

Title: Feasibility and Accuracy of Automated Three-Dimensional Echocardiographic Analysis of Left Atrial Appendage for Transcatheter Closure

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Highlights

- Accurate device sizing is of paramount importance for procedural success of LAAC
- A software for automated device sizing in 3D-TEE is assessed in a retrospective cohort.
- Automated device sizing achieved the highest success rate with 90.5% accuracy.
- Automated device sizing is reproducible and saves time for LAAC analysis.

Abstract

Background: Procedural success of transcatheter left atrial appendage closure (LAAC) is dependent on correct device selection. Three-dimensional transesophageal echocardiography (3D-TEE) is more accurate than the two-dimensional (2D) modality for evaluation of the complex anatomy of LAA. However, 3D-TEE analysis of LAA is challenging and highly expertise dependent. In this study, we sought to evaluate the feasibility and accuracy of a novel software tool for automated 3D analysis of the LAA using 3D-TEE data.

Methods: The intra-procedural 3D TEE data of 158 patients who underwent LAAC were retrospectively analyzed with a novel automated LAA analysis software tool. Based on the 3D TEE data, the software semi-automatically segmented the 3D LAA structure, determined the device landing zone (LZ), and generated measurements of the LZ dimensions and the LAA length, allowing manual editing if necessary. The accuracy of LAA pre-implantation anatomic measurement reproducibility, and time for analysis of the automated software were compared against expert manual 3D analysis. The software feasibility to predict the optimal device size was directly compared to implanted models.

Results: Automated 3D analysis of the LAA on 3D-TEE was feasible in all patients. There were excellent agreements between automated and manual measurements of LZ maximal diameter (bias:-0.32, LOA:-3.56; 2.92), area-derived mean diameter (bias:-0.24, LOA:-3.12, 2.64), and LAA depth (bias:0.02, LOA:-3.14; 3.18). Automated 3D analysis, with manual editing if necessary, accurately identified the implanted device size in 90.5% of patients, outperforming 2D-TEE (68.9%, $p<0.01$). The automated software showed results competitive against the manual analysis of 3D-TEE with higher intra- and inter-observer reproducibility and allowed quicker analysis ($101.9\pm9.3s$ vs. $183.5\pm42.7s$, $p<0.001$) compared to manual analysis.

Conclusions: Automated LAA analysis based on 3D-TEE is feasible and allows accurate, reproducible and rapid device sizing decision for LAAC.

Keywords: Left Atrial Appendage Closure, LAA device sizing, Automated software analysis; Interactive analysis; 3D transesophageal echocardiography.

Abbreviations:

ACP – Amulet Cardiac Plug

CA – Circumflex Artery

CT – Computed Tomography

FOV – Field of view

ICC - Intraclass correlation coefficient

LAA – Left Atrial Appendage

LAAC – Left Atrial Appendage Closure

LZ – Landing Zone

MPR – Multiplanar reconstruction

TEE – Transesophageal Echocardiography

WM – Watchman

Introduction

Occluder device sizing for transcatheter left atrial appendage closure (LAAC) is a challenging task requiring careful evaluation of the highly variable LAA anatomy on periprocedural transesophageal echocardiography (TEE), fluoroscopy, or computed tomography (CT)¹. Suboptimal device sizing has direct impact on the procedural time, safety and efficacy^{1,2}. Device under- or over-sizing may result in complications including device embolization, device-related thrombus, peri-device leak, prolonged procedural time, or cardiac tamponade³. Although two-dimensional (2D) TEE is currently the standard imaging modality for LAAC device sizing, it frequently underestimates LAA orifice size owing to foreshortening⁴, especially in cases where the orifices are oval-shaped. Three-dimensional (3D) TEE has clear advantages over 2D TEE in the evaluation of LAA anatomy^{1,3-5}. Volume rendering of the 3D TEE image allows *en face* visualization of the ellipticity of LAA orifice; moreover, through multiplanar reconstruction (MPR)^{3,4,6-8} the 3D volume can be reformatted to multiple 2D views (standard or modified) for measurements of LAA diameters and depths without foreshortening; additionally, MPR of the short-axis plane of LAA allows measurement of the area and other 3D-derived parameters of the device landing zone (LZ), which have been shown to be more useful for occluder device sizing compared to conventional 2D parameters⁵.

Nevertheless, 3D TEE has not yet been widely adopted in clinical practice for periprocedural LAAC device sizing, with several possible explanations: (i) 3D navigation using orthogonal planes is not straightforward, has to be done manually, requiring specific training and software; (ii) 3D TEE image analysis can be time-consuming, which may hamper its implementation in intraprocedural analysis; and (iii) interpretation and measurement of the LAA 3D anatomy, including the identification of device LZ plane, is highly expertise-dependent with relatively

reduced observer reproducibility. Automated analysis of 3D echocardiographic data has shown promise in overcoming these limitations in other scenarios such as chamber quantification and valve analysis^{9–11}. For LAA, automated segmentation in CT using image-based methods¹² and deep learning¹³ were proposed. However, TEE remains the most frequently used modality for preprocedural LAA imaging and is the only viable option that can provide 3D intra-procedural image guidance. Our group has developed an automated modeling algorithm that allows rapid segmentation of LAA volume data obtained by 3D TEE¹⁴ with automatic extraction of 3D LAA geometry from the segmented models¹⁵. Our methods were validated in a small number of datasets (~20 cases), demonstrating its feasibility in terms of 3D segmentation and 3D-based geometric measurements. In the present study, we sought to evaluate the diagnostic performance and reproducibility of the proposed automated 3D-TEE-based method for LAAC device sizing in comparison to the conventional manual approach in a larger patient cohort undergoing LAAC using two commonly used devices.

