

Disparity between Two-Dimensional Echocardiographic and Electroanatomic Left and Right Atrial Volumes in Patients Undergoing Catheter Ablation for Long-Standing Persistent Atrial Fibrillation

Short Title: 2D Echocardiographic and Electroanatomic Atrial Volumes

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Summary

Background: Left atrial (LA) volume (LAV) is used for the selection of patients with atrial fibrillation (AF) to rhythm control strategies. Calculation of LAV from the LA diameters and areas by two-dimensional (2D) echocardiography may result in significant error. Accuracy of atrial volume assessment has never been studied in patients with long-standing persistent AF (LSPAF) and significant atrial remodeling.

Methods: This study investigated correlation and agreement between 2D echocardiographic (Simpson method) and electroanatomic (CARTO, Biosense Webster) left and right atrial (RA) volumes (LAV_{ECHO} vs. LAV_{CARTO} and RAV_{ECHO} vs. RAV_{CARTO}) in patients undergoing catheter ablation for LSPAF.

Results: The study enrolled 173 consecutive subjects (females: 21%, age: 59 ± 9 years). There was only modest correlation between LAV_{ECHO} (92 ± 31 ml) and LAV_{CARTO} (178 ± 37 ml) ($R=0.57$), and RAV_{ECHO} (71 ± 29 ml) and RAV_{CARTO} (173 ± 34 ml) ($R=0.42$), respectively. LAV_{ECHO} and RAV_{ECHO} underestimated LAV_{CARTO} and RAV_{CARTO} with the absolute bias (± 1.96 standard deviation) of -85 (-148 ; -22) ml and -102 (-169 ; -35) ml, respectively, and with the relative bias of -48 (-75 ; -21)% and -59 (-88 ; -30)%, respectively (all $P < 0.000001$ for their mutual difference). Significant confounders of this difference were not identified.

Conclusion: In patients with LSPAF, 2D echocardiography significantly underestimated both LA and RA volumes as compared with electroanatomic reference. This disagreement was independent of clinical, echocardiographic and mapping characteristics.

Keywords: Long-Standing Atrial Fibrillation – Echocardiography – Electroanatomic Mapping – Atrial Volume

Introduction

Atrial fibrillation (AF) is frequently associated with left atrial (LA) enlargement which is also an acknowledged marker of resistance to pharmacological and non-pharmacological treatment of AF (Berruezo *et al.* 2007, Hof *et al.* 2009, Montefusco *et al.* 2010, Von Bary *et al.* 2012, Zhuang *et al.* 2012). Although LA antero-posterior diameter in long-axis parasternal (PLAX) view has been largely used as a simple index of the LA size, its correlation with the LA volume (LAV) was poor in multiple prior studies (Lester *et al.* 1999, Pritchett *et al.* 2003, Badano *et al.* 2008, Hof *et al.* 2009). Three-dimensional (3D) echocardiography, computed tomography (CT) or magnetic resonance (MR) imaging are not commonly used in routine clinical practice for more accurate assessment of LAV (Russo *et al.* 2010, Miyasaka *et al.* 2011, Mor-Avi *et al.* 2012, Shimada and Shiota 2012, Koka *et al.* 2012, Patel *et al.* 2003, Müller *et al.* 2010, Vandenberg *et al.* 1995, Rodevan *et al.* 1999, Maceira *et al.* 2010, Abhayaratna *et al.* 2006, Lang *et al.* 2005, Havranek *et al.* 2016). On the other hand, routinely employed automated algorithms for calculation of LAV from the LA diameters and areas by two-dimensional (2D) echocardiography may result in significant error.

