A Method for Quantifying Atrial Fibrillation Organization Based on Wave-Morphology Similarity

Luca Faes*, Giandomenico Nollo, Renzo Antolini, Fiorenzo Gaita, and Flavia Ravelli

***Abstract*—A new method for quantifying the organization of single bipolar electrograms recorded in the human atria during atrial fibrillation (AF) is presented. The algorithm relies on the comparison between pairs of local activation waves (LAWs) to estimate their morphological similarity, and returns a regularity index (ρ) which measures the extent of repetitiveness over time of the detected activations. The database consisted of endocardial data from a multipolar basket catheter during AF and intraatrial recordings during atrial flutter. The index showed maximum regularity ($\rho = 1$) for all atrial flutter episodes and decreased significantly when increasing AF complexity as defined by Wells (type I: $\rho = 0.75 \pm 0.23$; type II: $\rho = 0.35 \pm 0.11$; type III: $\rho = 0.15 \pm 0.08$; $P < 0.01$). The ability to distinguish different AF episodes was assessed by designing a classification scheme based on a minimum distance analysis, obtaining an accuracy of 85.5%. The algorithm was able to discriminate among AF types even in presence of few depolarizations as no significant ρ changes were observed by reducing the signal length down to include five LAWs. Finally, the capability to detect transient instances of AF complexity and to map the local regularity over the atrial surface was addressed by the dynamic and multisite evaluation of ρ, suggesting that our algorithm could improve the understanding of AF mechanisms and become useful for its clinical treatment.**

***Index Terms*—Atrial fibrillation (AF), endocardial signals, rhythm classification, signal processing, tachyarrhythmia organization, waveform morphology.**

I. Introduction

Atrial fibrillation (AF) is a commonly encountered cardiac disorder, which occurs in up to 10% of individuals older than 70 years of age [1], and is associated with increased risk for stroke and/or embolic events [2], [3]. Although it is not yet clear how AF occurs, human studies and animal models have demonstrated that it is associated with the propagation throughout the atrial tissue of multiple activation wavelets, resulting in complex ever-changing patterns of electrical activity [4], [5]. As a consequence, during AF, the electrogram morphology changes constantly both in time and space showing different levels of spatiotemporal organization, according to a definition of organization as repetitive wave morphologies in the AF signals. Since the various morphologies reflect different spatial activation patterns such as slow conduction, wave collision, and conduction blocks [6], the analysis of the waveform changes of the endocardial signals acquired during AF plays an important role in the understanding of the mechanisms responsible for its induction and maintenance. Furthermore, the analysis of the degree of complexity characterizing the shape of the activation waves provides an electrophysiologic, instead of anatomic, help for guiding the catheter ablative therapy of AF [7], [8]. Up to now, the evaluation of the morphological features of the atrial activations is performed by a subjective qualification of the extracellular recordings following predefined rules [9].

Several algorithms for the quantitative analysis of AF organization have been reported in the literature. Since a rigorous definition of organization does not exist, various approaches have been adopted including monovariate [10] and bivariate [11] frequency analysis, cross-correlation techniques [12], linear prediction [13], and nonlinear analysis [14], [15]. All these techniques proposed for evaluating the regularity of AF electrical pattern require a significant manipulation of the atrial waveforms and the lack of a direct evaluation of the characteristics of the activation waves limits their potentiality in distinguishing among different degrees of AF complexity. Moreover, these methods work on the complete atrial recording, including also part of the signal during which the analyzed atrial site is not activated by the depolarizing wave fronts. On the other hand, the signal morphology is often overlooked by analyzes that characterize AF by means of the occurrence time of the atrial activations [16] or the atrial interval [17], [18].