Methods

Study Population

A total of 183 AF patients who underwent LAAC at the Prince of Wales Hospital (Hong Kong) using WatchmanTM (WM, n=112; Boston Scientific, MA, USA) and AmplatzerTM Cardiac Plug 2/AmuletTM (ACP, n=71; Abbott, IL, USA), were retrospectively reviewed. All subjects had nonvalvular AF, CHA2DS2–VASc score ≥ 1 , and relative or absolute contraindications to long-term anticoagulation. Exclusion criteria were patients with no intra-procedural full cardiac-cycle 2D/3D TEE sequence available (n=20) and the impossibility to export TEE data for an open format (n=5). Finally, a total of 158 cases (98 WM and 60 ACP) were selected for the study. The study received the approval of the Ethics Committee of the Prince of Wales Hospital (Code 2020.139).

LAAC and Procedural Imaging

LAAC was performed using a transfemoral transseptal approach under monitored anesthesia care and guidance by 3D TEE and fluoroscopy in all patients. The transseptal puncture was guided using matrix-array biplane mode in the bicaval (90°) and short-axis (45°) views. Intraprocedural 2D TEE images of the LAA were acquired with transducer array rotated through 0°, 45°, 90°, and 135° in the mid-esophageal position¹⁶ after raising LA pressure to ≥ 10 mm Hg with intravenous normal saline. A team of expert interventionists and imagers assessed the acquired images and performed manual measurements of the device landing zone (LZ) and the LAA depth. For WM, LZ diameters from the circumflex artery (CA) inferiorly to a point superiorly 1–2 cm within the pulmonary vein ridge were recorded by sweeping through the standard imaging planes from 0° to 135°. The depth of LAA was subsequently measured from the orifice LZ to the tip of the deepest LAA lobe¹⁶. For ACP, LZ diameters were measured 1–1.5 cm distal to a line connecting the CA to the tip of the pulmonary vein ridge. The LAA depth was calculated as the distance of a perpendicular line from the LAA orifice to the roof of the appendage¹⁶. An illustration scheme of each sizing strategy is presented in Supplementary Material A.

3D TEE is the standard procedural imaging technique for LAAC at our center¹⁷. All patients underwent intraprocedural 3D TEE with a Philips EPIQ 7, CVx or IE33 ultrasound machine (Philips, Bothell, WA). Image acquisition was performed in the mid-esophageal position using the “3D zoom” mode, keeping the LAA body, CA, left pulmonary vein ridge, and part of LA and mitral valve in the field of view (FOV)². The average frame rate of the 3D images used in this study was $15 \text{ Hz} \pm 9 \text{ Hz}$ ($\sim 12 \pm 7$ frames per cardiac cycle). The resulting 3D image presented a resolution and size that varied from 0.22 to 0.86 mm and $112 \times 112 \times 208$ to $336 \times 320 \times 224$ voxels, respectively. The 3D datasets of LAA were assessed manually on-cart using the

multiplanar reconstruction (MPR) mode, which allowed manual alignment of the LAA in 3 orthogonal planes (2 long-axis, 1 short-axis). The LAA long-axis planes were aligned, and the short-axis plane was adjusted to visualize the device LZ plane. The area, maximum, and minimum diameter of the LZ were manually measured on the short-axis plane, and the depth was measured from the long-axis views. Moreover, the LAA morphology was classified as described in Di Biase *et al.*¹⁸.

Based on the obtained measurements, patients underwent implantation of the WM and ACP devices. WM is available in 5 different devices - 21, 24, 27, 30 and 33 sizes - while ACP has 8 different devices - 16, 18, 20, 22, 25, 28, 31 and 34 sizes. For each patient, device sizing at the time of implantation was made at the operator's discretion, using data from all available modalities (2D and 3D TEE and fluoroscopy), taking into account the LZ diameters and LAA depth^{1,3,7,16,19}, as well as other factors including LAA morphology and trabeculae, particularly in borderline situations (e.g. measurements between two consecutive sizes in the manufacturer's guidelines)¹⁷. After implantation, the device was evaluated to confirm correct sizing, position, and stability, as previously described^{1,2}. Peri-device leaks were assessed using Doppler echocardiography.

Automated LAA Software

Blinded to the procedural data, automated analysis of the 3D TEE datasets was performed retrospectively on the intraprocedural 3D TEE datasets using the LAA software tool integrated on a customized non-commercial MATLAB-based application (MathWorks, Natick, MA), termed Speple3D (KULeuven, Leuven, Belgium)¹¹. The data were exported in Cartesian DICOM format and converted to an isotropic voxel spacing for evaluation using the proposed software. For each patient, only the sequence before the implantation moment was evaluated by the proposed software. In this study, two automated operating modes based on the proposed LAA software were

assessed, namely: automated results without manual editing (henceforward referred Auto) and automated analysis followed by manual editing, if necessary (henceforward mentioned Interactive).

The software workflow is divided into three stages (Figure 1): (1) identification of the LAA centerline, through three or more points defined manually in the LAA anatomy, and the CA, based on one point or a 2D contour (Figure 1-A); (2) 3D segmentation of the LAA lumen boundaries (Figure 1-B)¹⁴; and (3) estimation of all required measurements for device sizing, i.e. device LZ short-axis level and LAA depth distance (Figure 1-C). While manual initialization is required in stage 1, the remaining stages of the software tool are automatic¹⁵. The operator starts by selecting the end-systolic frame with maximal LAA volume in the cardiac cycle. By navigation through 3 orthogonal reconstructed planes of the 3D volume, three points are manually located at the proximal, central, and distal parts (tip) of LAA, which are then interpolated for a 3D centerline, allowing manual corrections if required. Then, a specific navigation mode through a set of orthogonal planes (i.e. one short-axis and two long-axis) defined along the centerline (i.e. short-axis plane's normal is aligned with the LAA centerline) is automatically activated. The centerline-based navigation ensures that 2D views are centered and co-axial with the proximal LAA, simplifying the study of complex morphology particularly in high curvature portions. The approximate location of CA is then manually defined (Stage 1). The above manual steps initialize a mean 3D LAA deformable model¹⁴ that evolves to fit the patient-specific LAA anatomy using intensity-based and edge-based terms, segmenting the LAA lumen (Stage 2). Finally, the LAA device LZ short-axis plane is computed automatically by the software through alignment of the 3D segmented surface with a set of known 3D references through a weighted iterative closest point approach¹⁵. This alignment step is repeated with independent device-specific templates to estimate

the final LZ level as a consensus of all results (Stage 3). The 3D LAA surface was then clipped with the estimated LZ level, and the maximum and area-derived mean diameters of the LZ automatically computed. The LAA depth was computed as the Euclidean distance between the centroid of the LZ contour and the LAA tip.

