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# Higher Reproducibility of Phase Derived Metrics from Electrocardiographic Imaging During Atrial Fibrillation in Patients Remaining in Sinus Rhythm after Pulmonary Vein Isolation

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**Abstract**

**Background:** Electrocardiographic imaging (ECGI) allows evaluating the complexity of the reentrant activity of atrial fibrillation (AF) patients. In this study, we evaluated the ability of ECGI metrics to predict the success of pulmonary vein isolation (PVI) to treat AF.

**Methods:** ECGI of 24 AF patients (6 males, 13 paroxysmal, 61.8 ± 14 years) was recorded prior to PVI. Patients were distributed into two groups based on their PVI outcome 6 months after ablation (sinus vs. arrhythmia recurrence). Metrics derived from phase analysis of ECGI signals were computed for two different temporal segments before ablation. Correlation analysis and variability over time were studied between the two recorded segments and were compared between patient groups.

**Results:** Temporal variability of both rotor duration and spatial entropy of the rotor histogram presented statistical differences between groups with different PVI outcome ($p<0.05$). The reproducibility of reentrant metrics was higher ($R^2>0.8$) in patients with good outcome rather than arrhythmia recurrence patients ($R^2<0.62$). Prediction of PVI success based on ECGI temporal variability metrics allows for an increased specificity over the classification into paroxysmal or persistent (0.85 vs. 0.64).

**Conclusions:** Patients with favorable PVI outcome present ECGI metrics more reproducible over time than patients with AF recurrence. These results suggest that ECGI derived metrics may allow selecting which patients would benefit from ablation therapies.

**Keywords:** Atrial Fibrillation; Electrocardiographic Imaging; Reproducibility; Reentrant Activity; Pulmonary Vein Isolation

# Abbreviations

AF Atrial Fibrillation

AUC Area Under the Curve

ECGI Electrocardiographic Imaging

IVC Inferior Vena Cava

LIPV Left Inferior Pulmonary Vein

LSPV Left Superior Pulmonary Vein

PVI Pulmonary Vein Isolation

RIPV Right Inferior Pulmonary Vein

ROC Receiver Operating Characteristic Curve

RS Reproducibility Score

RSPV Right Superior Pulmonary Vein

SP Singularity Point

SVC Superior Vena Cava

VS Variability Score

## 1. Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia in the adult population [1], and it causes a major burden both in the patients and in health systems [2]. Although restoration of sinus rhythm would be desirable in the entire AF population of patients this is not always feasible. When drug therapies fail in restoring sinus rhythm or in minimizing AF-related symptoms, patients can be referred for catheter ablation [2]. Pulmonary vein isolation (PVI) is recommended for patients with paroxysmal AF and persistent AF with low risks of AF recurrence, but despite these recommendations, the percentage of AF recurrence in ablated patients is still high and around 40% [3]. It has been reported that driver-guided catheter ablation of atrial areas with other lesions can reduce AF recurrence after the ablation [4,5] but the most recent guidelines for AF management still recommend further evidence before changing the current recommendations [2].

Electrocardiographic imaging (ECGI) is a non-invasive technique that has shown its ability to estimate the electrical activity of AF patients. ECGI has been used with success to guide ablations based on driver identification [5,6,7] and more recent studies have reported a good correlation between invasively and ECGI-derived estimation of the complexity of the electrical patterns during AF [8]. ECGI derived metrics of complexity have been shown to be related to the disease progression, and more complex patterns are typically present in persistent AF patients as compared to paroxysmal AF patients [9]. However, these complexity metrics have not been related to a differential outcome prediction.

The objective of this study is to evaluate the potential of ECGI derived complexity metrics as an indicator of PVI success. We hypothesized that the reproducibility of ECGI complexity metrics can be related to the complexity of the arrhythmia and the outcome of PVI to a larger extent than the complexity estimated at a single temporal interval. We compared ECGI derived metrics of AF patients prior to PVI obtained at different time segments and evaluated its variability in time in patients with and without arrhythmia recurrence 6 months after PVI.