In this paper, a new algorithm for the evaluation of the organization of the atrial electrograms during AF based on wave-morphology similarity is presented. The algorithm quantifies the regularity of an atrial electrogram by measuring the extent of repetitiveness over time of its consecutive activation waves. Since the analysis is focused on the shape of the waveforms occurring in correspondence of the local activations of the atrial tissue, the morphology of the atrial activations is the element by which the algorithm differentiates among various degrees of AF organization. Thus, unlike other published algorithms the proposed method analyzes the signal only in correspondence of the depolarizing wave fronts, excluding parts with low informative content and poor signal-to-noise ratio (SNR). Furthermore, it provides a local measure of AF organization since the analysis is performed on single atrial signals. The performance of the

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proposed method in discriminating different organization states was assessed by applying the algorithm to a highly periodic and regular atrial arrhythmia such as atrial flutter and to a spectrum of atrial fibrillations of increasing complexity class [9]. Moreover, examples are provided showing the ability of the regularity index: 1) to detect short-time changes in AF organization by following beat-to-beat the time evolution of the regularity index and 2) to detect spatial changes in AF organization by mapping the index over the entire atrial surface.

II. Methods

A. Patients and Data Acquisition

The study group consisted of eleven patients with idiopathic AF with no demonstrable organic heart disease. All antiarrhythmic drugs had been discontinued for at least five half lives, and no patients had received Amiodarone within the preceding six months.

After informed consent was received, a multielectrode basket catheter (Constellation catheter, EP Technologies, Boston Scientific) with eight splines each carrying eight electrodes equally spaced (each 4 mm apart) was inserted via the femoral vein in the right atrium. Thirty-two bipolar intracardiac recordings were acquired by coupling adjacent pairs of electrodes. The exact position of each electrode was monitored by two orthogonal X-ray images. Bipolar electrograms from 31 endocardial signals and the lead II of the surface electrocardiogram (ECG) were simultaneously recorded (CardioLab System, 30–500 Hz [Prucka Engineering, Inc.]) and digitized at 1-kHz sampling rate and 12-bit precision. The gain of each channel was adjusted to fit the requirement of analog-to-digital conversion. When not spontaneously present, AF was induced with atrial extrastimuli or atrial bursts. The shortest duration of either spontaneous or induced episodes of AF chosen for analysis was at least 5 min. The period analyzed was chosen randomly, excluding the first and last minute of AF.

To test the proposed algorithm upon a reference data set of regular rhythms with repetitive morphology, 20 intra-atrial recordings of atrial flutter were selected from a database previously collected [19].

B. Data Preprocessing

Ventricular interference was first removed from atrial recordings by an averaging technique [20]. Briefly, an adaptive template of the ventricular artifacts was obtained by averaging 100-ms windows of atrial signal synchronized with the ventricular activation times detected on the R-waves of the surface ECG. At each R-wave, the last 20 detected atrial windows were used to update the template. The template was then subtracted from the atrial recording in correspondence to the detected ventricular activation times. The use of an adaptive template allowed us to take changes in the ventricular conduction during the evolution of the AF episode into account.

Secondly, atrial activation times were estimated from the bipolar recordings by measuring the barycenter of the local activation waves (LAWs). The process of atrial waveform recognition started by band-pass filtering (40–250 Hz, order-40, Kaiser window) the atrial signal $(s(t))$ to remove baseline shifts and high-frequency noise [21]. The filtered signal was then rectified, introducing low-frequency components related to the amplitude of the high-frequency oscillations of the original signal. The modulus of the filtered signal was further low-pass filtered (finite impulse response, cutoff at 20 Hz, order-40, Kaiser window) to extract a waveform $s_w(t)$ proportional to the amplitude of the components of $s(t)$ occurring at 40–250 Hz [12]. The atrial waveforms were then detected by threshold crossing. To account for variability in waveform amplitude, we set an adaptive threshold on the amplitude of the last ten detected peaks of $s_w(t)$ with exponentially decreasing weights. In addition, a blanking period of 55 ms was imposed to avoid multiple detection of a single LAW. After wave recognition, the atrial activation times were estimated by calculating the barycenter of the waveform, i.e., as the time that divided in two equal parts the local area of the modulus of the signal [22]. For this purpose, a moving average noncausal filter with 90 coefficients was applied to the modulus of the original electrogram $s(t)$

$$s_f(t) = \sum_{i=0}^{44} |s(t-i)| - \sum_{i=1}^{45} |s(t+i)|. \tag{1}$$

For each detected LAW, the activation time was set on the positive zero crossing of $s_f(t)$ which was closer to the local peak of $s_w(t)$.

