ORIGINAL RESEARCH

Association Between Cardiovascular Magnetic Resonance-Derived Left Atrial Dimensions, Electroanatomical Substrate and NT-proANP Levels in Atrial Fibrillation

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***Background*—**Enlargement of left atrial (LA) size indicates advanced disease stage in patients with atrial fibrillation (AF) and is associated with poor success of different AF therapies. Two dimensional echocardiographic LA measurements do not reliably reflect the true size of LA anatomy. The aim of the current study was: 1) to analyze cardiovascular magnetic resonance (CMR)-derived LA dimensions and their association with low voltage areas (LVA); and 2) to investigate the association between these parameters and NT-proANP (N-terminal proatrial natriuretic peptide) levels.

***Methods and Results*—**Patients undergoing first AF catheter ablation were included. All patients underwent CMR imaging (Ingenia 1.5T Philips) before intervention. CMR data (LA volume, superior–inferior, transversal and anterior–posterior LA diameters) were measured in all patients. LVA were determined using high-density maps and a low voltage threshold <0.5 mV. Blood plasma samples from femoral vein were collected before catheter ablation. NT-proANP levels were studied using commercially available assays. There were 216 patients (65±11 years, 59% males, 56% persistent AF, 26% LVA) included into analyses. NT-proANP levels in patients with LVA were significantly higher than in those without (median/interquartile range 22 [13–29] versus 15 [9–22] pg/mL, P=0.004). All CMR derived LA diameters correlated significantly with persistent AF (r^2=0.291–0.468, all P<0.001), LVA (r^2=0.187–0.306, all P<0.001), and NT-proANP levels (r^2=0.258–0.352, P<0.01). On logistic regression multivariable analysis, age (odds ratio=1.090, 95% confidence interval: 1.030–1.153, P=0.003), females (odds ratio=2.686, 95% confidence interval: 1.047–6.891, P=0.040), and LA volume (odds ratio=1.022, 95% confidence interval: 1.009–1.035, P=0.001) remained significant predictors for LVA.

***Conclusions*—**Left atrial CMR parameters are associated with persistent AF, low voltage areas and NT-proANP levels. LA volume is the most significant predictor for LVA. **(*J Am Heart Assoc*. 2018;7:e009427. DOI: 10.1161/JAHA.118.009427.)**

Key Words: atrial fibrillation • cardiovascular magnetic resonance • left atrial volume • low voltage areas • NT-proANP

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical routine associated with cardio- and cerebrovascular complications, dementia, and mortality. Catheter ablation is a cornerstone therapy in AF patients.[1] There are several variables associated with AF progression patterns and severity. Left atrial (LA) enlargement is known to be associated with advanced disease stages of AF.[2–5] There are several imaging modalities to assess the LA dimensions. Echocardiography is readily available and the most frequently used modality. LA size is a routine diagnostic criterion in patients before pulmonary vein isolation because of significant association with arrhythmia recurrences.[6,7]

However, echocardiographic LA measurements are often associated with significant inter- and intra-observer inaccuracies and do not reliably reflect the true size of LA anatomy. Novel imaging modalities such as cardiovascular magnetic resonance (CMR) revealed that this measurement has poor correlation with LA volume given the varying size.[8]

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Clinical Perspective

What Is New?

- Cardiovascular magnetic resonance derived left atrial diameters and volumes are associated with NT-proANP (N-terminal proatrial natriuretic peptide) levels, a blood marker of atrial stress
- Left atrial (LA) volume and several LA diameters are significantly associated with low voltage areas (LVA). However, LA volume seems to be the most powerful predictor for the presence of LVA.
- Furthermore, in a subgroup of echocardiographic derived LA dimensions, LA volume remained the best predictor for LVA, too.

What Are the Clinical Implications?

- Presence of LVA is associated with ablation success and can determine further AF progression.
- A non-invasive tool (eg, imaging, blood biomarkers) to predict LVA before ablation is important to optimize and individualize the ablative approach.