## 2. Methods

### 2.1. Study Population

A population of 24 atrial fibrillation patients (18 females and 6 males; 61.8 ± 14.3 years old) was studied prior to a wide antral circumferential pulmonary vein isolation procedure. Patients gave informed consent, and the protocol was approved by the ethics committee of Hospital Gregorio Marañón, Madrid, Spain (reference 475/14). Consecutive patients from this Clinical Trial that had two or more signal segments with AF recorded prior valvuloplasty and PVI were selected for being able to study the reproducibility of the metrics. Five patients of a totality of 29 did not present two AF signals prior the procedure with enough quality to be analyzed and were removed from the present study. Out of the 24 patients, 13 were classified as paroxysmal AF and 11 as persistent AF and 10 patients had valvular insufficiency. A percutaneous balloon mitral valvuloplasty was performed on patients with valvular diseases prior PVI. In procedure, patients in sinus rhythm, AF, it was induced by decremental pacing at the pulmonary veins. A total of 6 patients were under antiarrhythmic drugs (flecainide n=1, amiodarone n=5). Patients were followed 6 months after the ablation and then grouped into either sinus rhythm (N=13) or arrhythmia recurrence (atrial fibrillation, atrial tachycardia or atrial flutter, N=11, see Table 1). A 12 lead ECG and quality-of-life questionnaires were used for detecting arrhythmia recurrences 6 months after the PVI.

| | **All Patients (n = 24)** | **Sinus (n=13)** | **Arrhythmia Recurrence (n=11)** |
|---|---|---|---|
| **Male (%)** | 6 (25 %) | 5 (38.46 %) | 1 (9.1 %) |
| **Age (Years)** | 61.83 ± 14.03 | 59.23 ± 14.01 | 64.91 ± 13.43 |

| | | | |
|---|---|---|---|
| **Paroxysmal AF (%)** | 13 (54.17 %) | 9 (69.23 %) | 4 (36.36 %) |
| **Valvuloplasty (%)** | 10 (41.67 %) | 7 (53.85 %) | 3 (27.27 %) |
| **Medical Therapy** | Flecainide – 1<br>Amiodarone – 5 | Flecainide – 1<br>Amiodarone – 2 | Amiodarone – 3 |
| **Medical Therapy after Ablation** | Amiodarone – 6<br>Flecainide -2<br>Beta-Blockers - 8 | Amiodarone – 4<br>Flecainide -2<br>Beta-Blockers - 4 | Amiodarone – 2<br>Beta-Blockers - 4 |
| **Patients with Previous Ablations** | 23 (95.8%) | 12 (92.3%) | 11 (100%) |
| **Previous Ablations per Patient** | 1.21 ± 0.5 | 1.15 ± 0.55 | 1.27 ± 0.44 |
| **Left Ventricular Ejection Fraction (%)** | 56.48 ± 6.92 | 59 ± 6.14 | 53.73 ± 6.91 |
| **Left Atrium Size ($cm^2$)** | 32.7 ± 7.41 | 33.35 ± 8.27 | 31.94 ± 6.54 |

**Table 1.** Clinical description of the study population

## 2.2. Data Acquisition

We recorded surface ECG signals from the patients at 57 locations on the torso surface before pulmonary vein isolation and valvuloplasty. Signals were recorded with 0.05 to 500 Hz filtering

and a sampling frequency of 1 kHz [8]. The geometry of the torso of the patients and the electrode location were obtained using video recording and reconstructed by photogrammetry [10]. Images from the video were exported and common image pixels were used for 3D-torso reconstruction. A 3D-torso mesh and the corresponding texture was used for electrode location identification. MRI/CT scan images were also obtained before the intervention and both the atria and the torso were segmented semi-automatically when geometries were well defined or manually layer by layer using ITK-SNAP when necessary [8] [11]. Torso and atrial geometries were co-registered using the torso reference from MRI/CT images.

### 2.3. Data processing

To study the reproducibility among time of ECGI-extracted metrics, raw signals of two segments of each patient (4 ± 0.31s) were selected prior to PVI. The signals were preprocessed removing the baseline and were band-pass filtered between 2 and 45 Hz to eliminate noise using a $10^{th}$ order Butterworth filter, and ventricular activity (QRST segment) was canceled lead by lead by using the Principal Component Analysis approach [12]. Inverse computed electrograms were calculated by using zero-order Tikhonov regularization and L-curve optimization [13] for each segment. We applied Hilbert's transform to the ECGI signals to compute the instantaneous phase of each signal. Reentrant activity was defined as a phase progression from $-\pi$ to $+\pi$ around a single point in the epicardium. Singularity points (SP) were then defined as stable rotations around an atrial point for at least 1 turn in at least two out of three concentric rings of increasing radii as described elsewhere [14]. The distance threshold between SP at consecutive time instants to considered SP related to form a rotor was 1 cm [14]. SP histograms were constructed to represent the cumulative SPs in each node of the epicardium, where a higher accumulation of SP detected represent areas with more frequent pivoting electrical activity [8].

