Functional assessment of the left atrium by real-time three-dimensional echocardiography using a novel dedicated analysis tool: initial validation studies in comparison with computed tomography

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Aims

A novel real-time three-dimensional echocardiography (RT3DE) analysis tool specifically designed for evaluation of the left atrium enables comprehensive evaluation of left atrial (LA) size, global, and regional function using a dynamic 16-segment model. The aim of this study was the initial validation of this method using computed tomography (CT) as the method of reference.

Methods and results

The study population consisted of 34 prospectively enrolled patients with clinical indication for pulmonary vein isolation. A dynamic polyhedron model of the left atrium was generated using RT3DE. LA maximum and minimum volumes (LA\text{max}/LA\text{min}) and emptying fraction (LAEF) were determined and compared with the results obtained by CT. High correlations between RT3DE and CT were found for LA\text{max} (r = 0.92, P < 0.001), LA\text{min} (r = 0.95, P < 0.001), and LAEF (r = 0.82, P < 0.001). LA\text{max} and LA\text{min} were lower by RT3DE than by CT (95.0 ± 44.7 vs. 119.8 ± 50.5 mL, P < 0.001 and 58.1 ± 41.3 vs. 83.3 ± 52.6 mL, P < 0.001, respectively), whereas LAEF was measured higher by RT3DE (42.8 ± 15.2 vs. 34.2 ± 15.4%, P < 0.001, respectively). RT3DE measurements closely correlated in terms of intra-observer (intra-class correlation r = 0.99, r = 0.99, r = 0.96, respectively) and inter-observer variability (r = 0.97, r = 0.98, r = 0.88, respectively).

Conclusions

LA volumes and EF as assessed by RT3DE correlate highly with CT measurements, albeit there is some bias between the imaging modalities. Most importantly, RT3DE measurements using the novel dedicated LA analysis tool are robust in terms of observer variability and thus suitable for follow-up analyses.

Keywords

Three-dimensional echocardiography • Imaging left atrium • Computed tomography

Left atrial (LA) size is a prognostic factor in a variety of diseases. Increased LA dimensions are associated with development of atrial fibrillation (AF), stroke, and cardiovascular death.\(^1\)\(^–\)\(^3\) Although M-Mode echocardiography has traditionally been used as a convenient measure of LA size, assessment of LA volume seems to be superior, especially in patients with an enlarged left atrium.\(^4\)\(^–\)\(^7\) Calculations of the LA volume using the ellipsoidal formula or the modified Simpson method\(^8\)\(^,\)\(^9\) are, however, still
based on geometric assumptions. Recent studies using the real-time three-dimensional echocardiographic (RT3DE) approach have demonstrated the superiority of RT3DE over 2D techniques. However, RT3DE measurements of LA volumes have yet to be validated against independent reference methods. In addition, RT3DE studies to date have been based on contour tracing algorithms developed for the left ventricle, since no dedicated LA analysis software has been available. Recently, an analysis tool specifically designed for the reconstruction of a dynamic polyhedron LA model has been developed. The novel tool provides a number of analysis features enabling comprehensive assessment of LA size as well as global and regional LA function. The aim of the present study was the initial clinical validation of the novel RT3DE analysis tool using CT as the method of reference.

Methods

Study population

Forty-eight patients with clinically indicated pulmonary vein isolation (PVI) due to paroxysmal or persistent AF were prospectively enrolled during a 9-month period from July 2009 to March 2010. Patients were included regardless of the quality of the acoustic window. RT3DE and computed tomography (CT) were performed on the same day in order to avoid an impact of altered fluid loading conditions. Informed consent was obtained from all patients. The study protocol was approved by the local Ethics Committee.

