present study. Five patients were excluded due to technically inadequate echocardiographic images or inability to follow breath hold indications necessary for 3DE acquisition. The Advanced and Beginner users performed measurements of the LAV_ max and LAV_min on the echocardiographic images of the 30 patients (59±14 years, 20 males) with a main diagnosis of ischemic cardiomyopathy (10), dilated cardiomyopathy (7) and other pathologies such as valvular disease and various arrhythmias (13) (Table 1). The average resolution of the 2DE and 3DE datasets was 58±5 frames per second and 38±9 volumes per second, respectively, when the images were acquired by the Advanced user, and 60±5 frames per second and 45±7 volumes per second, respectively, for the images acquired by the Beginner user.

TABLE 1. Clinical characteristics of the study population

Sex	20 male
Age	59±14
Main diagnosis	
Ischemic cardiomyopathy	10
Dilated cardiomyopathy	7
Other	13

The Advanced user measured both 2DE and 3DE datasets in all patients. Mean LAV_max was 80±24 mL when calculated with 2DE by using the area-length method,78±16 mL using the disk summation method, and 84±34 mL when measured with 3DE. Mean LAV_min was 45±23 mL when calculated with 2DE using the area-length method, 40±23 mL using the disk summation method, and 40±16 mL when measured with 3DE.

Intra-observer variability

As expected, there was a good intra-observer reproducibility for the 2DE measurements, particularly for LAV_max (r=0.98 by AL and r=0.99 by BP). However, a similarly good reproducibility was documented for the 3D measurements of LAV_max (r=0.97) and superior reproducibility was documented for LAV_min (r=0.99 *vs* 0.95 with 2DE, regardless of formula to calculate the LAVs), when performed by a user with beginner level in 3DE (Table 2).

Agreement analysis using Bland-Altman plots revealed no systematic bias for LAV_max or LAV_min measured by 2DE or 3DE (Figure 4). The limits of agreement between the 2DE and the 3DE measurements of LAV_max were similar, however 3DE measurements of LAV_min

TABLE 2. Intra-observer comparison of left atrial volumes when measured by a user with advanced level in 2DE and beginner level in 3DE (ICC=intra-class coefficient, CI= confidence interval, LOA=limits of agreement)

	2D LAV_max Area Length	2D LAV_max Biplane	2D LAV_min Area Length	2D LAV_min Biplane	3D LAV_max	3D LAV_min
ICC	0.98	0.99	0.95	0.95	0.97	0.99
CI	0.97-0.99	0.98-0.99	0.91-0.98	0.90-0.98	0.95-0.99	0.995-0.999
Bias	0.42	0.16	1.17	1.28	-0.25	0.28
LOA	-10; 11	-8; 9	-15; 18	-15; 17	-10; 9	-3; 3

