

# High-rate pacing-induced atrial fibrillation effectively reveals properties of spontaneously occurring paroxysmal atrial fibrillation in humans

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## Aims

Research on paroxysmal atrial fibrillation (AF) assumes that fibrillation induced by rapid pacing adequately reproduces spontaneously occurring paroxysmal AF in humans. We aimed to compare the spectral properties of spontaneous vs. induced AF episodes in paroxysmal AF patients.

## Methods and results

Eighty-five paroxysmal AF patients arriving in sinus rhythm to the electrophysiology laboratory were evaluated prior to ablation. Atrial fibrillation was induced by rapid pacing from the pulmonary vein-left atrial junctions (PV-LAJ), the coronary sinus (CS), or the high right atrium (HRA). Simultaneous recordings were obtained using multipolar catheters. Off-line power spectral analysis of 5 s bipolar electrograms was used to determine dominant frequency (DF) at recording sites with regularity index  $>0.2$ . Sixty-eight episodes were analysed for DF. Comparisons were made between spontaneous ( $n = 23$ ) and induced ( $n = 45$ ) AF episodes at each recording site. No significant differences were observed between spontaneous and induced AF episodes in HRA ( $5.18 \pm 0.69$  vs.  $5.06 \pm 0.91$  Hz;  $P = 0.64$ ), CS ( $5.27 \pm 0.69$  vs.  $5.36 \pm 0.76$  Hz;  $P = 0.69$ ), or LA ( $5.72 \pm 0.88$  vs.  $5.64 \pm 0.75$  Hz;  $P = 0.7$ ) regardless of pacing site. Consistent with these results, paired analysis in seven patients with both spontaneous and induced AF episodes, showed no regional DFs differences. Moreover, a left-to-right DF gradient was also present in both spontaneous (PV-LAJ  $5.71 \pm 0.81$  vs. HRA  $5.18 \pm 0.69$  Hz;  $P = 0.005$ ) and induced (PV-LAJ  $5.62 \pm 0.72$  vs. HRA  $5.07 \pm 0.91$  Hz;  $P = 0.002$ ) AF episodes, with no differences between them ( $P =$  not specific).

## Conclusion

In patients with paroxysmal AF, high-rate pacing-induced AF adequately mimics spontaneously initiated AF, regardless of induction site.

## Keywords

Atrial fibrillation • Pulmonary veins • Dominant frequency • Inducibility • Left atrial diameter

## Introduction

Paroxysmal atrial fibrillation (AF) is characterized by recurrent and self-terminating episodes.<sup>1</sup> Although research on paroxysmal AF assumes that induced AF by rapid pacing is an adequate experimental model,<sup>2,3</sup> concerns exist about how artificially induced AF adequately reflects the pathophysiology of spontaneous paroxysmal AF episodes in patients arriving at the electrophysiology

laboratory in sinus rhythm for pulmonary vein (PV) isolation. Since the vast majority of paroxysmal AF episodes are not only triggered but also maintained by high-frequency discharges originating in pulmonary vein-left atrial junctions (PV-LAJ),<sup>4,5</sup> the coronary sinus (CS), or the high right atrium (HRA), we hypothesized that AF induced by rapid pacing from those sites adequately mimics the electrophysiological characteristics of spontaneously initiated paroxysmal AF in humans. To test this hypothesis, we

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compared the spatial distribution of atrial activation frequencies during spontaneous vs. pacing-induced AF in paroxysmal AF patients.

## Methods

Patients admitted for ablation treatment of drug-refractory paroxysmal AF were included in this protocol, as approved by the research and ethics committee of the Gregorio Marañón Hospital, Madrid, Spain. Self-terminating AF lasting <48 h was defined as paroxysmal. All patients gave informed consent. Patients arriving in AF to the electrophysiology laboratory were excluded. All antiarrhythmic and  $\beta$ -blocking agents were withheld at least 'five-half-lives' before the study. Amiodarone treatment was terminated at least 2 weeks in advance.

