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Extent and magnitude of low-voltage areas assessed by ultra-high-density electroanatomical mapping correlate with left atrial function

F. Hohendanner [a,b,*], I. Romero [c], F. Blaschke [a,b], F.R. Heinzel [a,b], B. Pieske [a,b,d], L.-H. Boldt [a,b], A.S. Parwani [a,b]

[a] Charité – Universitätsmedizin Berlin, Department of Internal Medicine and Cardiology, Campus Virchow-Klinikum, Augustenburgerplatz 1, 13353 Berlin, Germany
[b] DZHK (German Centre for Cardiovascular Research), partner site Berlin, Germany
[c] Boston Scientific Corp., Amsterdam, the Netherlands
[d] German Heart Center Berlin, Department of Internal Medicine and Cardiology, 13353 Berlin, Germany

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ABSTRACT

Introduction: The extent of left atrial (LA) adverse remodeling as a cardiac disease marker has become increasingly important. In patients with atrial fibrillation (AF), atrial remodeling (AR) is accompanied by increased mortality. The relation between LA function and the extent of low-voltage areas (LVAs) has not yet been systematically investigated.

Methods: In patients with AF undergoing catheter-ablation, LA was studied using echocardiography and ultra-high-density mapping (Rhythmia®). Fibrosis (i.e. extent of LVAs) was estimated by quantifying areas with bipolar electrogram amplitudes of ≤0.5, ≤0.4, ≤0.3, ≤0.2 or ≤0.1 mV.

Results: A total of 22 patients with a mean LVEF of 53 ± 2% was studied. Mean LA volume index (LAVI) was significantly increased at 39 ± 3 ml/m^2 indicating AR. Size of LVAs was 57 ± 7 cm^2 representing 47 ± 5% of the total LA area (low-voltage set to ≤0.5 mV). With low-voltage set to ≤0.4, ≤0.3, ≤0.2 and ≤0.1, total area decreased to 34 ± 6, 28 ± 6, 22 ± 5 and 12 ± 3 cm^2. LAVI positively correlated with the extent of LVAs at all cut-offs. Mean LA emptying fraction was 42 ± 3% and showed a negative correlation with LVAs with low-voltage set to ≤0.4 mV. Moreover, mean LA strain was 13 ± 2% and correlated with LVAs with low-voltage at all cut-offs further supporting the notion that the extent of LVAs impacts LA function. Notably, with low-voltage set to ≤0.2, ≤0.3 and ≤0.4 mV impaired LA strain was detected with an accuracy of >76% ($p < 0.05$).

Conclusion: Structural (i.e. LAVI) and functional (i.e. LA emptying fraction and LA strain) parameters of the LA correlate with the extent of LVAs.

1. Introduction

Atrial remodeling (AR) is the result of processes that lead to alterations in morphology and function of the atrial myocardium. Atrial fibrillation (AF), enlargement, fibrosis and mechanical dysfunction are hallmark features of AR. In a recent consensus statement of the EHRA, AR has been defined as 'any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations' [1]. AR is independently associated with increased mortality and patient deterioration [2,3] and has been linked to disease progression and arrhythmias (e.g. AF) [4–7]. Current evidence indicates that atrial function extends beyond the classical view of an "atrial kick" to improve ventricular filling [1]. In fact, mechanical atrial function throughout the whole cardiac cycle is considerably more complex. In addition, the atrial myocardium also acts as a (stretch) sensor and has secretory activity. AR may affect all these functions by altering cardiomyocyte (CM) function, extracellular matrix composition (fibrosis) and paracrine signaling, ultimately leading to an atrial phenotype termed atrial (cardio)myopathy.

Left AR is often quantified using echocardiography: LA volume corrected for body size (i.e. LA volume index; LAVI) relates to the reservoir function of the LA and its measurement allows determining atrial contractility (LA emptying fraction; LAEF). In addition atrial strain based on speckle tracking has been used for the differentiation of LA conduit and reservoir function [8].

AF is a hallmark feature of atrial cardiomyopathy associated with AR (i.e. atrial enlargement and atrial functional impairment) as fibrosis creates conduction obstacles that might perpetuate the AF [9].

Patients with AR and AF are at increased risk for stroke, tachycardiomyopathy, impaired ventricular function and often show symptoms (i.e. palpitations) that negatively impact their daily life.