C. Description of the Algorithm

Our algorithm attempted to quantify the regularity of an atrial signal defined as the degree of repetitiveness over time of its activation waves. The algorithm related the morphologies of all possible pairs of atrial activations extracted from the recording to estimate their similarity.

For an atrial recording in which N atrial activations were detected, LAWs $\{x_1, \ldots, x_N\}$ were defined as signal windows of p samples centered on the atrial activation times. In order to prevent the amplitude of the LAWs from affecting our regularity measure, each LAW was normalized by division by the standard norm of the p-dimensional real space

$$s_i = \frac{x_i}{\sqrt{\sum_{j=1}^{p} x_{ij}^2}} \tag{2}$$

where $x_i = [x_{i1}, \ldots, x_{ip}]$ and s_i represent, respectively, the ith LAW and the ith normalized LAW. As prior to normalization each LAW was represented as a point of the p-dimensional real space, the normalized LAWs $\{s_1, \ldots, s_N\}$ became points belonging to the p-dimensional unitary sphere. Hence, the morphological dissimilarity between two LAWs was evaluated by using the standard metric of the sphere to compute their distance

$$d(s_i, s_j) = \arccos(s_i \cdot s_j) \tag{3}$$

where s_i and s_j represent the ith and jth normalized LAW and $(\cdot)$ denotes the scalar product. The regularity index, $\rho(\varepsilon)$, was

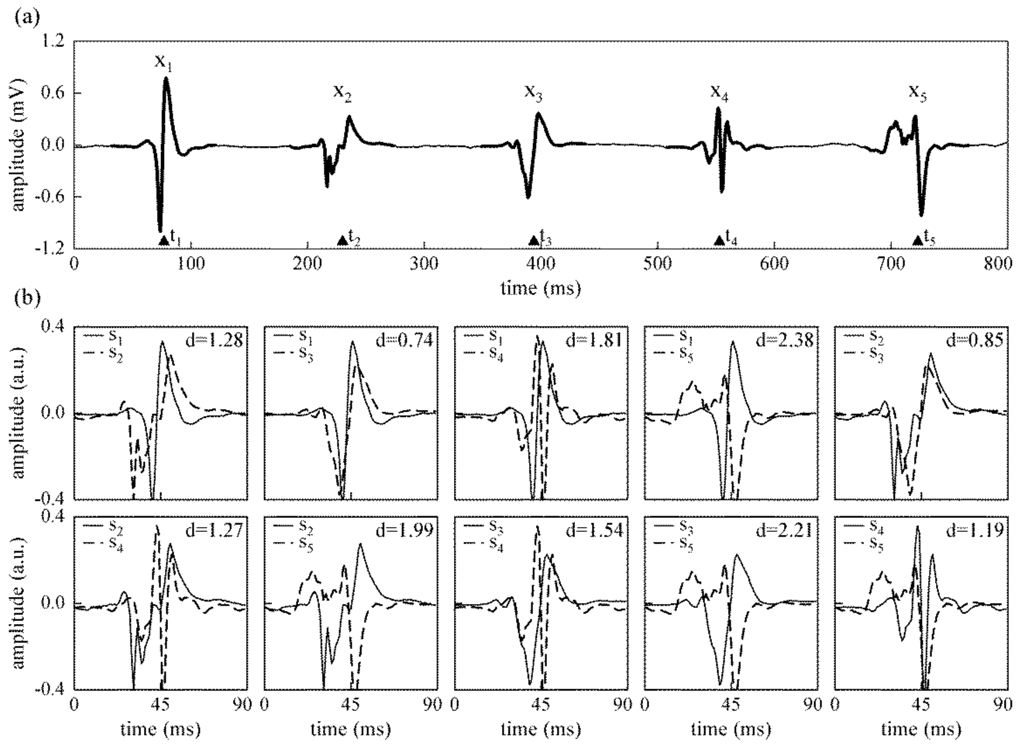

Fig. 1. Description of the algorithm running on a strip of 800 ms extracted from a bipolar electrogram during AF. (a) Local activation waves (LAWs: $x_1, \ldots, x_5$; thick lines) were determined as windows centered on the detected activation times ($t_1, \ldots, t_5$; filled triangles) and lasting 90 ms. (b) Normalized LAWs $(s_1, \ldots, s_5)$ were obtained and the distance (d) between all pairs of normalized LAWs was computed by (3). The distances were then used in (4) to calculate the regularity index.