### Electrophysiological study and recording protocol

The electrophysiological study was performed under general anesthesia. Immediately after transeptal puncture, a bolus of intravenous heparin (100 U/kg) was administered and additional periodic heparin boluses were administered to maintain activated clotting time between 300 and 350 s. Four recording catheters were positioned as follows: a tetrapolar catheter at the HRA, a tetrapolar catheter in the distal CS, an ablation catheter (Therapy Cool Path irrigated ablation catheter, St Jude Medical, St Paul, MN, or irrigated tip Navistar catheter, Biosense Webster, Inc., Diamond Bar, CA) positioned at a randomly selected PV-LAJ and a duodecapolar circular mapping catheter (St Jude Inquiry AFocus II or St Jude Inquiry Optima) at the contralateral PV-LAJ. The three-dimensional geometry of the left atrial (LA) chamber was reconstructed using either the EnSite NavX system version 8.0 (St Jude Medical) or the CARTO navigation system (Biosense Webster, Inc.).

### Atrial fibrillation initiation

After anatomic reconstruction of the LA and stabilization of the multipolar catheters, stimulation was applied from a randomly selected PV-LAJ. In a subset of patients, AF induction was attempted pacing from the distal CS or the HRA. The stimulation protocol consisted of 15–30 s atrial burst pacing attempts (strength, 10 mA; duration, 2 ms) at progressively shorter cycle lengths, starting at 600 ms, with a 10–15 s pause prior to each decrement, until 1:1 atrial capture was lost or AF was induced.<sup>6</sup> Once sustained AF was induced, no further induction attempts were made following cardioversion. Spontaneous AF episodes occurring during the recording time prior to ablation were also analysed. The origin of the ectopic discharges initiating spontaneous AF episodes was defined as the earliest atrial activity relative to the different intracardiac electrograms and the onset of the ectopic P wave, guided by the activation sequence on the intracardiac catheters.<sup>4</sup> The origin was confined to the LA when the left and right PVs activity was simultaneous with the onset of the P wave and earlier than the right atrial (RA) activity. Mechanically induced AF episodes due to catheter motion were excluded from analysis. Regardless of the AF initiation mode, only episodes lasting >5 min after initiation were included in the analysis if all catheters remained at fixed positions during the recording time.

### Spectral analysis

All signals were recorded using the Prucka system at a sample rate of 1 KHz and exported for off-line analysis. Pre-processing of all recording catheters was performed on 5 s segments, by a Hanning window,

rectification and with a non-biased 1–20 Hz band-pass filter to minimize baseline wander and high-frequency harmonics.<sup>6–8</sup> A 4096-point fast Fourier transformation (spectral resolution 0.24 Hz) was obtained for dominant frequency (DF) determination. The regularity index (RI), defined as the ratio of the power at the DF and adjacent frequencies ( $\approx 0.75$  Hz band) to the sum of the power in the 1–20 Hz band was also simultaneously obtained. To control for ambiguity in DF detection points with  $RI < 0.2$  were excluded.<sup>6–8</sup> All signals were visually inspected and spurious DFs were excluded or corrected. Dominant frequencies from the bipoles of the circular duodecapolar catheter were averaged during each 5 s segment, whereas distal bipoles were used to obtain DF in the remaining catheters or, alternatively, the proximal bipoles in case of poor distal bipolar signal. To allow AF stabilization and avoid non-sustained AF episodes, DF measurements were performed on 5 s segments obtained during the third minute following sustained AF initiation. To assess DF spatial distribution, we compared DFs for each recording site (HRA, CS, and LA), and condition (spontaneous vs. induced AF episodes). For the purpose of LA-to-RA gradient calculations, the RA DF was calculated from the HRA signal while LA DF was calculated from the PV-LAJ signal. In patients presenting both spontaneous and induced AF episodes, paired analysis was performed from segments with identical time following onset. Off-line analyses for all exported signals were performed in the Matlab environment (The MathWorks, Inc., Natick, MA).

### Real-time frequency mapping

In a subset of patients ( $n = 18$ ), three-dimensional reconstruction and real-time DF determination of the LA was created using either CARTO or EnSite NavX with embedded spectral analysis capabilities. High-density mapping of the LA was performed by sequentially acquiring bipolar electrograms. Real-time determination of DF for each point acquired was performed and colour-coded DF maps were superimposed on the atrial shell geometry, displaying low frequencies in red and high frequencies in purple.<sup>6,8,9</sup> Sites with the highest DF throughout the atria, showing DFs that were at least 20% higher than their surrounding points, were identified as primary and secondary maximal DF sites (i.e. the primary maximal DF site was that with the highest DF throughout the atria).<sup>8,9</sup>

