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Noninvasive Organization Analysis Along Consecutive Episodes of Paroxysmal Atrial Fibrillation

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***Abstract*— Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice. Although its mechanisms are incompletely understood, electrophysiological and structural remodeling of the atria seem to play an important role in the arrhythmia transition from paroxysmal to persistent. However, the time course of the atrial remodeling along onward episodes of non-induced paroxysmal AF has not been investigated yet. In this work, a non-invasive method, based on the regularity estimation of AF through sample entropy (SampEn), has been used to assess the organization evolution along onward episodes of paroxysmal AF. Given that AF organization has been associated to the number of existing wavelets wandering throughout the atrial tissue, SampEn could be considered as a concomitant estimator of atrial remodeling. The achieved results, in close agreement with previous findings obtained from invasive recordings, showed a progressive disorganization increase along onward episodes of AF for 63% of the analyzed patients and a stable AF organization degree in the remaining 37%. Additionally, a positive correlation between episode duration and SampEn was also noticed ($R = 0.541$, $p < 0.01$). As a consequence, it could be considered that atrial electrophysiological dynamics that occur along onward paroxysmal AF episodes are reflected and can be quantified from ECG recordings through non-invasive organization estimation.**

I. Introduction

ATRIAL fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in clinical practice, affecting up to 1% of the general population [1]. Although the mechanisms leading to the initiation, self-termination and maintenance of this arrhythmia have been under intensive investigation, their whole comprehension still is an open issue for the scientific community [1]. It is not completely known why AF is paroxysmal, i.e. self-terminating, in certain individuals but not in others, or why the duration of paroxysmal AF episodes varies from patient to patient and from episode to episode [2]. Nevertheless, electrophysiological and structural atrial remodeling during the arrhythmia are believed to play an important role in the progressive evolution from paroxysmal to persistent AF [3]. To this respect, it has been shown through studies in animals, that the shortening of the atrial effective refractory period and the loss of its normal adaptation rate are associated with an increase in AF stability, thus leading to the concept that "AF begets AF" [3], i.e., the electrophysiological changes provoked in the atria by the presence of AF facilitate the perpetuation of the arrhythmia. In humans, these findings have been replicated in induced AF [4] and endorsed in chronic AF by means of comparison with normal subjects [5]. However, no study about the atrial remodeling time course along onward episodes of patients with spontaneous, i.e. non-induced, paroxysmal AF has been published yet. To this respect, the possibility of gaining information about paroxysmal AF, its progressive degeneration and its rhythm of advance would be clinically very interesting, because effective treatments could be tailored and early applied.

In the present work, the time course of AF organization, defined as how repetitive is the AF signal pattern, along successive paroxysmal episodes is non-invasively evaluated making use of a non-linear regularity index, such as sample entropy (SampEn) [6]. This index has shown to be a robust non-invasive estimator of AF organization [7], [8]. In addition, several authors have hypothesized that a strict correlation between AF organization and the number of wavelets wandering throughout the atrial tissue exists, such that more wavelets imply a more disorganized AF [9], [10]. To this respect, the number of simultaneous wavelets depends on electrophysiological properties of the atrial tissue, such as the refractory period, mass and conduction velocity along the atria [1]. As a consequence, given that the presence of AF provokes profound changes in these atrial electrophysiological properties [3]–[5], this contribution proposes SampEn as a concomitant estimator of atrial remodeling.

II. Methods

A. Study population

Nineteen patients with paroxysmal AF detected for the first time, i.e., without previously known history of AF, and without associated antiarrhythmic drug treatment were enrolled in the study. They were selected to present more than 5 full AF episodes, i.e., without interruption during the recording time, lasting longer than 10 seconds, with the aim of appreciating clear and reliable intra-patient trends related to the AF organization time course along onward episodes. Thus, 243 episodes with a duration ranging from 10.74 seconds to 6.17 hours (median of 5.72 minutes, mean and standard deviation of 20.63 ± 33.22 minutes) were analyzed.

