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Validation of Surface Atrial Fibrillation Organization Indicators Through Invasive Recordings

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***Abstract*— Studies related to atrial fibrillation (AF) have shown that surface lead V_1 reflects mainly the dominant atrial frequency (DAF) of the right atrium (RA), which has been widely used to analyze this arrhythmia. AF organization and fibrillatory (f) waves amplitude are two recently proposed non-invasive AF markers, which have not been yet validated with invasive recordings. In this work, these two non-invasive metrics have been compared with similar measures recorded from two unipolar atrial electrograms (AEGs). Results obtained from 38 patients showed statistically significant correlations between the values measured from surface and invasive recordings, thus corroborating the usefulness of the aforesaid markers in the non-invasive study of AF. Precisely, for AF organization, the correlation coefficients between surface and both AEGs were $R = 0.926$ ($p < 0.001$) and $R = 0.932$ ($p < 0.001$), respectively. For f waves amplitude, slightly lower significant relationships were noticed, the correlation coefficients being $R = 0.765$ ($p < 0.001$) and $R = 0.842$ ($p < 0.001$), respectively. These outcomes together with interesting linear relationships found among the parameters, suggest that AF organization and f waves amplitude can characterize non-invasively the epicardial activity related to AF.**

I. Introduction

THE surface electrocardiogram (ECG) provides a widely used and non-invasive way to study atrial fibrillation (AF). This arrhythmia is the most commonly diagnosed in clinical practice and affects almost 5% of the population older than 69 years of age and 8% of the population older than 80 years [1].

Non-invasive methods for atrial activity (AA) analysis from the ECG have been advocated as becoming useful in AF research. These methods are capable of detecting or monitoring changes in the fibrillatory (f) waves due to interventional procedures [2]. In this sense, previous studies have shown that the dominant atrial frequency (DAF) is a widely used index that can be considered as a concomitant indicator of atrial refractoriness [3] and can be useful to predict the arrhythmia progression under different therapies [4]. However, the usefulness of this index depends on a reliable estimation of the DAF from the surface ECG. To this respect, its validation, by direct comparison with atrial electrograms (AEG), has shown that the DAF obtained from the standard lead V_1 is highly correlated with the fibrillatory rate of the right atrium (RA) [5], [6].

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Similarly as with the DAF, two recent non-invasive markers based on the f waves have shown a very interesting ability to deal with specific events associated to AF. In this sense, the f waves amplitude proved to be a successful predictor of AF recurrence after electrical cardioversion (ECV), with a diagnostic accuracy about 80% [7]. On the other hand, the estimation of AF organization based on a non-linear regularity index, such as sample entropy (SampEn), demonstrated a robust ability in the outlook of a number of AF events, such as prediction of paroxysmal AF termination, detection of normal sinus rhythm maintenance after electrical cardioversion or discrimination between paroxysmal and persistent AF episodes [8]. However, apart from the aforementioned applications of the f waves amplitude and SampEn to the surface ECG in AF, the way in which both markers could reliably reflect the dynamics of the internal fibrillatory activity still is a pending issue. As a natural consequence, this study uses SampEn to investigate the relationship in AF organization between two fibrillatory activities: the one present in the RA and the one observed from the surface ECG. Furthermore, the relationship between f waves amplitude obtained from RA electrograms and surface recordings is investigated as well.

II. Methods

A. Study population

The comparison between invasive and surface ECG recordings was performed in 38 patients undergoing cardiac surgery who developed postoperative AF. For each patient, 12 lead ECGs were recorded during a time interval varying between 50 and 150 seconds together with two epicardial recordings, which will be referred to as RA_1 and RA_2. In this latter case, unipolar electrodes were placed on two different positions of the RA anterolateral free wall after the surgical procedure. Both recordings were referred to the Wilson Central Terminal. The sampling frequency of both ECG and AEG signals was 1 kHz. From the 38 patients, 52 AF episodes were selected with a duration ranging from 41 to 146 s (64.87 ± 20.33 s in average).