AF ablation is a well-established method to mitigate the effects of a missing atrial mechanical contribution to ventricular filling [10],

* Corresponding author at: Charité – Universitätsmedizin Berlin, Department of Internal Medicine and Cardiology, Campus Virchow-Klinikum, Augustenburgerplatz 1, 13353 Berlin, Germany.
E-mail address: felix.hohendanner@charite.de (F. Hohendanner).

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alleviate tachycardiomyopathy [11] and to improve symptoms in patients. Invasive ultra-high-density mapping is becoming increasingly important to characterize the atrial substrate in atrial arrhythmia.

The extent of LVAs might provide a surrogate parameter for the extent of AR as it has been shown to correlate with atrial fibrosis [12–14]. LA fibrosis in AR has been reported to range from 13 to 27% [15,16]. However, to date a direct correlation between the extent of LVAs and atrial functional impairment remains elusive. In addition, cut-off values for LVAs, correlating with different states of atrial mechanical dysfunction are unknown.

This study provides data obtained from 3D ultra-high-density mapping and echocardiography to quantify different stages of AR according to electroanatomic and functional parameters. By that it might allow to assess patients with AR and AF at risk for stroke or worsening of heart failure more comprehensively and beyond traditional scoring systems like the CHA_2DS_2-Vasc [17]. This study might also contribute to the more comprehensive prediction of freedom from atrial fibrillation after ablation.

2. Methods

2.1. Patient cohort

The institutional review board (Charité – Universitätsmedizin Berlin ethics committee) approved this study (clinical research project EA2/133/15). Patients with paroxysmal or persistent AF (i.e. AF that lasts longer than seven days) undergoing catheter ablation (1st or 2nd procedure [1st procedure: exclusively pulmonary vein isolation]) were included in the study. Cases with chronic persistent (i.e. continuous AF lasting for ≥1 year) or permanent AF were excluded.

The patient cohort was divided into different stages (no AR to severe AR) according to the LA strain during conduit phase (εe; severe: ≤13%; moderate >13%; LA strain below 23% is considered impaired [18]), the LA emptying fraction (reduced: <37%; preserved ≥37%, from [19]) or mean LAVI (severe: ≥39 ml/m^2; normal to moderate <39 ml/m^2; LAVI ≥34 ml/m^2 is considered increased [20]).

2.2. Echocardiography

LA function was assessed in a blinded-fashion during sinus rhythm on the day prior to ablation by LA strain analysis using 2-dimensional speckle-tracking echocardiography (Philips QLAB, 4-chamber view, peak LA strain during conduit phase; εe).

LA volumes were measured by biplane Simpsons method. LA EF (total LA emptying fraction, a measure of reservoir function [21]) was calculated as $LAV_{max} - LAV_{min} / LAV_{max} * 100$.

Echocardiographic image analysis allowed to obtain LA strain, LA volume and LA EF in a subset of 17, 17 and 16 patients, respectively.

2.3. 3D voltage map

Complete LA voltage maps were created with a 3D ultra-high-density electroanatomic mapping system (Rhythmia®, Boston Scientific). Electroanatomic maps were created before ablation using a multipolar basket (64 mini-electrodes distributed along 8 splines with a separation of 2.5 mm center to center and a size of 0.4 mm^2 per electrode; Rhythmia®, Boston Scientific) catheter. Field threshold was reduced from 4 to 2 mm.

Electroanatomic mapping was done carefully using steerable introducer-systems with the intention to create accurate maps while avoiding low contact. All maps were reviewed retrospectively in a blinded-fashion. Fibrosis was estimated by areas with a bipolar electrogram amplitude of <0.5, <0.4, <0.3, <0.2 or <0.1 mV. The size of areas with low-voltage was calculated by exporting these voltage electroanatomic maps into a triangular geometric surface creating a mesh of vertices and triangles. This mesh was obtained by giving a voltage value to each vertex based on the collected measurements in the vicinity. Then, a voltage value was assigned to each triangle. The total area for a specific voltage range was calculated as the sum of the areas of all triangles with voltage value within that range. In all patients, pulmonary veins, mitral valve and LA appendage (i.e. tissue not contributing to atrial mechanical function) were not considered for the calculation of LVAs.

