LEFT ATRIAL FIBROSIS QUANTIFICATION BY LATE GADOLINIUM ENHANCEMENT MAGNETIC RESONANCE: A NEW METHOD TO STANDARDIZE THE THRESHOLDS FOR REPRODUCIBILITY.

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ABSTRACT

Background: Identification of left atrial (LA) fibrosis through late gadolinium-enhanced cardiac magnetic resonance (LGE-CMR) remains controversial due to the heterogeneity and lack of reproducibility of proposed methods. Our aim is to describe a normalized, reproducible, standardized method to evaluate LA fibrosis through LGE-CMR.

Methods and Results: ECG- and respiratory-gated 3-TeslaLGE-CMR was performed in 10 healthy young volunteers and 30 patients with atrial fibrillation (AF): 10 with paroxysmal AF, 10 with persistent AF, and 10 with a previous AF ablation procedure. Local Image Intensity Ratio (IIR) of the LA was calculated as the absolute pixel intensity to mean blood pool intensity ratio. The healthy atrial tissue threshold was defined in young healthy volunteers (upper limit of normality set at IIR tissue mean plus 2 standard deviations). Dense atrial scarring was characterized in patients with previous radiofrequency-induced scarring (post-AF ablation patients). Validation groups consisted of patients with paroxysmal and persistent AF.

The upper limit of normal IIR was IIR=1.20; IIR values higher than 1.32 (60% of mean maximum pixel intensity in post-ablation patients) were considered dense scar. IIR values between 1.2 and 1.32 identified interstitial fibrosis. Patients with paroxysmal and persistent AF had less atrial fibrotic tissue compared to post-ablation patients. Endocardial bipolar voltage was correlated to IIR values.

Conclusions: An IIR=1.2 identifies the upper limit of normality in healthy young individuals. An IIR >1.32 defines dense atrial fibrosis in post-ablation patients. Our results provide a consistent, comparable, and normalized tool to assess atrial arrhythmogenic substrate.

KEYWORDS: atrial fibrillation; atrial fibrosis; late gadolinium enhancement; magnetic resonance; catheter ablation.

ABBREVIATIONS

LA: Left atrial

AF: Atrial Fibrillation

(LGE-)CMR: (Late gadolinium-enhanced) cardiac magnetic resonance

IIR: Image intensity Ratio

MPI: Maximum pixel intensity

TI: Inversion time

EAM: Electroanatomic Voltage Map

HV: Healthy volunteers

AFpx: Paroxysmal AF

AFpt: Persistent AF

P-Ab: Post-ablation patients

CONDENSED ABSTRACT

LGE-CMR remains a promising tool to non-invasively identify atrial fibrosis. We found that a signal intensity ratio (IIR)=1.20 identifies the upper limit of normality in a cohort of healthy volunteers; an IIR>1.32 identifies dense scarring in post-ablation patients. These results allow identifying AF substrate providing prognostic information and guiding ablation.

INTRODUCTION

Left atrial (LA) structural and functional adaptation to haemodynamic overload (so-called atrial *remodelling*) contributes to the onset, progression, and perpetuation of atrial fibrillation (AF). In addition, LA remodelling develops as a consequence of repeated episodes of AF, leading to the well-known refrain, "AF begets AF".

Collagen deposition in the myocardial interstitial space is a hallmark of LA structural remodelling[1]. Total atrial fibrosis might appear as interstitial fibrosis or dense scarring[1]. Fibrosis has been shown in patients with AF but no structural heart disease (*lone AF*), but is more intense in patients with structural cardiac disease[2].

Non-invasive assessment of myocardial fibrosis has proven useful as a diagnostic, prognostic, and therapeutic tool. Gadolinium is a paramagnetic metal that accumulates in the extracellular space of the myocardium and modifies magnetic properties of water. Visualization and quantification of gadolinium in LGE-CMR sequences estimate the extracellular matrix volume and has been used as a myocardial fibrosis surrogate.[3]

In the left ventricle, late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) identifies those patients at an increased risk of sudden death, accurately characterizes ventricular myocardial scar, and has been successfully used to support ventricular tachycardia ablation procedures[4]. Nevertheless, a reliable and reproducible method to locate and quantify myocardial fibrosis in the atrium is still lacking. In recent years, several groups tested the ability of LGE-CMR to detect both pre-existing[5, 6] fibrosis and post-ablation scarring[7]. Although these reports suggested that the extent of fibrosis may predict recurrences after ablation procedures, the lack of reference values for normality has prompted the publication of several image acquisition and post-

processing protocols and thresholds to identify fibrosis, eventually limiting the external validation and reproducibility of this technique. Thereby, despite promising findings, the assessment of LA fibrosis has not been yet widely adopted in the clinical practice.

The aims of our study were 1) to establish LA LGE-CMR signal intensity normality in a young healthy population and 2) to provide a normalized, systematic, consistent, and reproducible method to identify LA fibrotic tissue.

METHODS

A detailed version of the Methods is available in the Supplementary Material.

Sample population

Ten young healthy volunteers (aged 18-30 years with no previous cardiac or other conditions) and 30 patients with a previous diagnosis of AF (10 patients with paroxysmal AF; 10 patients with persistent AF; 10 patients who had previously undergone an AF ablation procedure) were included in this study. Exclusion criteria included claustrophobia, major renal impairment (glomerular filtration rate <30 mL/min), and gadolinium allergy.

LGE-CMR exams were obtained at baseline in healthy volunteers, shortly (<2 weeks) before an AF ablation procedure in paroxysmal or persistent AF patients, and 3 months (±1 week) after a first radiofrequency AF ablation procedure in patients with previous AF ablation. Healthy volunteers and post-ablation patients were used to establish LGE-CMR signal intensity normality and fibrosis thresholds; paroxysmal and persistent AF patients served as validation groups.