### 2.4. Atrial fibrillation complexity quantification

To evaluate the reentrant activity and the complexity of the arrhythmia in each patient, different metrics of the signals were computed in the two segments recorded of each patient. Total singularity points were computed as the number of phase singularities detected scaled by time (SP/ms). Mean rotor duration (Rduration) was computed as the mean duration in seconds of the detected rotors in the signal. Finally, the Shannon spatial entropy of the SP histogram was computed.

## 2.5. Reproducibility measurements

To study the reproducibility of each metric, the variability of AF complexity metrics in time was computed as the absolute difference between the metrics extracted from the two different temporal segments: ΔSP/ms, ΔRduration and ΔEntropy were computed as the absolute differences between SP/ms, Rduration and Entropy measured in interval 1 and 2, respectively. In addition, the Coefficient of determination ($R^2$) between the first and second metrics was computed.

An additional quantification of the reproducibility of the different metrics was computed as the ratio between the intra-patient variability and the variability between subjects: the variability score (VS), see Equation 1[15].

$$VS = \frac{Intrasubject\ Variability}{Intersubject\ Variability} = \frac{\frac{|(X1 - X2)|}{|(X1 + X2)|/2}}{\frac{\sigma_{X1}}{\mu_{X1}}} \quad (1)$$

Where X1 is any metric at time interval 1 (namely SP/ms, mean rotor duration, or spatial Shannon's entropy), X2 is the same metric computed for interval 2, $\sigma_{X1}$ is the standard deviation of X1 and $\mu_{X1}$ is the mean value of X1. The lower the VS values, the higher the reproducibility of the metric. Overall, a VS value lower than 1 is assumed to represent a reproducible metric.

## 2.6. Statistical analysis

In order to compare complexity metrics between groups (restoration of sinus rhythm vs. arrhythmia recurrence or paroxysmal vs. persistent), mean values of the metrics of the first and

second interval were computed. Normality of the values of each patient's group was computed using the Kolmogorov-Smirnov test. To study differences between groups, student's t-test was computed to compare normal samples and Wilcoxon rank-sum test was computed to compare non-normal samples. A p-value<0.05 was considered statistically significant. Statistical differences in the $R^2$ between groups were computed using a tail t-test after Fisher r-to-z transform.

### 2.7. Outcome prediction based on ECGI reproducibility

A reproducibility score (RS) was computed as the average between ΔRduration and ΔEntropy in order to predict 6-months outcome of PVI. Univariate logistic regression of RS was performed to predict the PVI outcome. Sensitivity and specificity were also computed based on the threshold determined from the regression analysis and subsequent receiver operating characteristic curves (ROC) and area under the curve (AUC) were computed. Furthermore, univariate logistic regression was computed using AF type as a predictor of PVI outcome, to compare the proposed method with the current standards for selecting PVI candidates. Finally, univariate logistic regression was also computed for the determination of the AF type (paroxysmal vs. persistent) based on the reproducibility score to see if RS is related to AF type.

## 3. Results

Two sample cases and their phase maps and SP histograms are represented in Fig. 1, including one patient that maintained sinus rhythm 6 months after PVI (Fig 1A) and one patient in which AF recurred (Fig. 1B). Phase maps from the first and second time interval in a patient with an effective PVI do show reentries, mainly around the Right Inferior Pulmonary Vein (RIPV) and therefore rotor histogram maps show a larger incidence at the RIPV, together with some occurrences at other pulmonary veins. Phase maps of the patient with an ineffective PVI show a more complex pattern, with a more inhomogeneous propagation. Rotor histogram in this patient,

therefore, showed more reentries in both atria, including the pulmonary veins but also the inferior vena cava (IVC) and other sites in the right atrium. Although rotor maps obtained from the same patient at different time instants do show large incidence areas at similar locations, the reproducibility is larger in the patient in which PVI was effective.