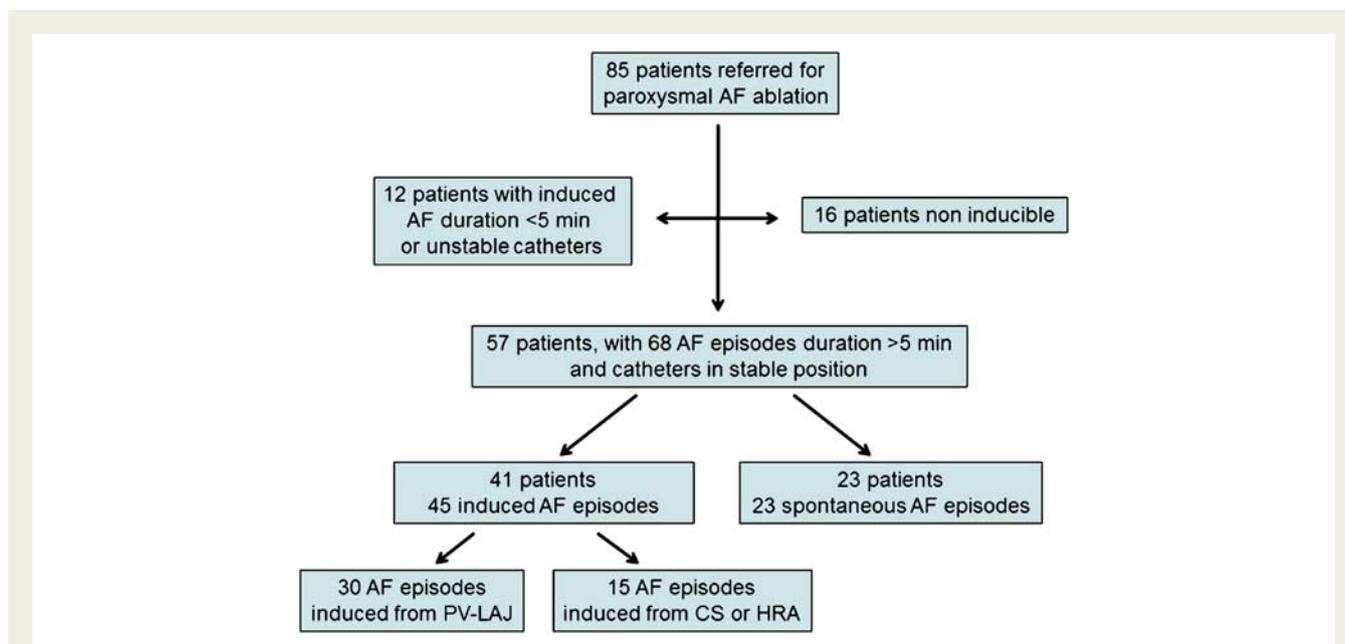
### Statistical analyses

Continuous variables are reported as mean  $\pm$  standard deviation (SD) and assessed for normality using the Kolmogorov–Smirnov test. Statistical significance was assessed using the paired or unpaired Student's *t*-test, as appropriate. Non-parametric tests were used in cases of non-normally distributed continuous variables; median and interquartile ranges are reported for such cases. Bonferroni correction was used for multiple comparisons. Categorical variables are reported as number and percentage, and were analysed using the  $\chi^2$  test or Fisher exact test. To analyse independent predictive factors of AF inducibility, all univariate factors presenting  $P < 0.1$  together with other relevant variables were introduced into a stepwise logistic regression model. Analyses were performed with SPSS version 17.0 and statistical significance was established at  $P < 0.05$ .

## Results

### Population

Eighty-five consecutive patients (age  $53 \pm 10$ ; 76% male) with paroxysmal AF arriving to the electrophysiology laboratory in sinus rhythm were included in the study. In 69 patients, AF either



**Figure 1** Patient inclusion flowchart. AF, atrial fibrillation; PV-LAJ, the pulmonary vein to left atrial junctions; CS, coronary sinus; HRA, high right atrium.