In the Interactive approach, manual editing of the automated results is allowed, if deemed necessary, on two levels: (i) plane correction and (ii) LAA contour correction (Figure 2). For plane correction, the operator can manually adjust the LZ plane position/orientation and/or provide a new 3D location of the LAA tip (Points 1 and 2 of Figure 2-A). For contour correction, the LAA body contour can be corrected manually by adding anchor points (Point 3 of Figure 2-A). The LAA measurements are automatically updated (Figure 2-C).

Manufacturer-recommended sizing guidelines were applied for each patient based on the LAA anatomic measurements generated by the software. Moreover, recent recommendations⁷ were also considered. According to previous studies^{4,20,21}, the maximum diameter and area-derived mean diameters were used for the WM and ACP, respectively. The accuracy of the software to identify the correct occluder device size was assessed by comparing the device chosen based on the automated measurements against the size of the implanted device. For WM, as the manufacturer's recommendations use rounded limits (i.e. device 21: 17-19 mm, device 24: 20-22 mm, device 27: 23-25 mm, device 30: 26-28 mm, device 33: 29-33 mm) thus presenting undefined regions (i.e. 19-20 mm, 22-23 mm, 25-26 mm, 28-29 mm) between two consecutive devices, both upper and lower sizes were considered valid options in these undefined regions.

Reproducibility of LAA measurements by the Auto and Interactive approaches was determined by repeating analysis 15 days after the initial analysis by the same observer (intra-observer) and a different one (interobserver) in 50 randomly selected cases (25 WM, 25 ACP), blinded from

previous results except the analyzed frame. Finally, the total time taken to perform the analysis using the LAA software tool (Auto and Interactive) was assessed. The time of analysis corresponds to the period between loading/displaying the data into the workstation and the extraction of all clinical indexes to size the device. All results were computed using an Intel (R) i7 CPU at 2.8 GHz and 16 GB of RAM.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 20 (IBM, Armonk, NY) and Microsoft Excel 365 (Microsoft, Redmond, WI). Variables were expressed as mean $\pm$ standard deviation or number (percentage) where appropriate. The D'Agostino-Pearson test was used to test the normality of the data. A 2-tailed $P < 0.05$ was considered statistically significant. To evaluate the performance of the proposed software, it was compared against standard manual measurements (both 2D and 3D) and against the implanted device model. Manual measurements were used as gold standard to assess the reproducibility/agreement of the automated pre-implantation measurements, while the actual implanted device size was used to quantify the success rate in terms of automated implant device prediction. Note that 2D and 3D manual references were extracted by one expert after the intervention blinded to the selected device. Bland-Altman plot and Pearson's correlation were used to assess the agreement between Auto and Interactive methods and the standard 3D manual practice. The accuracy of the software to identify the correct occluding device size was assessed by comparing the device size chosen based on the extracted measurements against the size of the implanted device. The accuracy of the Auto and Interactive methods in correct identification of the implanted device size was assessed and compared to the conventional sizing method based on manual analysis of 2D and 3D TEE using McNemar statistics. The percentages of under-sizing and over-sizing situations were calculated. Intra- and

inter-observer variability of LZ and depth measurements using automated methods were assessed by intraclass correlation coefficient (ICC). The influence of the LAA shape for each sizing strategy (manual or automated) was also assessed through Fisher's exact test. The time of analysis of each sizing strategy was compared through an analysis of variance (ANOVA) with Bonferroni's multiple comparison test.

Results

Patient characteristics and procedural outcome

Automated 3D segmentation and anatomic measurements of the LAA by the software was feasible in all subjects. Table 1 presents the baseline clinical characteristics of the study population. All device implantations were successful. Multiple implantation attempts were required in 18 patients (11% of all cases; 11 WM and 7 ACP). One post-procedural complication was found at 6 weeks follow-up where TEE showed ACP device migration; one patient was lost to TEE follow-up. All cases achieved peri-device leak <3mm on immediate post-procedural TEE. 122, 30, 4 and 1 cases registered a peri-device leak of < 1mm, 1-3 mm, 3-5 mm, >5 mm, respectively (with a total mean value of 0.6 ± 1.1 mm), measured on post-procedural follow-up TEE (at 40 days post LAAC).

Agreement Between Automated and Manual LAA Measurements

Agreement and correlations in the anatomic measurements of the LZ between the automated and manual methods are presented in Figure 3. There were excellent agreements and correlations in area-derived mean and maximal diameters, and LAA depth for both Auto and Interactive methods with reference to manual measurements. The Interactive method, however, demonstrated a narrower limits-of-agreement than the Auto method. Most of the manual editing in Interactive analysis was related to the modification of the LZ plane (75% for WM and 83% for ACP),

requiring a small and quick translation/rotation of the plane. Manual correction of the contour was mainly required in LAA cactus shapes (43% of all contour corrections). Representative results of the proposed software are depicted in Figure 4, namely: (i) a good result with reduced user interaction (Figure 4A); (ii) a case where a large modification of the LZ level was required (Figure 4B); (iii) a case where manual correction of the 3D surface was needed (Figure 4C).