B. Signal processing and AF organization estimation

A 24-h Holter ECG recording from each patient under study was acquired with a sampling rate of 125 Hz and 12-bit resolution. Although three leads (V_{II}, aV_F and V_1) were recorded, only V_1 was considered in the study and

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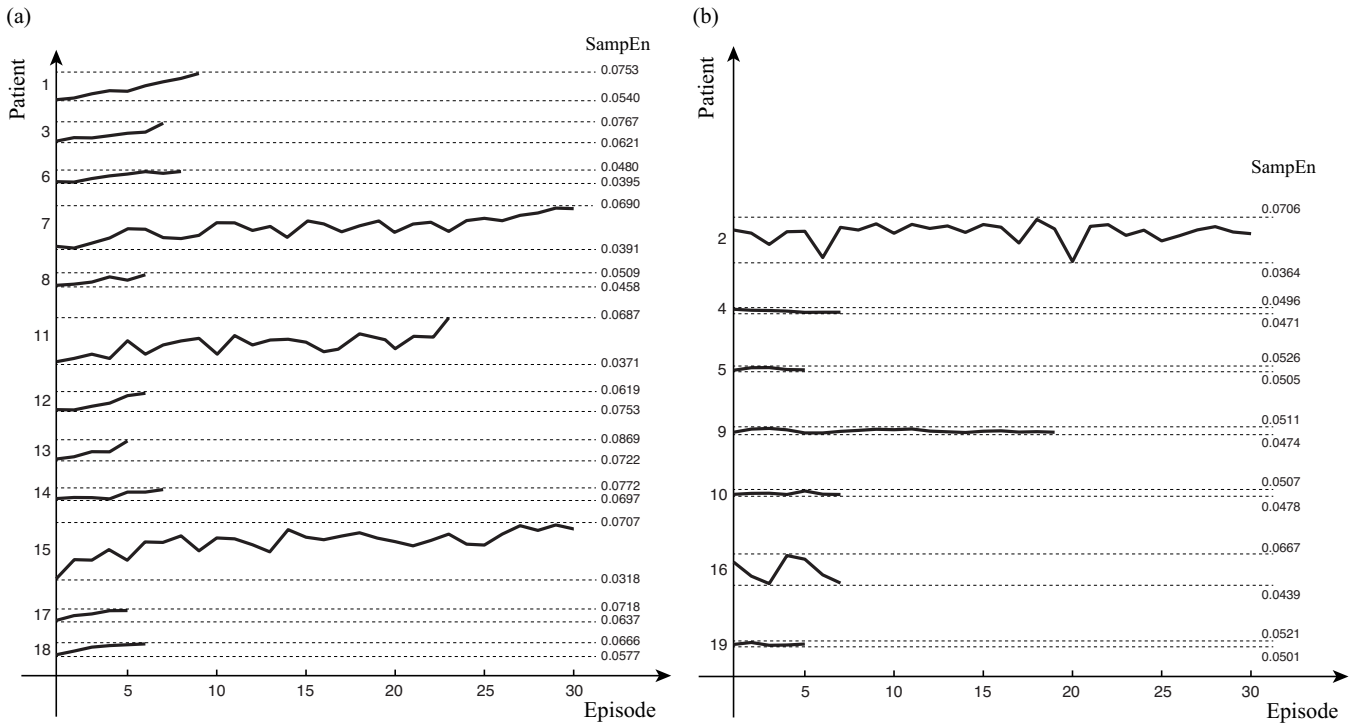

Fig. 1. Individual AF organization time course along onward episodes for each analyzed patient. The subjects with progressive AF disorganization (SampEn increase) are in panel (a). Patients with stable or decreasing disorganization trend are in panel (b). For patients suffering more than 30 AF episodes, only the first 30 are plotted because the organization trend is easy to appreciate.

filtered out with cut-off frequencies of 0.5, 70 and 50 Hz to remove baseline wander, high frequency noise and powerline interference, respectively. Additionally, to facilitate a better alignment for QRST complex subtraction, this lead was upsampled to 1 kHz [11].

To estimate AF organization, the application of SampEn to V_1 requires the fulfillment of several steps. Firstly, the ventricular activity has to be removed making use of a cancellation technique [12]. Next, the main atrial wave (MAW) has to be extracted from the atrial activity (AA) signal by applying a selective filtering centered on the dominant atrial frequency (DAF), i.e. the frequency corresponding to the highest spectrum magnitude within the 3–9 Hz range. Finally, SampEn computation can be applied to the MAW for quantifying the predictability of its fluctuations, thus assigning a non-negative number with a larger value corresponding to more irregularity in the data. This approach has been described in detail in previous works [8].