Additionally to atrial enlargement, symmetry changes and shape of the 3D LA structure have been associated with reduced ablation success.[9]

Another important variable associated with AF progression patterns and severity stage is a periprocedural evidence of low voltage areas (LVA) representing advanced remodeling processes in LA.[10] LVA are present in ≈20% to 25% of all AF patients and may require additional ablation strategies, continuation of antiarrhythmic drugs, as well as more intensive clinical follow-up because of higher AF recurrence rates.[10]

To improve and tailor an individualized AF treatment strategy, several blood biomarkers have been analyzed in epidemiological and clinical studies.[11] Among them are natriuretic peptides (NP) which levels correlate with cardiovascular diseases (eg, coronary heart disease, heart failure, and hypertension).[12] NPs also associate with AF, cardiovascular risk in AF patients, and AF recurrence following intervention.[13] Recently we demonstrated that NT-proANP (N-terminal proatrial natriuretic peptide) levels are significantly higher in AF patients with increased LA diameter and in patients with LVA.[14]

The aim of current study was to analyze CMR derived LA dimensions and their association with low voltage areas (LVA). Furthermore, we investigated the association between these parameters and NT-proANP levels.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. All data generated or analyzed during this study are included in this published article and its supplementary information files. The studies were approved by the local Ethical Committee (Medical Faculty, University Leipzig) and patients provided written informed consent for participation. All methods were performed in accordance with the relevant guidelines and regulations.

In this study we included 216 patients who presented to our tertiary clinic from October 2015 to April 2017 for AF catheter ablation. Inclusion criteria was a highly symptomatic AF, refractory to the antiarrhythmic treatment. Exclusion criteria were pregnancy, aged <18 or >75 years, valvular AF, cancer, acute or systemic inflammatory diseases.

Paroxysmal and persistent AF were defined according to current guidelines.[15] Paroxysmal AF was defined as self-terminating within 7 days after onset. Persistent AF lasted longer than 7 days or required drugs or direct current cardioversion for termination. In all patients, transthoracic and transesophageal echocardiography were performed before ablation. All patients underwent CMR and had CMR-based left atrial anatomy measures. All class I or III antiarrhythmic medications with exception of amiodarone were discontinued for at least 5 half-lives before the AF ablation procedure.

Cardiovascular Magnetic Resonance

Before AF ablation, patients underwent 1.5T CMR (Ingenia, Philips Medical) 1 to 2 days before the intervention. A contrast-enhanced magnetic resonance angiography of the left atrium and the pulmonary veins was acquired during breath holding without ECG gating (TR/TE/flip angle: 2.5 msec/8 msec/30°; spatial resolution: $1.0\times1.0\times1.0$ mm^3) using real-time bolus tracking with a bolus injection of 0.1 mmol/kg Gd-DTPA (injection rate 4.0 mL/s). CMR data were reviewed and total LA volume (LAV) was determined after exclusion of the left atrial appendage and the pulmonary veins. LA was centered on all 3 cutting planes and the superior–inferior (SI), transversal (TV) and anterior–posterior (AP) diameters were measured (Figure 1). In addition, the asymmetry index was calculated as previously described.[16] The total left atrial volume was therefore divided by a cutting plane, between the anterior segment of the pulmonary veins ostia and the left atrial appendage and parallel to the posterior wall. The partial LA volumes, the anterior (LA-A) and the posterior (LA-P) were calculated and the ratio LA-A/LAV was defined as an asymmetry index (Figure S1).

Catheter Ablation

The electroanatomical mapping was performed in sinus rhythm. In patients presenting with AF, the arrhythmia was terminated