**Table 1** Clinical characteristics

	Inducible (n = 69)	Non-inducible (n = 16)	Univariate P-value	Multivariate P-value
Age (years)	51.6 ± 9	50.7 ± 9	0.75	
Gender (male)	51 (74)	13 (81)	0.75	
AF duration (years)	6.6 ± 4.9	4 ± 2.6	0.04	0.03
Hypertension	23 (33)	6 (38)	0.77	
Structural heart disease	18 (26)	3 (19)	0.75	
Prior ablation	24 (35)	5 (31)	1.00	
LVEF (%)	59.4 ± 6.1	57.2 ± 13	0.32	
Telediastolic LV diameter (mm)	47.7 ± 5.2	49.7 ± 8.1	0.24	
Left atrial diameter (mm)	42.6 ± 6.4	38.9 ± 5.3	0.03	0.02

LVEF, left ventricular ejection fraction.

occurred spontaneously or was induced, whereas in 16 patients AF was not inducible according to the required criteria (Figure 1). As shown in Table 1, the only independent predictors of AF inducibility were longer history of AF [odds ratio (OR): 1.25, 95% confidence interval (CI): 1.02–1.54;  $P = 0.03$ ] and larger LA diameter (OR: 1.12, 95% CI: 1.02–1.23;  $P = 0.02$ ).

In 12 patients, AF episodes lasted for <5 min and/or the catheters moved during the recording time, and these patients were not considered for spectral analysis. Overall, we analysed 68 AF episodes in 57 patients. In 41 patients, 45 (66%) AF episodes were induced by high-rate stimulation, 30 of them pacing from the PVs, 11 from the CS and 4 from the HRA. Twenty-three patients presented 23 (34%) spontaneous AF episodes while the catheters were in stable position. The origin of the spontaneous ectopic

discharges initiating AF were the PVs in 9 cases (39%), the LA in 11 (48%), and the RA in 1 patient (4%); it could not be documented in 2 patients (8%). In seven patients, both spontaneous and induced episodes were recorded. Table 2 shows the clinical characteristics of patients in whom spectral analyses were performed. Eight patients received isoproterenol during the procedure, but no differences were observed according to inducibility or AF spectral characteristics (data not shown).

### Atrial activation frequency in induced vs. spontaneous atrial fibrillation

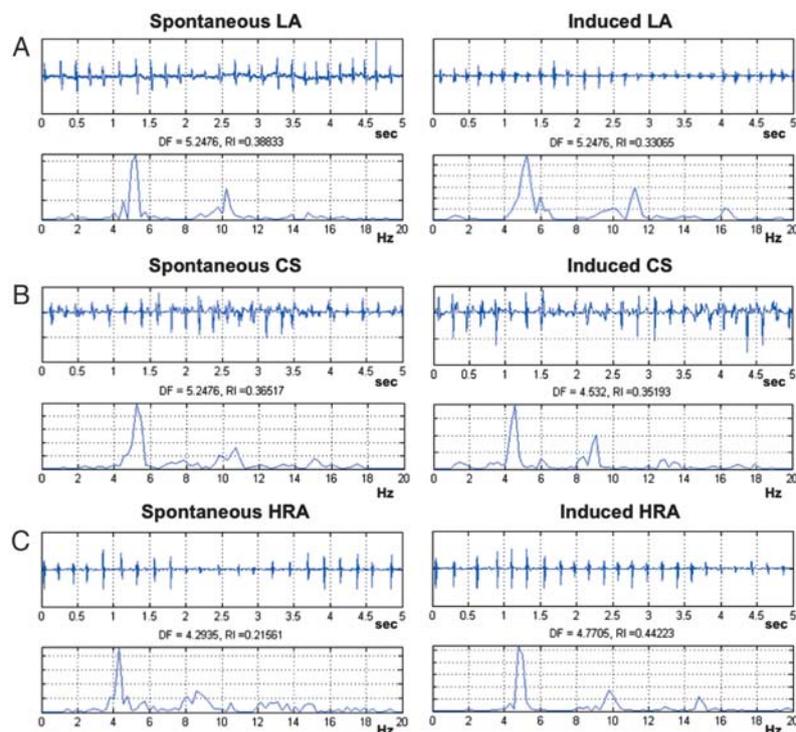
The proportions of the total number of recordings excluded due to  $RI < 0.2$  (low regularity of activity) were similar in patients

with spontaneous (LA 34%, CS 45%, and HRA 25%) and induced (LA 30%, CS 33%, and HRA 30%) AF episodes for all locations ( $P = ns$ ). Dominant frequencies were determined for the AF episodes with  $RI \geq 0.2$ . Figure 2 shows representative examples of 5 s recordings from the LA, CS, and HRA and corresponding