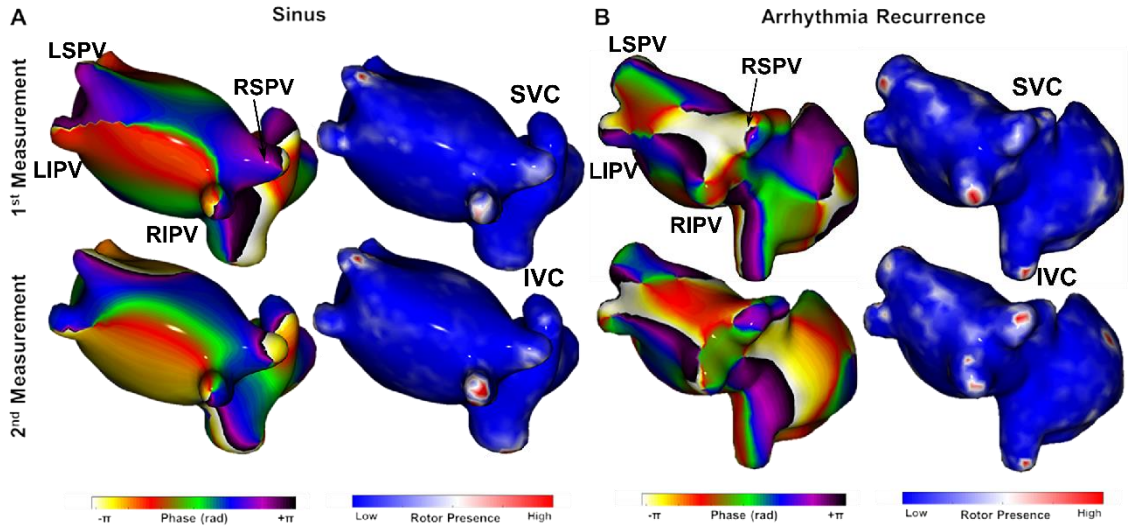
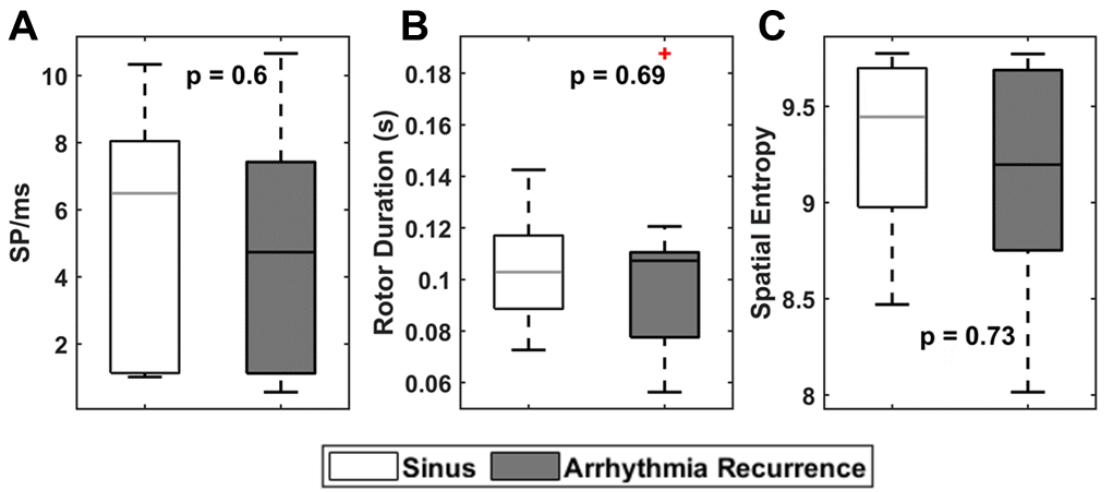



**Fig. 1.** Phase map and singularity points histogram of the first and second segment of the signal of a patient that had sinus rhythm 6 months after PVI (A) and a patient with arrhythmia recurrence after ablation (B).

### 3.1. Reproducibility of ECGI metrics vs. patient outcome

Values for all the complexity metrics for patients with an effective and an ineffective PVI are presented in Figure 2. As it can be observed no statistical differences between the two groups were found in any of the parameters and, therefore, neither the amount of SP/ms found nor their duration or the entropy of the rotor histogram maps may allow anticipating in which patients PVI might be effective.