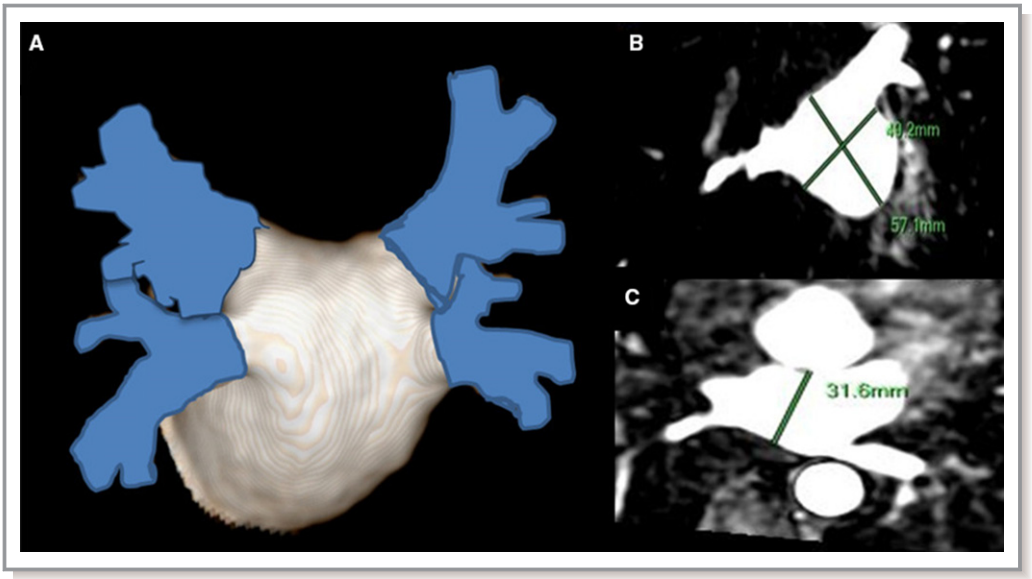

Figure 1. CMR LA Volume after excluding the pulmonary veins and the LAA (A) and CMR derived diameters: superior-inferior and transversal diameter (B) and anterior–posterior diameter (C). CMR indicates cardiovascular magnetic resonance; LAA, left atrial appendage.

by electrical cardioversion and the mapping was further performed in sinus rhythm. End point of the catheter ablation was isolation of the pulmonary veins with proof of both exit and entrance block. The electroanatomical voltage maps of the left atrium excluding the pulmonary veins were created using multielectrode spiral catheter with interelectrode distance 2–5–2 mm and an ablation catheter with a 3.5-mm electrode tip and contact measurement properties (SmartTouch Thermocool, Biosense Webster, Diamond Bar, CA and TactiCath, St Jude Medical (SJM), Saint Paul, MN) as mapping catheter. Electroanatomical mapping was performed using 3D electroanatomical mapping systems (Carto, Biosense Webster, Diamond Bar, CA or EnSite Precision, SJM). In both mapping systems the cut-off values for defining LVA were identical: <0.5 mV for low voltage and <0.2 mV for dense scar, >0.5 mV for normal voltage. Patients underwent high-density mapping (Figure 2) of left atrial voltage using multipolar catheters in combination with auto-annotation algorithms (AutoMap in Precision and ConfiDense in Carto 3). The voltage mapping points were obtained in sinus rhythm before ablation or after ablation of the pulmonary veins. Here the number of points was >1000. Points with insufficient catheter-to-tissue contact or inside ablation lines were excluded to obtain an accurate electroanatomical map. According to the presence of LVA additional ablation lines were added after the electroanatomical map. After ablation the electroanatomical map was stored in our clinical database.

At the end of the procedure, an attempt to induce AF or left atrial macro-reentry tachycardia (LAMRT) was performed using a standardized protocol (burst stimulation with 300, 250, 200 ms from coronary sinus). According to the underlying LVA and inducible left atrial macro-reentry tachycardia additional ablation lines were applied.

Blood Samples

Blood samples were obtained in EDTA test tubes in fasting state prior ablation procedure from femoral vein and processed within 1 hour of collection. Blood plasma was prepared (1000×g for 10 minutes at 20°C) and aliquots were stored at −70°C for subsequent analysis. NT-proANP levels were studied using Luminex Screening Assay (R&D/biotechne, Minneapolis).

Statistics

Data are presented as mean and standard deviation for normally distributed or median (interquartile range) for skewed continuous variables and as proportions for categorical variables. Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. The differences between continuous values were assessed using an unpaired t test or the Mann–Whitney, and a chi-square test for categorical variables. Correlations were performed using Spearman rank correlation method. Logistic regression analysis was used to identify factors associated with LVA. Multivariable analysis, which included variables with a $P<0.05$ found on univariable analysis, was performed to identify independent predictors for the presence of LVA. We performed multivariable analyses separately with LA volume analyzed in CMR (model 1) and in echocardiography (model 2).