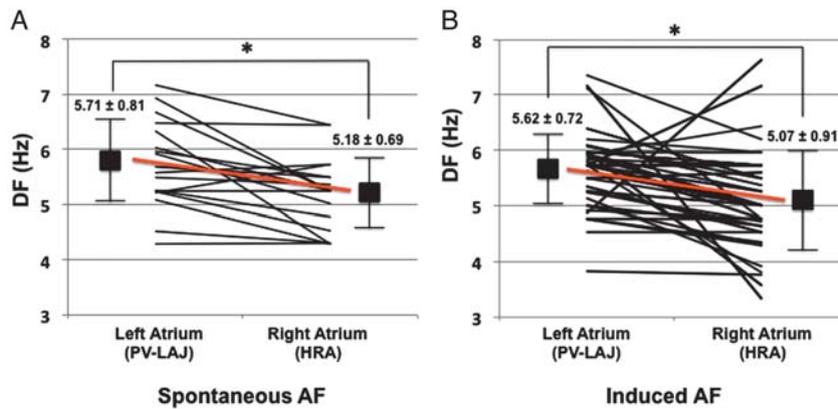
power spectra from one spontaneous and one induced AF episode. On comparison, DF values in the three locations differ by  $<0.5$  Hz. On average, our analysis demonstrates no significant differences in regional atrial activation frequencies between spontaneous and induced AF episodes at the HRA ( $5.18 \pm 0.69$  vs.  $5.06 \pm 0.91$  Hz;  $P = 0.64$ ), the CS ( $5.27 \pm 0.69$  vs.  $5.36 \pm 0.76$  Hz;  $P = 0.69$ ), and the LA ( $5.72 \pm 0.88$  vs.  $5.64 \pm 0.75$  Hz;  $P = 0.7$ ). Similarly, a separate analysis of AF induced by pacing at different sites showed also consistent regional activation frequencies: Compared with spontaneous AF episodes, regional DFs during AF induced from the PV (HRA,  $5.11 \pm 1$  Hz;  $P = 0.8$ ; CS,  $5.48 \pm 0.73$  Hz;  $P = 0.37$ ; and LA,  $5.71 \pm 0.71$  Hz;  $P = 0.76$ ) or AF induced from the CS/HRA (HRA,  $4.99 \pm 0.74$  Hz;  $P = 0.46$ ; CS,  $5.16 \pm 0.81$  Hz;  $P = 0.69$ ; and LA,  $5.51 \pm 0.84$  Hz;  $P = 0.47$ ) showed no differences. These results were not influenced by prior AF ablations (data not shown). As shown in Figure 3, a left-to-right DF gradient was observed in both spontaneous (PV-LA)  $5.71 \pm 0.81$  vs. HRA  $5.18 \pm 0.69$  Hz;  $P = 0.005$ ) and induced AF episodes (PV-LA)  $5.62 \pm 0.72$  vs. HRA  $5.07 \pm 0.91$  Hz;  $P = 0.002$ ), with no differences between them ( $P =$  not specific). Consistent with these results, paired analysis in a subset of seven patients presenting with both spontaneous and induced AF sustained episodes, showed no regional DFs differences, respectively, at the HRA ( $4.88 \pm 0.75$  vs.  $4.9 \pm 1.32$  Hz;  $P = 0.92$ ), the CS ( $4.95 \pm 0.83$  vs.  $5.4 \pm 0.99$  Hz;  $P = 0.16$ ), and the LA ( $5.49 \pm 0.78$  vs.  $5.23 \pm 0.79$  Hz;  $P = 0.35$ ).

