SUPPLEMENTARY DATA

SUPPLEMENTARY METHODS

Cohorts under study

A total of 53 individuals who underwent LGE-CMR for research purposes were included in consecutive stages of this study. Initially, thresholds to identify fibrosis in the RA were determined in healthy volunteers (individuals aged 18- 30 years without any relevant comorbidity, who had been recruited to assess LA fibrosis threshold,[1] n = 9) and in patients who had undergone typical atrial flutter and AF ablation in the same procedure (n = 9). Later, patients with paroxysmal (n = 10) or persistent (n = 10) AF were used for validation. Finally, the correlation between the IIR and EAM in an additional prospective cohort of patients undergoing a first AF ablation procedure was evaluated (n = 15). The exclusion criteria were as follows: age less than 18 years, poor quality of LGE-CMR, severe renal failure (glomerular filtration rate < 30 mL/min), known gadolinium allergy, implanted cardiac electronic device, and pregnancy or lactation.

LGE-CMR imaging

An LGE-CMR scan was obtained in all individuals included in the present study. Details of the healthy volunteers have also been reported previously.[1] In the postablation group, LGE-CMR was obtained 3 months after the index ablation procedure. In the validation groups (paroxysmal and persistent AF), an LGE-CMR was performed less than 2 weeks before the ablation procedure.

Acquisition protocol

Images were obtained with a 3.0 Tesla CMR (Magnetom Prisma Siemens Healthcare, Germany) and a dedicated 32-channel cardiac coil, as described previously.[1,2] Electrical cardioversion was performed, if necessary, prior to the LGE-CMR to improve image acquisition and quality. LGE-CMR scans were acquired 20 minutes after an intravenous bolus injection of 0.2 mmol/kg gadobutrol (Gadovist, Bayer Hispania) using a free-breathing 3D navigator and ECG-gated inversion-recovery gradient-echo sequence applied in the axial orientation. The gadolinium dose was selected for consistency with previous research from our and other groups, and according to current recommendations.[3] The voxel size was 1.25 x 1.25 x 2.5 mm. Repetition time/echo time was 2.3/1.4 ms; flip angle, 11°; bandwidth, 460 Hz/pixel; inversion time (TI) 280 to 380 ms; and parallel imaging with GRAPPA technique, with reference lines of R = 2 and 72. A TI scout sequence was used to nullify the left ventricular myocardial signal and determine optimal TI. Typical scan time for an LGE-CMR sequence was 15 [11-18] minutes, depending on heart rate and breathing patterns.

Postprocessing

Both the RA and LA of each patient were initially segmented by an expert investigator and reviewed by a second expert investigator to ensure optimum image processing. RA and LA segmentation was performed using ADAS 3D software (ADAS, Spain). Atrial contours of the wall were manually drawn by 2 expert operators in each axial plane of the LGE-CMR, without invading the interatrial common septum, and a 3-dimensional model was constructed. ADAS automatically builds a 3D shell. Subsequently, pulmonary veins at the ostium level, mitral valve plane and left appendage were excluded in the LA, and the superior and inferior vena cava at the ostium level, tricuspid valve plane and coronary sinus were excluded in the RA.

Signal intensity was internally (within each patient) normalized to blood pool intensity to provide an absolute signal intensity value that would allow comparisons between patients. The LA blood pool was automatically identified by the software. Image intensity ratio (IIR) was calculated as the ratio between the signal intensity of each single pixel and the mean blood pool intensity for each patient. IIR values were colour-coded, projected into the atrial shell, and presented in histograms.

Assessment of total fibrosis and dense scar thresholds

Signal intensity was obtained from each pixel of the RA wall and normalized to the mean LA blood intensity to calculate the IIR; an analogous process in the LA wall was performed as a reference. The LA blood pool intensity was chosen for RA wall normalization because it was found to be less variable than the RA blood pool, and because it enabled comparison between the 2 atria. Notably, the correlation between LA- and RA-blood pool adjusted IIR was very high ($r = 0.95$, supplementary figure). All the IIR values of each subgroup were represented in histograms, and thresholds were calculated as follows. Using a common definition of normality (ie, mean ± 2 standard deviations [SD] of a normal cohort),[1] the fibrosis threshold was defined as the mean IIR value in the healthy volunteer group plus 2 SD. By definition ≈ 97.5% of all pixels in the healthy volunteers group fell below this threshold. The dense scar threshold was defined using previously clinically validated algorithms for identifying gaps in the LA after PV isolation[4] and ventricular scar heterogeneity,[5] as the IIR value corresponding to 60% of the maximum normalized signal intensity pixel in the RA of patients who had undergone cavotricuspid isthmus ablation.

We established an upper limit of healthy tissue IIR in the RA and a threshold discriminating interstitial fibrosis from dense scar. For validation purposes, both values were then used to quantify total, interstitial fibrosis and dense scar in all participants and groups.

Correlation between LGE-CMR and electroanatomical map

In 15 consecutive patients undergoing AF ablation (8 paroxysmal/7 persistent), intraprocedural high density point-by-point electroanatomical bipolar voltage maps (EAM) of the RA and LA (CARTO 3, Biosense Webster) were obtained with a multipolar catheter (Lasso, Biosense Webster or Pentarray, Biosense Webster) before ablation. Standard voltage thresholds of 0.1 mV and 0.5 mV were used to characterize the atrial tissue, as follows: dense scar <0.1 mV; 0.1 mV < interstitial fibrosis < 0.5 mV; 0.5 mV < healthy tissue.[6]

The EAM was merged with the previously built RA/LA LGE-CMR 3D shell. Both structures were aligned, and only EAM points projected on the CMR 3-dimensional image less than 10 mm apart were used. The correlation between bipolar voltage (in the EAM) and normalized IIR (in the LGE-CMR) values was calculated for each patient. The accuracy of LGE-CMR and the EAM in classifying areas as healthy tissue, interstitial fibrosis or dense scar was also calculated.