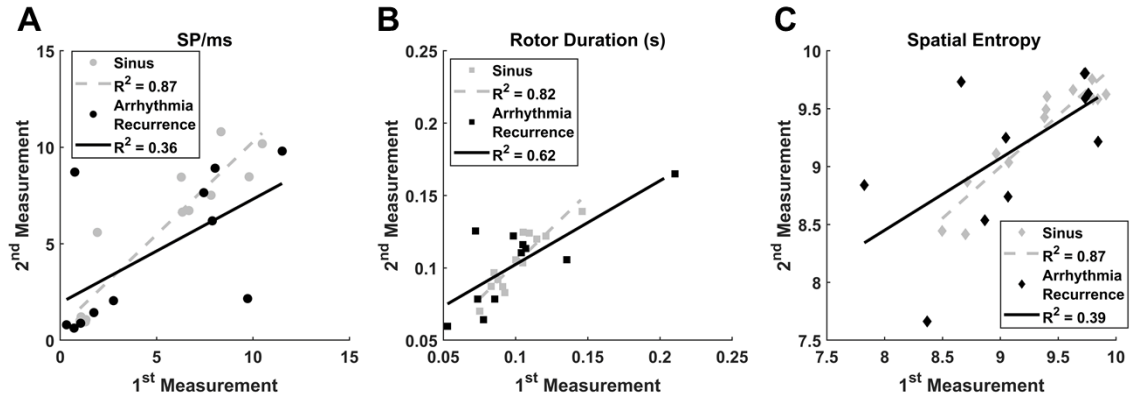



195

196 **Fig. 2.** Mean values between first and second measurements for each metric for each patient group
197 (white: good PVI outcome, black: bad PVI outcome) and p-value from the Wilkoxon rank-sum
198 test between groups of singularity points per millisecond (A), mean rotor duration (B) and spatial
199 entropy (C).

200

201 Scatter plots of the metrics in the first segment versus the second temporal segment for both
202 groups of patients and each metric are presented in Fig. 3. As it can be observed, there is some
203 reproducibility in the measurements since metrics from the first temporal segment are closely
204 related to those in the second temporal segment and this correlation is higher for patients with a
205 successful PVI than for patients with an unsuccessful PVI. In fact, the $R^2$ values are higher for
206 patients with favorable outcome and all measurements: SP/ms ($R^2$=0.87 vs. 0.36, p=0.04), spatial
207 entropy ($R^2$=0.87 vs. 0.39, p=0.05) or mean rotor duration (0.82 vs. 0.62, p=n.s).

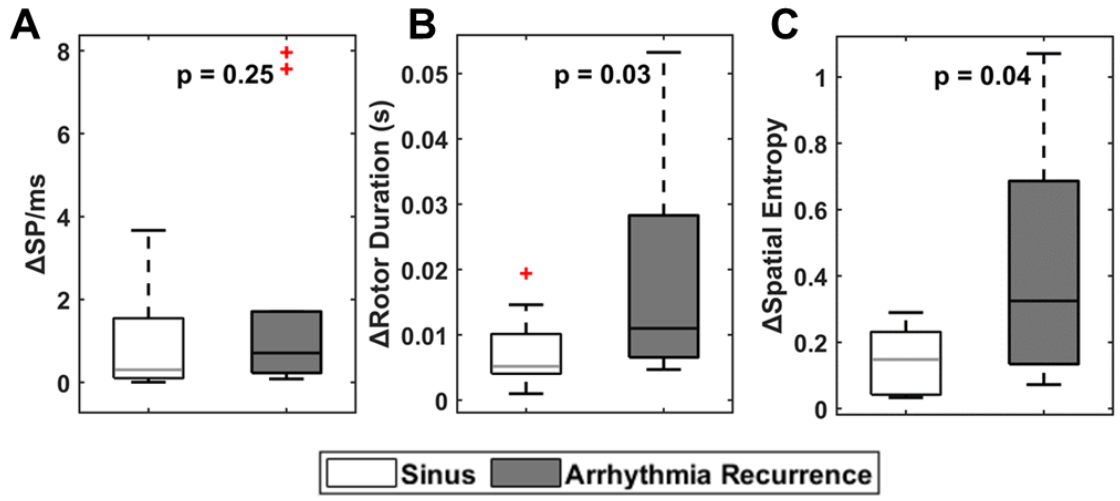



208

209 **Fig. 3.** Scatter plots of the first and second measurements for each metric classified by PVI
210 outcome (gray: good outcome), black (bad outcome): singularity points per millisecond (A), mean
211 rotor duration (B) and spatial entropy (C).