**Table 2** Clinical characteristics of patients with spectral analysis ( $n = 57$ )

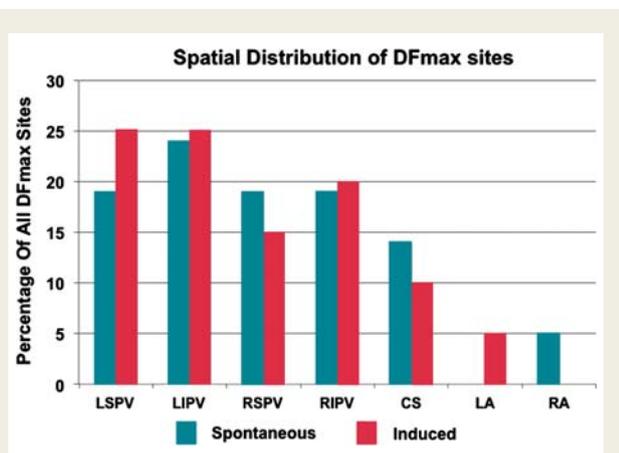
Age (years)	$51.75 \pm 9.9$
Gender (male)	43 (75)
AF duration (years)	$6.7 \pm 4.9$
Hypertension	18 (32)
Coronary artery disease	2 (5)
Prior antiarrhythmic treatment	
Amiodarone	13 (23)
Class I	32 (56)
Betablockers	17 (30)
Prior AF ablation	18 (31)
LVEF (%)	$59.1 \pm 6.5$
Telediastolic LV diameter (mm)	$47.7 \pm 5.6$
Left atrial diameter (mm)	$41.9 \pm 6.4$



**Figure 2** Spectral analyses of 5 s recordings obtained from spontaneous (left panel) and induced (right panel) atrial fibrillation episodes in the same patient. Each panel shows a 5 s electrogram with its corresponding power spectrum. DF, dominant frequency; RI, regularity index; HRA, high right atrium; CS, coronary sinus; LA, left atrium.



**Figure 3** Paired comparisons between the pulmonary vein-left atrial junctions and high right atrium dominant frequencies in spontaneous (A) vs. induced (B) atrial fibrillation episodes, demonstrating the presence of a left to right frequency gradients. DF, dominant frequency; HRA, high right atrium; PV-LAJ, pulmonary vein-left atrial junction.



**Figure 4** Spatial distribution of maximal dominant frequency sites in spontaneous vs. induced atrial fibrillation. LSPV: left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; CS, coronary sinus; LA, left atrium; RA, right atrium.

### Spatial distribution of activation frequencies

In a subset of 18 patients (8 spontaneous and 10 induced), real-time DF maps of the LA were obtained by acquiring a mean of  $81 \pm 25$  points. There was no difference in the number of maximal DF (DFmax) sites ( $2.1 \pm 0.84$  vs.  $1.8 \pm 0.92$ ;  $P = 0.45$ ) or the DFmax values ( $7.46 \pm 1.37$  vs.  $7.93 \pm 1.42$  Hz;  $P = 0.5$ ) between spontaneous and induced AF maps, respectively. Maximal DF sites, up to three in both circumstances, were preferentially located either at the PV antrum or a specific PV ostium, without significant differences ( $P = 0.88$ ) in the percentage of DFmax sites according to atrial chamber location (Figure 4). As shown in Figure 5, there were no significant differences in DFmax sites distribution at the LA in spontaneous vs. induced AF episodes.