B. Data preprocessing and atrial activity extraction

From the 12 standard ECG leads, precordial lead V_1 was chosen for the analysis, because f waves are more prominent in this lead [3]. Furthermore, from an anatomic point of view, lead V_1 is considered to be the closest one to the RA [3] and the frequency of the RA fibrillatory activity seems to be mostly reflected in this lead [6]. This surface lead together with RA_1 and RA_2 were filtered to remove baseline wander,

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high frequency noise and powerline interference. Thereafter, a method based on average ventricular beat cancellation was employed for extracting the AA both from ECG and AEG recordings. This method was used because it has provided an optimized ventricular cancellation for ECGs [9] and for unipolar AEGs, especially when the fibrillatory activity is not extremely organized [10].

C. Time and frequency markers

The power spectral density of the AA signal was obtained using the Welch Periodogram. A Hamming window of 4096 points in length, a 50% overlapping between adjacent windowed sections and a 10240–points Fast Fourier Transform were used as computational parameters. The frequency with the highest amplitude within the AF typical range of 3–9 Hz was selected as the DAF [3].

On the other hand, AF organization has been defined as how repetitive the AA signal pattern is [11]. In this study, AF organization was estimated by applying SampEn over the main atrial wave (MAW) signal, i.e., the fundamental waveform associated to the AA [12]. The MAW was obtained by applying a selective band-pass filtering with a 3 Hz bandwidth to the AA centered on the DAF [8] and its use is justified because the presence of QRST residua and noise in the AA signal degrades notably AF organization estimation using non-linear regularity indexes [12]. SampEn examines a time series for similar epochs and assigns a non-negative number to the sequence, with larger values corresponding to more irregularity in the data. A detailed description of SampEn can be found in [13].

Finally, the amplitude of surface and epicardial f waves was estimated by means of their mean power, which is refereed to as fWP. This power represents the energy carried by the f waves within the time interval under analysis and, hence, it could be considered as a robust indicator of the signal amplitude, such as it has been shown in prediction of electrical cardioversion outcome [7]. It is noteworthy that before extracting the AA signal from the ECG, each recording was normalized to its maximum R peak amplitude. The two AEGs associated to the ECG were also normalized by the same factor in order to preserve the relationship between the surface and epicardial f waves. This intra-patient normalization avoided all the effects that can turn the ECG amplitude higher or lower as a function of the different gain factors during recording, electrodes impedance, skin conductivity, etc.

D. Statistical analysis

Pearson correlation analysis and a Student's t-test for paired data were used to compare statistically the values of the DAF, SampEn and fWP obtained from the recordings V_1, RA_1 and RA_2. A two-tailed value of statistical significance (p) lower than 0.05 was considered significant.

III. Results

The three analyzed parameters were computed from 10 s-length segments with a 50% overlapping, yielding a total of 334 segments studied. The mean value of the DAF measured in the two unipolar AEGs was 5.243 $\pm$ 1.206 Hz for RA_1 and 5.245 $\pm$ 1.207 Hz for RA_2, respectively. Hence, both values were very similar and, indeed, non-significant statistical differences were noticed, given that $p = 0.941$. Moreover, as can be appreciated in Fig. 1, the DAF values computed for both AEGs were highly correlated with the DAF from the lead V_1, whose mean was 5.270 $\pm$ 1.156 Hz. The correlation coefficients were $R = 0.939$ ($p < 0.001$) for RA_1 and $R = 0.952$ ($p < 0.001$) for RA_2, respectively.