212

213 Differences in the metrics between the first and second segment showed a similar trend than the
214 $R^2$ values: differences were significant both of the mean rotor duration and spatial entropy (Fig.
215 4), (p=0.03 and p=0.04, respectively).




216

217 **Fig. 4.** The absolute difference between the two measurements for each metric and group of
218 patients (white: good PVI outcome, black: bad PVI outcome) is presented with the p-value from

the Wilkoxon rank-sum test of singularity points per millisecond (A), mean rotor duration (B) and spatial entropy (C).

Intersubject variability against the intrasubject variability of each metric is shown in Fig. 5A. All the metrics presented a good reproducibility based on this criterium: variability among patients was higher than for the same patient and therefore, all pairs of values are below the identity line. Patients with a successful PVI presented both a lower intrasubject variability and intersubject variability for all metrics (white colored in Fig. 5A and B), showing a better reproducibility in comparison with the unsuccessful PVI. The number of SP/ms and spatial entropy presented higher differences between groups of the patients regarding intersubject variability. Mean rotor duration presented the lowest differences between groups. Variability scores, shown in Fig.5.B show the same tendency of the $R^2$ values: patients with good PVI outcome showed lower variability scores than patients with arrhythmia recurrence. Furthermore, differences in the value of $R^2$ and variability score between these two groups of patients are consistent, observing the highest differences in SP/ms and spatial entropy.

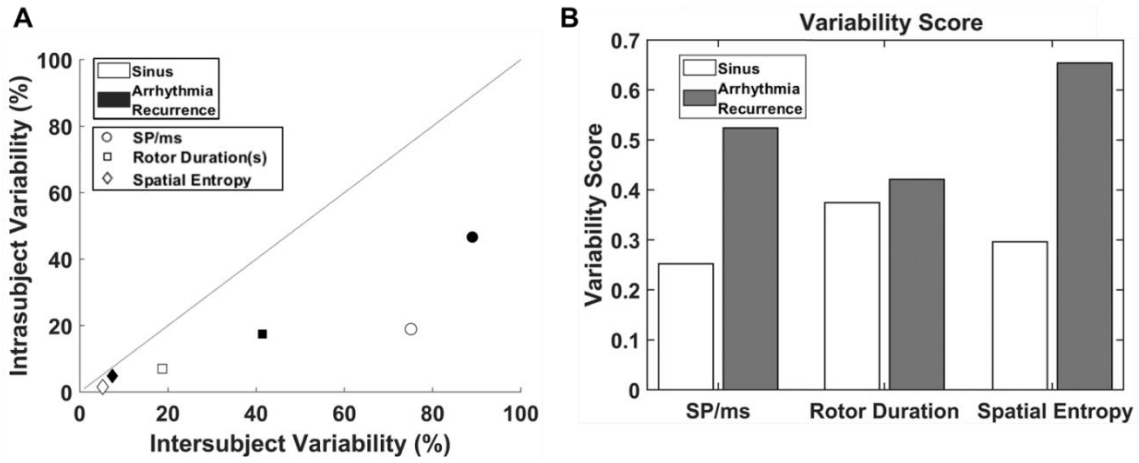



**Fig. 5.** A. Intersubject variability vs intrasubject variability of the metrics calculated. Color indicates the classification of the patients and shape the metric. The area under the line shows the metrics that are in the optimal area where intersubject variability is lower than the variability

between patients. B. Results for the variability score between the studied metrics and patients classified by PVI outcome.

### 3.2. ECGI Reproducibility vs. AF type

A comparison between metrics and their variability between groups of patients based in AF type (paroxysmal/persistent) is presented in Fig. 6. When patients are classified by AF type, there are no major differences in the mean value of metrics, as it happens when grouping the patients according to the PVI outcome. Differences between first and second measurements, however, were significant for the number of singularities detected, but not on the rotor duration or spatial entropy.