Electroanatomic mapping in patients undergoing catheter ablation for AF offers an alternative tool of 3D atrial reconstruction and volume assessment independent of geometric assumptions (Patel *et al.* 2003, Müller *et al.* 2010). The LAV derived from electroanatomic mapping (LAV_{CARTO}) poorly corresponded with 2D-echocardiographic LAV (LAV_{ECHO}) in patients ablated for predominantly paroxysmal AF in prior studies (Patel *et al.* 2003, Havranek *et al.* 2016). No prior study; however, compared LAV_{CARTO} and LAV_{ECHO} in the subjects with long-standing persistent AF (LSPAF), the most difficult-to-ablate AF type because of extensive LA remodeling. In addition, although arrhythmogenic substrate of LSPAF involves RA in up to 30% of cases (Rostock *et al.* 2008, Narayan *et al.* 2012, Haissaguerre *et al.* 2014), RA is not routinely mapped during AF ablation and correspondence

between 2D echocardiographic and electroanatomic RA volumes (RAV_{ECHO} and RAV_{CARTO}) is generally unknown.

This study aimed at investigating the relationship between the 2D echocardiographic LAV_{ECHO} and RAV_{ECHO} calculated by the Simpson method and the LAV_{CARTO} and RAV_{CARTO} derived from 3D electroanatomic mapping in patients undergoing catheter ablation for LSPAF.

Methods

Study Population

The study included 173 consecutive patients who underwent their first ablation for LSPAF between August 2007 and December 2011 and met the following criteria: 1) age 18-80 years; 2) symptomatic LSPAF lasting >12 months without intervening sinus rhythm; 3) refractory to oral amiodarone; 4) resistant to electrical cardioversion or recurring within 7 days after.

Ethical approval was obtained for the study protocol, and all patients gave written informed consent.

Electroanatomic Mapping

Electroanatomic LA and RA maps (CARTO, Biosense Webster, Diamond Bar, CA, USA) were acquired during AF by mapping/ablation catheter with a 3.5-mm irrigated-tip electrode (NaviStar ThermoCool, Biosense Webster, Diamond Bar, CA, USA). The maps were based on 3D virtual LA/RA shells reconstructed by software interpolations over the co-ordinates of multiple endocardial points. Efforts were made to obtain high-density maps consisting of evenly distributed contact points. Transition of the tubular segment of pulmonary vein (PV) into the PV antrum was identified by combined information obtained from fluoroscopy, recording of PV and LA potentials, and impedance drop. Intracardiac echocardiography

assisted in visualization of critical atrial structures in a majority of cases. The LAV_{CARTO} and RAV_{CARTO} were automatically derived from 3D electroanatomic maps that comprised broader PV antra and entire appendages. The CT image was registered in the electroanatomic map by an automated algorithm that minimizes the distance between mapping points and the CT surface. The match between both merged maps was optimized by eliminating inner and outer electroanatomic points due to inadequate contact or excessive pressure against the atrial wall as well as respiration-related shifts. LAV_{CARTO} and RAV_{CARTO} were automatically provided by a built-in computation function of the Biosense system. In addition to volume assessment, the proportions of mapping points arbitrarily divided into 3 groups exhibiting voltage <0.2 mV (severe interstitial fibrosis), $0.2-1.0$ mV, and >1 mV (normal atrial myocardium) were obtained as described previously (Fiala *et al.* 2010).

Echocardiographic Examination

Transthoracic echocardiography using an echocardiograph iE 33 (Phillips, Bothell, WA, USA) were completed by 3 experienced physicians prior to the ablation according to the guidelines (Pritchett *et al.* 2003⁷, Abhayaratna *et al.* 2006, Lang *et al.* 2005). Left ventricular diameters were measured in PLAX view using M-mode when possible, or 2D echocardiography if more accurate. Antero-posterior LA diameter in PLAX view, and LA and RA long- and short-axis diameters in apical four-chamber (A4CH) and apical two chamber (A2CH) views were measured as the maximum end-systolic linear dimensions not including venous ostia or appendages. Atrial volumes were automatically obtained by biplane (A2CH and A4CH) and single-plane (A4CH) modified Simpson method for LAV_{ECHO} and RAV_{ECHO} , respectively (Lang *et al.* 2005).