Real-time 3D echocardiography

RT3DE examinations were performed using a Philips IE33™ ultrasound system equipped with a matrix array transducer (X3–1 transducer, Philips Medical Systems, Andover Massachusetts). All acquisitions were performed using an apical view encompassing the entire left atrium. 3D data sets were obtained by combining subvolumes derived from seven consecutive cardiac cycles. On average, four to six data sets were acquired per patient. The observer selected the data set with the highest image quality for the final analysis. Patients in AF with a highly variable R–R interval had to be excluded due to artefacts within the RT3DE data set. Trigger delay was set to 300 ms ensuring coverage of the entire diastole. Analysis of the 3D data sets was performed offline using the novel software (LA-Function©, TomTec Imaging Systems, Inc., Unterschleissheim, Germany). Usually, analysis of a 3D data set takes less than 5 min. The workflow of the LA analysis software consists of four steps: Step 1 View adjustment; three main cut-planes (apical four-chamber, three-chamber and two-chamber view) are selected. The observer defines the end-diastolic and end-systolic frame as well as the frame before onset of atrial contraction (‘pre-A’) (Figure 1). Step 2 Setting of initial contours: the software provides an end-systolic and end-diastolic frame of each view. The observer draws the end-systolic (maximal LA volume) and end-diastolic (minimal LA volume) contours in each view. The observer defines the end-diastolic and end-systolic frame as well as the frame before onset of atrial contraction (‘pre-A’) (Figure 1). Step 2 Setting of initial contours: the software provides an end-systolic and end-diastolic frame of each view. The observer draws the end-systolic (maximal LA volume) and end-diastolic (minimal LA volume) contours in each view.
The LA appendage and the pulmonary vein confluence were excluded from the LA tracings. Step 3 Contour revision: based on the initial manual contour drawings, a polyhedron model of the left atrium is created. Adaptation to the endocardial surface over all frames of the cardiac cycle results in a dynamic LA model. Optionally, the contours can be manually corrected. Step 4 LA analysis: finally, the dynamic LA polyhedron model and a table with the quantitative values of LA volumes and function are displayed (Figure 2). Further, the regional movement pattern based on a 16-segment model of the left atrium is displayed (Figure 3, see Supplementary data online, Videos S1–S3).

Computed tomography
CT image acquisition and reconstruction
CT studies were performed using a 64-detector row CT scanner (Sensation 64, Siemens Medical Solutions, Forchheim, Germany). Sixty
millilitre i.v. contrast agent (Ultravist 370, Bayer Schering Pharma, Berlin, Germany; iodine concentration of 370 mg/mL) was administered with a flow rate of 2.5 mL/s using a bolus tracking technique. The scan was started when the threshold of 80 Hounsfield Units was reached in the left atrium. Tube current was automatically adjusted using an ECG-controlled dose modulation technique. The remaining acquisition parameters were identical in all patients: tube potential 120 kV, collimation 1.2 mm; pitch 0.2; reconstructed slice thickness 3 mm; reconstruction increment 1.5 mm; reconstruction kernel B35f (soft tissue). Retrospective ECG-gating was used and the cardiac cycle was reconstructed in 3%-steps of the RR-interval from 31 to 100%.

CT image analysis
Images were processed using a dedicated software tool (Argus©, Siemens Medical Solutions, Forchheim, Germany) by contouring the LA border in left ventricular end-systole (defined as last image before opening of the mitral valve) and left ventricular end-diastole (defined as first image after closure of the mitral valve) on every slice (Figure 4). Based on these contours, LA diastolic and systolic volume and emptying fraction were calculated by the summation-of-disks-method. The LA appendage and the pulmonary veins were excluded corresponding to the echocardiographic measurements.

Statistics
RT3DE measurements were performed by two different observers for the assessment of inter-observer variability. For intra-observer variability, one of the observers performed a second measurement at least 30 days after the first evaluation. The RT3DE data set used for the initial measurement was also used for assessment of intra- and inter-observer variability.

Measurement reproducibility was evaluated in all patients in a blinded fashion. Data are presented as means ± SD for continuous variables and as absolute numbers and relative percentages for categorical variables. Paired data were compared using the Wilcoxon signed-rank test. Relations between two methods, two measurements, or two observers were determined using linear regression analysis and the respective intra-class correlation coefficient was calculated. Intra- and inter-observer agreement and agreement between methods were assessed by the Bland–Altman analysis. Significance was defined as a P-value < 0.05 (two-sided). The SAS 9.2 16.0 Software Package (SAS Institute, Inc., Cary, NC, USA) was used for statistical data analysis.

Results
A total of 48 patients were enrolled into the study. Three patients were excluded due to insufficient quality of the RT3DE data set owing to a highly variable R–R interval during acquisition, two patients due to storage failure of the RT3DE data. In one patient, contrast-enhanced CT was not performed in order to avoid worsening of renal failure. In five patients, the mitral valve could not be delineated exactly within the CT data set. Three patients did not have the same cardiac rhythm during RT3DE and CT.

Finally, RT3DE and CT data were compared in 34 patients. Of these, 2 had normal-sized left atria, 6 had mildly, 7 moderately and 19 severely enlarged left atria according to ASE (American Society of Echocardiography) cut-offs as measured by the biplane modified Simpson’s rule. Twenty-nine subjects were in sinus rhythm and five in AF during acquisition. Baseline characteristics of the 34 patients are given in Table 1.