Written informed consent was obtained from all participants. The study protocol was reviewed and approved by the Hospital Clinic Ethics Committee.

Image acquisition and LGE-CRM post-processing

The acquisition protocol has been previously reported[7] and is extensively described in the Methods section of the Supplementary Material. Briefly, images were acquired 20 min after an intravenous bolus injection of 0.2 mmol/kg gadobutrol (Gadovist, BayerShering, Germany) in a 3-Tesla CMR scanner (Magnetom Trio, Siemens Healthcare, Germany).

LA was segmented using ADAS® image post-processing software (Galgo Medical SL, Barcelona, Spain). Epicardial and endocardial LA wall contours were manually drawn in each axial plane. In order to minimize endocardial and epicardial segmentation artefacts, ADAS constructed a mid-myocardial (50% thickness) layer and built a 3Dshell. Pulmonary veins at their ostia and the mitral valve were removed for fibrosis analysis. Pixel signal intensity maps were calculated and projected into the shell (Figure 1).

Signal intensity was normalized to blood pool intensity. Image Intensity Ratio (IIR)[8] was calculated as the ratio between the signal intensity of each pixel and the mean blood pool intensity. IIR values were colour-coded, projected into the atrial mid-myocardial shell and presented in histograms.

Normality and assessment of atrial myocardial fibrosis threshold.

Two threshold points were sought in IIR histograms: the first delimited an upper limit of healthy tissue signal intensity and the second discriminated between interstitial and dense fibrosis. Both threshold points were thereafter used to quantify total and dense atrial fibrosis in all groups.

Normal LA IIR values were characterized in healthy volunteers. All IIR values were plotted in a histogram, and the upper limit of normality was set at 2 standard deviations above the mean (mean+2SD, encompassing 97.5% of all signal intensity values of a healthy population).

Dense scarring was characterized in individuals who had previously undergone a pulmonary vein isolation procedure. The ablation procedure in these patients had been conducted according to our centre usual practice. The target of ablation (paroxysmal and persistent AF) was pulmonary vein isolation; additional lines were performed in persistent AF patients at the discretion of the treating electrophysiologist. Dense fibrosis was defined as those IIR values above the 60% of the maximum pixel intensity (MPI) in patients who had previously undergone an AF ablation procedure, as previously validated to predict conduction gaps in re-do patients.[7]

A subset of 14 randomly selected LGE-CMR scans were analysed by a second investigator to assess fibrosis assessment inter-observer reproducibility.

LGE-CMR intensity and electroanatomic map correlation

In 15 patients undergoing a first pulmonary vein isolation procedure, a point-by-point electroanatomic bipolar voltage map (EAM)(CARTO® 3, Biosense-Webster) was obtained with a multipolar catheter (Lasso NAV®, Biosense-Webster; interelectrode spacing 2-6-2 mm) before ablation. The EAM was merged with the 50%-layer LGE-CMR LA shell and their correlation was assessed. Only EAM and CMR-shell points that were <2 mm apart were used for the correlation analysis[8].

Statistical analysis

Continuous variables are shown as mean ± standard deviation (SD) or median (25^{th}–75^{th} quartiles) and compared with a t-test/Mann-Whitney test or one-way ANOVA/Kruskal-Wallis test. Categorical variables are summarized as total number (percentage) and compared with a Fisher exact test. The correlation between atrial EAM and IIR was fitted in a generalized linear mixed model. Inter-observer concordance was analysed using the Lin correlation coefficient. A two-sided type I error of 5% was used for all tests. All analyses were performed using R v3.2.0 (R project for Statistical Computing; Vienna, Austria)

RESULTS

Baseline characteristics of the 10 healthy volunteers and 30 AF patients are shown in Table 1. Mean age was 22 years for healthy volunteers and 58±10 years for patients with AF. Hypertension was the only factor significantly differing in the four groups.

Echocardiographic (Table 1) and standard CMR measurements (Table 2) showed no differences between groups for left ventricular ejection fraction or diameters. In CMR, LA volume progressively increased from healthy volunteers to patients with paroxysmal AF to patients with persistent AF. Post-ablation patients showed smaller volumes.

LGE-CMR image post-processing and fibrosis analysis

LGE-CMR was analysed in all individuals except for one healthy volunteer who was excluded because of multiple artefacts and poor image quality. A total of 901,390 IIR

values were obtained (averaging 23,113±12,137 points per patient). Four IIR histograms including all individuals in the same group were generated: healthy volunteers (HV) and paroxysmal AF (AFpx), persistent AF (AFpt) and post-ablation (P-Ab) patients.

The histograms for all groups are shown in Figure 2. The morphology of the four LA IIR histograms was significantly different ($p<0.001$ for all pairwise comparisons, multiple-comparison adjusted Kolmogorov-Smirnov test). The mean IIR for each group showed a progressive increase from healthy volunteers to post-ablation patients (Table 2).

The skewness statistic assesses the symmetry of a distribution, with 0 denoting perfect symmetry, positive values a right-tailed distribution and negative values a left-tailed distribution. Skewness ranged from -0.75 (left-tailed to "healthy" tissue values) for HV to +0.78 (right-tailed to fibrotic tissue values) in P-Ab. Patients with AFpx and AFpt remained in intermediate, slightly right-tailed skewness values at 0.08 and 0.22, respectively.

Threshold assessment

Normal IIR values were identified in a population of healthy individuals. The upper limit of IIR normality was accordingly set at IIR=1.20 (mean tissue IIR+2SD) (Figure 3A), and was similar in male and female individuals (1.20±0.04vs. 1.21±0.09, $p=0.53$). Hence, all IIR values >1.20 were considered as fibrotic tissue.

Dense scarring was characterized in P-Ab patients as previously described[7]. The MPI in the whole atria was recognized, and its 60% calculated. All IIR values above IIR=1.32 (60% of MPI) were therefore considered to localize dense scarring.