Statistical Analysis

Continuous variables were expressed as a mean with standard deviation and compared by 2-tailed t-test for independent samples. Categorical variables were expressed as a percentage and compared by χ^2 -test. Pearson's correlation and multivariate linear regression were used to analyze the relationship between LAV_{ECHO} and RAV_{ECHO} together with other clinical covariates as independent variables and LAV_{CARTO} and RAV_{CARTO} as dependent variable. Stepwise forward method was used for all variables with univariate relationship of $P \leq 0.20$. The agreement between atrial volumes was analyzed using the modified method of Bland-Altman assuming that LAV_{CARTO} and RAV_{CARTO} are substantially more accurate than LAV_{ECHO} and RAV_{ECHO}. P-value < 0.05 was considered significant. All analyses were performed using the STATISTICA vers.12 software (Statsoft, Inc., Tulsa, USA).

Results

Baseline characteristics of the study population are shown in Table 1. Pre-ablation LAV_{ECHO} and LAV_{CARTO} were compared in all 173 patients; comparison of RAV_{ECHO} and RAV_{CARTO} was available in 169 patients. Echocardiographic and electroanatomic mapping parameters are summarized in Tables 2 and 3. The distribution of LAV_{ECHO} (92 ± 31 ml) / RAV_{ECHO} (71 ± 29 ml) and LAV_{CARTO} (178 ± 37 ml) / RAV_{CARTO} (173 ± 34 ml) is shown in Figure 1.

There was only modest correlation between LAV_{ECHO} and LAV_{CARTO} ($R=0.57$), and RAV_{ECHO} and RAV_{CARTO} ($R=0.42$), respectively ($P < 0.0001$ for both coefficients) (Figure 2). LAV_{ECHO} and RAV_{ECHO} underestimated LAV_{CARTO} and RAV_{CARTO} with the absolute bias (± 1.96 standard deviation) of -85 (-148 ; -22) ml and -102 (-169 ; -35) ml, respectively, and with the relative bias of -48 (-75 ; -21)% and -59 (-88 ; -30)%, respectively (all $P < 0.000001$ for their mutual difference) (Figure 3). The proportions of patients exhibiting difference between echocardiographic and electroanatomic LAV and RAV that exceeded predefined level of error are shown in Table 4. No significant and independent covariates of the difference between

LAV_{ECHO} and LAV_{CARTO} and between RAV_{ECHO} and RAV_{CARTO} were identified by multivariate regression analysis.

Discussion

This study demonstrated that the LAV derived from electroanatomic endocardial map was approximately twofold larger than that assessed by the 2D echocardiographic Simpson method and, importantly, that the limits of agreement were considerably wide. Such disagreement was for the first time shown in patients with intractable LSPAF and significant left atrial enlargement. This is also the first study that revealed similarly poor correspondence between electroanatomic and echocardiographic RAV.

The present study corroborated previously reported systematic underestimation (by ~30%) of LAV assessed by 2D echocardiography when compared with the assessment by CT or MR (Koka *et al.* 2012, Rodevan *et al.* 1999). LAV obtained by echocardiographic biplane Simpson method was also lower by 20-30% when compared with electroanatomic LAV; this study reported excellent correlation ($r=0.9$) between electroanatomic and echocardiographic LAV; however, it included a relatively small number of patients with only paroxysmal AF (Patel *et al.* 2003). Our concurrent analysis of a larger population with all AF types showed an increasing scatter of differences between LAV_{ECHO} and LAV_{CARTO} as well as trend to greater both absolute and relative underestimation of true LA size in patients with excessive LA enlargement (Havranek *et al.* 2016).

Electroanatomic instead of CT atrial volumes were used in our study. We are convinced that they can be used promiscuously because excellent match between high-density electroanatomic map and CT image can be invariantly achieved during AF ablation procedures. This is supported by prior study which showed that electroanatomic reconstruction could display true LA 3D anatomy as defined by the CT with high accuracy in

most of the LA regions (Piorkowski *et al.* 2006). Recently, the LAV derived from electroanatomic mapping correlated and agreed well with the LAV calculated by MR (Rabbat *et al.* 2015).