Accuracy in Device Sizing

Figure 5A depicts the diagnostic performance of the proposed software (Auto and Interactive) and standard manual approaches (2D and 3D TEE) in occluder device sizing. The highest accuracy was found for the Interactive approach for sizing of both WM (90%) and ACP (92%) devices. Both under- and over-sizing were less frequent using the interactive 3D TEE method compared to conventional 2D TEE and manual 3D TEE approaches (Figure 5B). The influence of the LAA morphology in the device sizing prediction is depicted in Figure 6, showing no statistically significant differences in the distribution of accurate and inaccurate cases per LAA morphology predicted through manual and automated approaches.

Reproducibility

Table 2 summarizes the intra- and inter-observer variability of different operation modes of the LAA software and 3D manual analysis. Overall, higher inter- and intra-observer reproducibility was obtained by both Auto and Interactive analyses compared to the manual approach for both devices.

Analysis time

Figure 7 shows the analysis time for each of the evaluated operation modes. The ANOVA showed statistically significant differences between all operation modes ($p < 0.0001$). Bonferroni's multiple

comparison test ($p < 0.05$) registered statistically significant differences between all operation mode pairs (adjusted p-value < 0.0001 for Auto vs Interactive and Auto vs Manual, and adjusted-p value = 0.0160 for Interactive vs Manual). Overall, both Auto and Interactive methods allowed quicker analysis when compared to the traditional manual practice (Auto vs Interactive vs manual, $101.9 \pm 9.3s$ vs. $154.6 \pm 20.3s$ vs. $183.5 \pm 42.7s$, $p < 0.01$).

Discussion

We reported a novel customized software tool for automated sizing of LAA occluder devices based on 3D TEE image. We found that automated LAA analysis and occluder device sizing with the proposed software is feasible and accurate, allowing rapid 3D visualization of the LAA anatomy in intraprocedural 3D TEE data. Our results suggest that the proposed automated software (with or without manual editing) is a competitive and potential alternative to the standard 3D manual practice. Auto analysis achieved similar accuracy but reduced processing time and observer variability compared to expert manual analysis of 3D TEE. The semi-automated Interactive method showed the highest device sizing agreement in our results. The curvilinear MPR navigation mode, semi-automatic fast segmentation of LAA boundaries, and automatic estimation of the device LZ on 3D data are the key features of the proposed software tool. The interactive approach combines the advantages of both automatic and manual analyses, i.e., allows faster and more reproducible analysis while keeping the high accuracy of measurements performed by a manual observer. Similar to other studies^{9,11,22}, minor manual corrections of the automated results (mainly the LZ) further improve the accuracy of the automated software. Thus, with the full interactive pipeline, a higher accuracy in identifying the device size for successful implantation was achieved when compared to other studies in the literature^{23,24} that used CT for preprocedural device sizing.

Similarly to other studies^{1,3-5}, our results show the limitation of 2D TEE with a notably inferior accuracy in device sizing compared to both manual and automated 3D TEE analysis.

Our software failed to identify the implanted device size in about ~10% of cases, even after manual editing. This result reflects that factors other than measured LAA dimensions were evaluated at the implantation moment and affected the device decision. In some cases, the implanter may prefer a modification of the implantation site (more proximally/distally), allowing him/her to implant a larger/smaller device. All failure cases were reanalyzed by one expert after the intervention. The expert agreed with the automated result in 5 cases, namely: (i) in one case the device was deployed too deep into the LAA; and (ii) in four cases the device was too big for the anatomy, showing a strawberry-shaped device in post-implantation imaging. Overall, while reviewing all cases, the automated 3D result showed a superior performance than the standard manual practices in cases of LAA clot/sludge/spontaneous echo contrast, where the smoke or sludges makes the LAA boundary very vague and hard to delineate (see supplementary material – Figure D-A). In contrast, the automated result was considered as sub-optimal in 5 cases, due to: (i) incorrect axis initialization at the LAA proximal part (2 cases); (ii) incorrect identification of the optimal frame (i.e. the end-systolic frame with maximal LAA volume in the cardiac cycle, 1 case); and (iii) incomplete acquisition of the LAA with small portions found out of FOV (see supplementary material - Figure D-B). For the remaining 5 failure cases, a different sizing strategy based on our own clinical practice was applied, namely: (i) modification of the LZ site due to a well-pronounced chicken wing shape (1 case); and (ii) oversizing of the extracted measurements due to the presence of prominent trabeculations in the LZ (4 cases).

The standard imaging modality for procedural guidance during LAAC remains to be TEE in many centers, and 2D TEE is still recommended by device manufacturers for standard device sizing.

However, 2D TEE often underestimates LAA dimensions compared to 3D modalities, including CT and 3D TEE. 3D imaging allows reconstruction of anatomically correct planes allowing measurements of LAA dimensions without foreshortening. Nevertheless, manual reconstruction of the LAA 3D datasets is time-consuming; this is particularly undesirable for intraprocedural analysis when decisions must be made rather quickly to avoid prolonging the procedural time. Furthermore, the LAA anatomy is highly complex, and deciding the device implantation level can be difficult, with high observer variability. The present study involved a larger cohort of patients undergoing LAAC using two commonly used devices and provides new insights into the clinical utility of automated LAA analysis by demonstrating a high accuracy in correct device size identification and efficiency, as well as reproducibility in LAA anatomical measurements. Additionally, the automated software achieved similar performance for all LAA morphologies. Nevertheless, we must mention that a slightly inferior performance (not statistically significant) was found in morphologies with high anatomical heterogeneity at the distal portion (e.g., large pectinate muscles), most common in cactus and cauliflower morphologies. In contrast, the manual analysis was more challenging in high curvature cases (i.e., chicken wing and windsock). Nevertheless, these results are still preliminary, requiring further studies with a similar representation of all LAA shapes.