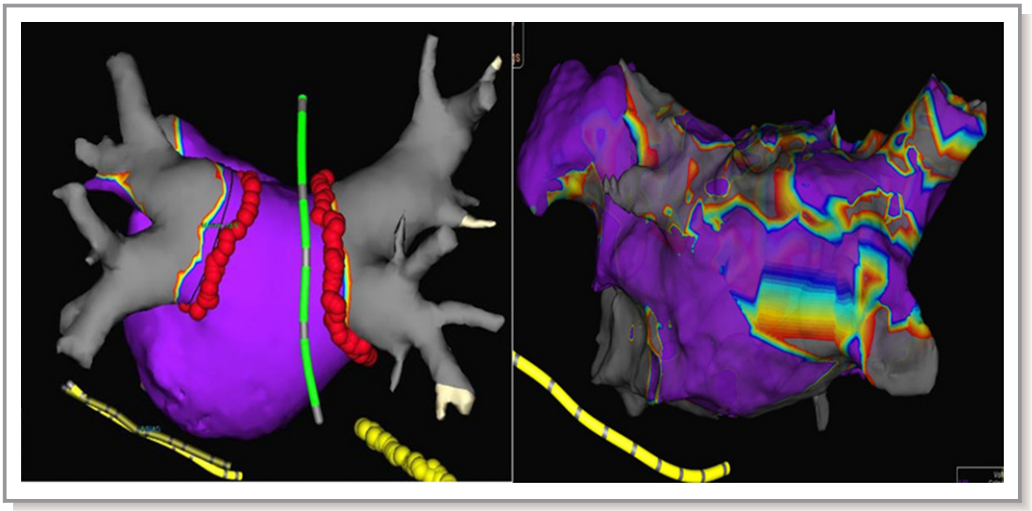

Figure 2. Electroanatomic voltage mapping from the anterior–posterior view without (left, purple color bipolar voltage >0.5 mV) and with (right, multicolored areas, bipolar voltage <0.5 and >0.2 mV; bipolar voltage <0.2 mV is displayed as grey).

A $P<0.05$ was considered statistically significant, and all analyses were performed with SPSS statistical software version 23 (SPSS Inc, Chicago).

Results

Clinical Characteristics of Study Population

In total, 216 patients (65±11 years, 59% males, 56% persistent AF, 26% LVA) with available clinical, CMR, and laboratory data undergoing primary AF ablation were included into analysis. Clinical characteristics of study population are summarized in Table 1. Patients in the LVA group were significantly older, had more frequently persistent AF, and lower estimated glomerular filtration rate (all $P<0.01$). LVA presence was significantly higher in females than in males ($P=0.004$). CMR derived LA dimensions correlated significantly with LVA ($r^2=0.306$, 0.228, 0.267, and 0.277 for anterior–posterior, SI, LA-A, and LAV, $P<0.001$), persistent AF ($r^2=0.468$, 0.324, 0.404, 0.423, and 0.435 for AP, transversal, SI, LA-A, and LAV ($P<0.001$) and NT-proANP levels ($r^2=0.285$, 0.258, 0.304, 0.352 and 0.335 for anterior–posterior, transversal, SI, LA-A and LAV [$P<0.001$, Table 2, Figure 3]).

There was significant correlation between echocardiographic LA diameter and CMR LAV in a subgroup of 87 patients with available echocardiographic data, respectively, all $P<0.001$, Figure S2).

Low Voltage Areas

There were significant differences in all LA parameters in patients with and without LVA. However, there was no significant difference in asymmetry index between patients with and without LVA ($P=0.625$, Table 1). NT-proANP levels in patients with LVA were significantly higher than in those without LVA (median (IQR) 22 (13–29) versus 15 (9–22) pg/mL, $P=0.004$).