Table 1 Patient characteristics (n = 34)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>(Range)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>57.0 ± 9.0</td>
<td>(31–70)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177.8 ± 8.3</td>
<td>(164–194)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.4 ± 16.0</td>
<td>(53–120)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.0 ± 4.3</td>
<td>(18.8–37.6)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>138.3 ± 17.5</td>
<td>(105–170)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85.2 ± 10.0</td>
<td>(60–110)</td>
</tr>
<tr>
<td>Sinus rhythm (%)</td>
<td>85.3</td>
<td></td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>66.3 ± 18.4</td>
<td>(41–140)</td>
</tr>
<tr>
<td>Number of frames (RT3DE)</td>
<td>27.5 ± 3.1</td>
<td>(15–31)</td>
</tr>
</tbody>
</table>

BMI, body mass index.

RT3DE vs. CT
Maximal (LA_{max}) and minimal (LA_{min}) left atrial volumes throughout the cardiac cycle were lower by RT3DE than by CT (95.0 ± 44.7 vs. 119.8 ± 50.5 mL, P < 0.001, 58.1 ± 41.3 vs. 83.3 ± 52.6 mL, P < 0.001), whereas the left atrial emptying fraction (LAEF) obtained by RT3DE was higher than LAEF obtained by CT (42.8 ± 15.2 vs. 34.2 ± 15.4%, P < 0.001) (Figure 5). The scatter plots in Figure 6 illustrate the high correlations between RT3DE and CT, correlation coefficients ranged from 0.82 to 0.95 (P < 0.001 for all correlation analyses). Mean difference (95% CI for agreement) as assessed by the Bland–Altman analysis was −24.8 ± 20.3 mL (−64.6 to 15.1 mL) for LA_{max}, −25.2 ± 19.5 mL (−63.4 to 13.0 mL) for LA_{min} and 8.6 ± 9.2% (−9.5 to 26.6%) for LAEF (Figure 6).

Figure 5 Mean values of LA maximum and minimum volumes and emptying fraction obtained by CT vs. RT3DE. Error bars indicate the standard deviation of measurements. LA_{max}, maximum LA volume; LA_{min}, minimum LA volume; LAEF, LA emptying fraction; CT, computed tomography; RT3DE, real-time 3D echocardiography; LA, left atrium.
Intra- and Inter-observer variability

Figures 7 and 8 illustrate the results for intra- and inter-observer variability, respectively. Regarding intra-observer variability, the mean time between measurements was 99 ± 56.3 days. The intra-class correlation coefficients ranged from 0.96 to 0.99 between measurements (performed by one observer) and from 0.88 to 0.98 between observers.

Discussion

In the present study, a novel RT3DE analysis package specifically designed for the left atrium was tested—to the best of our knowledge the first validation study using this dedicated LA analysis tool. RT3DE measurements were highly correlated to those obtained by CT. This applied to the assessment of LA size as well as to quantification of LA function as expressed by diastolic emptying fraction. RT3DE proved to be remarkably robust in terms of intra-observer and inter-observer variability. This is of utmost significance regarding the value of the method for follow-up analyses. Adequate RT3DE data sets could be obtained in >90% of patients and the analysis of a data set usually takes less than 5 min. Thus, the new RT3DE analysis package may be an appropriate tool for relatively simple and rapid, robust yet low-cost quantitative assessment of LA size and function.

Evolution of 3D echocardiography for the assessment of the left atrium

An initial approach to using three dimensions for improved reproducibility of measurements of LA size was reported by King et al. in 1992.14 Several studies using the rotational or free-hand technique reported good agreement with magnetic resonance imaging (MRI)
for the assessment of LA volume.\textsuperscript{15–17} A volumetric system developed at Duke University enabled the first real-time acquisitions.\textsuperscript{18,19} It could be demonstrated in comparison studies with 2D techniques that RT3DE is at least comparable and may be superior to 2D measurements.\textsuperscript{10,11,20,21} Consequently, RT3DE was used in recent studies to evaluate LA size and/or function in various diseases.\textsuperscript{22–27} However, as stated by Mor-Avi et al.\textsuperscript{12} there is still a lack of validation studies against independent reference techniques.

**Bias between RT3DE and the method of reference**

Underestimation of volumes by RT3DE has been nearly consistently reported in studies on the left and right ventricle.\textsuperscript{28,29} Not surprisingly, we also found a bias between the LA measurements obtained by RT3DE and CT. Both maximum and minimum LA volume showed a mean difference of about –25 mL. This is in good agreement with the results of recent studies on the left atria. A difference of –24 mL was found comparing 2DE with CT.\textsuperscript{30} Artang et al.\textsuperscript{31} reported a bias of about –20 mL comparing RT3DE with MRI. Müller et al.\textsuperscript{32} found a mean difference of –30 mL for the maximum volume using electro-anatomic mapping and a mean difference of –38 mL using biplane angiography as a method of reference. A plausible explanation for the observed differences lies in the limited spatial resolution of ultrasound-based techniques, leading to a blurred depiction of the endocardial surface. This results in a wider band of grey shades, prompting the observer to track the endocardium inside these shades causing volume underestimation.\textsuperscript{33} Thus, LA volumes obtained by the reference methods should not be used as baseline value for follow-up by RT3DE.\textsuperscript{32}