From our results, we propose that IIR values between 1.2 and 1.32 identify interstitial fibrosis while an IIR>1.32 involves dense scarring. We therefore quantified the percentage of fibrosis (IIR>1.20) in all participants, which progressively increased from healthy volunteers to post-ablation patients (2.46% [1.52-4.21] HV; 8.53% [4.12-12.47] AFpx; 11.73% [4.62–22.57] AFpt; 34.62% [14.57-43.18] P-Ab; p<0.001) (Figure 3B). Similarly, atrial dense scar percentage was 0.02% [0.01-0.04] for HV, 1.27% [0.51-2.21] for AFpx, 1.64% [0.07-2.8] for AFpt, and 14.5% [4.88-22.13] for P-Ab patients (p<0.001) (Figure 3B). Data for male and female individuals is shown in the Online Supplemental Figure.

The inter-observer Lin concordance correlation coefficient for mean IIR, IIR+2SD, and global fibrosis percentage were 0.948, 0.987 and 0,998 respectively.

Electroanatomic voltage map and IIR correlation

The point-by-point correlation between the atrial EAM and IIR shells was assessed in 15 patients (10 persistent AF, 5 paroxysmal AF) undergoing AF ablation after CMR evaluation. Overall, 1729 valid voltage points were obtained (124±81 points per patient). The correlation plot for each of the individuals is shown in Figure 4. A negative correlation between EAM voltage and IIR was found for all individuals, generally of a moderate intensity; correlation coefficients ranged from r=-0.19 to r=-0.58 (r^2 from 0.036 to 0.34). When all individuals were modelled with GLMM, *r* was estimated at 0.2 (p<0.001). Similarly, a negative correlation was obtained after categorizing IIR data into clinically meaningful groups (<1; 1-1.20; 1.20-1.32; >1.32) (Figure 5). Mean IIR values were 1.45V±1.51; 1.07V±1.39; 0.94V±1.16 and 0.72V±0.89, respectively (p<0.001).

DISCUSSION

In this study we provide a normality range for atrial LGE-CMR signal intensity in young healthy individuals and propose a reproducible, normalized method to assess total and dense left atrial fibrosis. Specifically, we define the IIR cut-off point of >1.20 for identification of abnormal signal intensity as the threshold for atrial fibrosis, while the IIR>1.32 cut-off point is the threshold for dense atrial fibrosis. To our knowledge, this is the first study that uses a healthy volunteer population to characterize a LGE-CMR signal intensity threshold in the LA to identify atrial fibrosis.

Atrial fibrosis assessment

In the atrium, total fibrosis might result from interstitial reactive fibrosis or from confluent replacement fibrosis after myocyte apoptosis or necrosis[1]. Our work provided a threshold to identify both total and dense fibrosis.

Atrial fibrosis assessment – Native fibrosis

Several groups have proposed a variety of algorithms to identify native fibrosis, but most of them remain controversial. While most reports agree that a higher signal intensity correlates to a larger amount of fibrosis and a worse recurrence prognosis after AF ablation, a threshold has not been uniformly established.

The most widely validated algorithm was published by the Marrouche group[5] and is currently supported by a growing core of evidence[6]. Rather than using a fixed algorithm, their method largely relies on an expert decision to use a certain, variable threshold ranging from 2 to 4 SDs above the mean for healthy myocardium intensity. The need for this expertise hampers external validation, with inconsistent findings[9].

Most algorithms rely on a certain number of SDs over mean atrial signal intensity to identify fibrosis, likely under- or over-estimating atrial fibrosis[10]. Indeed, we have shown that pixel intensity histogram morphology is deeply influenced by patient characteristics (Figure 2), which might lead to inaccurate changes in fibrosis quantification due to differences in the mean and SD between healthy individuals and post-ablation patients.

Khurram et al. first proposed a normalized signal intensity ratio (IIR) to homogenize CMR from all individuals and establish an absolute fibrosis threshold that could be used in all patients[8]. Nevertheless, a normality threshold (IIR<0.97) was set after correlating to bipolar voltage maps in patients with AF. Most groups have exclusively relied on CMR images from patients with AF; the lack of a healthy volunteer group poses a risk of inaccurate identification of normality limits and the under- or over-estimation of atrial fibrosis.

A novel approach in our study incorporated a healthy population in which no fibrosis is expected, in order to obtain a standardized upper limit of normality that is able to provide an objective value beyond which fibrosis is defined and define systematic thresholds. Our healthy volunteer cohort encompasses exclusively young individuals aged 22 years old, excluding the pro-fibrotic effects of aging or other co-morbidities such as hypertension. On this basis, an IIR>1.20 identifies atrial fibrosis, independent of patient characteristics.

Notably, we used young healthy volunteers as the reference population to ensure obtaining normality values from an ***atrial fibrosis-free*** population. Ageing has been suggested to associate with progressive atrial collagen deposit, a process likely underlying an increase of AF prevalence over years[11]. An elderly or middle-aged

reference population, even if providing a normal-for-age threshold, would miss ageing-related fibrosis. When apparently healthy middle-aged individuals have been used as a control group, average fibrosis burden ranged from 1.7%[5] to 8.9%[12]. Our method identifies all ageing- and risk-factor-related atrial fibrosis, both of which may contribute to AF pathology.

Atrial fibrosis assessment – Dense scarring

Post-ablation scarring is characterized by large areas of coagulative necrosis and fibrotic replacement, and is a hallmark of dense fibrosis. Dense fibrosis is also present in confluent areas in patients with native atrial fibrosis[1]. Specific studies focusing on the identification of atrial post-ablation injury with LGE-CMR have been recently carried out, with uneven conclusions[6, 13, 14].