Table 1. Clinical Characteristics of Study Population

	Low-Voltage Areas		
	No (n=160)	Yes (n=56)	*P* Value
Age, y	63 (55–71)	69 (64–75)	<0.001
Females, %	35	57	0.004
Persistent AF, %	49	82	<0.001
eGFR, mL/min per 1.73 m^2	79 (68–91)	68 (58–82)	0.001
BMI, kg/m^2	29 (26–33)	30 (26–33)	0.314
AP, mm	44 (40–49)	50 (45–54)	<0.001
TV, mm	61 (54–65)	66 (60–71)	0.001
SI, mm	61 (55–68)	66 (61–72)	<0.001
LAV, mL	112 (88–137)	137 (116–162)	<0.001
LA-A	76 (58–93)	96 (73–110)	<0.001
LA-P	34 (27–46)	42 (31–53)	0.008
Asymmetric index, %	69 (63–74)	69 (65–73)	0.625
Asymmetric index >65%, %	57	52	0.399
EF, %	57 (48–61)	55 (47–59)	0.219
LA-EDV mL (biplane, echocardiography)	78 (61–100)	97 (80–113)	0.002
NT-proANP ng/mL	15 (9–22)	22 (13–30)	0.004

AF indicates atrial fibrillation; AP, anterior–posterior diameter; BMI, body mass Index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; LA-A, left atrial anterior volume; LA-EDV, left atrial end diastolic volume; LA-P, left atrial posterior volume; LAV, total left atrial volume; NT-proANP, N-terminal proatrial natriuretic peptide; SI, superior inferior diameter; TV, transversal diameter.

Table 2. Correlation of LA Parameters With LVA, Persistent AF, and NT-proANP

	AP	TV	SI	LA-A	LA-P	LAV	Asymmetry Index
	r^2/*P* Value	r^2/*P* Value	r^2/*P* Value	r^2/*P* Value	r^2/*P* Value	r^2/*P* Value	r^2/*P* Value
LVA	0.306/<0.001	0.187/<0.006	0.228/0.001	0.267/<0.001	0.090/0.181	0277/<0.001	0.036/0.620
Persistent AF	0.468/<0.001	0.324/<0.001	0.404/<0.001	0.423/<0.001	0.181/0.006	0.435/<0.001	−0.073/0.3
NT-pro-ANP	0.285/<0.001	0.258/0.001	0.304/<0.001	0.352/<0.001	0.140/0.078	0.335/<0.001	0.125/0.127

AF indicates atrial fibrillation; AP, anterior–posterior diameter; LA-A, left atrial anterior volume; LA-P, left atrial posterior volume; LAV, total left atrial volume; LVA, low-voltage areas; NT-proANP, N-terminal proatrial natriuretic peptide; SI, superior inferior diameter; TV, transversal diameter.

In logistic regression univariable analysis, age, sex, persistent AF, NT-proANP, CMR-derived LA diameters (AP, transversal, SI), total LA volume and LA anterior volume as well as echocardiographic biplane LA volume were predictors for low voltage areas (Table 3). In multivariable analysis with CMR data, only age (odds ratio [OR]=1.090, 95% confidence interval [CI]: 1.030–1.153, *P*=0.003), females (OR= 2.686, 95% CI: 1.047–6.891, *P*=0.040), and LAV (OR= 1.022, 95% CI: 1.009–1.035, *P*=0.001) remained significant predictors for LVA. Similar findings had been found in multivariable analysis with echocardiographic LA volume data, where only echocardiographic left atrial volume remained a significant predictor for LVA (OR=1.028, 95% CI: 1.002–1.054, *P*=0.033). In contrast to MV model 1, the sex and age were not significantly associated with LVA. However, this might be explained by smaller patient number with available echocardiographic data.

Discussion

Main Findings

In the current paper, we report associations between different CMR-derived LA size measurements and LVA, indicating advanced electroanatomical remodeling. We found that besides age and sex, LA volume, among several LA parameters, was significantly associated with LVA. To the best of our knowledge this is the first study to report on a significant association between CMR-derived LA dimensions and NT-proANP.

LA Size and Low Voltage Areas

The accurate measurement of the LA diameter before pulmonary vein isolation is required, since the LA diameter is a marker of advanced electroanatomical remodeling and a strong predictor for the success after different AF management strategies.[17–20] We assessed LA anatomy with CMR as it is superior in quantifying the real 3D LA volume and shape compared with 2D echocardiographic measurements.

The prognostic value of LVA for AF recurrences is well established in the current literature.[10,21,22] In times of emerging cryoballoon ablation, the clinical decision of pulmonary vein isolation 'only' versus pulmonary vein isolation with additional substrate modification is of crucial importance. Therefore, analyzing clinical characteristics, imaging and biomarker profiles might be very helpful for the prediction of LVA and individualized AF management decisions before intervention.