C. Data analysis

Previous works, dealing with paroxysmal AF, have shown that AF disorganization presents a gradual increase along the first 3 minutes from the onset before reaching the plateau. In the same manner, it decreases from the plateau within the last minute prior to the arrhythmia termination [7], [13]. Hence, given that the most disorganized AA is constantly present after the first and before the last minutes of the episode, SampEn was computed for the central 10 second interval of the excerpt. This fact could make it possible to study the evolution of organization in onward AF episodes of the same patient. On the other hand, Bollmann et al [14] have shown that the duration of an AF episode is directly associated to the DAF magnitude. Given that this frequency is directly related to atrial refractoriness [15], in the present work, the relationship between SampEn and the AF episode duration has been also analyzed.

III. Results

A. Evolution of AF organization along onward episodes

A clear increasing trend in SampEn was observed in 12 patients along onward episodes, such as can be seen in Fig. 1(a). In average, for each patient, the relative rate of SampEn increase ranged from 1.74 to 7.28% among patients in Fig. 1(a). On the other hand, for the remaining 7 subjects, a stabilized or decreasing trend in AF disorganization along onward episodes was observed, such as Fig. 1(b) shows. Additionally, whereas a strictly increasing, decreasing or stable SampEn time course was noticed for those patients with less than 10 AF episodes, a notable variability was observed for those with higher number of AF episodes. Nevertheless, in this last case, a clear trend was also identified easily for all the patients.

Another interesting observation from Fig. 1 is that the patients showing a clear increasing trend in AF disorganization also presented higher SampEn values than those in whom AF disorganization remained stable or slightly increased from episode to episode. Moreover, as an average for all the episodes, patients with increasing AF disorganization

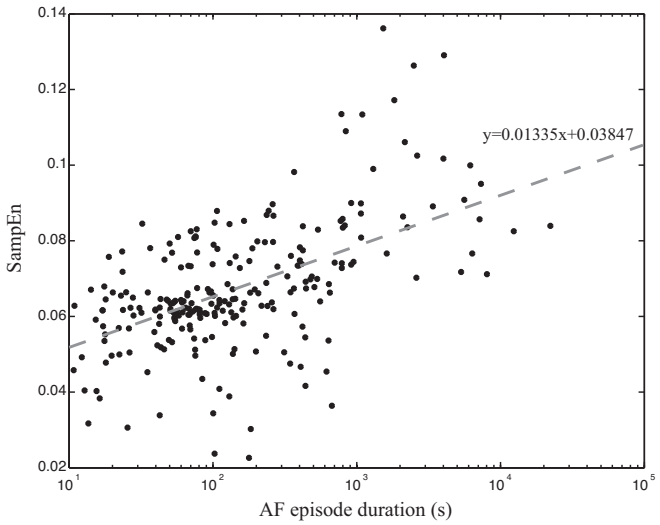

Fig. 2. Relationship between SampEn computed for each AF episode and its duration. Note that the AF episode duration is expressed on a logarithmic scale for easy visualization.

presented a mean SampEn of 0.0657 ± 0.0116, whereas this value was 0.0519 ± 0.0044 ($p < 0.0001$) for those presenting a constant or slightly decreasing AF disorganization episode by episode.

B. AF organization and episode duration

A positive correlation between SampEn and its duration was found, such as Fig. 2 shows. It is noteworthy that the AF episode duration is expressed on a logarithmic scale for easy visualization. In this case, the least means linear fit shows a line ($y = 0.01335x + 0.03847$, $R = 0.541$, $p < 0.01$) with a SampEn increase of 0.013 for every decade of the AF episode duration. The linear regression was computed after the logarithmic transformation of all the individual values associated to every AF episode duration.

IV. Discussion

A. Evolution of AF organization along onward episodes

Regardless of the higher or lower rhythm of rise, 12 of the analyzed patients exhibited an increasing SampEn trend along onward episodes, see Fig. 1(a). Hence, a more disorganized AA signal will be reached for each new paroxysmal AF onset. Despite the substantial intra-individual variability, happening in some patients with a high number of episodes, this finding is in close agreement with similar observations obtained from invasive studies in humans [4], [16] and animals [3]. These previous works reported how brief episodes of induced AF, even with a few minutes of duration, were enough to shorten atrial refractoriness [3], [4], to produce the loss of atrial refractory period adaptability to the changes in heart rate [3], [4], and to induce atrial contractile dysfunction [16]. These changes in the atrial electrophysiological properties were evolving during AF presence, thus provoking a progressively shorter atrial cycle length. This fact implies a gradual increase in the number of wavelets wandering throughout the atrial tissue, which could increase the probability of arrhythmia perpetuation when AF has been present during some days [3]. On the contrary, the remaining 7 patients presented a stable or decreasing AF disorganization episode by episode, such as Fig. 1(b) shows. This observation could suggest that the presence of AF provokes no significant alterations on their atrial electrophysiological properties, which could be indicative of stabilized paroxysmal AF in these patients or, at least, that the arrhythmia is not degenerating to persistent AF.