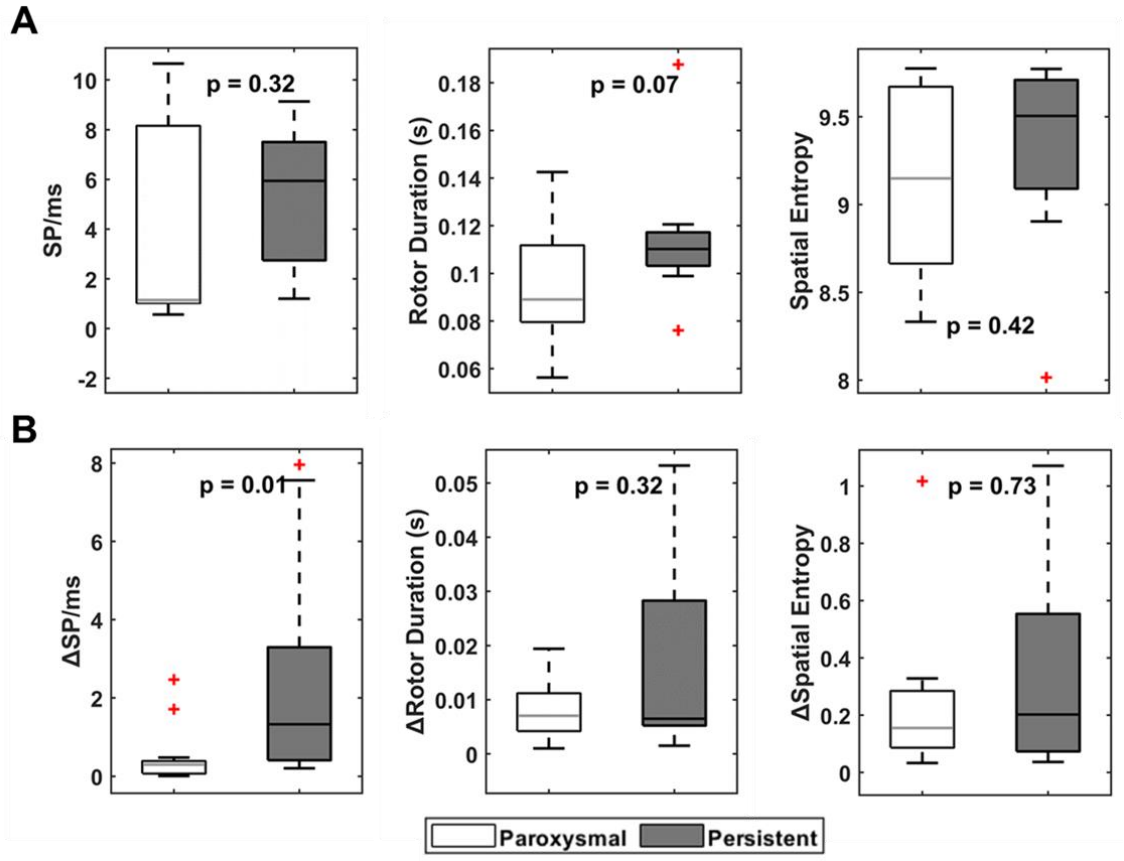



**Fig. 6.** Mean values between first and second measurements for each metric are presented in A for each patient group based on AF diagnosis (white: paroxysmal AF, black: persistent AF) and

p-value from the Wilkoxon rank-sum test between groups. The absolute difference between the two measurements for each metric and group of patients is presented with the p-value from the Wilkoxon rank-sum test in B.

### 3.3. Association of PVI success based on ECGI variability metrics

Univariate logistic regression of the proposed reproducibility score was computed with the two metrics that showed lower p-values when compared groups based on PVI outcome (ΔRduration and ΔEntropy). Results showed an area under the curve of 0.77. Area under the curve of RS for classification into paroxysmal or persistent AF was lower: 0.59, which highlights that the proposed reproducibility score based on ECGI metrics is more closely related to the PVI outcome than the AF classification.

Prediction of PVI success according to their diagnosis into paroxysmal or persistent AF, assuming that patients with paroxysmal AF will have a favorable outcome of PVI whereas patients with persistent AF will have a poor PVI outcome offered a sensitivity of 0.63 and a specificity of 0.69. Prediction based on our reproducibility score, in contrast, resulted in a sensitivity of 0.64 and a specificity of 0.85, and therefore, the use of ECGI reproducibility measurements may allow in better selecting patients that will not benefit from PVI.

## 4. Discussion

In this work, we have evaluated the variability of reentrant activity metrics extracted before PVI in AF patients and found a relation between this variability and PVI outcome six months after the procedure. We have found that the electrical patterns of patients with a successful PVI are more stable in time than those of patients with an unsuccessful PVI. Temporal variability of ECGI

metrics during AF may allow for a better prediction of PVI outcome than the classification into paroxysmal or persistent AF.

