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Predicting Catheter Ablation Outcome in Persistent Atrial Fibrillation Using Atrial Dominant Frequency and Related Spectral Features

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***Abstract*— Pre-procedural atrial fibrillation dominant frequency (AFDF) has been reported to play a role as a predictor of catheter ablation (CA) outcome for the treatment of persistent atrial fibrillation (AF). The present study analyzes some spectral features of the atrial signal aimed at evaluating the quality of surface AFDF estimation and discusses their predictive power. First, automated extraction of surface atrial activity (AA) on pre-procedural 12-lead ECG recordings is performed by means of an independent component analysis (ICA) method. AFDF is then estimated by means of short-time Fourier analysis of the extracted atrial sources and simultaneous endocardial electrograms (EGM) used as reference. On a database of 20 patients in persistent AF undergoing CA, AFDF does not appear to play a role as a predictor of CA outcome at follow-up, neither on ECG nor on EGM recordings. The quality of surface AFDF estimation is assessed by means of the correlation coefficient r between surface and EGM AFDF, as well as the spectral concentration (SC) of the estimated atrial signal. It is shown that the quality of surface AFDF estimation is significantly lower for non-terminating CA procedures, both in terms of r and SC. The latter, in particular, seems to play a significant role in distinguishing terminating from non-terminating CA procedures and therefore in the non-invasive prediction of CA outcome.**

I. INTRODUCTION

Atrial fibrillation (AF) is a supraventricular arrhythmia in which the electrical activation in the atria shows an uncoordinated pattern. AF is the most common arrhythmia in elderly people and a potential risk factor for stroke. Hemodynamic impairment and thromboembolic events result in significant morbidity, mortality, and cost [1]. In its persistent form, AF continues until some measure is taken to terminate it. Radiofrequency catheter ablation (CA) has been proven to terminate persistent AF and maintain sinus rhythm, typically in association with temporary antiarrhythmic-drug therapy after ablation and one or more cardioversions [2]. Nevertheless, CA is a difficult and time-consuming procedure, as it requires to scar several targeted regions within the atria in order to disrupt the sources of abnormal electrical activity. Furthermore, the success rate in case of persistent and long-lasting AF is lower compared to other supraventricular arrhythmias [3]. The introduction of new technologies able to map the ablation regions allows doctors to create ablation scars with a high level of precision and to decrease the risks for the patient, but it also makes the procedure very expensive. For these reasons, it is desired to predict ablation outcome, so that this time-consuming procedure can be spared in patients that are unlikely to result in sinus rhythm restoration.

Several works have focused on the determination of clinical parameters able to predict the termination of paroxysmal and persistent AF by CA [4], [5], [6], [7]. All the cited works present several limitations: either the proposed approaches for parameter computation are manual [4], [6], [7], either the investigations are limited to invasive measures [5], [4], or paroxysmal AF is the only form taken into account [4]. Atrial fibrillation dominant frequency (AFDF) is the frequency at which the peak of the power spectrum of the atrial activity (AA) is found and represents the rate of depolarization of the atrial substrate. In [6] AF cycle length, i.e., the reciprocal of AFDF, was manually estimated from single-lead ECG recordings and was found to serve as a predictor of AF termination by CA ablation.

In the present work, the role of pre-procedural AFDF and related spectral features as predictors of CA outcome is investigated on both surface 12-lead ECG and endocardial electrograms (EGM) from the left atrial appendage (LAA) by means of a fully automated approach. On a database of 20 patients undergoing CA for the treatment of long-lasting persistent AF, an independent component analysis (ICA) algorithm, the RobustICA-f method of [8], is performed on the multi-lead surface ECG recording to suppress ventricular activity and noise, and concentrate the AA into one atrial source. Time-frequency analysis is then performed on the extracted atrial signal in order to obtain an estimation of AFDF. The correlation r between EGM- and surface-estimated AFDF is then used as a parameter to assess the quality of surface AFDF estimation, as recently proposed in [9]. The SC of the extracted atrial source is also employed for evaluating surface AFDF estimation performance, as this parameter was shown to correlate with atrial extraction quality in [10]. The role of these spectral measures as predictors of AF termination by CA is finally investigated. As opposed to [6], AFDF does not predict CA success. By

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contrast, the SC is able to predict the termination of persistent AF by CA.