2.4. Statistical methods

For between-group statistical analyses 2-way ANOVA tests were used. If not stated otherwise, correlations between variables were determined using Pearson correlation coefficients. To determine the specificity and sensitivity of the different low-voltage cut-offs a ROC analysis [22] was performed. LA emptying fraction was considered normal ≥37% [19]. For the ROC analysis of LAVI, patients were stratified according to the mean LAVI into an either severely affected (>39 ml/m^2 LAVI) or unaffected to moderately affected (≤39 ml/m^2) group. For the ROC analysis of LA (conduit) strain, patients were again stratified into severe or moderate according to the value of the mean strain with a cut-off of 13%. $p < 0.05$ was considered significant.

3. Results

A total of 22 patients with preserved left ventricular ejection fraction (mean LVEF 53 ± 2%) were studied (see Suppl. Table 1 for patient characteristics). Mean age of patients was 62 ± 2 years and mean LAVI was significantly increased at 39 ± 3 ml/m^2 indicating AR. 68% of patients showed paroxysmal atrial fibrillation with a mean EHRA class of 2.7 ± 0.6. Mean CHA_2DS_2-vasc score was 2.4 ± 0.5 and showed no correlation with LAVI, LA strain, LA emptying fraction or LVAs (Suppl. Fig. 5).

We automatically determined LVAs with different cut-offs and calculated the respective percentage of the total endocardial atrial surface (Fig. 1). Using this approach, mean total area of LVAs in our patient cohort was 57 ± 7 cm^2 representing 47 ± 5% of the total LA area (defining low-voltage as ≤0.5 mV; see Fig. 2).

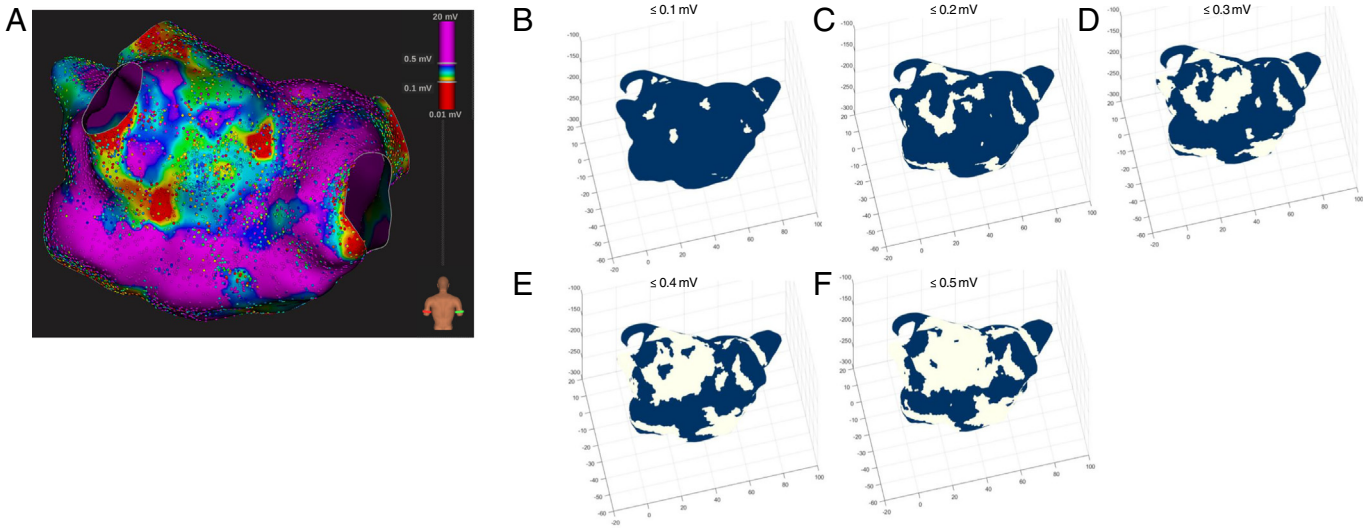

Fig. 1. A. Anterior-posterior view of a ultra-high-density electroanatomic map during pacing of the left atrium of a patient with extensive AR as obtained with a multipolar basket (64 mini-electrodes) catheter. B–F. Example binary image of the left atrium from a patient with AR showing regions with a bipolar electrogram amplitude with a cut-off of ≤0.5, ≤0.4, ≤0.3, ≤0.2 or ≤0.1 mV in yellow and "healthy" myocardium i.e. myocardium above the cut-off in blue. The size of areas with low-voltage was calculated from these voltage electroanatomic maps. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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