then defined by calculating the relative number of similar pairs of LAWs in the analyzed recording as

$$\rho(\varepsilon) = \frac{2}{N(N-1)} \sum_{i=1}^{N} \sum_{j=i+1}^{N} \Theta(\varepsilon - d(s_i, s_j)) \qquad (4)$$

where Θ is the Heaviside function [$\Theta(x) = 0$ for $x \leq 0$ and $\Theta(x) = 1$ for $x > 0$]. The parameter ε is a threshold in evaluating the similarity between pairs of LAWs on the basis of their distance, that is, two LAWs are considered to be similar when their distance is lower than ε. For a given value of ε, the index $\rho(\varepsilon)$ in (4) estimates the probability of finding similar LAWs in the analyzed recording. The dependence of ρ on the parameter ε is discussed in Section III-A.

For the choice of the length of the LAWs care was taken to cover the duration of the whole atrial waveform and to avoid the superposition between two consecutive LAWs. In our study, the optimal window length was equal to 90 ms. As a consequence, the parameter p was set to 90 being the sampling period equal to 1 ms. Fig. 1 describes the algorithm working on a recording of 800 ms of AF. After the detection of five LAWs $\{x_1, \ldots, x_5\}$, the distance between all pairs of normalized LAWs $\{s_1, \ldots, s_5\}$ is computed. For $\varepsilon = 0.8$ rad, only s_1 and s_3 are similar, thus, (4) gives $\rho = 0.1$. For $\varepsilon = 1.6$ rad, six pairs of normalized LAWs are similar and the regularity index is $\rho = 0.6$.

D. Verification of the Algorithm

First, validation of the barycenter method to estimate the local activation times was performed on a set of AF signals subdivided by an expert cardiologist in type I (AF1), type II (AF2), and type III (AF3) AF according to the Wells' classification [9]. Ten signals lasting 4 s (corresponding to 15–30 LAWs) were analyzed for each class. The activation times were estimated on a beat-to-beat basis by the barycenter method and by two traditional methods calculating the occurrence time of the local maximum peak and maximum slope of the atrial depolarization [16], [23]. The three methods were compared by taking the manual measurement performed by the expert reader as reference. Moreover, to evaluate the influence of detection errors on similarity analysis the regularity index ρ was calculated after manual and barycenter-based estimation of the activation times.

To verify that the proposed method can discriminate atrial arrhythmias with different degree of organization, the algorithm was applied to a data set constituted by 20 strips of atrial flutter, 35 of AF1, 30 of AF2, and 35 of AF3, each 4 s wide. Since the distribution of ρ evaluated on atrial flutter and AF1 strips was not normal (Kolmogorov–Smirnov test), nonparametric tests were used for the statistical analysis. The difference among the four distributions of ρ was tested by the Kruskal–Wallis analysis of variance (ANOVA), while the Mann–Whitney U test was used to focus on the difference between pairs of distributions. The statistical analysis was repeated for all values of ε ranging from 0 to π, step 0.05.

In order to assess the ability of our algorithm to characterize AF episodes with different complexity, a classification scheme was designed by dividing the AF data set into a training set of 45 strips (15 AF1, 15 AF2, and 15 AF3) and a test set of 55 strips (20 AF1, 15 AF2, and 20 AF3). The classifier made use of a single classification parameter (ρ) to discriminate between