**Figure 7** Intra-observer variability of RT3DE measurements ($n = 34$). Results of linear regression and correlation analyses (left) as well as Bland–Altman plots (right) are given. The dotted line represents the line of identity. $L_{A_{\text{max}}}$ maximum LA volume; $L_{A_{\text{min}}}$ minimum LA volume; LAEF, LA emptying fraction; RT3DE, real-time 3D echocardiography; LA, left atrium; SD, standard deviation.
Robustness of measurements

Although one has to be aware of a bias between two imaging modalities, this does not preclude the clinical usefulness of a quantification tool. For the interpretation of baseline measurements, normal reference ranges for LA volumes and emptying fraction have to be defined. More importantly, good reproducibility is a prerequisite to reliable follow-up analyses. High correlation coefficients and close limits of agreement were observed for intra- as well as for inter-observer variability. Thus, the novel RT3DE technique enables a remarkably robust quantification of LA volumes and function.

Future developments and clinical implications

As to technical refinements of RT3DE acquisition, transducers with larger pyramidal imaging will enable acquisition within one single heart cycle. In particular, this will facilitate acquisitions in patients with various cycle lengths due to AF. The precision of volume determination could be enhanced by increased temporal resolution. In an experimental setting, frame rates of up to 168 Hz could be realized for 3D echocardiography.

RT3DE opens new perspectives regarding the assessment of LA size and function for risk stratification. Two recently published studies have demonstrated for the first time that LA volume as assessed by RT3DE is a predictor of clinical events. LA remodelling and reverse remodelling have gained increasing attention in patients undergoing cardiac resynchronization therapy or ablation of AF. In initial studies, RT3DE was used as a novel approach to assess reverse remodelling in these patient groups. Hence, the novel LA analysis tool presented in this study may be of special interest in this emerging field of research. In addition to the parameters validated in this study, it

Figure 8 Inter-observer variability of RT3DE measurements (n = 34). Results of linear regression and correlation analyses (left) as well as Bland–Altman plots (right) are given. The dotted line represents the line of identity. LA\text{max}, maximum LA volume; LA\text{min}, minimum LA volume; LA\text{EF}, LA emptying fraction; RT3DE, real-time 3D echocardiography; LA, left atrium; SD, standard deviation.
contains additional features for the assessment of atrial emptying fraction and atrial stroke volume as well as LA synchrony or dysynchrony. A recent study using myocardial strain imaging has pos-
tulated a predictive significance of LA dysynchrony. In a very interesting initial approach, Azar et al. used RT3DE for the assessment of reference values of atrial synchrony in subjects without cardiovascular disease. The dedicated LA analysis package presented in our study has the potential to expand our knowledge in this new field of research providing a comprehensive and specific LA analysis including information on the presence of LA dysynchrony.

Limitations

There are several limitations that need to be acknowledged and addressed regarding the present study. The first limitation is whether the findings can be generalized in a population with no structural heart disease and normal-sized atria. As stated by Shimada et al., in fact larger volumes contribute to larger under-
estimation. A larger cohort, including patients with a wide range of underlying clinical conditions as well as patients lacking structural heart disease is needed to standardize the normal values for LA volume and function.

Second, a considerable number of patients had to be excluded from the present study (14 of the 48 initially enrolled patients). In 11 patients, technical aspects and medical reasons led to exclusion. Only three patients were excluded due to poor image quality.

We did not compare RT3DE with more conventional echocardiographic methods. However, previous studies have consistently shown that measurements using M-Mode echocardiography are inferior, especially in patients with enlarged left atria. Different 2D techniques allow a more reliable volume determination of the left atrium. Russo et al. found good correlations between 2DE and RT3DE. RT3DE, however, was found to be superior to differ-
ent 2D methods in terms of reproducibility, suggesting that this technique is to be preferred for sequential measurements.

Conclusion

In this initial validation study using a novel RT3DE analysis package it could be shown that LA volumes and EF are highly correlated with CT measurements. There is some bias between the imaging modalities resulting in lower volumes by RT3DE. Most importantly, RT3DE measurements are remarkably robust in terms of observer variability.

Supplementary data

Supplementary data are available at European Journal of Echocardiography online.

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Conflict of interest: none declared.

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