One of the most significant and novel findings of this study is the association between LVA and CMR-derived left atrial diameters and volumes. We demonstrated that besides age

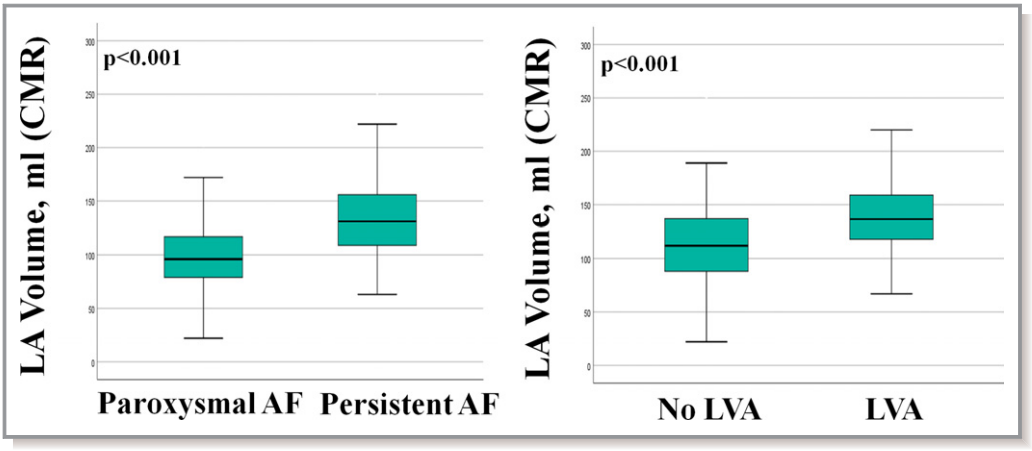

Figure 3. LA volume according to AF type and presence/absence of low-voltage areas. AF indicates atrial fibrillation; CMR, cardiovascular magnetic resonance; LA, left atrial; LVA, low voltage areas.

Table 3. Prediction of Low-Voltage Areas

	Univariable Analysis			Multivariable Analysis 1			Multivariable Analysis 2		
Variables	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age, y	1.086	1.045 to 1.129	<0.001	1.086	1.027 to 1.149	0.004	1.061	0.985 to 1.143	0.121
Females	2.476	1.331 to 4.608	0.004	2.612	1.009 to 6.763	0.048	2.120	0.529 to 8.494	0.289
Persistent AF	4.716	2.226 to 9.993	<0.001	1.840	0.651 to 5.203	0.250	2.701	0.614 to 11.885	0.189
NT-proANP ng/mL	1.033	1.010 to 1.056	0.005	1.013	0.987 to 1.040	0.333	0.997	0.96 to 1.035	0.861
AP, mm	1.102	1.054 to 1.150	<0.001						
TV, mm	1.046	1.012 to 1.081	0.007						
SI, mm	1.060	1.023 to 1.098	0.001						
LA volume, mL (biplane, CMR)	1.016	1.007 to 1.025	<0.001	1.019	1.006 to 1.033	0.005			
LA-A, mL	1.023	1.010 to 1.035	<0.001						
LA-P, mL	1.009	0.996 to 1.023	0.186						
Asymmetric index	0.991	0.956 to 1.027	0.619						
LA-EDV mL (biplane, echocardiography)	1.061	1.020 to 1.105	0.004				1.028	1.002 to 1.054	0.033
LA-EDV Index, mL/cm^3 (echocardiography)	1.025	1.006 to 1.044	0.008						

AF indicates atrial fibrillation; AP, anterior–posterior diameter; CI, confidence interval; CMR, cardiovascular magnetic resonance; LA-A, left atrial anterior volume; LA-EDV, left atrial end-diastolic volume; LA-P, left atrial posterior volume; LVA, low-voltage areas; NT-proANP, N-terminal proatrial natriuretic peptide; OR, odds ratio; SI, superior inferior diameter; TV, transversal diameter.

and sex, LA anterior volume, total LA volume, anterior-posterior, transversal, and superior- inferior diameters are significant predictors for the presence of LVA.