Inaccuracy of LAV/RAV_{ECHO} may be influenced by availability of suitable echocardiographic window, observer-dependent adjustment of angulation and gain for endocardial contour visualization, and correct timing of measurement at the end of ventricular systole (Lester *et al.* 1999, Ujino *et al.* 2006). The image quality and anatomically correct projection are frequently competing factors, so that the planes may not be aligned to geometric centre of the chamber in order to achieve maximum cross-sectional area, and biplane assessments may not be strictly orthogonal. Thus, the disparity between the methods might results from: (i) failure of simple geometric assumptions applied by 2D echocardiography to assess adequately the true volume of complex atrial shape (Cozma *et al.* 2007) and/or (ii) failure to acquire the proper images for biplane assessment in terms of orthogonality and nice endocardial contour. Although the Simpson method is less dependent on simple geometric assumption (like, for example, prolate ellipsoid method), we believe that both are important sources of error. One can easily imagine that non-spherical structure is prone to either overestimation or underestimation, while more spherical structure is prone to underestimation only. Therefore, bidirectional deviations are mutually cancelled in small, non-spherical atria in patients with paroxysmal AF while unidirectional deviations aggregate in significantly remodelled and more spherically shaped atria in patients with LSPAF. Besides spherical remodelling of the LA (Bisbal *et al.* 2013), other factors may also play a role: enlargement of the funnel-shaped PV antra (Tsao *et al.* 2001), LA roof reshaping (Kurotobi *et al.* 2011), and dilation of the anterior LA including the LA appendage (Nedios *et al.* 2011).

The results of our study are clearly biased by the volume of LA appendage that was mapped, i.e. included into the LAV_{CARTO} . Biplane 2D echocardiography does not display LA

appendage that was, therefore, principally excluded from the LAV_{ECHO} calculation. LA appendage volume ranges between 10-30 ml according to different studies, so that the sizeable difference between LAV_{CARTO} and LAV_{ECHO} in our study would hardly have been eliminated if electroanatomic maps had been edited in this respect.

Importantly, there is also bias in the opposite direction that relates to the timing of LAV/RAV assessment. While echocardiographic readings are performed at the end-systolic maximum of atrial volume, the electroanatomic mapping is triggered by the QRS complexes, i.e. points are acquired at the end-diastolic phase when atrial volume is consistently lower by approximately 20-30 ml, which may offset the bias related to the LA appendage (see above).

The difference between LAV_{CARTO} and LAV_{ECHO} was substantially greater than in prior studies and we were not able to find any clinical or morphological variables responsible for this disagreement as in our previous study (Havranek *et al.* 2016). However, this study investigated a significantly larger and more heterogeneous population of AF patients and consequently was more powered to identify individual confounders.

Limitations

Because of retrospective nature of our investigation, the study has several limitations: Readings of CT-derived atrial volumes were not available. We have no centre-specific data on within- and inter-examiner reproducibility of 2D echocardiographic LAV/RAV. The same applies for LAV/RAV assessed by means of electroanatomic mapping which was performed only once per patient by single experienced operator.

Finally, despite limitations of 2D echocardiography for the assessment of atrial volume, the vast majority of prognostic data is derived from this method. Therefore, before adoption of other imaging methods into clinical practice, their prognostic value should be assumed as unknown.

Conclusions

In patients with LSPAF and significant atrial remodeling, the 2D echocardiography with the use of single/biplane Simpson method significantly underestimated the atrial size compared to the electroanatomic reference. Therefore, the results of this method should be interpreted with caution, especially when used for selection of suitable candidates for rhythm control strategies including catheter ablation. More focused studies are needed to disclose the main source of inaccuracy in atrial volume assessment by 2D echocardiography in patients with severe atrial dilation.