On the basis of histological findings and validation in an animal model, Harrison et al. proposed that blood pool intensity mean plus a certain number of SDs could be used to identify linear radiofrequency lesions in the right atria of sheep[14]. Nevertheless, this algorithm was not able to reliably predict previously ablated areas in patients undergoing a second PVI ablation procedure[15]. Similarly, Hunter et al. confirmed that a 5-SD threshold above the mean atrial tissue intensity likely underestimates radiofrequency-induced atrial fibrosis[10]. Only 34% of all electrically isolated pulmonary veins were completely encircled by radiofrequency lesions using the Utah criteria[16]..

Bisbal et al. found a 79% correspondence between the electrical site of reconnection and anatomical gaps by using a value 60% of the MPI to threshold post-ablation scarring[7]. Our study used the definition by Bisbal et al. to distinguish dense fibrosis. By using this criterion in our study, large fibrotic patches predominantly encircling pulmonary veins were detected in a 3-month post-ablation LGE-CMR

(14.5%[4.88-22.13], Table 2), while it was negligible in young, healthy individuals (0.02% [0.01-0.04]).

Value of CMR-identified fibrosis – Clinical implications

The non-invasive assessment of atrial myocardial fibrosis extent provides important data on atrial structural remodelling, which might be translated into clinically useful information for daily clinical practice, from primary prevention to prognosis and the guidance of AF therapy. Such knowledge of the arrhythmogenic state of the LA should pave the way for future AF therapy personalization.

The selection of patients at high risk of AF might allow optimization of primary prevention programs. Hypertension is the most common AF risk factor in the community, but the positive predictive value for AF is relatively low[17]. The AF risk of structural heart disease is higher (6- to 14-fold increased risk), but its prevalence in overall AF is much lower than hypertension. A set of 14 clinical and ECG markers proposed by the CHARGE consortium predicts AF incidence, but accuracy remains moderate (AUC 0.66 – 0.71 in validation cohorts)[18]. The non-invasive assessment of the structural arrhythmic substrate by means of LGE-CMR might provide a more direct estimation of AF risk; those patients with extensive fibrosis and at high risk of AF might benefit from a closer rhythm follow-up, more intensive antihypertensive drugs, or even early instauration of antiarrhythmic therapies.

Atrial fibrillation outcomes after an ablation procedure remain unsatisfactory. Plasmatic biomarker profiles suggesting enhanced collagen turnover predict a higher recurrence rate after an AF ablation procedure. Non-invasive estimation of atrial fibrosis by means of LGE-CMR might be a valuable tool to improve patient selection

for AF ablation[6]. Ablation gaps assessed by LGE-CMR predict AF recurrences after an AF ablation procedure[19].

The pre-procedural identification of fibrotic areas might not only serve to foresee a group of patients with an ominous recurrence prognosis, but also to guide AF ablation procedures. A recent subanalysis of the DECAAF trial suggested that encircling atrial fibrosis is beneficial to prevent AF recurrences after pulmonary vein isolation[20]. Identifying dense fibrotic lesions in patients undergoing repeated AF ablation procedures localize conduction gaps surrounding pulmonary veins and simplify re-do procedures[7]. Confirmation in larger, randomized trials is warranted.

LIMITATIONS

Some limitations of our work need to be acknowledged. First, individual factors are an indisputable source of variability. Individual characteristics such as body mass index, renal function, and haematocrit might deeply change gadolinium wash-in and -out limit the validity of our (and most other) algorithms. Blood pool normalization partially accounted for these potential biases in our study and allowed inter-individual comparability.

Second, technical and post-processing parameters might influence IIR estimation. Our work was conducted in a 3T setup, as it provides a higher signal-to-noise ratio and enhanced temporal and spatial resolution in thin-walled atrium than 1.5T setups. The accuracy of manual and semi-automated identification of the LA endocardial and epicardial boundaries remains a critical aspect of image post-processing protocols, largely depending on investigator experience. Nevertheless, these errors were minimized by using a mid-myocardial layer (50% of atrial wall thickness) that prevents against mild inaccuracies in boundary segmentation. Moreover, reproducibility of our

technique was confirmed by a high Lin correlation coefficient. Further studies are needed to guarantee external validity in 1.5T setups, different patient groups and operators experience.

Third, we describe a normality threshold value for LGE-CMR and liken it to fibrosis burden. Although LGE-CMR has been commonly used as a myocardial fibrosis surrogate, it is possible that other causes increasing extracellular volume such as oedema or infiltration could also contribute to LGE.[3]

Last, collagen deposition in the myocardial interstitial space is likely continuously distributed with a variable degree of overlap between HV and AF patients, thus making any threshold arbitrary. Small changes in any threshold of a continuous variable might result in large changes in the percentage of fibrosis[14]. Nevertheless, we believe that finding an upper limit of normality that encompasses the 97.5% of all values in a healthy population is the more appropriate way to discriminate healthy vs. pathological tissue. As in any normality threshold, external replication is required.

CONCLUSION

In healthy individuals, the LGE-CMR threshold for healthy atrial tissue is IIR≤1.2. Higher values identify variable degrees of fibrosis. An IIR>1.32 identifies dense atrial scar. Our results provide a consistent, reproducible, and normalized tool to identify atrial fibrosis that might be useful for prognostic and therapeutic purposes.

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DISCLOSURES

David Andreu is an employee of Biosense-Webster. Dr. Mont and Dr. Berruezo participate in Galgo Medical Company. The other authors report no conflicts.

REFERENCES

[1] Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. *J Am Coll Cardiol* 2008; **51**: 802-9.

[2] Kottkamp H. Human atrial fibrillation substrate: towards a specific fibrotic atrial cardiomyopathy. *Eur Heart J* 2013; **34**: 2731-8.

[3] Ambale-Venkatesh B, Lima JA. Cardiac MRI: a central prognostic tool in myocardial fibrosis. *Nat Rev Cardiol* 2015; **12**: 18-29.