Asymmetry index has recently been suggested as an important predictor for rhythm outcomes after catheter ablation.[23] Despite significant associations between rhythm outcomes and LVA,[10] the association between asymmetry index and LVA is unknown. In our study, we did not find an association between asymmetry index and LVA.

Data regarding LVA and fibrosis distribution are inconsistent. While an earlier study suggested LVA being predominantly located at the posterior wall,[24] a study by Rolf et al described low-voltage areas to be mostly located in the anterior/septal LA part,[10] which is consistent with our correlation between LVA and the LA anterior volume. In other publications regarding fibrosis distribution in CMR, fibrosis is mostly found in the posterior LA or below the left inferior pulmonary vein ostium.[25] Nevertheless LA visualization via CMR can be helpful for the non-invasive indication of low voltage areas before AF ablation and consequently improve patient selection for different therapeutic strategies.[26]

In our study, total LA volume remained the strongest predictor for LVA irrespectively of the imaging modality (CMR or echocardiography). Furthermore, as already found in a previous study, where LA volume in CMR was associated with AF recurrence after AF ablation,[27] we demonstrated significant association with LVA. It is known, that the presence of LVA has an impact on the ablation modality. Therefore, our results demonstrate usefulness of non-invasive biomarkers of advanced LA remodeling, which would be helpful individualizing the AF treatment.

Associations Between NT-proANP, LVA, and LA Size

NT-proANP and NT-proBNP are expressed by cardiomyocytes, but ANP expression is highest in atria while BNP expression is higher in the left ventricle.[28] ANP has antihypertrophic, antifibrotic, antiproliferative and anti-inflammatory effects and is thus involved in cardiovascular remodeling.[29–31] Of note, progressing AF increases imbalance in ANP homeostasis.[32] Recently we found that NT-proANP levels are significantly higher in AF patients with larger echocardiographic LA diameter and in patients with LVA.[14] Furthermore, there were significant associations between NT-proANP and AF progression stage. NT-proANP levels were lowest in patients with paroxysmal AF and no LVA and highest in patients with persistent AF and LVA. In current study we confirm our previous results and demonstrate that diverse CMR-derived LA size parameters were significantly associated with NT-proANP. Also, the NT-proANP levels were associated with LVA in univariable analysis.

Furthermore, we found that besides age and LA volume, female sex is an important predictor for LVA. This is in line with other reports, too.[33–35] Female sex is associated with a 2-fold risk for LVA[33,34] and also has an almost 3-fold increased risk for AF recurrence following catheter ablation.[35] It is only to speculate that females probably might present with clinical AF in a later state of fibro-fatty infiltration, which

could explain a higher presence of electroanatomical substrate and worse rhythm outcomes after catheter ablation.

Strengths and Clinical Implications

The strength of the current study was the assessment of LA anatomy using CMR-derived measurements. LA dilatation and presence of LVA directly reflect pathophysiologic changes (eg, electroanatomical remodeling) and are known risk factors for worse therapy outcomes in AF patients. Whether an application of peripheral biomarkers—eg, NT-proANP—would improve the prediction of left atrial substrate in the daily practice, should be addressed in larger studies.

In our study total LA volume was the strongest predictor for LVA irrespectively of the imaging modality—CMR or echocardiography. Clear advantages of an echocardiographic study are its cost effectiveness, quick performance and a wide availability in the clinical routine. Also, as already demonstrated in multiple studies, initially the antero-posterior LA diameter was for a while the one of the most important indicators of LA remodeling.[7] However, some patients groups (eg, with obesity, lung disorders, or with a narrow ultrasound window) remain a big challenge even for the experienced echocardiographers and therefore determine interobserver inaccuracies. In these patients the CMR remains a gold standard.

We believe that our finding could improve individualized AF management, and AF patients should be screened non-invasively for characteristics of AF progression (eg, LA size, biomarker profiles) to refine therapy and follow-up strategies.

Limitations

Our study design aimed to detect correlations between circulating molecules in peripheral blood and CMR parameters that are relevant in AF pathophysiology. Whether these findings are applicable for cardiac tissue is unknown and could not be addressed in our study. We are aware that our observations do not prove any pathomechanistic processes but it is hypothesis-generating. The biomarkers were examined in a single blood sample before ablation; no repeated blood samples were obtained. Therefore, it remains unclear, what impact the biomarker fluctuations may have. Our correlations are significant, although it was limited by moderate R^2 values.