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Tables

Table 1: Baseline Characteristics	
Age (years)	59±9 (32-79)
Females	37 (21 %)
Total AF history (months)	median 60, IQR 31-93 (13-504)
Persistent AF duration (months)	median 26, IQR 17-48 (13-254)
Arterial hypertension	107 (62 %)
Diabetes mellitus	20 (12 %)
Stroke/TIA	22 (13%)
Coronary artery disease	13 (8 %)
Pulmonary disease	21 (12 %)
History of heart failure	34 (19%)
LVEF ≤40% before ablation	28 (16%)
Hypothyroidism	13 (8%)
CHADS ₂	1.2±1.0 (0-4)
CHA ₂ DS ₂ VASC	1.7±1.4 (0-6)
Body mass index (kg/m ²)	31±4 (19-44)
LV end-diastolic diameter (mm)	52±7 (37-79)
LV end-systolic diameter (mm)	37±8 (21-67)
LVEF (%)	median 58, IQR 51-60 (25-67)
Data shown as mean ± standard deviation (range) or Median with interquartile range (IQR) (range) or count (percentage). AF = atrial fibrillation; LV = left ventricular; LVEF = left ventricular ejection fraction; TIA = transitory ischemic attack.	

Table 2. Left and Right Atrial Echocardiographic Parameters	
LA antero-posterior diameter (mm)	48±5
LA long-axis diameter (mm)	68±6
LA short axis diameter (mm)	47±6
RA long-axis diameter (mm)	61±6
RA short axis diameter (mm)	44±8
LAV _{ECHO} (ml)	92±31
RAV _{ECHO} (ml)	71±29
Data shown as mean ± standard deviation (range). LA = left atrial; RA = right atrial; LAV _{ECHO} , RAV _{ECHO} = left and right atrial volumes assessed by 2D echocardiography (Simpson method).	

Table 3. Left and Right Atrial Electroanatomic Mapping Parameters	
LA mapping points	222±39
RA mapping points	177±29
LA points <0.2 mV (%)	24±18
LA points >1.0 mV (%)	19±11
RA points <0.2 mV (%)	17±11
RA points >1.0 mV (%)	35±16
LA maximum voltage (mV)	5.5±2.4
RA maximum voltage (mV)	6.2±2.5
LAV _{CARTO} (ml)	178±37
RAV _{CARTO} (ml)	173±34
Data shown as mean ± standard deviation (range). LA = left atrial; RA = right atrial; LAV _{CARTO} , RAV _{CARTO} = left and right atrial volumes derived from electroanatomic mapping.	

Table 4. Proportions of Subjects with Relative Deviation of Echocardiographic from Electroanatomic Atrial Volume		
	LAV _{ECHO} vs. LAV _{CARTO}	RAV _{ECHO} vs. RAV _{CARTO}
Magnitude of error >10%	99%	97%
Magnitude of error >20%	95%	97%
Magnitude of error >30%	92%	93%
Magnitude of error >50%	46%	73%
Results are shown for 4 categories defined by lower limit of error. LAV _{ECHO} , RAV _{ECHO} = left and right atrial volumes automatically assessed by 2D echocardiography (Simpson method); LAV _{CARTO} , RAV _{CARTO} = left and right atrial volumes assessed by electroanatomic mapping.		

Legend to Figures

Figure 1. Distribution of left and right atrial volumes. Abbreviations: LAV_{ECHO} , RAV_{ECHO} – left and right atrial volume assessed by 2D echocardiography (Simpson method); LAV_{CARTO} , RAV_{CARTO} – left and right atrial volumes derived from electroanatomic mapping.

Figure 2. Pearson's correlation between two-dimensional echocardiographic and electroanatomic volumes. Correlation of left atrial volumes (panel A) and right atrial volumes (panel B). Abbreviations as in Figure 1.

Figure 3. Agreement between two-dimensional echocardiographic and electroanatomic atrial volumes. Scatterplots for absolute (panels A and B) and relative (panels C and D) differences between left atrial (panels A and C) and right atrial (panels B and D) volumes obtained by 2D echocardiography and electroanatomic mapping. Dashed line – identity line; solid line – bias; dotted line – limits of agreement (± 1.96 standard deviation). Abbreviations as in Figure 1.