[4] Bisbal F, Fernandez-Armenta J, Berruezo A, Mont L, Brugada J. Use of MRI to guide electrophysiology procedures. *Heart* 2014; **100**: 1975-84.

[5] Oakes RS, Badger TJ, Kholmovski EG, Akoum N, Burgon NS, Fish EN, et al. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. *Circulation* 2009; **119**: 1758-67.

[6] Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA* 2014; **311**: 498-506.

[7] Bisbal F, Guiu E, Cabanas-Grandio P, Berruezo A, Prat-Gonzalez S, Vidal B, et al. CMR-guided approach to localize and ablate gaps in repeat AF ablation procedure. *JACC Cardiovasc Imaging* 2014; **7**: 653-63.

[8] Khurram IM, Beinart R, Zipunnikov V, Dewire J, Yarmohammadi H, Sasaki T, et al. Magnetic resonance image intensity ratio, a normalized measure to enable interpatient comparability of left atrial fibrosis. *Heart rhythm : the official journal of the Heart Rhythm Society* 2014; **11**: 85-92.

[9] Sramko M, Peichl P, Wichterle D, Tintera J, Weichet J, Maxian R, et al. Clinical value of assessment of left atrial late gadolinium enhancement in patients undergoing ablation of atrial fibrillation. *Int J Cardiol* 2015; **179**: 351-7.

[10] Hunter RJ, Jones DA, Boubertakh R, Malcolme-Lawes LC, Kanagaratnam P, Juli CF, et al. Diagnostic accuracy of cardiac magnetic resonance imaging in the detection and characterization of left atrial catheter ablation lesions: a multicenter experience. *J Cardiovasc Electrophysiol* 2013; **24**: 396-403.

[11] Fabritz L, Guasch E, Antoniades C, Bardinet I, Benninger G, Betts TR, et al. Expert consensus document: Defining the major health modifiers causing atrial fibrillation: a roadmap to underpin personalized prevention and treatment. *Nat Rev Cardiol* 2016; **13**: 230-7.

[12] Habibi M, Lima JA, Khurram IM, Zimmerman SL, Zipunnikov V, Fukumoto K, et al. Association of left atrial function and left atrial enhancement in patients with atrial fibrillation: cardiac magnetic resonance study. *Circulation Cardiovascular imaging* 2015; **8**: e002769.

[13] Lim HS, Yamashita S, Cochet H, Haissaguerre M. Delineating atrial scar by electroanatomic voltage mapping versus cardiac magnetic resonance imaging: where to draw the line? *J Cardiovasc Electrophysiol* 2014; **25**: 1053-6.

[14] Harrison JL, Jensen HK, Peel SA, Chiribiri A, Grondal AK, Bloch LO, et al. Cardiac magnetic resonance and electroanatomical mapping of acute and chronic atrial ablation injury: a histological validation study. *Eur Heart J* 2014; **35**: 1486-95.

[15] Harrison JL, Sohns C, Linton NW, Karim R, Williams SE, Rhode KS, et al. Repeat Left Atrial Catheter Ablation: Cardiac Magnetic Resonance Prediction of Endocardial Voltage and Gaps in Ablation Lesion Sets. *Circ Arrhythm Electrophysiol* 2015.

[16] Parmar BR, Jarrett TR, Burgon NS, Kholmovski EG, Akoum NW, Hu N, et al. Comparison of left atrial area marked ablated in electroanatomical maps with scar in MRI. *J Cardiovasc Electrophysiol* 2014; **25**: 457-63.

[17] Lau YF, Yiu KH, Siu CW, Tse HF. Hypertension and atrial fibrillation: epidemiology, pathophysiology and therapeutic implications. *J Hum Hypertens* 2012; **26**: 563-9.

[18] Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* 2013; **2**: e000102.

[19] Andreu D, Gomez-Pulido F, Calvo M, Carlosena-Remirez A, Bisbal F, Borras R, et al. Contact force threshold for permanent lesion formation in atrial fibrillation ablation: A cardiac magnetic resonance-based study to detect ablation gaps. *Heart rhythm : the official journal of the Heart Rhythm Society* 2016; **13**: 37-45.

[20] Akoum N, Wilber D, Hindricks G, Jais P, Cates J, Marchlinski F, et al. MRI Assessment of Ablation-Induced Scarring in Atrial Fibrillation: Analysis from the DECAAF Study. *J Cardiovasc Electrophysiol* 2015; **26**: 473-80.

Table 1:Patient demographics (AF: Atrial fibrillation; OSA: obstructive sleep apnoea; LA: Left atrial; AP: antero-posterior; LV left ventricle)

	Healthy volunteers	Paroxysmal AF	Persistent AF	Post-ablation	p
Age (years)	22±0	60±12	57±8	56±12	<0.001
Men	5 (50%)	9 (90%)	9 (90%)	8 (80%)	0.12
Hypertension	0 (0%)	3 (30%)	5 (50%)	7 (70%)	0.01
Diabetes mellitus	0 (0%)	0 (0%)	2 (20%)	1 (10%)	0.27
OSA	0 (0%)	1 (10%)	1 (10%)	0 (0%)	0.55
Structural heart disease	0 (0%)	1 (10%)	1 (10%)	0 (0%)	0.41
Echocardiography data					
LA AP diameter (mm)	_	38±4	44±5	39±4	0.03
LV ejection fraction (%)	_	59,4±65,5	59,3±32,9	60.5±43.6	0.82

Table 2:Standard CMR and post-processed LGE-CMR results. (AF: Atrial fibrillation, LVEF: Left ventricle ejection fraction; EDV/ESV: End diastolic/systolic volume; LA: left atrial; IIR: Image intensity ratio)