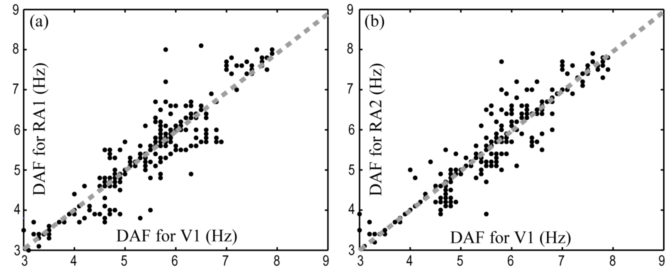

Fig. 1. DAF values computed from surface lead V_1 in comparison to those others measured from (a) RA_1 and (b) RA_2, respectively. Note that the gray dashed line is the best fit regression line for each case.

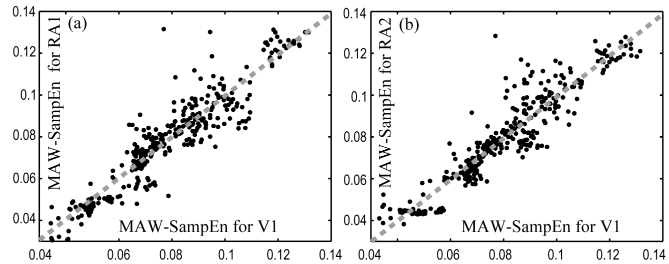

Fig. 2. Comparison of MAW-SampEn values computed over surface lead V_1 with MAW-SampEn of (a) RA_1 and (b) RA_2, respectively. As before, the gray dashed line is the best fit regression line for each case.

On the other hand, notably significant linear relationships were found when SampEn was computed over the MAW of lead V_1 and compared with SampEn of the MAW in RA_1 ($R = 0.926$, $p < 0.001$) and RA_2 ($R = 0.932$, $p < 0.001$), as can be seen in Fig. 2. In addition, statistically non-significant differences between SampEn mean values of RA_1 (0.079 $\pm$ 0.023) and RA_2 (0.078 $\pm$ 0.023) were observed ($p = 0.193$). These mean values were also very similar to the MAW-SampEn of lead V_1 (0.079 $\pm$ 0.022).

Fig. 3 represents the fWP values computed over V_1 as a function of those obtained from RA_1 and RA_2. A significant correlation between the surface ECG and both unipolar AEGs was observed, the correlation coefficients being $R = 0.765$ ($p < 0.001$) for RA_1 and $R = 0.842$ ($p < 0.001$) for RA_2, respectively. Nevertheless, significant differences between the fWP mean values obtained from the two RA electrograms, 0.104 $\pm$ 0.125 squared normalized units (n.u.^{2}) for RA_1 and 0.123 $\pm$ 0.145 n.u.^{2} for RA_2, were noticed, given that the statistical significance was slightly lower than 0.05. Additionally, these mean values were very dissimilar to the one obtained from the lead V_1, 0.253×10^{-2}

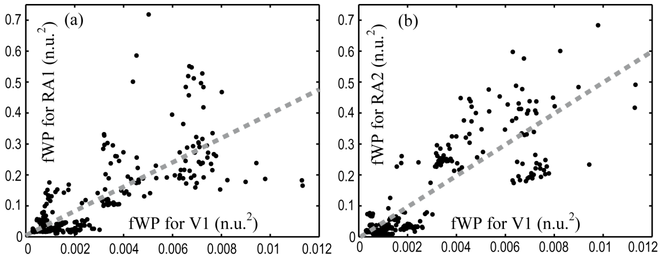

Fig. 3. Representation of the fWP values computed from surface lead V_1 as a function of the fWP from the invasive recordings (a) RA_1 and (b) RA_2, respectively. As aforesaid, the gray dashed line is the best fit regression line for each case.