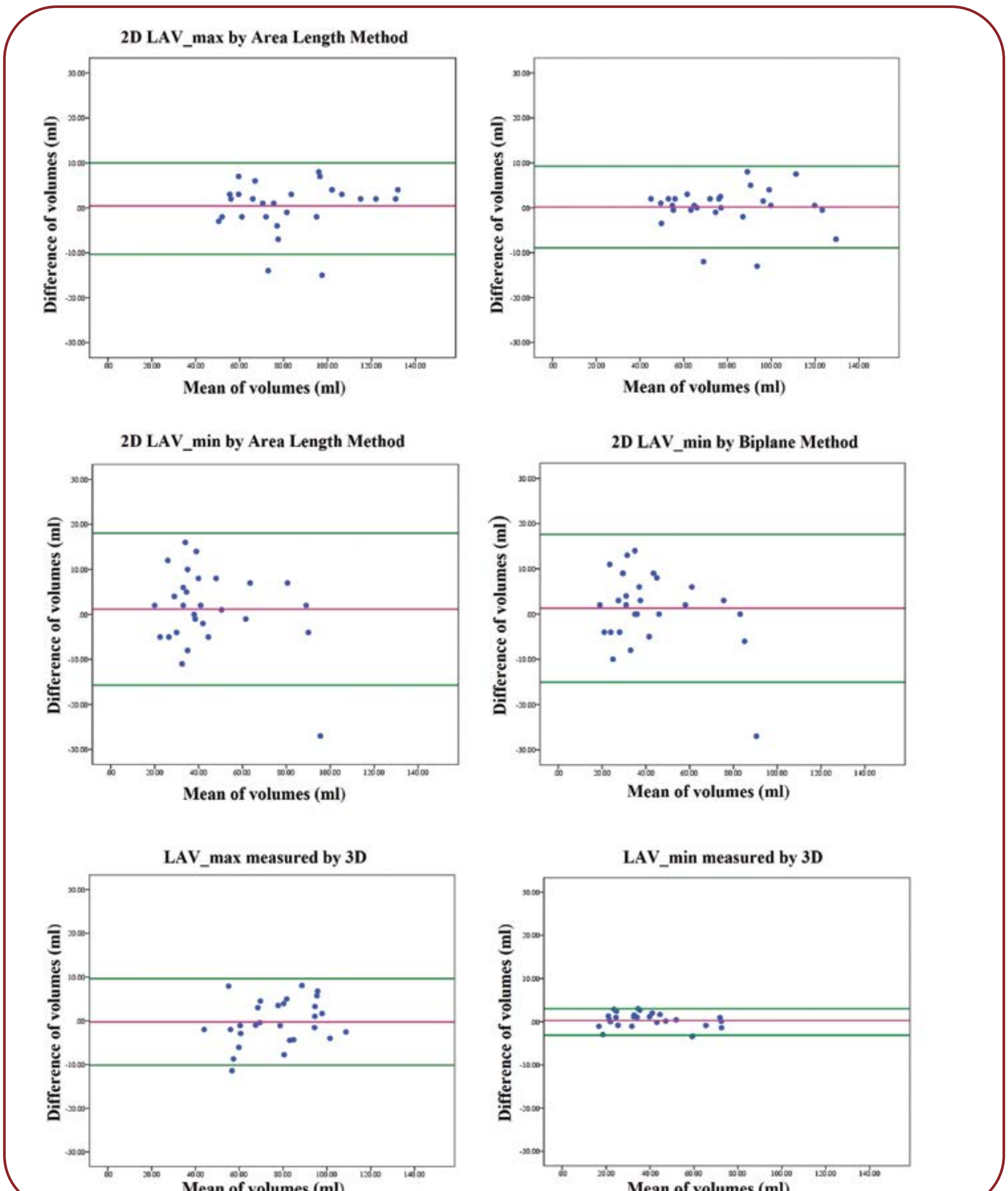

FIGURE 4. Bland-Altman plots for the intra-observer measurement of left atrial volumes (LAV) by 2DE and 3DE

TABLE 3. Inter-observer comparison of left atrial volumes between a user with advanced level in 2DE and 3DE and a user with advanced level in 2DE, but only beginner level in 3DE (ICC=intra-class coefficient, CI=confidence interval, LOA=limits of agreement)

	2D LAV_max Area Length	2D LAV_max Biplane	2D LAV_min Area Length	2D LAV_min Biplane	3D LAV_max	3D LAV_min
ICC	0.98	0.98	0.97	0.96	0.98	0.98
CI	0.96-0.99	0.97-0.99	0.94-0.98	0.91-0.98	0.96-0.99	0.97-0.99
Bias	-2.17	-1.58	2.17	3.17	-0.51	-0.45
LOA	-13;9	-11;8	-10;15	-13;19	-9;8	-8;7