CMR data	Healthy volunteers	Paroxysmal AF	Persistent AF	Post-ablation	p
LVEF (%)	59±3	59±4	57±5	60±5	0,51
EDV (mL)	161.3±38.8	168.0±23.4	157.3±38.9	164.3±37.5	0.91
ESV (mL)	67.4±18.3	70.9±12.5	64.9±15.0	67.6±15.5	0.86
LA (area, cm^2)	18.6±3.1	26.9±7.0	30.6±4.3	28.2±4.6	<0.001
LA Volume (cm^3)	32.5±8.2	83.9±31.5	100.7±23.3	74.5±19.8	<0.001
LA BS-indexed volume(cm^3/m^2)	18.9±4.36	45.32±18.45	52.52±10.7	38.2±11.71	<0.001
Post-processed LGE-CMR histogram data					
Mean IIR	0.91 ±0.15	0.98±0.2	0.97±0.2	1.04±0.3	<0.001
% Overall fibrosis (IIR >1,20)	2.46% (1.52-4.21)	8.53% (4.12-12.47)	11.73% (4.62-22.5)	34.62% (14.57-43.18)	<0.001
% Dense fibrosis (IIR > 1.32)	0.02% (0.01-0.04)	1.27% (0.51-2.21)	1.64% (0.07-2.8)	14.5% (4.88-22.13)	<0.001
Asymmetry (Skewness)	-0.75	0.08	0.22	0.78	

Figure legends

Figure 1: Segmentation process of a healthy volunteer. 1) Original 3D LGE-CMR image. 2) Manually drawn epicardial and endocardial contours. 3) Deformation of 50% layer. 4) Pulmonary veins and mitral withdrawal. 5) Three-dimensional colour-coded LGE-CMR shell. 5a-posterior view. 5b-anterior view.

Figure 2: Histogram distribution (IIR) superimposed in all groups**.**

Figure 3: A- Left panel: Histogram distribution (IIR) in all groups. Red line: Upper threshold IIR. Green line: Low threshold IIR. Right panel: Examples of postero-anterior and antero-posterior view in each group. B- Fibrosis quantification in each patient.

Figure 4: Individual patient point-by-point atrial correlation with IIR-bipolar voltage(log-transformed)

Figure 5: A) Representative example of an electroanatomic map and IIR LGE-CMR shell merge. B) Voltage distributions in the threshold IIR cut-offs in all patients.

