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Discrepancy Between LGE-MRI and Electro-Anatomical Mapping for Regional Detection of Pathological Atrial Substrate

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Abstract: Atrial fibrillation (AF) is the most common sustained arrhythmia posing a significant burden to patients and leading to an increased risk of stroke and heart failure. Additional ablation of areas of arrhythmogenic substrate in the atrial body detected by either late gadolinium enhancement magnetic resonance imaging (LGE-MRI) or electro-anatomical mapping (EAM) may increase the success rate of restoring and maintaining sinus rhythm compared to the standard treatment procedure of pulmonary vein isolation (PVI). To evaluate if LGE-MRI and EAM identify equivalent substrate as potential ablation targets, we divided the left atrium (LA) into six clinically important regions in ten patients. Then, we computed the correlation between both modalities by analyzing the regional extents of identified pathological tissue. In this regional analysis, we observed no correlation between late gadolinium enhancement (LGE) and low voltage areas (LVA), neither in any region nor with regard to the entire atrial surface ($-0.3 < r < 0.3$). Instead, the regional extents identified as pathological tissue varied significantly between both modalities. An increased extent of LVA compared to LGE was observed in the septal wall of the LA ($\tilde{a}_{\mathrm{sept.,LVA}} = 19.63\,\%$ and $\tilde{a}_{\mathrm{sept.,LGE}} = 3.94\,\%$, with $\tilde{a}$ = median of the extent of pathological tissue in the corresponding region). In contrast, in the inferior and lateral wall, the extent of LGE was higher than the extent of LVA for most geometries ($\tilde{a}_{\mathrm{inf.,LGE}} = 27.22\,\%$ and $\tilde{a}_{\mathrm{lat.,LGE}} = 32.70\,\%$ compared to $\tilde{a}_{\mathrm{inf.,LVA}} = 9.21\,\%$ and $\tilde{a}_{\mathrm{lat.,LVA}} = 6.69\,\%$). Since both modalities provided discrepant results regarding the detection of arrhythmogenic substrate using clinically established thresholds, further investigations regarding their constraints need to be performed in order to use these modalities for patient stratification and treatment planning.

Keywords: Atrial fibrillation, LGE-MRI, electro-anatomical mapping, pathological substrate, regionalization of the atria

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1 Introduction

Worldwide more than 43.6 million individuals are affected by AF, which is the most common sustained arrhythmia associated with cardiovascular mortality [1, 2]. The current treatment option for restoring and maintaining sinus rhythm consists of the isolation of the pulmonary veins (PVs) by performing catheter ablation, since triggers of AF are frequently located in these areas [3]. However, the long-term success rate regarding the freedom from AF recurrence for patients with continuously sustained (persistent) AF is below $50\,\%$ [4, 5]. A possible reason may be the presence of non-PV triggers, such as electrical rotors or focal sources in combination with a vulnerable substrate for AF maintenance [6, 7]. The latter may occur due to electrical or structural remodeling, which includes interstitial fibrosis or cellular degeneration. Additionally targeting these structures may result in an increased success rate of freedom from AF recurrence [8–10]. Commonly used acquisition modalities to detect arrhythmogenic substrate are LGE-MRI and EAM. To compare locally if LGE-MRI and EAM identify equivalent substrate as potential ablation targets, we divided left atrial geometries into six clinically important regions. Then, we used this division to quantitatively assess the correlation between both modalities by analyzing the regional extents of LGE measured by LGE-MRI and LVA measured by EAM.

2 Methods

2.1 Data Acquisition

For this study, we investigated a data set consisting of ten (P01-P10) LA geometries acquired at the University-Heart-Center in Freiburg-Bad Krozingen [11]. All patients provided written

informed consent and the protocol was approved by the institutional ethics committee of the University of Freiburg.

LGE-MRI was performed on a 3 T cardiovascular magnetic resonance scanner (Siemens Healthineers, Munich, Germany) and the LA geometries were segmented using ADAS® software (Galgo Medical, Barcelona, Spain). To distinguish between pathological substrate and healthy tissue, we used the image intensity ratio (IIR) with a threshold of IIR > 1.2 [12, 13]. Normalizing the image intensities by the mean blood pool value results in a decreased influence of parameters such as contrast dose, time of delay for image acquisition after contrast dose injection and body mass index [12].

Bipolar voltage electrograms from high-density mapping were obtained by using the CARTO® 3 mapping system (Biosense Webster, Irvine, USA). All patients were mapped during sinus rhythm prior to PVI. To distinguish between pathological substrate and healthy tissue, we considered a threshold of $V_{\mathrm{bi}} < 0.5\,\mathrm{mV}$ [9, 14].