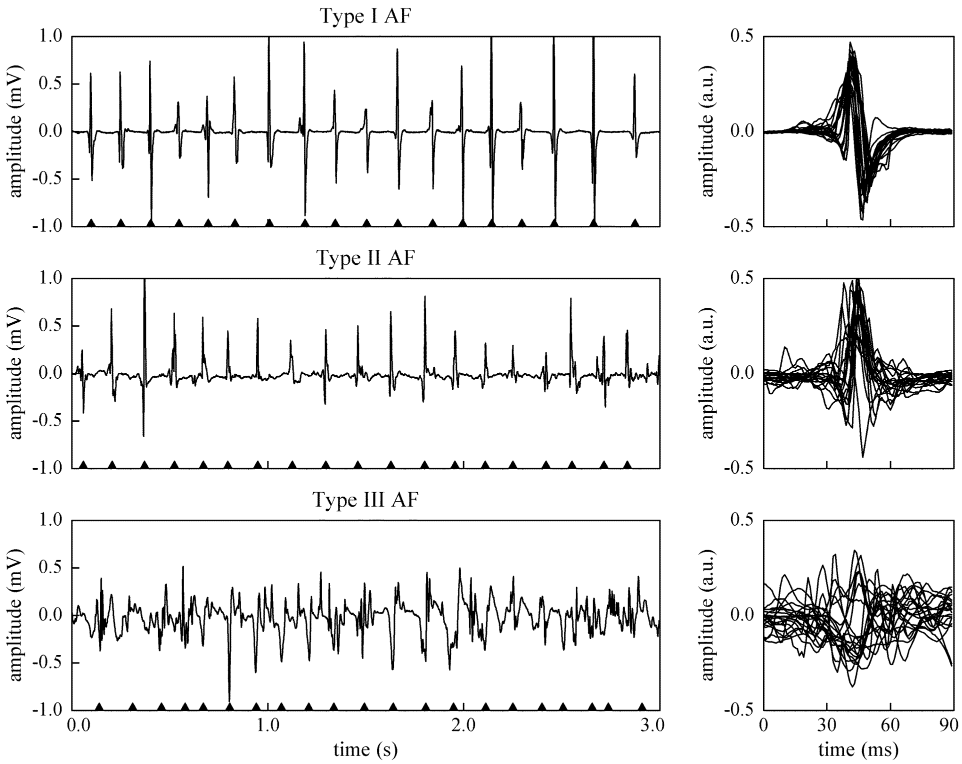

Fig. 2. Analysis of the LAWs for AF episodes with different complexity class. From top to bottom, bipolar electrograms of type I, type II, and type III AF. Filled triangles indicate the time of LAWs detection. On the right, superposition of the normalized LAWs obtained from the signals of the left panels.

three classes (AF1, AF2, or AF3). The thresholds for discriminating between AF1 and AF2, and between AF2 and AF3, were calculated as the values of ρ that minimized the classification error for the training set. For each class, the performance of the classifier was then evaluated on the test set by computing its sensitivity and specificity. The strips belonging to the examined class were labeled as positive, whereas the others as negative. The accuracy of the classifier, defined as the percentage ratio between the strips correctly classified and the total number of strips of the test set, was also calculated.

The discriminative power of the regularity measure proposed in (4) was compared to that of two alternative procedures for processing the distance between LAWs. The investigated procedures were the average distance of the LAWs to the average LAW, and the average distance between pairs of LAWs. The comparison was performed for atrial flutter, AF1, AF2, and AF3 episodes. Fifteen signals per class, each containing 20 LAWs, were analyzed.

The dependence of the regularity index on the number of atrial depolarizations included in the analyzed epoch was investigated by selecting strips containing at least 50 LAWs belonging to the same class (atrial flutter, AF1, AF2, or AF3) and computing the algorithm for different values of N in the set $\{5, 10, 20, 30, 40, 50\}$. Fifteen signals per class were selected for the analysis. Differences among AF types at fixed values of N were assessed by the Kruskall–Wallis ANOVA and the Mann–Whitney U test, while within-type differences were investigated by the Friedman ANOVA for repeated measures.

Finally, the ability of the algorithm to detect transient instances of AF complexity was assessed by evaluating the time course of the regularity index during an AF episode showing spontaneous changes in the arrhythmia organization. Moreover, the ability of the algorithm to detect regional differences in AF regularity was evaluated by mapping the index over the right atrial surface.

III. Results

A. Validation of the Regularity Index

The ability of the algorithm to discriminate between different types of AF is shown in Fig. 2 where an example of bipolar electrograms recorded during three instances of fibrillation with increasing complexity, classified respectively as type I, type II, and type III by the expert cardiologist, is reported. The corresponding normalized LAWs are well superimposed for the signal with repetitive morphologies corresponding to type I AF, slightly scattered for the type II AF signal, and highly scattered for the signal showing complex morphologies corresponding to type III AF. As a consequence, the distances between pairs of LAWs increase as the signal organization decreases being on average 0.6 rad for type I, 1.2 rad for type II, and 1.7 rad for type III, while the regularity index decreases (0.73 type I, 0.38 type II, 0.16 type III with $\varepsilon = 1$ rad).