Figure 1

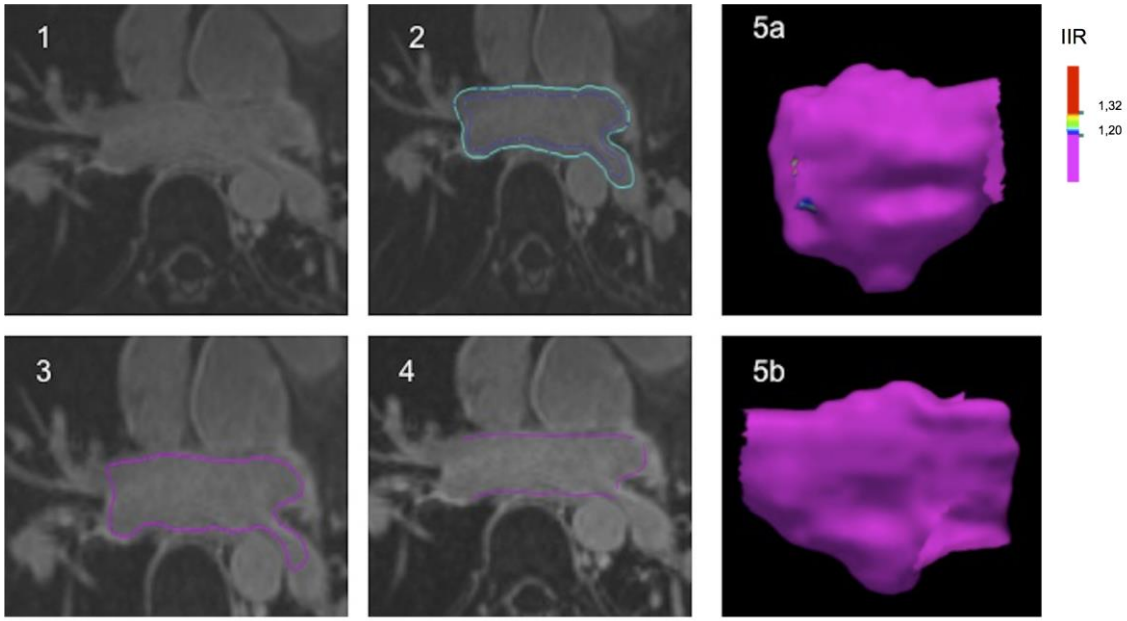


Figure 2

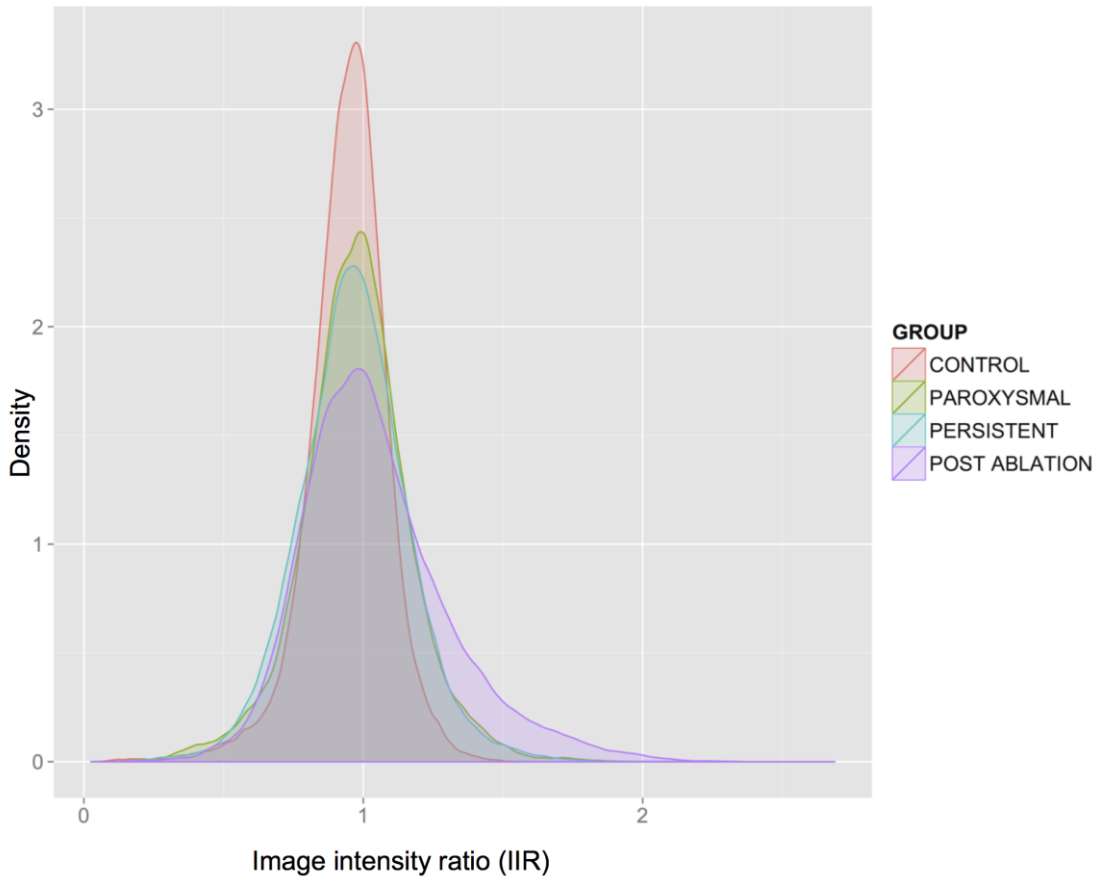

Density
3
2
1
0
0
1
2
Image intensity ratio (IIR)
GROUP
CONTROL
PAROXYSMAL
PERSISTENT
POST ABLATION

Figure 3

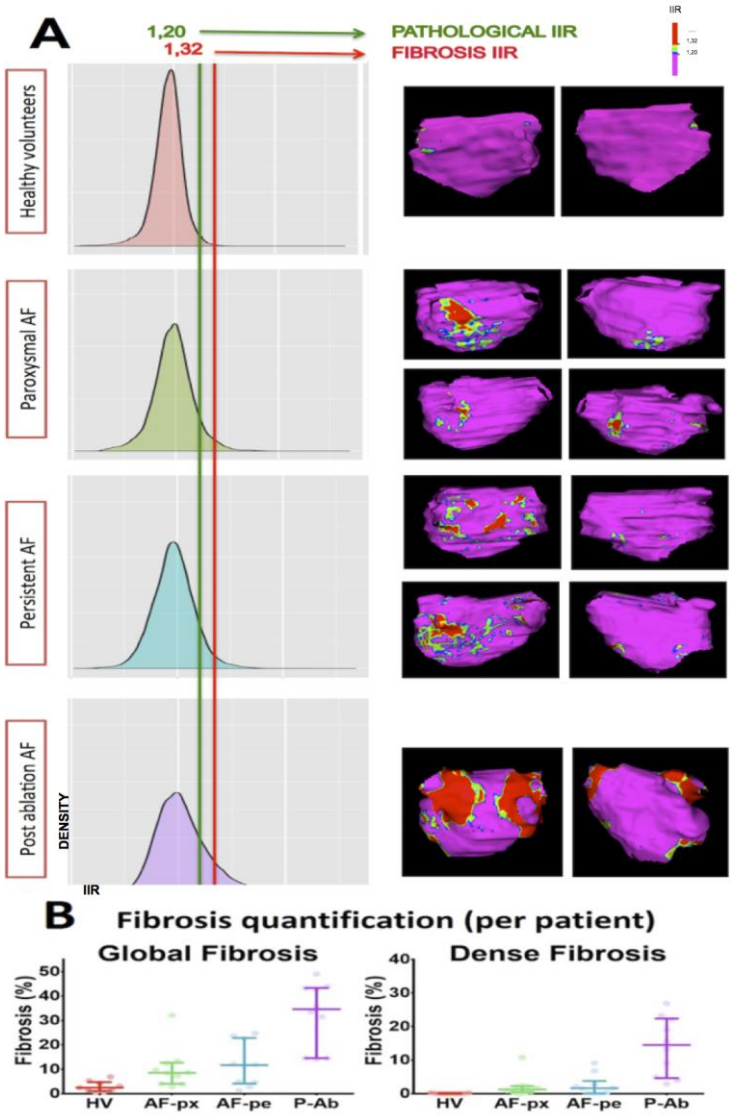

A
1,20
1,32
PATHOLOGICAL IIR
FIBROSIS IIR
IIR
Healthy volunteers
Paroxysmal AF
Persistent AF
Post ablation AF
DENSITY
IIR
B
Fibrosis quantification (per patient)
Global Fibrosis
Dense Fibrosis
Fibrosis (%)
HV
AF-px
AF-pe
P-Ab