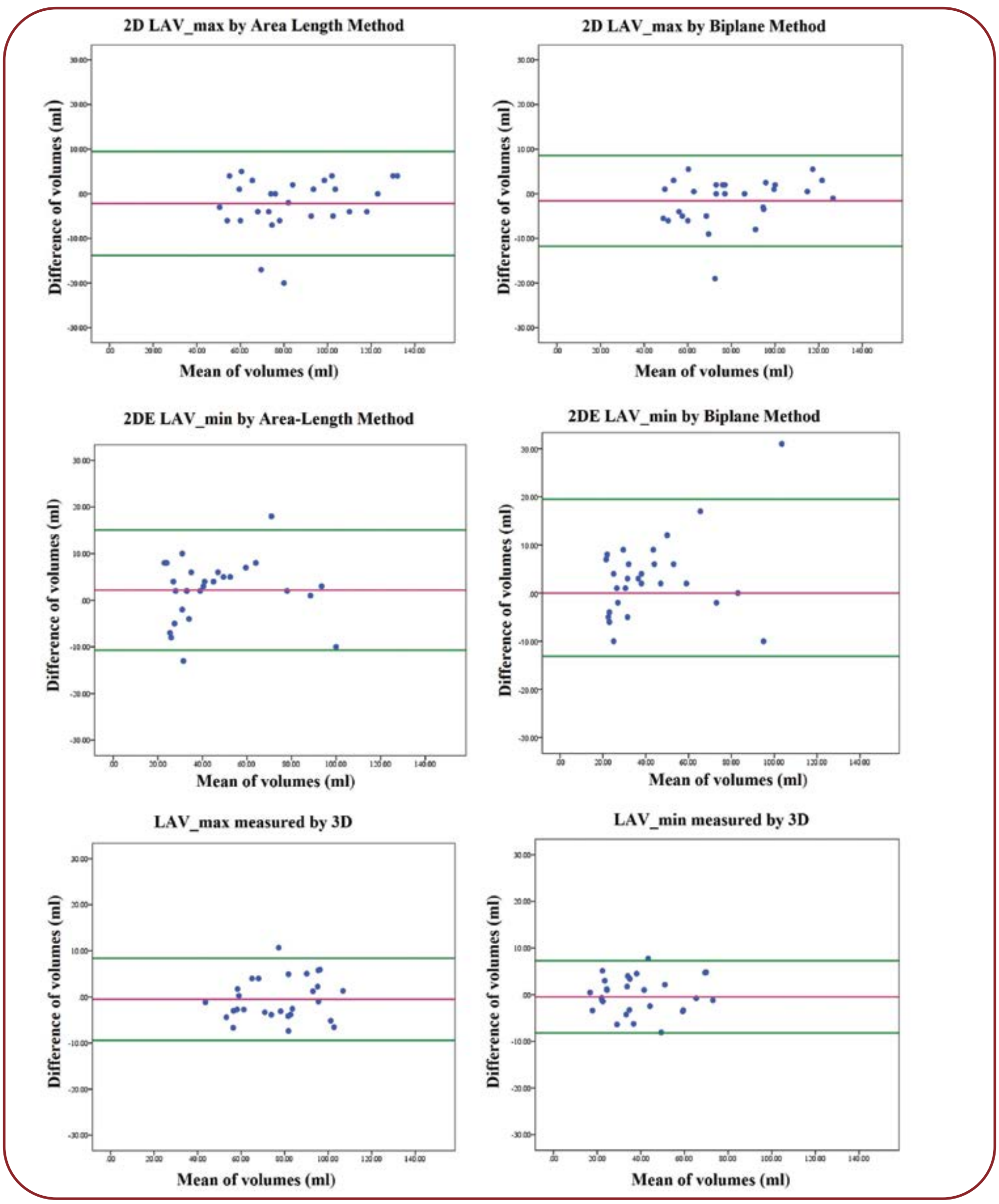

FIGURE 5. Bland-Altman plots for the inter-observer measurement of left atrial volumes (LAV) by 2DE and 3DE

TABLE 4. Test-retest comparison of left atrial volumes, when 3DE acquisitions were performed by an advanced user in 3DE and a beginner user in 3DE (ICC=intra-class coefficient, CI=confidence interval, LOA=limits of agreement)

	2D LAV_max Area Length	2D LAV_max Biplane	2D LAV_min Area Length	2D LAV_min Biplane	3D LAV_max	3D LAV_min
ICC	0.84	0.92	0.85	0.86	0.97	0.95
CI	0.66-0.92	0.91-0.98	0.69-0.93	0.71-0.93	0.94-0.98	0.91-0.98
Bias	4.39	1.82	2.35	2.32	-0.73	1.93
LOA	-22;31	-13;17	-22;27	-20;25	-11;10	-10;14