II. METHODS

A. Database and Signal Processing

Standard 12-lead ECG as well as EGM LAA recordings were performed on 20 patients affected by long-lasting persistent AF and undergoing stepwise catheter ablation at the Cardiology Department of Princess Grace Hospital, Monaco. The typical procedural steps were pulmonary veins isolation, followed by roof lines ablation and complex fractionated atrial electrograms (CFAE) ablation. Procedural end-point was the ablation of CFAE, independently of AF termination. In the event that AF was not terminated during the ablation procedure, electrical cardioversion was performed. A medium-long term follow-up of CA outcome is available (4 to 19 months) with a success/failure ratio of 13/7. Medium-long term success was defined as maintenance of sinus rhythm at follow-up. Recordings were acquired before the beginning of ablation procedure at a sample rate of 977 Hz and lasted about 60 s each. They were filtered by a third-order zero-phase band-pass Chebyshev filter with a lower cutoff frequency of 0.5 Hz and an upper cutoff frequency of 30 Hz, in order to remove low-frequency baseline wandering due to physiological interference (e.g., breathing) and high frequency artifacts, such as power-line and myoelectric interference.

B. AA extraction in ECG recordings

ICA is a statistical tool belonging to the family of blind source separation techniques that aims to separate the statistically independent sources contributing to an observed linear mixture. ICA does not require sources to be spatially orthogonal nor Gaussian, thus resulting more suitable for atrial source extraction compared to other BSS techniques such as principal component analysis (PCA) [11]. We employed the RobustICA-f algorithm proposed in [8], since it has been shown to compare favorably to other non-invasive atrial signal extraction techniques in multi-lead recordings [8], [9]. RobustICA-f's search for directions of maximum independence within the space of data relies on higher order statistics (kurtosis contrast). Therefore, the time-series to be analyzed should contain an amount of samples sufficiently large. On the other hand, the analysis should be performed on segments sufficiently short so as to guarantee the adaptability to possible non-stationarities within the ECG during AF. A suitable trade-off was found dividing the ECG signals into 8 s long segments and performing source separation on each segment. Overlap between segments was set to 6 s. Data were spatially prewhitened in the time domain using PCA and then transformed into the frequency domain using a T_f-point FFT, with T_f chosen as:

$$T_f = 2^{\lceil log_2 T \rceil} \tag{1}$$

where T is the length of the recording in the time domain, expressed in number of samples, and function $\lceil \cdot \rceil$ denotes the closest integer equal or larger than its argument. The search for directions of maximum independence was performed in the frequency domain and the extracted sources were then transformed back to the time domain. To identify the AA among the 12 independent sources, RobustICA-f exploits the fact that the AA typically shows a narrowband frequency spectrum, whereas ventricular activity is a wideband signal. Hence, SC was employed as an indicator of AA quality [10]. To account for the quasi-periodic character of AA in AF, the fundamental frequency f_p and the second harmonic $2f_p$ were considered for the computation of SC in the present study:

$$\text{SC} = \sum_{k=1}^{2} \frac{\sum_{0.82kf_p}^{1.17kf_p} P_{AA}(f)}{\sum_{0}^{f_s/2} P_{AA}(f)} \tag{2}$$

where P_{AA} is the Power spectrum of the estimated AA and f_s is the sampling frequency. The atrial source was detected among the 12 independent components by selecting the one with highest SC and dominant peak in the 3-9 Hz range, which is considered the typical AF frequency band. Segments whose atrial source presents a SC below a threshold of 50% were considered of unacceptable quality and excluded from further analysis.

C. AFDF Measurement

From the atrial signal provided by RobustICA-f, the AFDF was computed as follows. In order to make AFDF estimation more robust to the presence of potential non-stationarities, the obtained atrial signal was windowed as for the RobustICA-f described above (8 s segments, 6 s overlap). The power spectrum density (PSD) of each segment was computed using Welch's averaged modified periodogram as in [10], [11] (4096-point Hamming window, 2048-point overlap and 8192-point FFT). AFDF was then calculated as the peak frequency of the PSD in the 3-9 Hz range. The median of the AFDF among the different segments was finally taken as the AFDF estimate for a given patient, because of the robustness of this measure to outliers compared to the sample mean. The choice of reducing the time-frequency distribution obtained to a single AFDF value (median value) relies on the assumption that AF can be considered quasi-stationary on a short-term basis. EGM recordings were analyzed as for ECG recordings, but were first preprocessed using the method proposed in [12] to overcome the difficulties brought about by the sharp biphasic morphology of the atrial depolarization waves in bipolar EGMs. In order to validate the automatic approach described above, AFDF was also manually measured from 10 s-long segments on the EGM recordings.