The regularity index was calculated as a function of the threshold distance ε over the 4-s segments of atrial flutter and type I, II, and III AF. Fig. 3 evidences the strong dependence of the regularity index on the parameter ε for each analyzed type of rhythm. It exhibited a monotonic trend with increasing the threshold distance, moving from zero with $\varepsilon = 0$ rad to one with $\varepsilon = \pi$ rad. Its average values were always higher for atrial flutter than for AF1, for AF1 than for AF2, and for AF2 than for AF3. Nonparametric ANOVA was significant

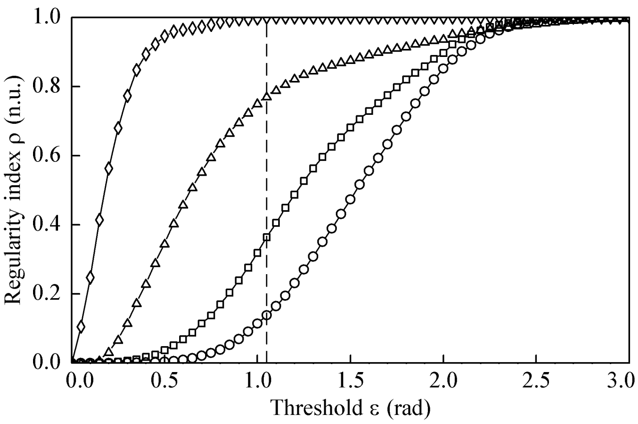

Fig. 3. Average values of the regularity index (ρ) calculated on the 4-s strips of atrial flutter (rhombs), type I AF (triangles), type II AF (squares), and type III AF (circles) as a function of the threshold distance ε. The four distributions were statistically different for ε ranging from 0.05 to 2.9 rad (ANOVA, $P < 0.01$), with maximum significance at $\varepsilon = \pi/3$ rad (dashed line).

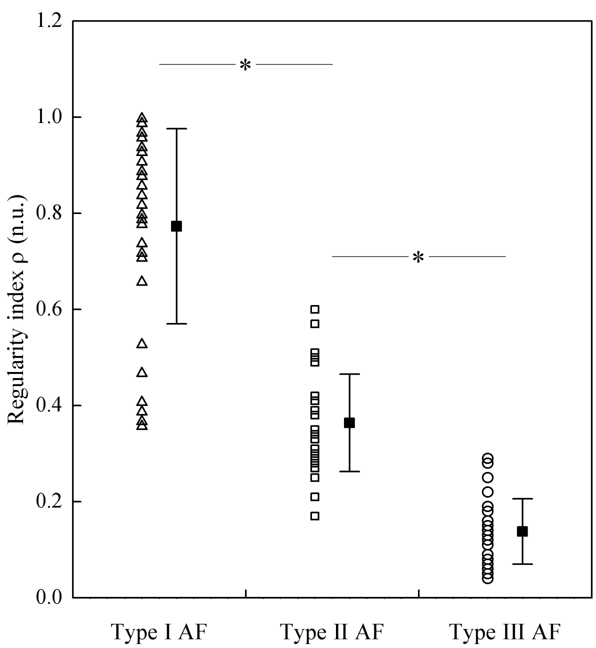

Fig. 4. Distribution of the regularity index (ρ) evaluated with $\varepsilon = \pi/3$ rad on the segments of type I, II, and III AF. The mean (box) and standard deviation (whiskers) of the three distributions are also shown. The differences between pairs of distributions were statistically significant (Mann–Whitney, *:$P < 0.00001$).