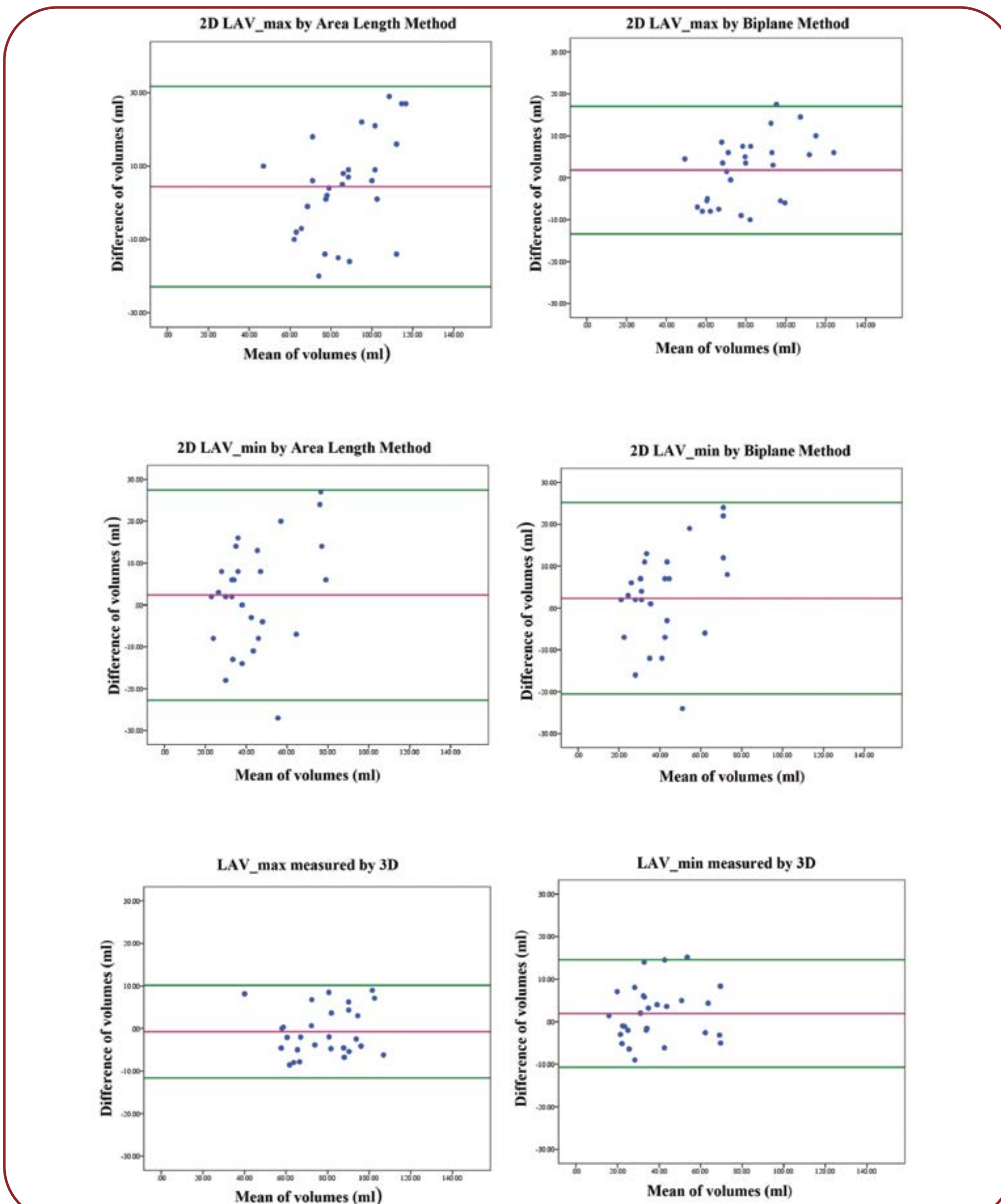

FIGURE 5. Bland-Altman plots for the test-retest measurement of left atrial volumes (LAV) by 2DE and 3DE

were considerably tighter (2SD: 16/15 mL for 2DE *versus* 2SD: 3 mL for 3DE) (Table 2).