### 4.1. Mechanism of AF and PVI outcome

Prior studies by Haissaguerre *et al.* [5], Narayan *et al.* [6], and others [4, 16] have demonstrated that ablation of rotors and focal sites does result in a better prognosis than PVI only. In this same direction, Gao *et al*. reported higher reentrant activity in ECGI maps for patients with acute termination of PVI [9]. These previous studies used a vest of 252 electrodes for ECGI calculation, and in the present study, 57 individual electrodes were used. Despite that a lower number of electrodes used, it was demonstrated in previous studies [17][18] that 32 electrodes are enough for a proper ECGI reconstruction. Furthermore, a good correlation of ECGI and intracardiac AF complexity evaluation with this electrode configuration has been previously shown [8]. Although we were anticipating that patients with successful PVI ablations would present differences in either the number of rotors or their duration as compared with patients with unsuccessful ablations we have not found significant differences in rotor metrics. Zaman *et al.* [19], found that patients with paroxysmal AF recurrence after PVI had extra-PV sources, matching with our observations with more unstable reentrant activity in arrhythmia recurrence patients independently of the diagnosis. Therefore, the presence of rotors outside the pulmonary vein area in some patients may be one of the reasons behind our unobserved differences in primary rotor metrics in our patients with successful versus unsuccessful ablations. However, we believe that this observation can also be attributed to the characteristics of our cohort of patients since most of them presented a very damaged atrial substrate as a consequence of an increased atrial pressure due to the valvular impairment that may result in a low incidence of driving rotors.

### 4.2. Temporal reproducibility of ECGI derived metrics

We have found that patients with a good prognosis after PVI showed a more stable electrical activity in terms of the variability in time of rotational quantification metrics. This is consistent

with many reports in the literature that have demonstrated a lower temporal recurrence on electrophysiological metrics in patients with persistent AF versus patients with paroxysmal AF [20]. Lim et al [21] and others [20, 21] found that the complexity of persistent AF drivers is higher when AF duration increases.

Our observation would also be consistent with other studies that have related an electrical temporal instability with lower rates of maintenance of sinus rhythm either after PVI [24] or electrical cardioversion [25].

### 4.3. Clinical implications

Catheter ablation is mainly recommended for paroxysmal AF patients based on overall lower AF recurrence after ablation in this group of patients [2]. However, there are both paroxysmal AF patients that do not benefit from PV ablation and persistent AF patients that do benefit from PVI. In our study, we have observed that temporal stability of ECGI derived rotor metrics may help to predict the success of PVI and, therefore, better select patients likely to benefit from PVI and discard the ones that will not, to tailor the treatment to AF in an individual basis with electrophysiological measurements from individual patients instead of the "one approach fits all" approach currently used today.

## 5. Limitations

The results of this study should be confirmed in larger datasets and compared to endocardial data. Our results may also be influenced by our study population, with a large proportion of patients with valvular disease. Although we did not find statistical differences in any of the variability of metrics when comparing valvular impaired patients with non-valvular impaired AF patients, we cannot rule out the possible effect of a substantially damaged atrial substrate that may not be representative of a more general AF population. Time separation between signals was established between 15s to 10 minutes due to the difficulties of some patients of maintaining AF during the

procedure and reproducibility in time was not considered during the PVI protocol. Furthermore, it should be noted that the outcome of the studied patients could be influenced by changes in the medication, the extent and durability of transmural ablation lesions and that this could influence the results. Follow up of the patients was done 6 months after PVI and could not determine if the recurrence of the arrhythmia would be caused by PVI reconnection and not because of the atrial substrate. The fact that durable PVI can occur although the substrate of the atria may remain abnormal should be considered together with the possibility of arrhythmia recurrence after the 6 months follow up.

## 6. Conclusions

This study shows that ECGI derived metrics of reentrant activity in atrial fibrillation patients are reproducible over time and the degree of this reproducibility may be indicative of their electrical substrate since patients with more reproducible metrics are associated with a more favorable outcome. Therefore, variability of rotor metrics derived from ECGI may be suggestive of the ability of PVI to terminate the arrhythmia and may serve for selecting the best treatment option in AF patients.

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## Disclosures

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