To measure the feasibility of the proposed software in terms of correct identification of the LAA device, multiple experimental scenarios were defined and compared offline with retrospective data from real interventions. Since the LAA is a fluid mediator with the capability to change its dimensions⁴, a variation of its size with the increase in LA pressure is expected which may result in differences between preprocedural and intraprocedural clinical indexes. Thus, all analyses of this study were performed based on intra-operative TEE images. Nevertheless, the application of

the proposed software in other interventional stages (namely pre-procedural 3D TEE imaging) is also viable. Many investigators have explored the clinical value of preprocedural measurements by using CT-based measurements ^{25,26}. Different strategies have been assessed to minimize the influence of possible LAA anatomical expansion throughout the intervention ^{25,26}. This typically is performed by upsizing of the preprocedural measurements through a pre-defined rule^{3,26}. Nevertheless, since the increase of the LAA diameter between pre- and intraprocedural stages varies between subjects ^{27,28}, the identification of the optimal upsizing value is still highly dependent on the operator which makes it suboptimal for clinical practice. Thus, in our clinical practice, when CT data is pre-procedurally acquired, intraoperative 3D TEE images are still mandatory to confirm the anatomy and the device sizing at the implantation moment, making the proposed automated 3D software of high clinical interest.

In this study, all image volumes were acquired by expert echocardiographers in their normal clinical routine and were of high quality; whether our automated approach applies to poorer quality images acquired by non-expert or how much its performance depends on operator expertise needs further evaluation. Our preliminary analysis (see supplementary material E) suggests that the operator's expertise does not have a high impact on the performance of the automated software (i.e. Auto mode), with experts and average users achieving a similar success rates in terms of device prediction. The interactive and auto modes performed by an average user proved feasible, achieving a success rate higher than manual analysis by the nonexpert. In contrast, for 3D manual analysis, the expert clearly outperformed the average user.

The current software is versatile and allows automated and reproducible computation of the area and perimeter of device LZ, which may be more accurate for device sizing than maximal LZ diameters, as suggested by previous studies^{4,28}. Furthermore, it allows fast automatic 3D

segmentation of the LAA, which may potentiate the development of quicker 3D printing techniques². 4D analysis (i.e. 3D segmentation plus tracking) is currently under investigation and may provide clinically relevant functional information of the LAA²⁹.

Study limitations

Our study has limitations. First, it was a single-center and single vendor retrospective study. Nevertheless, the study cohort is relatively large, with a variety of LAA sizes and morphologies. Moreover, the 3D TEE images tested in this study were prospectively acquired following a standard LAAC imaging protocol¹⁷. Although the current study relies on 3D TEE datasets from a single vendor, the software was already tested in volumes from a different vendor (see our previous studies^{14,15}) maintaining its high performance and feasibility. Second, only the WM and ACP occluders were used, while there are other devices available in the market. However, WM and ACP represent the two most frequently used endocardial LAAC devices adopting two different types of designs (i.e. “parachute” and “lobe and disk”), supporting the applicability of our software in common practice. It might be noted that the application of the proposed software to other devices (e.g. Lambre) is also possible, simply requiring the generation of a set of 3D reference anatomical models with the values of the manufacturer-recommended target clinical levels for device sizing. Third, our automated software was applied to only 3D TEE images; we did not test the feasibility of automated analysis on CT images, which is used in some centers for preprocedural planning^{3,23}. Nonetheless, we believe applying automated LAA analysis on TEE is clinically more relevant than applying it on CT because the former is the standard imaging modality used intraprocedurally. Although CT provides excellent image quality for accurate preprocedural LAA evaluation, the final device sizing decision is often made intraprocedurally after volume loading²⁸. Fourth, although we benchmarked against the clinically implanted device size, this is not necessarily the

best or only suitable size. Multiple factors may influence the implantation result, namely modification of the implantation site in specific anatomies or oversizing/undersizing of the extracted measurement based on the operator experience. In light of this, the reported accuracy (~90%) is extremely good and higher accuracy is unlikely. Moreover, due to all these sources of potential variability, the comparison between the automated software and manual analysis in terms of device size prediction must be considered a proof of concept of the potential clinical value of our software and not as a direct comparison between different sizing strategies. Finally, our approach remains semi-automatic requiring initial manual definition of the LAA centerline. A fully automatic approach could further reduce processing time; however, we believe our semi-automatic interactive approach is suitable for clinical use, allowing expert input in device sizing, with demonstrable superior performance and efficiency compared to the traditional fully manual practice.

Conclusions

This study provides validation of a novel 3D software for automated LAAC device sizing using 3D TEE images. The described software proved to be feasible, accurate, and reproducible. The interactive approach, with automation and manual editing when necessary, proved to be a potentially useful clinical option, showing a performance comparable to the standard manual practice. Overall, the obtained results indicate that automated 3D analysis of the LAA with the proposed software has the potential to be integrated into clinical practice, promoting routine use of 3D TEE for procedural guidance of LAAC.

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Figures:

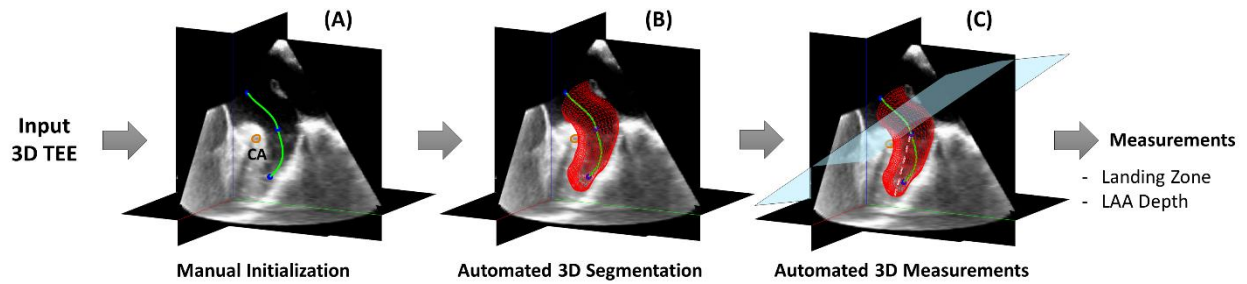


Figure 1 – Overview of the automated LAA software. After (A) initial manual definition of the LAA centerline, the automated software (B) three-dimensionally segments the LAA, and (C) automatically locates the device landing zone for automated anatomic measurements relevant to device sizing. The cyan plane is the LZ. The white dotted line represents the LAA depth. CA – Circumflex artery.