D. Surface AFDF Estimation Quality and Statistical Analysis

Linear regression analysis and Pearson's correlation coefficient r were used to study the correlation between the manually measured and the automatically estimated EGM AFDF. As for the AFDF estimation described above, the median of the SC among the different segments was taken as the SC estimate for a given patient. SC and r were estimated on the two groups of patients (terminating and non-terminating), in order to investigate significant differences

TABLE I

CORRELATION BETWEEN MANUALLY AND AUTOMATICALLY MEASURED EGM AFDF FOR THE TERMINATING (T) AND NON-TERMINATING (NT) PATIENTS IN THE DATABASE UNDER STUDY.

	T Group	NT Group	All (T+NT)
ρ	0.96	0.97	0.96
(p-value)	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$

TABLE II

SUMMARY OF RESULTS OBTAINED FOR THE TWO CATEGORIES OF PATIENTS. SC IS EXPRESSED IN %, AFDF IS EXPRESSED IN HZ AS MEAN$\pm$STANDARD DEVIATION.

	T Group	NT Group	p-value
r	0.77	0.69	-
(p-value)	< 0.01	0.09	
SC	75.9 ± 6.61	65.6 ± 6.34	$4 \cdot 10^{-3}$
ICA AFDF	5.83 ± 0.44	5.57 ± 0.99	0.41
EGM AFDF	5.97 ± 0.64	6.44 ± 0.80	0.16

among them in terms of surface AFDF estimation quality. Statistical significance was tested using Student's t-test for parametric data and the Wilcoxon rank-sum test for non-parametric data. Gaussianity of the distributions was verified using Lilliefors test. Null hypothesis was rejected for p-values below 0.05. Receiver operating characteristic (ROC) curve was analyzed and its area under curve (AUC) was determined to evaluate the performance of SC in distinguishing the two groups of patients.

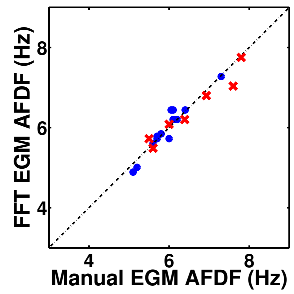

Fig. 1. Scatter plot showing the correlation between manually-estimated and Fourier analysis-estimated EGM AFDF. Circle markers represent the terminating patients; cross markers represent the non-terminating patients. The dash-dotted line represents $x = y$.

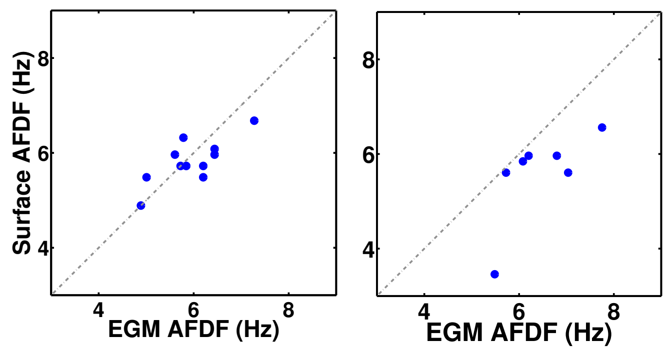

Fig. 2. EGM/surface AFDF correlation for terminating patients (left) and non-terminating patients (right). The dash-dotted line represents $x = y$.

III. RESULTS

The values of correlation ρ between manually- and automatically-estimated EGM AFDF are reported in Table I for the two groups of patients, together with the associated p-values. The analysis of correlation shows that the results provided by the automated approach for EGM AFDF estimation are highly correlated to those provided by manual measurements. The scatter plot in Fig. 1 confirms these results.

Non-significant differences in AFDF were found between the terminating and non-terminating groups. The mean value of AFDF measured on the body surface was 5.83 ± 0.44 Hz for the terminating patients and 5.57 ± 0.99 Hz for the non-terminating ones, yielding $p = 0.41$. For the LAA EGM recordings the difference was also non-significant, as the mean value of AFDF was 5.97 ± 0.64 Hz and 6.44 ± 0.80 Hz for the terminating and non-terminating group, respectively ($p = 0.16$).