Statistical analysis

Continuous variables are shown as mean ± SD or median [interquartile range] unless otherwise stated, and comparisons among groups were performed with 1 -way ANOVA. Categorical variables are summarized as total number and percentages. Skewness and kurtosis were computed to characterize the IIR histograms for each group. The Lin concordance correlation coefficient was used to test interobserver agreement. The correlation between IIR and EAM was assessed using the Pearson correlation coefficient (r), and a generalized linear mixed model with random intercept accounted for repeated IIR measurements per patient. The strength of association was evaluated according to the following criteria: weak ≤ 0.3; 0.3 > moderate ≥ 0.7; good > 0.7. Since bipolar voltage was not normally distributed, its log-transformation was used. Overall agreement was calculated as the ratio between the number of pixels in which EAM and MRI yielded the same classification (ie, healthy tissue, dense scar, interstitial fibrosis), and the overall number of pixels. A 2-sided type I error of 5% was used for all tests. Because the study was not designed to be a hypothesis testing study involving a null and alternative hypothesis, a sample size was estimated using a similar number of participants to that in previous work in the field.[1,7] For IIR histogram, but also correlation, analyses were performed in several thousands of data points. All analyses were performed using R v3.5.1 (R project for Statistical Computing).

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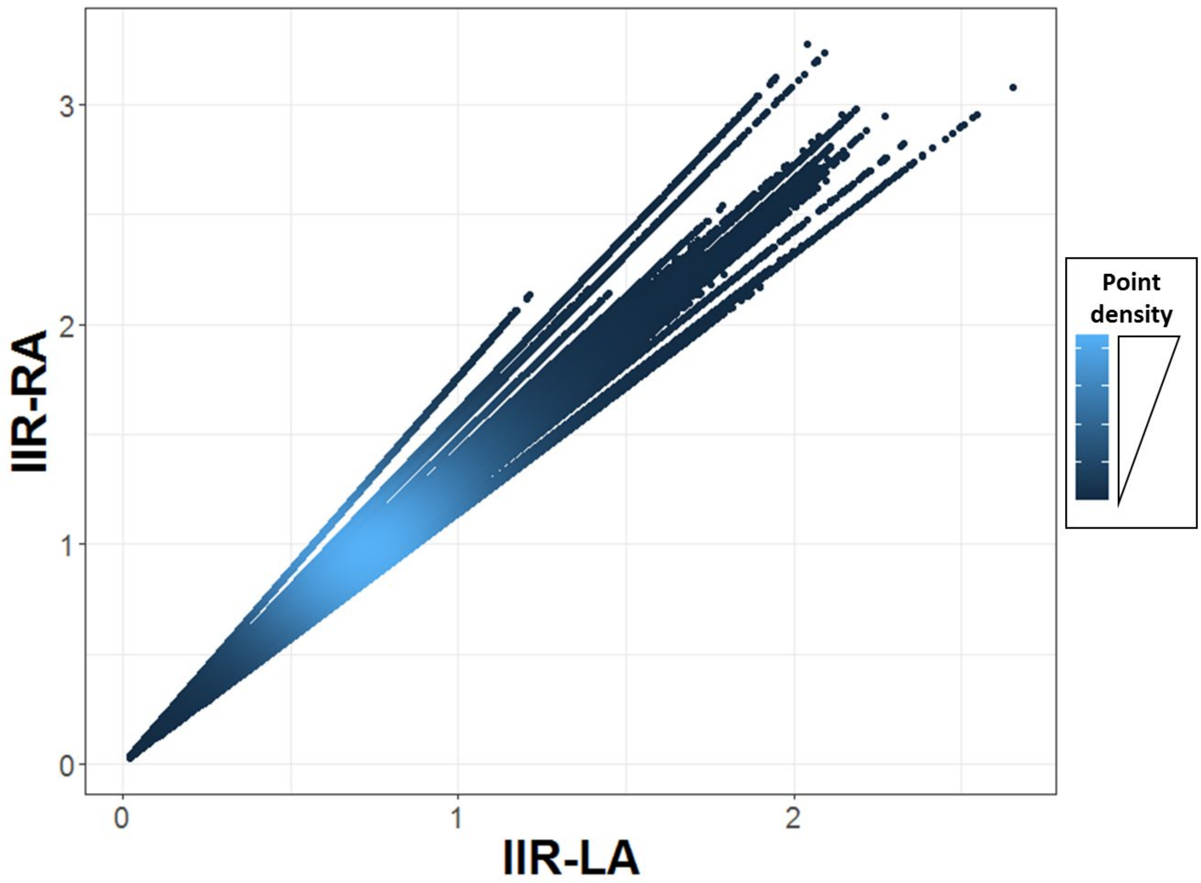
Figure 1 of the supplementary data



Correlation between left atrium (LA) blood pool- and right atrium (RA) blood pool-standardized image intensity ratio**.** Correlation, estimated by the Pearson correlation coefficient was found to be very high (r = 0.95).