2.2 Analysis

2.2.1 Atrial Division

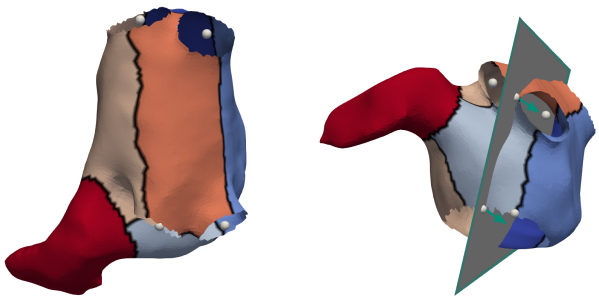
To perform regional quantitative comparisons between both modalities, we divided the LA geometries into six clinically important regions: Septal wall, inferior wall, lateral wall, anterior wall, posterior wall and left atrial appendage (LAA). To achieve a consistent and reproducible regionalization of the atria, we developed a semi-automatic division procedure. First, all geometries were re-meshed to a uniform mesh size [15]. Then, information on the PVs and the mitral valve (MV) were excluded by semi-automatically clipping these structures [16]. For the regional division, the shortest geodesic paths between the centers of the PV ostia were computed, as shown in Figure 1a. To determine the connections between the PV ostia and the MV annulus, a plane defined by the mean of the left PV (LPV) centers, the mean of the right PV (RPV) centers and the MV center was established (see Figure 1b). Then, the vectors from the mean of the LPV or RPV center to the LSPV/LIPV or RSPV/RIPV center were calculated. By adding these vectors to the corresponding septal or lateral intersection of the defined plane with the MV ostium, the closest points on the MV ostium were obtained. The boundary of the LAA was determined by the location where the salient structure merged into the body of the LA. The center of the LAA was also used as a reference point for the computation of the anterior boundary of the lateral wall.

2.2.2 Statistical Analysis

The regional extent of pathological tissue was calculated by dividing the number of mesh nodes exceeding the defined thresholds by the total number of mesh nodes of the corresponding region. This measure was applied, since the number of nodes directly corresponded to the surface area due to the uniform mesh size. The correlation between both modalities in each region was determined by the Pearson correlation coefficient.

3 Results

Using the clinically established thresholds, there was no correlation between the extent of detected LGE and LVA (Figure 2), neither in any analyzed region nor with regard to the entire atrial surface ($-0.3 < r < 0.3$). Moreover, in this study cohort, we observed a tendency towards a negative association between the extent of LVA and LGE, except for the anterior wall. The septal wall showed an increased extent of LVA compared to LGE ($\tilde{a}_{\mathrm{sept.,LVA}} = 19.63\,\%$ and $\tilde{a}_{\mathrm{sept.,LGE}} = 3.94\,\%$, with $\tilde{a}$ = median of the extent of pathological tissue in the corresponding region). In contrast, in the inferior and lateral wall, the extent of LGE was higher than the extent of LVA for most patients ($\tilde{a}_{\mathrm{inf.,LGE}} = 27.22\,\%$ and $\tilde{a}_{\mathrm{lat.,LGE}} = 32.70\,\%$ compared to $\tilde{a}_{\mathrm{inf.,LVA}} = 9.21\,\%$ and $\tilde{a}_{\mathrm{lat.,LVA}} = 6.69\,\%$). In the posterior wall, we either observed an increased extent of LVA and a lower extent of LGE or vice versa. Regarding the LAA, no LVA was detected, while minor extents of LGE $< 30\,\%$ were observed. Lastly, P02 and P03 showed an increased extent of LGE compared to LVA across all regions, as exemplified for the inferior wall of P03 in Figure 3.



(a) Top view: Paths between the PV ostia

(b) Lateral view: Computation of the points on the MV ostium

Fig. 1: Boundaries creation of the LA: Septal wall, inferior wall, lateral wall, anterior wall, posterior wall, LAA