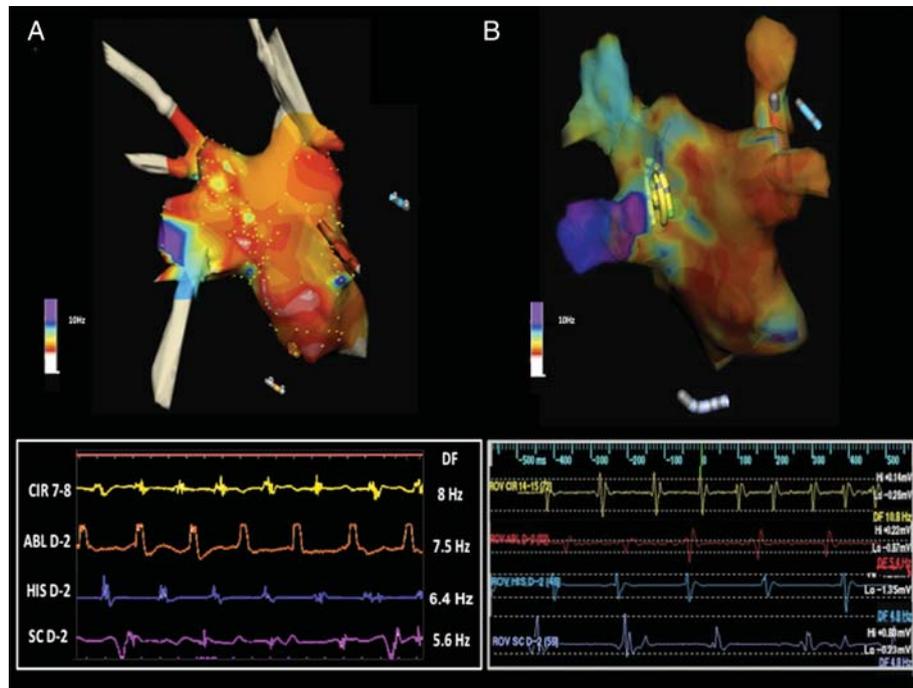
## Discussion

The present study demonstrates that, in patients with paroxysmal AF undergoing an ablation procedure, both the local DF and its spatial distribution during pacing-induced AF are not significantly different from spontaneously occurring AF, regardless of the atrial induction site. Moreover, the degree of irregularity in the intracardiac activation was similar in induced vs. spontaneous AF, as indicated by the similar proportion of recordings with  $RI < 0.2$ . An additional finding of the study is that AF inducibility is influenced by the duration of AF and the diameter of the LA.

Prior investigators have demonstrated that intermittent bursts of PV tachycardia not only trigger but also can maintain AF in some cases.<sup>4,5</sup> Oral et al.<sup>5</sup> showed that the intermittent bursts of PV tachycardia that occur during AF play the same role in sustaining AF as do intermittent bursts of rapid atrial pacing. Other extrapulmonary atrial sources may also trigger and sustain AF, although with much lower prevalence.<sup>4,8,10</sup> However, a significant proportion of paroxysmal AF patients (45–96%) are in sinus rhythm upon arrival to the electrophysiology laboratory.<sup>6–11</sup> For these reasons, it is generally assumed that induced AF by rapid pacing adequately reproduces spontaneous paroxysmal AF in humans.<sup>2,3,6–9,11</sup> However, to our knowledge, the validity of such an assumption had not been tested previously.

### Complexity of atrial fibrillation recordings and spectral analysis

The extremely complex patterns of spatio-temporal activation recorded during AF preclude straightforward analysis and interpretation in the time domain alone, while analyses in the frequency domain enable reliable measurement and quantitative analysis of the local frequency of activation. In most cases spectral analysis of AF demonstrates spatially distributed frequency domains with narrow-band peaks, suggesting that AF is spatiotemporally organized.<sup>2,3,6–11</sup> Using similar signal processing methods, experimental studies have demonstrated that acute cholinergic AF is maintained



**Figure 5** Representative examples of left atrium high-density dominant frequency maps (upper panels) together with the corresponding 1 s intracardiac electrograms time-series (lower panels) from paroxysmal atrial fibrillation patients with spontaneous (A) and pacing-induced (B) atrial fibrillation. Both maximal dominant frequency sites in purple are preferentially located to one pulmonary vein antra (left inferior pulmonary vein). OPT, circular catheter at the left inferior pulmonary vein antrum; ABL, ablation catheter at the right superior pulmonary vein; HIS, high right atrium; CIR, circular catheter; SC, coronary sinus.

by LA high-frequency reentrant sources (drivers), which results in a left-to-right gradient of atrial frequencies.<sup>2</sup> Recently, several studies have shown the existence of a hierarchical organization in the rate of activation of different regions in the atria of patients with paroxysmal and chronic AF.<sup>7–11</sup> Simultaneous time and frequency domain analyses have demonstrated a high correlation between the location of DFmax areas and the origin of incoming waves, strongly suggesting that during episodes of organized AF the posterior LA wall is passively activated from high-frequency sources located at one of the PV-LAJs.<sup>6</sup> As a natural consequence of those results, real-time spectral mapping techniques have been used to identify and ablate high-frequency sites in patients with AF. Using such an ablation strategy terminated AF in two-thirds of the patients and was associated with an excellent rate of long-term freedom from AF.<sup>10</sup>