Figure 4

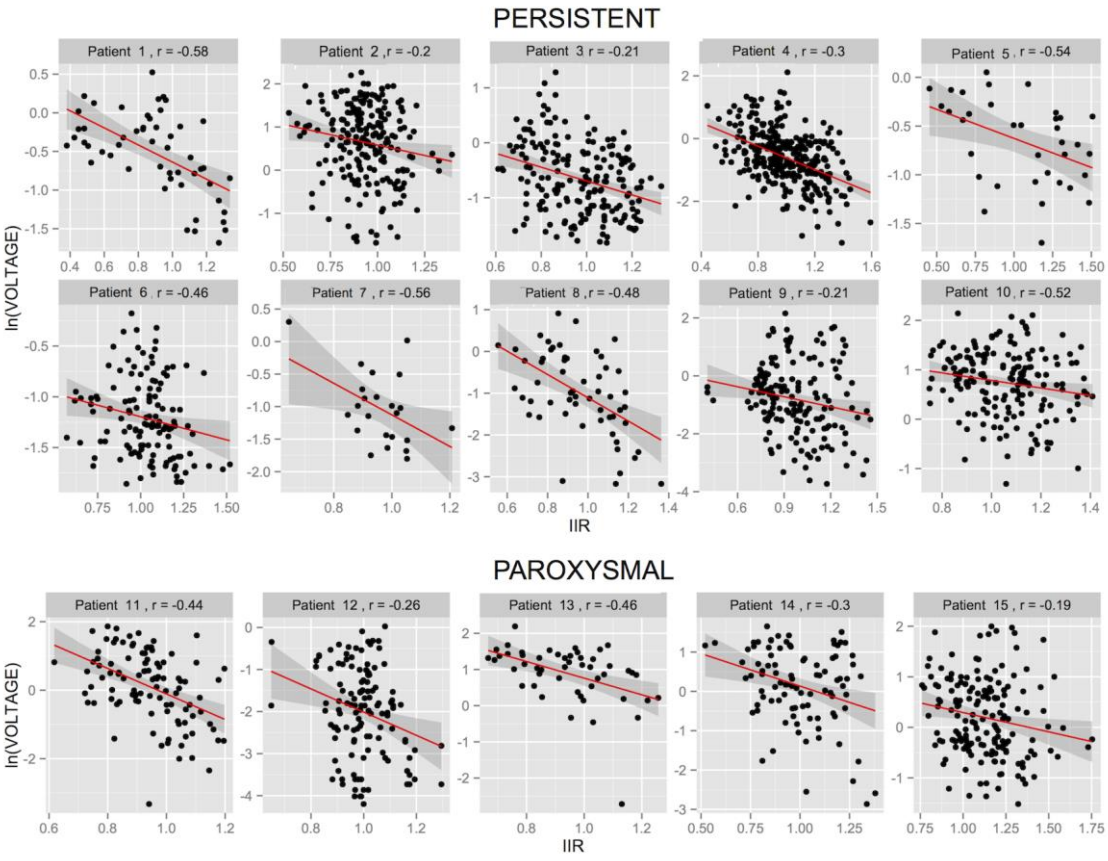
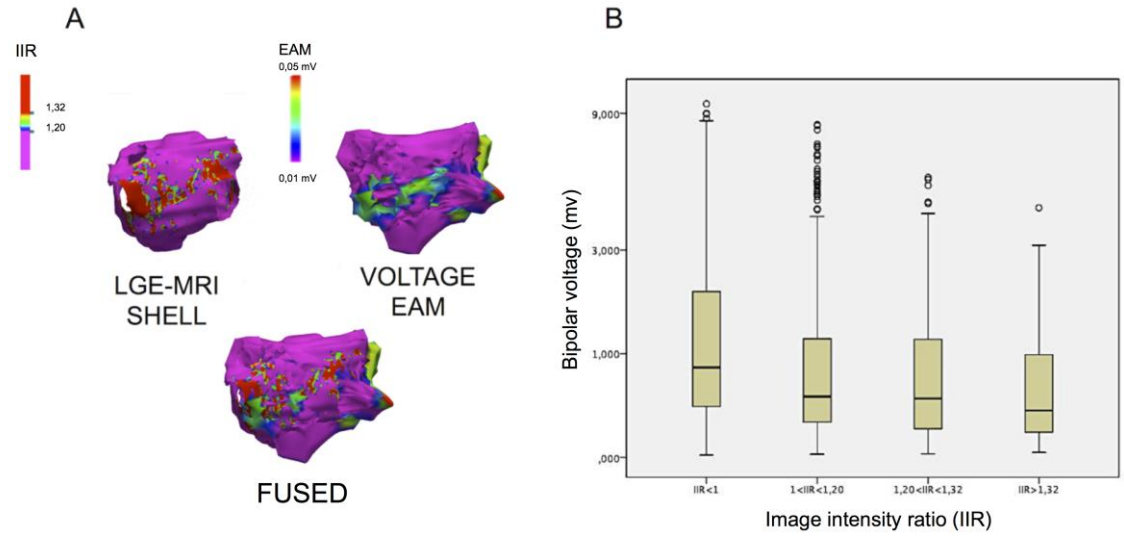

PERSISTENT
Patient 1 , r = -0.58
Patient 2 , r = -0.2
Patient 3 r = -0.21
Patient 4 , r = -0.3
Patient 5 , r = -0.54
Patient 6 , r = -0.46
Patient 7 , r = -0.56
Patient 8 , r = -0.48
Patient 9 , r = -0.21
Patient 10 , r = -0.52
ln(VOLTAGE)
IIR
PAROXYSMAL
Patient 11 , r = -0.44
Patient 12 , r = -0.26
Patient 13 , r = -0.46
Patient 14 , r = -0.3
Patient 15 , r = -0.19
ln(VOLTAGE)
IIR

Figure 5


A
IIR
1,32
1,20
EAM
0,05 mV
0,01 mV
LGE-MRI
SHELL
VOLTAGE
EAM
FUSED
B
Bipolar voltage (mv)
9,000
3,000
1,000
,000
IIR<1
1<IIR<1,20
1,20<IIR<1,32
IIR>1,32
Image intensity ratio (IIR)