Inter-observer variability

There was good inter-observer reproducibility for 2DE LAVs when measured by observers with similar levels of expertise in 2DE (r=0.98 for LAV_max regardless of method to calculate the LAVs, and r=0.97 by AL and r=0.96 by BP, respectively for LAV_min) (Table 3). However, similarly reproducible results were obtained for the 3DE LAVs, when measured by users with significantly different levels of training in 3DE (r=0.98 for both the LAV_max and the LAV_min) (Table 3).

Agreement analysis using Bland-Altman plots revealed no systematic bias between the two users for the LAV_max or LAV_min measurements performed by both 2DE and 3DE (Figure 5). The 3DE measurements showed lower bias compared to the 2DE measurements for LAV_max and LAV_min (2SD: 8 mL for LAV_max and 7 mL for LAV_min with 3DE, compared to 2SD: 11/10 mL for LAV_max and 12/16 mL for LAV_min with 2DE) (Table 3).

Test-retest variability

There was lower, yet acceptable (r>0.8) reproducibility for the 2DE LAVs when measured on separately acquired datasets, by users that acquired the respective datasets, both with advanced level of training in 2DE (r=0.84 by AL and r=0.92 by BP for LAV_max, r=0.85 by AL and r=0.86 by BP respectively for LAV_min) (Table 4). However, reproducibility was superior for 3DE LAVs, when measured by the Beginner and Advanced Users in 3DE (r=0.97 for LAV_max and r=0.95 for LAV_min) (Table 4).

Agreement analysis using Bland-Altman plots revealed no systematic bias for the LAV_max or LAV_min, regardless of the method used (Figure 6). The limits of agreement were significantly tighter for the 3DE measurements (2SD: 10 mL for LAV_max and 12 mL for LAV_min with 3DE, compared to 2SD: 27/15 mL for LAV_max and 25/22 mL for LAV_min with 2DE) (Table 4).

Feasibility

Scanning times for the 2DE and 3DE images were measured for both users (Table 5). The time necessary for the measurements of the LA parameters on 2DE and 3DE datasets were also computed for both the Advanced and the Beginner users.

TABLE 5. Measurement and acquisition times for 2DE and 3DE according to the level of expertise

	2D left atrial volume	3D left atrial volume Advanced	3D left atrial volume Beginner
Acquisition time, s	47±16	77±10	89±18
Measurement time, s	84±13	79±23	117±5

The acquisition timings for 2DE were shorter than for 3DE. However, there was no significant difference between the time necessary to acquire a full LAV by 3DE between the Beginner and Advanced users (Table 5). As expected, there was a significant difference between the time necessary for the Beginner user to measure a full 3DE volume acquisition of the LA, when compared to the Advanced user ($p<0.05$). However, the time necessary for the Advanced user to measure a 3DE dataset was not significantly different from the time necessary to measure a 2DE dataset. ❑

DISCUSSIONS

Three-dimensional echocardiography is a technique which has emerged in the last decade and has slowly gained ground in the chamber quantification guidelines (7). However, 3DE is not the technique currently used in clinical practice, being limited to scientific work and experienced echo labs. Measurements of LAVs by 3DE has been shown to be more accurate and reproducible than 2DE in several studies (10-12). Some of these studies have included large cohorts in a prospective manner, some in a multicentric setting. However, the studied populations were variable and the software used to assess the LA was also different. Furthermore, investigators were generally well versed in the use of the specific 3DE software for LAV measurement.

As such, our aim was to identify whether the measurement of LAVs using 3DE in a real-world cohort, with commercially available dedicated software, was feasible and reproducible in the

TABLE 6. Percentage bias for all the measurements, according to the method used

	2D LAV_max Area Length	2D LAV_max Biplane	2D LAV_min Area Length	2D LAV_min Biplane	3D LAV_max	3D LAV_min
Intra-observer	0.4%	0.3%	4%	5%	1%	0.8%
Inter-observer	3%	2%	4%	5%	1%	0.2%
Test-retest	3%	4%	3%	3%	1%	2%

hands of users with different levels of expertise in 3DE, when compared to the standard of 2DE measurements.