Conclusion

CMR-derived left atrial measurements are associated with persistent AF, LVA, and NT-proANP levels. LA volume is the most significant predictor for LVA. Using non-invasive diagnostic tools, it could be helpful to improve patient selection for different therapeutic strategies as well as individualize AF management.

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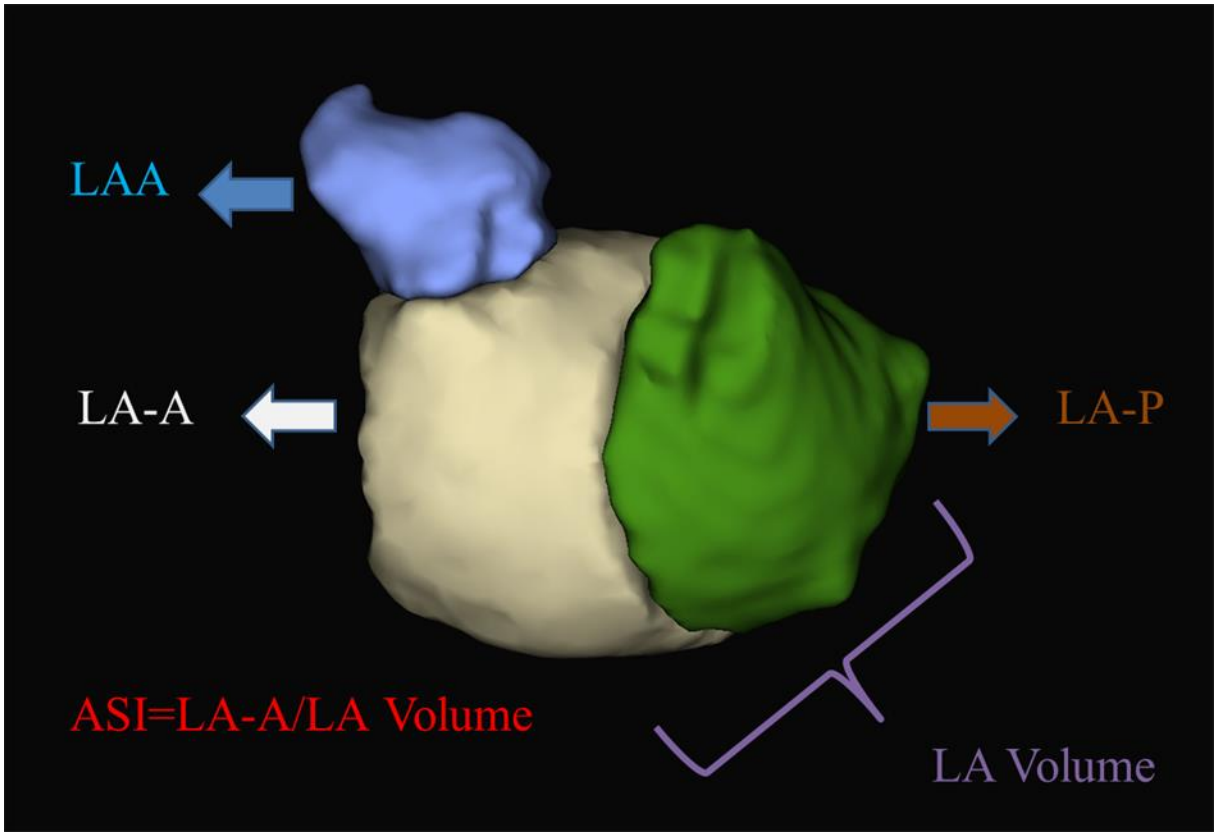
SUPPLEMENTAL MATERIAL

Figure S1. Calculation of the Asymmetry Index.



LAA - left atrial appendage, LA-A - left atrial anterior volume, LA-P - left atrial posterior volume, ASI - Asymmetry Index

Figure S2. Correlation between echocardiographic LA diameter and CMR derived LA Volume.