By contrast, the correlation r between automatically computed EGM and surface AFDF resulted significant only for the patients belonging to the terminating group (0.77, $p < 0.01$ versus 0.69, $p = 0.09$ for terminating and non-terminating patients, respectively), as visually illustrated by the scatter plots in Fig. 2. Index SC also resulted significantly higher for the terminating patients (75.9 ± 6.61 versus 65.6 ± 6.34, $p < 0.01$). The ROC analysis provided an AUC of 89.3%. Tab. II summarizes the values of the parameters obtained for the two categories of patients.

IV. DISCUSSION

In the present study surface and endocardial AFDF were automatically estimated for 20 patients undergoing CA for the treatment of AF. The patients were separated in two groups, depending whether the medium-long term outcome of CA was positive (terminating group) or negative (non-terminating group). The quality of AFDF estimation was then assessed for these two groups. Results showed that the EGM AFDF estimated by means of the method proposed in [12] and Fourier transform is highly correlated to the manually measured EGM AFDF. This holds both for the patients in the terminating as well as in the non-terminating group, thus supporting the reliability of the automatic approach based on the Fourier transform for EGM AFDF estimation. On the other hand, the surface AFDF appeared to be better correlated to the endocardial reference when the patients in the terminating group were considered.

As opposed to the findings presented in [6], pre-procedural surface AFDF was not found to distinguish successful from unsuccessful procedures in the present work. This result was found for ECG AFDF and confirmed for the endocardial reference. The reason of the discrepancy with [6] may be primarily attributed to the different database size. In [6], 90 patients were included in the study, whereas in the present contribution only 20 were available. Among these, only 7 belonged to the non-terminating group, against the 14 of [6]. The definition of procedural end-point of CA was also different between the two studies. In [6] a procedure was not interrupted until sinus rhythm restoration. Herein, the procedural end-point was the ablation of CFAE and, if sinus rhythm was not restored, electrical cardioversion was performed after CA. Therefore, patient labeling in the two works may not be comparable. Nonetheless, this procedural difference seems less likely to have an impact on the long-term outcome of CA, since AF termination during CA is not predictive of long-term AF recurrence [13]. Furthermore, it is noteworthy that in the present contribution the p-value for the ECG AFDF has been found to be higher than for the automatically estimated LAA EGM AFDF (refer to Table II). This result should be linked to the findings of the study of EGM/ECG AFDF correlation. As Figure 2 shows, for the non-terminating group ECG AFDF appears underestimated with respect to the endocardial LAA reference. Hence, the estimation of AFDF from the independent component with highest SC appears less reliable for non-terminating patients. This result may find its explanation in the electrophysiology of AF: this disease is characterized by the presence of multiple wavefronts (e.g., prompted by multiple reentrant circuits and/or ectopic foci) propagating across the atria with possibly different AFDFs. If the number of these propagating wavefronts is assumed to increase as AF advances to more complex forms, then focusing on only one of them (e.g., the one with highest SC) may not be sufficient to explore the underlying electrophysiological process. Hence, the source with highest SC is less likely to correspond to the activation pattern within the LAA for the non-terminating patients.

This physiological interpretation seems to be confirmed by the results of SC analysis. SC appeared to be significantly higher for the patients in the terminating group and high value of AUC obtained suggests that SC plays a role in the non-invasive prediction of AF termination by CA. The complexity of wavefront propagation may have an impact on the spectral characteristics of the AA recorded on surface ECG. In particular, the presence of multiple activation patterns may broaden the spectrum of the extracted atrial source, which can be seen as a mixture of these patterns, and consequently make the corresponding SC value decrease. Therefore, the difficulty encountered in the estimation of surface AFDF may be due to the presence of a complex pattern of atrial substrate depolarization and reflects on smaller SC values. Hence, the hypothesis that SC may reflect the complexity of AF electrophysiology may explain its ability to predict CA outcome in persistent AF patients and the results of EGM/ECG AFDF correlation.

V. CONCLUSIONS

Pre-procedural AFDF and related spectral parameters were investigated in the context of CA outcome prediction. On a database of 20 patients, surface AFDF was not found to be a predictor of CA outcome at follow-up. This result was corroborated by EGM recordings. On the other hand, correlation between surface and EGM AFDF was found to be statistically significant only in terminating patients, indicating that AFDF estimation from the body surface appears more difficult for non-terminating patients. Index SC was found to be significantly higher for terminating patients and can thus play a role in the non-invasive prediction of AF termination by CA ablation. Further investigation is needed to understand whether the AFDF complexity of wavefront propagation can be indeed described by the ICA of multi-lead surface ECG recordings. Clarifying this point may open the way to the use of SC as a non-invasive index of AA complexity and predictor of persistent AF termination.

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