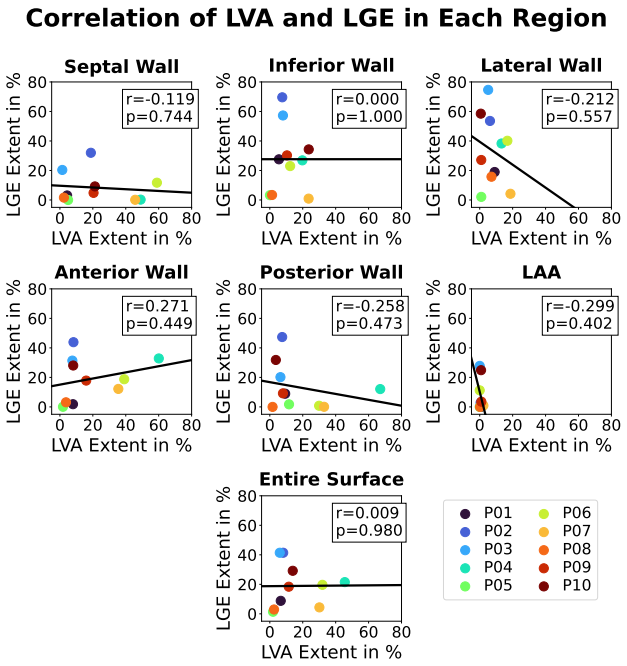


Fig. 2: Correlation of LVA and LGE extent in each region of the LA

4 Discussion

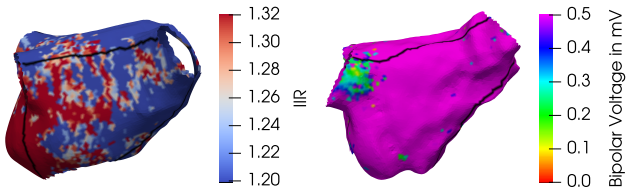
The examination of regional extents of LGE and LVA showed no correlation between LGE-MRI and EAM using the established thresholds per modality. Instead, we observed significant discrepancies between both modalities across all regions, mostly in accordance with previous reports [11, 17–19]. The anterior wall is the only region in which a positive correlation was found in our cumulative study, which is in line with the highest concordance found there for point-by-point comparison [11]. A possible explanation for the discrepancy may be the presence of smaller patches of pathological substrate located on the epicardium, which are detected by LGE-MRI but are hidden to the endocardial catheters of EAM [11]. Moreover, the identification of LVAs is not limited to the presence of fibrotic tissue. Besides multiple technical implications affecting the characteristics of the bipolar voltage map, such as tissue contact force or angle of incidence, atrial dilatation and mechanical stress influence the existence of LVA [20]. Another possible reason explaining the observed discrepancies might be the lack of standardization with regard to the acquisition procedure of LGE-MRIs, such as the time between injection and image acquisition or the applied contrast agent and dose [12]. Lastly, histological validation of native atrial fibrosis would be desirable [19, 20].

Since some patients showed an increased extent of LGE across all regions compared to LVA or vice versa, one might suggest a global mismatch of the applied thresholds [11] - e.g. P02 and P03 indicated an increased extent of LGE, while P07 showed an increased extent of LVA across all regions. However, other patients such as P04 or P06 exhibited an increased extent of LVA compared to LGE in the septal and anterior wall, whereas they showed an increased extent of LGE compared to LVA in the inferior and lateral wall contradicting this suggestion. Rather, this observation may be explained by anatomical heterogeneities affecting e.g. the amplitude of bipolar voltages. Consequently, the application of regional thresholds may be more suitable [20, 21].

The increased extent of LGE compared to LVA in the inferior and lateral wall may be caused by the proximity of the descending aorta. Besides the possibility of friction or mechanical pressure leading to fibrotic development, this might be due to partial volume artifacts of LGE in the wall of the aorta [19, 22, 23].

Results regarding the LAA need to be interpreted with caution, since the LAA was not entirely mapped for most geometries explaining the low extent of LVA in this region.

These findings need to be investigated further, since the analyzed data set of ten patients in total might not capture the variability of the tissue properties present in both modalities.



(a) IIR values obtained by LGE-MRI

(b) Bipolar Voltages in mV obtained by EAM

Fig. 3: Comparison of pathological tissue detected by LGE-MRI and EAM in the infero-posterior view of P03. In the inferior wall, we observed high extents of LGE spatially distributed across the entire region (a), whereas only a small patch of LVA was identified near the LIPV (b).

5 Conclusion

In this study, we show discrepancies between LGE-MRI and EAM in the LA for regional cumulative analysis. The regional extents of pathological tissue detected by LGE-MRI and EAM exhibit noteworthy differences. To effectively utilize these modalities for patient stratification and treatment planning, additional research is necessary to explore the constraints of each modality.