($P < 0.01$) for all ε values from 0.05 to 2.9 rad, and the differences between all pairs of distributions were significant ($P < 0.05$) for all ε values from 0.3 to 1.95 rad. The statistical significance was maximum ($P < 10^{-5}$ for both ANOVA test and Mann–Whitney tests) with $\varepsilon = 1.05$ rad. Moreover, for $\varepsilon \geq 1.05$ rad, the algorithm returned $\rho = 1$ for all atrial flutter recordings. Therefore, $\varepsilon = \pi/3$ rad was chosen as the optimal threshold distance for discriminating among various degrees of organization of the atrial bipolar recordings.

TABLE I
CLASSIFICATION OF AF EPISODES IN RELATION TO THE EXPERT APPRAISAL BASED ON WELLS' CRITERIA

		AF1	AF2	AF3	Sensitivity	Specificity
	AF1	17	3	0	85 %	94.3 %
EXPERT	AF2	2	10	3	66.7 %	92.5 %
	AF3	0	0	20	100 %	91.4 %

TABLE II
CHANGES IN THE REGULARITY INDEX RELATIVE TO THE THREE TYPES OF AF FOR DIFFERENT RECORD LENGTHS

N	AF1	AF2	AF3
5	$0.74 \pm 0.31^{\#}$	$0.42 \pm 0.22^{\circ}$	0.19 ± 0.19
10	0.80 ± 0.19*	$0.34 \pm 0.16^{\S}$	0.15 ± 0.11
20	0.75 ± 0.23*	$0.35 \pm 0.11^{\S}$	0.15 ± 0.08
30	0.72 ± 0.24*	$0.34 \pm 0.10^{\S}$	0.14 ± 0.08
40	0.73 ± 0.23*	$0.32 \pm 0.09^{\S}$	0.13 ± 0.07
50	0.74 ± 0.23*	$0.32 \pm 0.09^{\S}$	0.13 ± 0.06

The distributions of the regularity index evaluated with $\varepsilon = \pi/3$ rad over AF1, AF2, and AF3 segments are shown in Fig. 4. Even though the statistical analysis indicates that discrimination is possible, Fig. 4 evidences some overlap in ρ values between the three groups. Thus, a classifier was designed on the AF data set to fully assess the ability of our algorithm to distinguish episodes with different organization degrees. Table I reports the confusion matrix for the classification analysis along with the sensitivity and specificity values. The accuracy of the classifier was 85.5%. The optimal thresholds for distinguishing AF1 from AF2, and AF2 from AF3 resulted, respectively, in $\rho = 0.52$ and $\rho = 0.28$.

Two alternative procedures for measuring LAWs morphological similarity were tested on a subset of signals of typical length ($N = 20$). The average distance of the LAWs to their average resulted equal to 0.26 rad for atrial flutter, 0.87 rad for AF1, 1.28 rad for AF2, and 1.48 rad for AF3. The average distance between pairs of LAWs was 0.24 rad for atrial flutter, 0.85 rad for AF1, 1.30 rad for AF2, and 1.52 rad for AF3. For both measures, values were statistically different (Mann–Whitney, $P < 0.02$) when analyzing atrial flutter versus AF1 or AF1 versus AF2, while the distributions of AF2 and AF3 resulted overlapped ($P > 0.05$). On the contrary, the discriminative power of the regularity index was fully verified on the same data (atrial flutter: $\rho = 1$, AF1: $\rho = 0.75$, AF2: $\rho = 0.35$, AF3: $\rho = 0.15$; Mann–Whitney, $P < 0.001$ for all pairs). The average computational time of the regularity index was 30 ms. Correspondingly, computing the average distance between LAWs and the average distance to the average LAW took, respectively, 25 and 5 ms.