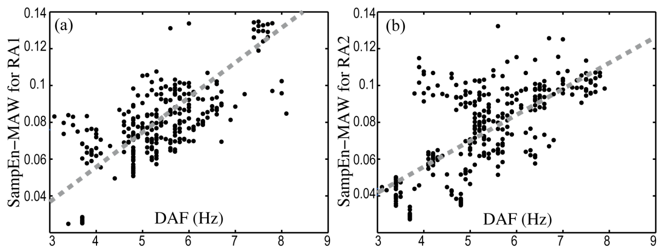

Fig. 4. Relationship between DAF and SampEn values computed from the AA of (a) RA_1 and (b) RA_2, respectively. Note that the gray dashed line is the best fit regression line for each case.

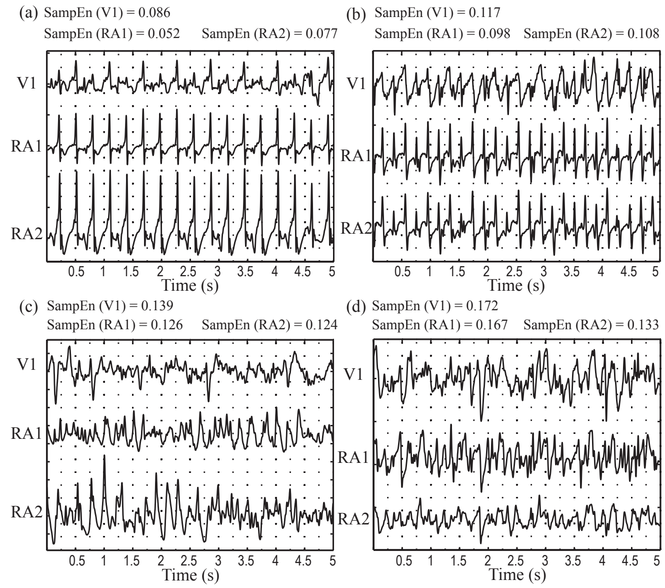

Fig. 6. Illustration on the SampEn ability to reliably estimate different organization status in the AEG. The presented sequence shows decreasing organization AEGs from (a) to (d), that can also be recognized by an increasing arduousness to distinguish local activations in RA_1 and RA_2 [14]. Accordingly, the SampEn values are increasing from (a) to (d) following the disorganization progression.

$\pm$ 0.243×10^{-2} n.u.^{2}., such as it could be *a priori* expected.

Finally, relationships among the three validated parameters were analyzed. To this respect, Fig. 4 shows a positive correlation between SampEn and DAF values computed from the AA of RA_1 and RA_2, the correlation coefficients being $R = 0.721$ ($p < 0.01$) and $R = 0.699$ ($p < 0.01$), respectively. On the other hand, the representation of the fWP values, obtained from lead V_1, as a function of the DAF and as a function of the MAW-SampEn also provided slightly significant linear correlations, such as Fig. 5 shows, given that the correlation coefficients in this case were $R = 0.117$ ($p = 0.036$) and $R = 0.136$ ($p = 0.013$), respectively.

IV. Discussion

This study presents the validation with epicardial recordings of two non-invasive markers, such as organization and amplitude, for f waves characterization. Similarly, previous works have carried out similar studies, but all of them have been only related to the DAF [5], [6]. Results obtained by these works agreed that lead V_1 mainly reflects the internal fibrillatory frequency of the RA, which is in strong agreement with the results obtained in the present study, since a close correlation between the DAF values measured from RA electrograms and from lead V_1 was observed.

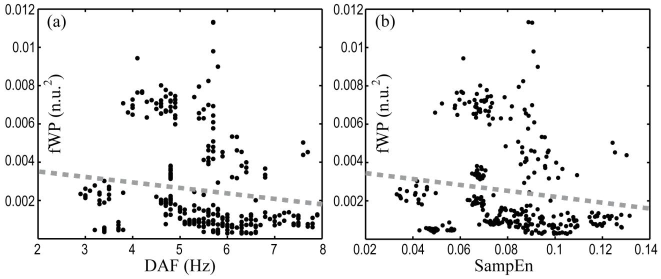

Fig. 5. Relationship (a) between DAF and fWP values and (b) between fWP and MAW-based SampEn values obtained from the surface lead V_1. Note that the gray dashed line is the best fit line regression for each case.