Previous studies provided results pointing in the same direction. In an elegant study, Lazar *et al.*<sup>7</sup> analysed the activation frequency distribution in 18 patients with paroxysmal AF: 3 patients presented to the electrophysiology laboratory in AF, while AF induction by isoproterenol-provoked atrial ectopies was required in the rest (84%). They found no significant differences in atrial activation frequencies between patients who developed spontaneous AF before the procedure and the paroxysmal group with 'provoked' AF. Recently, we performed high-density mapping in 30 paroxysmal AF patients, using the CARTO electroanatomic mapping

system, by sequentially acquiring 5 s long bipolar recordings from ~117 points during either spontaneous or induced AF.<sup>10</sup> Maximal chamber DF values were similar between paroxysmal patients with spontaneous AF vs. those in whom AF was induced, demonstrating a consistent left-to-right gradient of atrial activation in both groups. However, these studies analysed a limited number of patients/episodes, used heterogeneous induction methods (isoproterenol together with occasional pacing from the CS) and recorded AF at different times following initiation. In contrast, the induction protocol used in the present study was directly relevant to the manner in which spontaneous triggers initiate AF,<sup>4,5</sup> analysis of dominant frequencies and their spatial distribution was conducted at precisely the same time following initiation, and patients with self-terminating AF (<5 min) were excluded. On the basis of such a rigorous methodology, our results demonstrate that the degree of fractionation, the hierarchical distribution of frequencies, and the left-to-right gradients are similar regardless of whether AF was spontaneously generated or pacing induced. Despite their functional nature, the similar proportion of fractionated electrograms also suggests a similar electrophysiological behaviour in both AF types.<sup>6,12</sup> Analysis of high-density DF maps in a subset of patients with either spontaneous or induced AF further confirmed these results. Thus, induced AF by rapid pacing adequately reveals conditions for spontaneously initiated paroxysmal AF in humans, regardless of induction site.

## Implication of atrial fibrillation inducibility

By definition, individual paroxysmal AF episodes self-terminate within 48 h following their onset.<sup>1</sup> As such, patients undergoing AF ablation procedures frequently arrive at the electrophysiology laboratory in sinus rhythm.<sup>7–11</sup> In those cases, AF induction is required to study the mechanisms responsible for AF maintenance. Moreover, AF inducibility is often used as an endpoint after radiofrequency ablation due to its predictive value of long-term freedom from AF.<sup>13</sup> Here, 31% of patients with documented AF were unable to sustain AF lasting longer than 5 min prior to AF ablation. In agreement with our results, Haïssaguerre *et al.*<sup>13</sup> found that AF was inducible in ~65% of patients prior to ablation, using various pacing sites. Larger LA diameters and longer history of AF were predictors of inducibility in our study. Repetitive AF episodes cause electrical remodelling due to alterations in both normal ion channel density and function. In addition, structural changes leading to fibrosis and chamber dilatation can also occur.<sup>14</sup> These alterations depend on the duration of the AF itself, and in turn, promote AF initiation, maintenance and perpetuation. Recent clinical observations showing that larger LA diameters are associated with increased AF burden and progression from paroxysmal to persistent AF provide further support to this contention.<sup>15</sup> Several other factors may influence AF inducibility, such as the use of a specific decremental pacing protocol,<sup>16</sup> isoproterenol infusion at incremental doses<sup>17</sup> or sympato–vagal interactions causing focal triggers/drivers in the presence of an increased vagal tone.<sup>18</sup>

## Limitations

Our study has several potential limitations. The study was performed in patients under general anesthesia and a possible effect of anesthetic drugs cannot be ruled out. However, propofol alone or in combination with remifentanyl, the most commonly used drugs in our patients, has a negligible impact on the atrial electrophysiological parameters.<sup>19</sup> A higher inducibility rate could have been obtained using a decremental pacing protocol.<sup>16</sup> Knowledge of high density spatial distribution of frequencies is limited to the LA. However, extrapulmonary sources could be reasonably excluded by catheters positioned at the most likely areas (i.e. CS and HRA). Moreover, the results are consistent with prior studies that showed that the vast majority of DFmax sites in paroxysmal AF patients are located at the LA and PV-LA).<sup>8,9</sup> Finally, a larger sample of patients presenting with both spontaneous and induced AF episodes would be desirable, but paired analyses showed a similar trend than non-paired overall analyses.

## Conclusions

Our results support the use of pacing-induced AF as an appropriate experimental approach to study the mechanisms of paroxysmal AF maintenance.

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