Author Statement

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References

[1] Hindricks G, Potpara T, Dagres N et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation. Eur Heart J 2021;42:373-498

[2] Martignani C, Massaro G, Biffi M et al. Atrial fibrillation: an arrhythmia that makes healthcare systems tremble. J Med Econ 2020;23:667-669

[3] Haissaguerre M, Jaïs P, Shah DC et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. NEJM 1998;339:659-666

[4] De Greef Y, Schwagten B, Chierchia GB et al. Diagnosis-to-ablation time as predictor of success: early choice for pulmonary vein isolation and long-term outcome in atrial fibrillation: results from the Middelheim-PVI Registry. Europace 2018;20(4):589-595

[5] Tilz RR, Rillig A, Thum AM et al. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. J Am Coll Cardiol 2012;60(19):1921-1929

[6] Sánchez-Quintana D, López-Mínguez JR, Pizarro G et al. Triggers and anatomical substrates in the genesis and perpetuation of atrial fibrillation. Curr Cardiol Rev 2012;8(4):310-326

[7] Krummen DE, Hebsur S, Salcedo J et al. Mechanism Underlying AF: Triggers, Rotors, Other? Curr Treat Options Cardiovasc Med 2015;17(4):371

[8] Huo Y, Gaspar T, Schönbauer R et al. Low-Voltage Myocardium-Guided Ablation Trial of Persistent Atrial Fibrillation. NEJM Evidence 2022;1(11):220141

[9] Jadidi AS, Lehrmann H, Keyl C et al. Ablation of Persistent Atrial Fibrillation Targeting Low-Voltage Areas With Selective Activation Characteristics. Circ Arrhythm Electrophysiol 2016;9(3)

[10] Cutler JM, Sattayaprasert P, Pivato E et al. Low voltage-guided ablation of posterior wall improves 5-year arrhythmia-free survival in persistent atrial fibrillation. J Cardiovasc Electrophysiol 2022;33(12):2475-2484

[11] Nairn D, Eichenlaub M, Müller-Edenborn B et al. LGE-MRI for diagnosis of leaft atrial cardiomyopathy as identified in high-definition endocardial voltage and conduction velocity mapping. medRxiv 2022. doi:10.1101/2022.02.02.22269817

[12] Khurram IM, Beinart R, Zipunnikov V et al. Magnetic resonance image intensity ratio, a normalized measure to enable interpatient comparability of left atrial fibrosis. Heart Rhythm 2014;11(1):85-92

[13] Benito EM, Carlosena-Remirez A, Guasch E et al. Left atrial fibrosis quantification by late-gadolinium enhanced magnetic resonance: a new method to standardize the thresholds for reproducibility. Europace 2017;19(8):1272-1279

[14] Seitz J, Bars C, Théodore G et al. AF Ablation Guided by Spatiotemporal Electrogram Dispersion Without Pulmonary Vein Isolation: A Wholly Patient-Tailored Approach. JACC 2017;69(3):303-321

[15] Muntoni A, Cignoni P. PyMeshLab 2021. doi:10.5281/zenodo.4438750

[16] Nuñez-Garcia M, Bernardino G, Alacrón F et al. Fast Quasi-Conformal Regional Flattening of the Left Atrium. IEEE Transactions on Visualization and Computer Graphics 2020;26:2591-2602

[17] Chen J, Arentz T, Cochet H et al. Extent and spatial distribution of left atrial arrhythmogenic sites, late gadolinium enhancement at magnetic resonance imaging, and low-voltage areas in patients with persistent atrial fibrillation. Europace 2019;21(10)1484-1493

[18] Sramko M, Peichl P, Wichterle D et al. Clinical value of assessment of left atrial late gadolinium enhancement in patients undergoing ablation of atrial fibrillation. Int J Cardiol 2015;179:351-357

[19] Eichenlaub M, Müller-Edenborn B, Minners J et al. Comparison of various late gadolinium enhancement magnetic resonance imaging methods with high-definition voltage and activation mapping for detection of atrial cardiomyopathy. Europace 2022;24(7):1102-1111

[20] Sim I, Bishop M, O'Neill M, Williams SE. Left atrial voltage mapping: defining and targeting the atrial fibrillation substrate. J Interv Card Electrophysiol 2019;56(3):213-227

[21] Whitaker J, Rajani R, Chubb H et al. The role of myocardial wall thickness in atrial arrhythmogenesis. Europace 2016;18(12):1758-1772

[22] Higuchi K, Cates J, Gardner G et al. The Spatial Distribution of Late Gadolinium Enhancement of Left Atrial Magnetic Resonance Imaging in Patients With Atrial Fibrillation. JACC Clin Electrophysiol 2018;4(1):49-58

[23] Caixal G, Althoff T, Garre P et al. Proximity to the descending aorta predicts regional fibrosis in the adjacent left atrial wall: aetiopathogenic and prognostic implications. Europace 2021;23(10):1559-1567