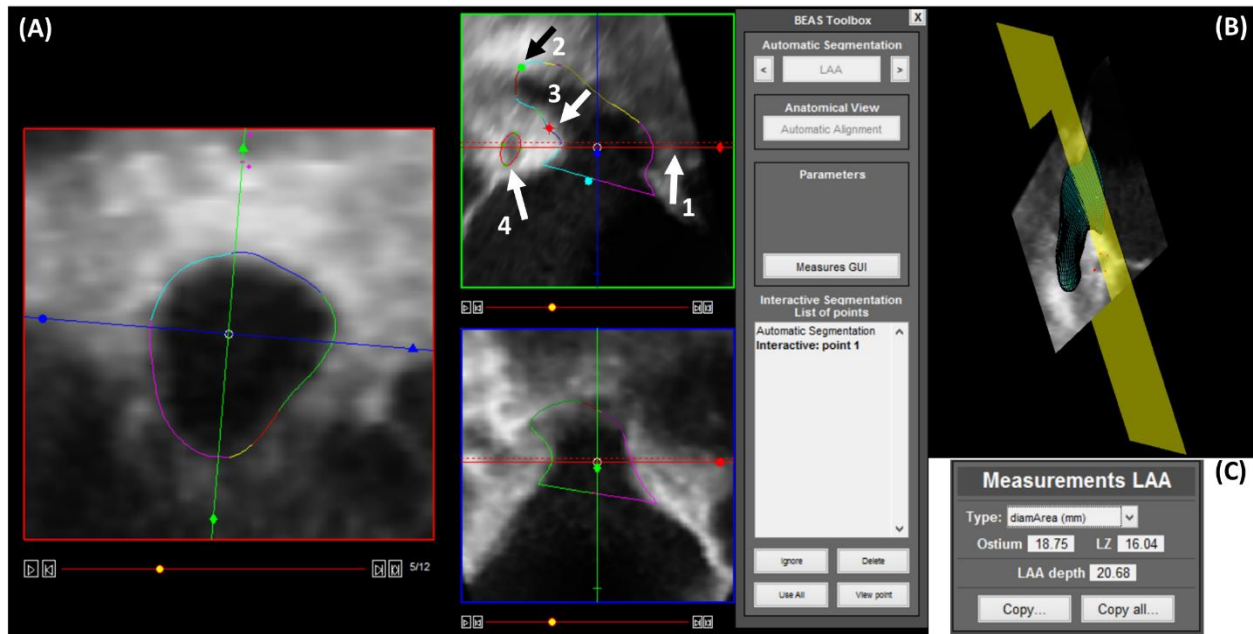


Figure 2 – Automated LAA anatomic measurements on Speple3D. (A) Image volume navigation using 3 orthogonal planes; (B) 3D representation of the LAA and LZ; (C) Extracted measurements. Manual interaction options: 1–modification of the LZ; 2- identification of the LAA tip; 3-correction of the LAA contour; 4–identification of the CA.

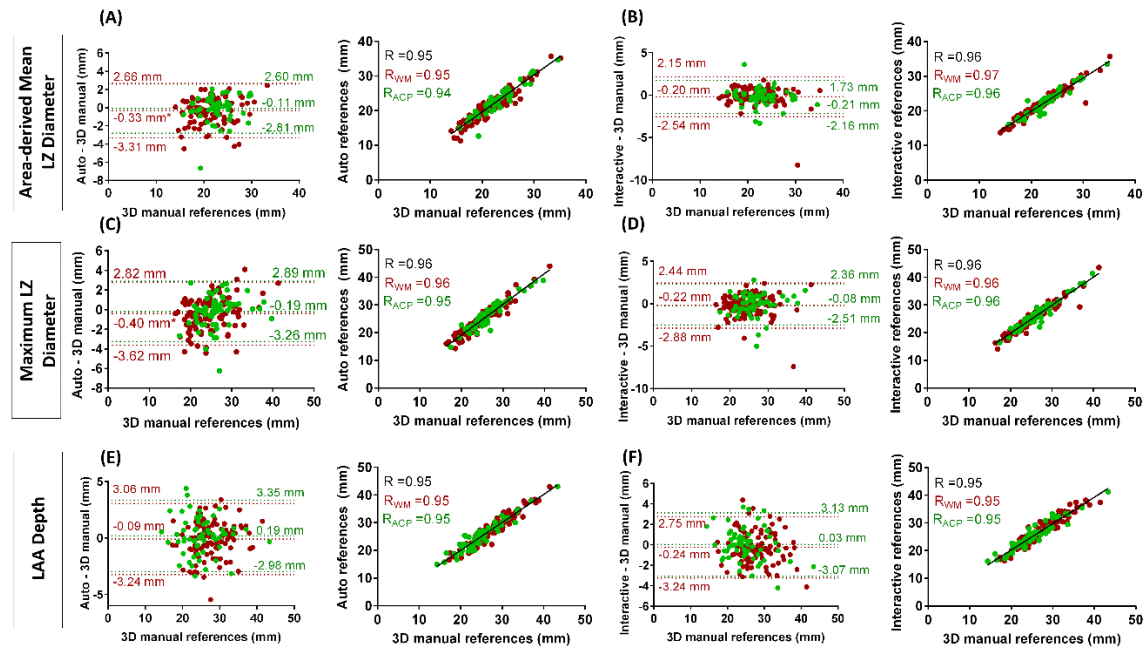


Figure 3 – Agreement and Correlation between automated (Auto and Interactive modes) and manual methods for LAA measurements. Bland-Altman analysis and Pearson correlation of the Auto (A,C,E) and Interactive (B,D,F) methods against manual references from 3D TEE for the area-derived mean (1st line, A-B) and maximum LZ diameter (2nd line, C-D) and the LAA depth (3rd line, E-F). * $p < 0.05$, two-tailed t-test against zero.