The reproducibility of the 2DE measurements in our study was similar to that previously reported (12). Regarding the agreement between the 2DE measurements, there was no systematic bias. However, the limits of agreement, while acceptable for intra-observer measurements, were arguably significant for inter-observer and test-retest measurements, reaching values up to 31 mL for the LAV_max by the area-length method for test-rest measurements (Table 4). Given the normality limit for LAV_max, which is 35 mL/m^2, this value appears significant, even if it must be noted that the percentage bias was below 10% for all measurements (Table 6). Similar values were reported in previous studies (10), some reporting even higher bias for 2DE, particularly for the test-retest measurements (12). This bias is believed to emerge from the variation in the acquisition of the LA with 2DE, even when significant efforts are made to obtain the maximum longitudinal axis, as was the case in our study.

In our study, we reported non-inferior reproducibility of the 3DE measurements compared to the 2DE measurements, which is an important finding, given the limited training in 3DE the Beginner user had received. The agreement between the 3DE measurements was superior to the 2DE ones when measurements were performed by users with different levels of training in 3DE. In previous studies, reproducibility for LAV measurements by 3DE has been shown to be superior to 2DE, when measured by experienced operators (11, 12). Badano *et al* (10) also reported on the reproducibility of 3DE between advanced operators and trainees, showing a decrease in reproducibility with less experience but still superior to the reproducibility of 2DE. In the same study, it has been shown that the reproducibility of LAV_min and LA ejection fraction measurements was more significantly impacted by the level in training in 3DE than for LAV_max measurements. In our study, 3DE LAV_min measurements had better limits of agreement than LAV_max ones, regardless of the level of training in 3DE. We believe this is the result of a more heterogenous population in our study, with a higher variability in LA shapes and sizes, while the previously cited study included a large population of normal subjects. This could imply that a larger LA might have clearer margins in its end-diastolic phase, when the inlet of the pulmonary veins is not visible, therefore a confounding factor is eliminated, allowing for a better delineation of its contours.

The reproducibility of the 3DE measurements remained comparably high even for the test-retest measurements, when one of the acquisitions was obtained and measured by a user with limited training in 3DE, and one by the Advanced user. To our knowledge, this variant of the test-retest method has not been evaluated for the reproducibility of 3DE LAV.

Regarding feasibility, the acquisition timings were longer for 3DE compared to 2DE, but were significantly shorter compared to those reported in the initial studies using dedicated LA software (11), showing the significant advancement in the technology. The same can be stated about measurement timings for LAVs with 3DE, which are now comparable to 2DE, when the operator is experienced in the method. Importantly, the current 3DE LA dedicated software automatically reports several other parameters other than LAV_max and LAV_min, including atrial strain, in a relatively short time, making the method more time efficient.

Study limitations

The negative impact of image quality on 3DE data analysis has been previously reported. One of the limitations of our study is not factoring in the image quality of the 3D images. Furthermore, 3DE acquisitions of the LA are hindered by the presence of AF. This issue has been partially resolved by single-beat acquisitions, at the expense of image quality, according to Badano *et al*. (10). However, we used multi-beat acquisitions and did not include any patients in AF, so we relied on images with a high resolution and had no representatives of this frequent arrhythmia in the general population, which is yet another limitation of our study.

Another limitation of our study is the lack of comparison to the "gold standard", cardiac magnetic resonance. However, our study aimed not to test the accuracy of 3DE *versus* CMR, which was already tested in previous studies, but to assess the reliability of 3DE compared to 2DE, according to level of expertise in 3DE. ❑

CONCLUSION

Three-dimensional echocardiography is a technique that promises to improve the overall assessment of patients, showing a good feasibility and better reproducibility than two-dimensional echocardiography for the measurement of LAVs, regardless of the level of training in the method. However, several issues still need to be addressed such as image quality in patients with irregular rhythms. Considering the advancements the technique has already had since the early 2000s, with significant improvements in acquisition and measurement timings as well as in quality of images, we believe this to be foreseeable in the near future. ❑

Conflicts of interest: none declared.

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