Unipolar AEGs have shown a well-defined relationship with the upstroke of the action potential, which is generally accepted as a fiducial point for marking local activations [14]. In this sense, a low number of wavelets will provoke discrete and clear activations in the AEG, separated by an isoelectric baseline, see Figs. 6 (a) and (b). On the contrary, the difficulty of distinguishing between discrete activations, as in Figs. 6 (c) and (d), will indicate the presence of a high number of wavelets wandering simultaneously throughout the atrial tissue [14]. As can be appreciated in Fig. 6, the decreasing epicardial organization in the presented sequence of AEGs, from (a) to (d), was reliably and quantitatively evaluated by SampEn for the invasive recordings. Additionally, a more detailed visual inspection of Figs. 6 (a) and (b) allows to observe a direct association between the discrete activations in RA_1 and RA_2 and the f waves in lead V_1. As a consequence, the organization of unipolar AEGs, computed via SampEn, can be reliably estimated from surface lead V_1. This observation also corroborates the finding reported in previous works, in which it was suggested that the MAW-SampEn based organization of lead V_1 may offer information on the complexity of the underlying electrophysiological patterns [8].

In a similar way, the DAF has also been previously associated to the complexity of activation wavefronts within the atrial. To this respect, Konings et al [15], by using high-density mapping of the RA free wall, reported a clear correlation between the DAF and the arrhythmia complexity. Therefore, it could be considered that both DAF and SampEn provide estimates of the same electrophysiological phenomenon, which could justify the statistically significant linear relation found between them and presented in Fig. 4. Anyway, remark that the MAW-SampEn strategy applied to V_1 can be considered as a more accurate marker than the DAF since, in previous works, SampEn has revealed a higher diagnostic ability to detect paroxysmal AF termination, to predict ECV outcome and to discern between paroxysmal and persistent AF episodes [8].

With regard to the comparison between surface and epicardial recordings in terms of f waves amplitude, a close correlation between the fWP obtained both from RA_1 and RA_2 and lead V_1 was noticed, such as Fig. 3 shows. To this day, the surface f waves amplitude has not been compared yet with invasive recordings, however, its relation with other intraatrial metrics has been previously analyzed. To this respect, Bollmann et al [16] showed a negative correlation between the DAF and the normalized f waves amplitude, which was weakly significant when both parameters were computed over lead V_1. In agreement with this work, a slight negative linear relation between the DAF and fWP values obtained from lead V_1 was also observed in the present study, see Fig. 5 (a). On the other hand, Roithinger et al [14] compared the surface f waves amplitude with the atrial activation organization in bipolar AEGs. A RA organized activation was identified to be associated with coarse AF (f waves amplitude > 0.12 mV), whereas a disorganized pattern was noticed in fine AF (f waves amplitude < 0.12 mV). Coherently, in the present work, a weak statistically significant linear relation with negative slope was found between the fWP and SampEn values computed from the lead V_1, as can be appreciated in Fig. 5 (b). Hence, the surface f waves amplitude could be considered as other quantitative and non-invasive estimator of the underlying atrial electrophysiological pattern complexity. However, previous works have shown that this metric is more inaccurate than SampEn and DAF, since it provided a lower diagnostic ability to predict paroxysmal AF termination, to discern between paroxysmal and persistent episodes [8] and to predict AF response to ibutilide [16].

V. Conclusions

Atrial events recorded at the right atrium free wall, which are related to the organization of AF, can be reliably analyzed from surface lead V_1 by time or frequency markers. These indices, such as the dominant atrial frequency, regularity of the main atrial wave and mean power of the f waves, have proven their ability to characterize epicardial activity from the surface ECG and, thereafter, could be used to explore non-invasively the mechanisms of AF and improve its treatment.

VI. Acknowledgments

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