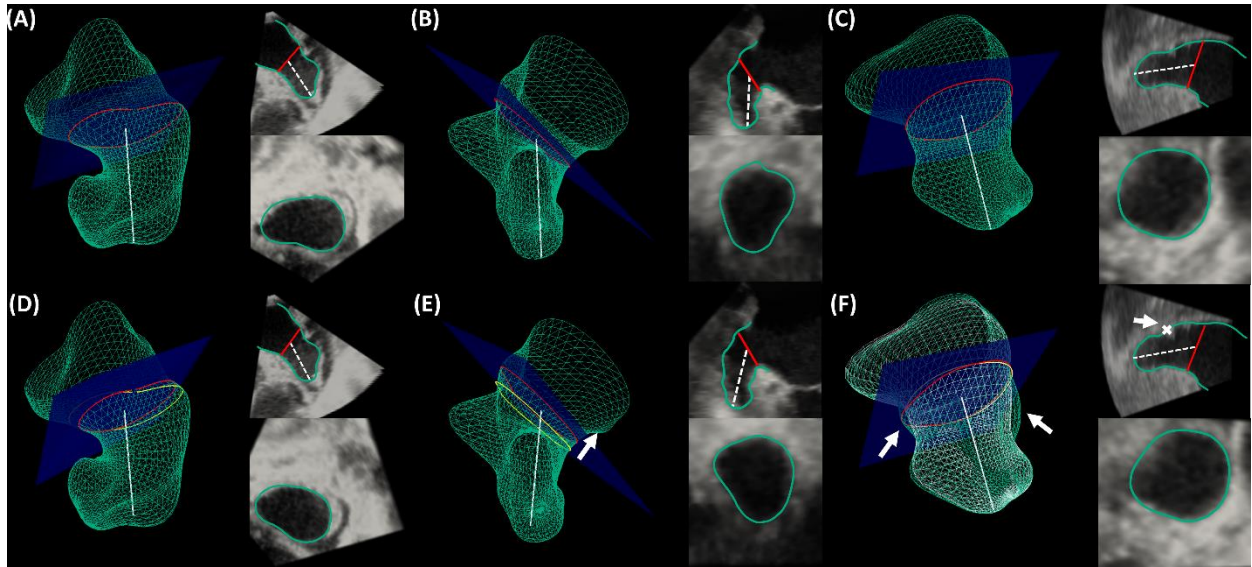
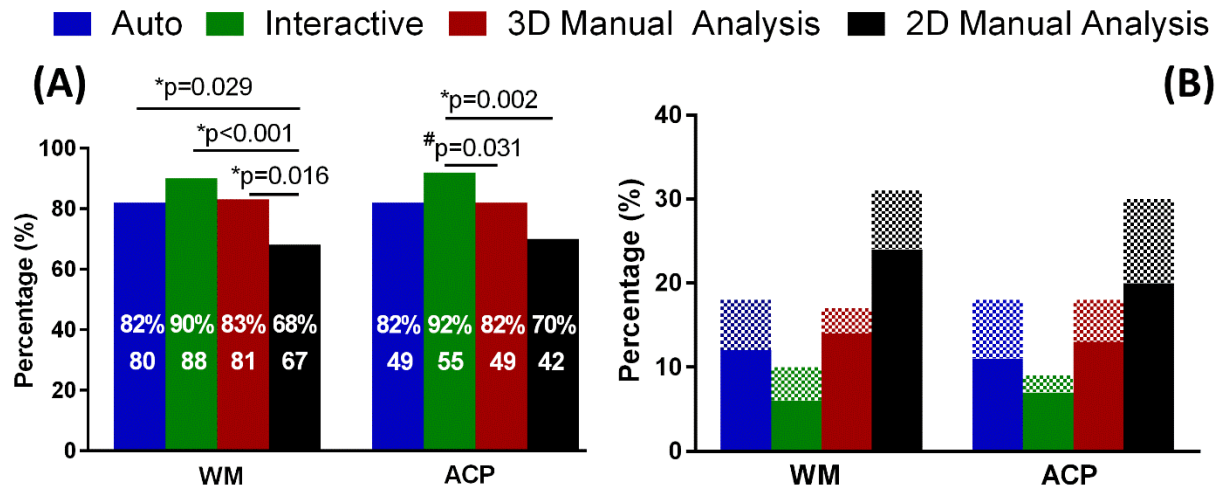


Figure 4 - Representative results obtained with the (A-C) Auto and (D-F) Interactive methods in 3 patients. The blue plane and the red contour represent the LZ and the corresponding LAA contour, respectively. The white arrows indicate sites of the manual corrections. In (D-F) the automated LZ is also shown as a yellow line. In patient 1 (A, D), slight tilting of the LZ plane was performed. In patient 2 (B, E), the LZ plane was manually adjusted to a more proximal position. In patient 3 (C, F), a major correction of the automated contour (white surface) was performed.



*p<0.05, in McNemar's test against 2D Manual Analysis; #p<0.05, in McNemar's test against 3D Manual Analysis;

Figure 5 – Accuracy of device sizing by automated software (Auto and Interactive modes) compared to manual 2D and 3D TEE analyses. (A) Percentage (and the absolute value) of correct device sizing using the implanted device size as reference. (B) Frequency of device under-sizing (solid color) and over-sizing (checkerboard). WM, Watchman device. ACP, Amulet or Amplatzer cardiac plug device.