As a consequence of the previous findings, it could be considered that results showed different intra-patient rates with which AF was disorganized along onward episodes. This aspect suggests that atrial remodeling could advance with different rhythms for each patient [3], [4]. Thus, the possibility of getting *a priori* knowledge on the intra-patient progression of AF disorganization, episode by episode, could be helpful in predicting both the possible termination or perpetuation of the arrhythmia and the timing and progressive advance that turns the arrhythmia from paroxysmal to persistent. This observation could have significant implications in AF management, thus allowing a better selection of patients for the most suitable therapy, like antiarrhythmic drug treatment or the implantation of atrial defibrillators [17]. To this respect, the risk of progression from paroxysmal to persistent AF is significantly higher in patients with a higher rate of disorganization along onward recurrences of AF [18]. This finding can also be corroborated by the fact that patients showing an increasing trend of AF disorganization, presented higher SampEn values than those in whom disorganization was stable or slightly decreasing. In this sense, previous works have shown that the risk of arrhythmia chronification is higher in groups of patients with greater SampEn values, and, more precisely, with entropy values greater than an established threshold of 0.09, approximately [19].

B. AF organization and episode duration

In line with the results, the estimation of AF organization via SampEn was positively correlated with the duration of paroxysmal AF episodes. The higher the episode duration, the higher the AF disorganization. This relationship is in close agreement with previous studies, obtained from invasive recordings, in which it was reported that atrial remodeling is dependent on AF episode duration and may promote the arrhythmia perpetuation [3], [4]. From non-invasive studies, a direct relationship between the AF episode duration and atrial fibrillatory rate (i.e., DAF multiplied by 60) was also found in patients with new-onset [20] and paroxysmal AF [14]. Atrial fibrillatory rate has been shown to reflect local atrial refractoriness [15], therefore, this measurement could be considered as a concomitant and quantitative marker of AF organization. Thus, low frequency values suggest a reduced number of simultaneous depolarization wavefronts wandering throughout atrial tissue, whereas high frequency values suggest a larger number of atrial wavelets [14].

Although SampEn shows a significant correlation with AF episode duration, it is not the only electrophysiological parameter determining AF subsistence or termination. Con-

duction velocity, dispersion of refractoriness and anisotropy may also contribute to maintain AF. To this respect, Wijffels et al [3] found no statistically significant differences in the measurement of spatial differences in atrial refractory period. Moreover, no significant changes were observed in atrial conduction velocity during the first days of AF in goats. However, Kumagai et al [21] showed that the P wave duration was significantly longer in paroxysmal AF patients than in control subjects, suggesting a reduction of intra-atrial conduction velocity in the presence of AF. Therefore, further studies would be required to analyze the influence of these properties on AF maintenance.

C. Limitations

Given the inter-patient variability observed in this study, the results must be considered with caution. However, the agreement between these results and those provided by previous works, together with the fact that clear and stable AF disorganization trends along onward episodes were observed, allow us to consider that the presented results are reliable and reproducible. Nonetheless, further studies are required in order to provide more confidence in their reliableness and reproducibility. On the other hand, onward paroxysmal AF episodes with initiation and termination recorded during regular sessions of electrophysiology are rarely encountered in the daily practice. Therefore, long-term surface ECG recordings provide the best way to document these events. Nevertheless, these recordings may not allow the detection of local events in small volumes of the atrial tissue, for example, in the pulmonary veins, that may be very relevant in the initiation and termination of paroxysmal AF.

V. Conclusions

Results showed that atrial electrophysiological dynamics ocurring along onward AF paroxysms can be quantified from ECG recordings through a non-linear regularity index, such as sample entropy. According to previous invasive studies, a positive correlation between episode duration and its disorganization was also noticed. As a consequence, sample entropy could be considered as a non-invasive and concomitant marker of atrial remodeling, which is associated to an increased likelihood of future AF paroxysms recurrence.

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