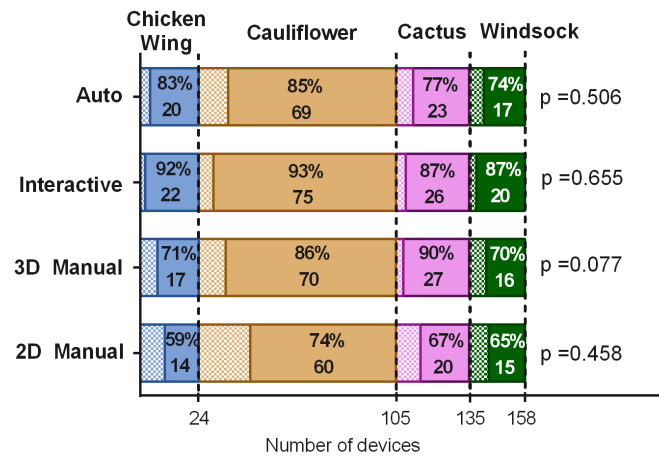


Figure 6 – Influence of the LAA morphology in the accuracy of device sizing performed by the automated software or standard manual practice. For each morphology, the percentage of correctly (solid color) and incorrectly (checkerboard shape) identified cases is presented. The result of Fisher’s exact test is also presented.

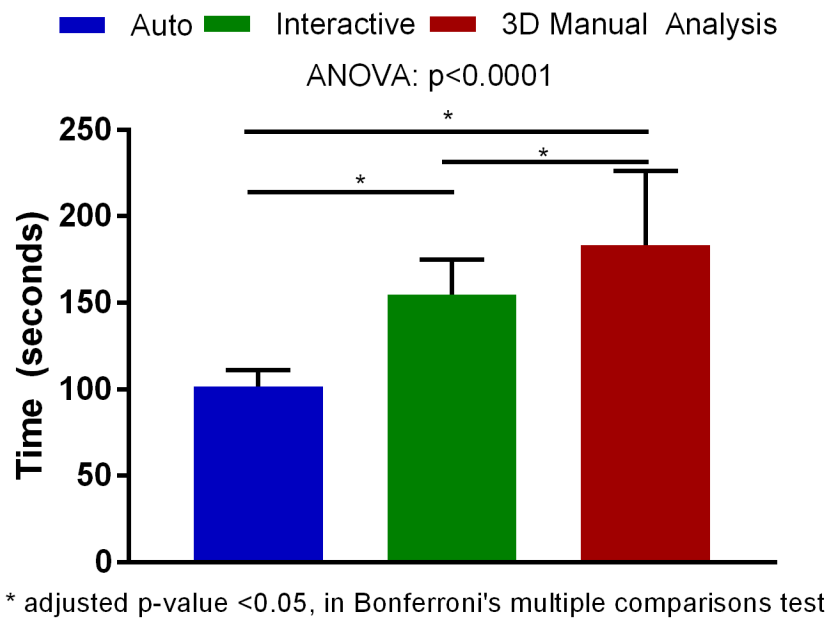


Figure 7 – Time for complete 3D LAA analysis of automated (Auto and Interactive modes) and manual methods on 3D TEE. Automated analysis, both fully Auto and Interactive operation modes, allows quicker analysis than traditional manual 3D analysis of the LAA.

Table 1 - Patients' baseline characteristics

Parameter	Value
Age, years	73.5±7.8
Men, n(%)	104 (66%)
LAA Morphology, n(%)	
Chicken Wing	24 (15%)
Windsock	23 (15%)
Cauliflower	81 (51%)
Cactus	30 (19%)
Medical History	
Paroxysmal AF, n(%)	63 (40%)
Non-paroxysmal AF, n(%)	95 (60%)
CHA2DS2-VASc score	4.4±1.5
1-3, n(%)	43 (27%)
4-6, n(%)	103 (65%)
7-9, n(%)	12 (8%)
HAS-BLED score	3.0±1.0
1-2, n(%)	42 (27%)
3-4, n(%)	107 (68%)
5-6, n(%)	9 (6%)
LV Ejection Fraction, %	57.7±9.0
Reduced (<40%), n(%)	8 (5%)
Mid-range (41%-49%), n(%)	6 (4%)
Normal (50%-70%), n(%)	142 (90%)
High (>70%), n(%)	2 (1%)

Table 2 – Intra- and inter-observer variability for LZ area-derived mean diameters, maximum diameters, and LAA depth of automated (Auto and Interactive modes) and manual analyses

		WM		ACP	
		Intra	Inter	Intra	Inter
		ICC (95% CI)	ICC (95% CI)	ICC (95% CI)	ICC (95% CI)
Mean LZ	Auto	0.93 (0.89-0.95)	0.82 (0.78-0.89)	0.91 (0.85-0.95)	0.86 (0.82-0.91)
	Interactive	0.93 (0.90-0.96)	0.85 (0.80–0.91)	0.92 (0.86-0.95)	0.84 (0.80-0.90)
	3D manual analysis	0.90 (0.87-0.94)	0.80 (0.70-0.88)	0.90 (0.72-0.95)	0.78 (0.68-0.87)
Maximum LZ	Auto	0.90 (0.84-0.94)	0.82 (0.77–0.88)	0.84 (0.81-0.90)	0.78 (0.74-0.85)
	Interactive	0.92 (0.90-0.95)	0.80 (0.75-0.86)	0.88 (0.84-0.93)	0.80 (0.74-0.86)
	3D manual analysis	0.86 (0.80-0.90)	0.76 (0.69-0.84)	0.80 (0.71-0.88)	0.71 (0.61-0.81)
LAA Depth	Auto	0.82 (0.74-0.88)	0.80 (0.71-0.85)	0.85 (0.72-0.90)	0.80 (0.68-0.90)
	Interactive	0.84 (0.75-0.91)	0.76 (0.69-0.83)	0.86 (0.73-0.92)	0.78(0.73-0.82)
	3D manual analysis	0.75 (0.65-0.83)	0.70 (0.65–0.76)	0.84 (0.75-0.87)	0.67 (0.60-0.74)