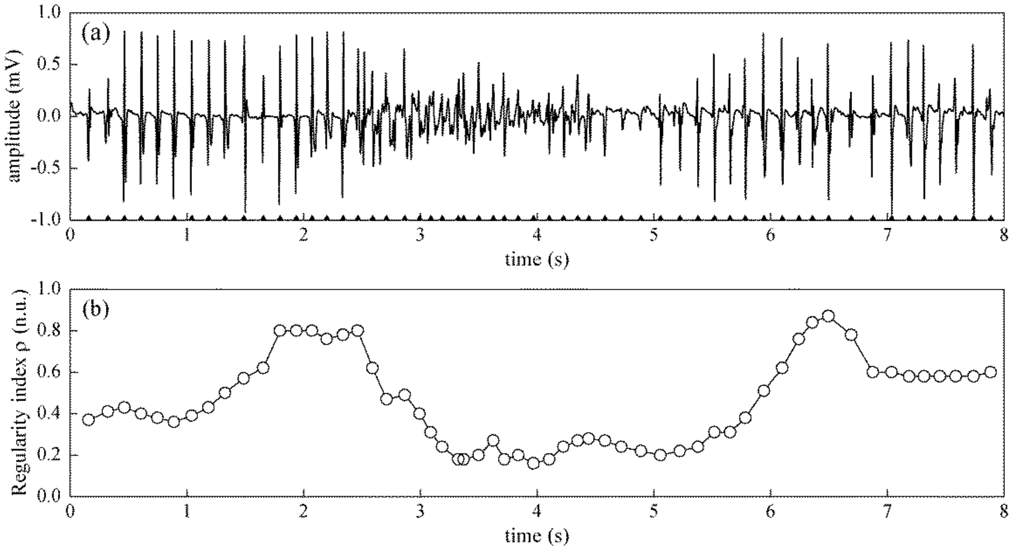

Fig. 5. Dynamic evaluation of the regularity index during an episode of AF showing spontaneous changes in complexity. (a) Bipolar endocardial electrogram showing a transient increase in AF complexity occurring between two periods of more regular electrical activity. (b) Beat-to-beat values of the regularity index ρ measured on the past ten local activations [filled triangles in (a)] with $\varepsilon = \pi/3$.

Algorithms were developed with Matlab[1] on a personal computer with a 400-MHz Pentium II processor.

B. Dependence on Signal Length

With a threshold distance ε set to $\pi/3$ rad, the application of the algorithm to atrial flutter episodes resulted in $\rho = 1$ for all the selected strips, independently on the number of LAWs involved into the analysis. Thus, the statistical analysis of the dependence of the algorithm on the record length was turned to AF episodes. The regularity index evaluated for AF1, AF2, and AF3 strips as a function of N is reported in Table II. For each value of N, the distributions of ρ calculated on the three different types of AF were significantly different. Inside a single AF type, no statistical differences in the regularity index were found by varying N (Friedman ANOVA, $P = NS$). The dispersion of ρ values was larger, and the statistical significance of the difference among AF types weaker, by decreasing the record length up to five depolarizations of the same type.

C. Validation of the Activation Times Estimation

To test the accuracy of the barycenter method for local activation time estimation and to quantify the influence of misalignments on the regularity index, 630 LAWs were recognized in the 30 analyzed AF signals. The average difference between automatic and manual activation times resulted lower for barycenter estimation (AF1: 2.6 ms; AF2: 4.5 ms; AF3: 12.7 ms) than for maximum slope (AF1: 2.7 ms; AF2: 5.9 ms; AF3: 20.2 ms) and maximum peak (AF1: 3.0 ms; AF2: 7.6 ms; AF3: 18.9 ms) estimations. No significant differences were observed in the distributions of the regularity index ρ based on manual and barycenter LAWs detection (AF1: 0.73±0.24 versus 0.71±0.26; AF2: 0.44±0.13 versus 0.39 ±0.13; AF3: 0.15±0.06 versus 0.12±0.05; $\varepsilon = 1$ rad).

[1]v. 5.3, The MathWorks Inc., Natick, MA.

D. Time Evolution and Spatial Mapping of Organization

The possibility to perform a beat-to-beat evaluation of the regularity index and, thus, the capability to detect short-time changes in AF organization is shown in Fig. 5 where an example of spontaneous changes in AF complexity is presented. In this case, the bipolar endocardial signal showed a transient increase of complexity occurring between two periods of more regular electrical activity. The estimated activation times are indicated on the horizontal axis by filled triangles. In correspondence to each activation time, the regularity index was calculated on the last detected LAWs ($N = 10$; $\varepsilon = \pi/3$ rad) and its temporal evolution was beat-to-beat evaluated [Fig. 5(b)]. It is well evident as the regularity index time course follows temporal changes in the signal organization, by evidencing not only marked changes in AF signal complexity, but also smaller variations of LAWs morphology occurring during the different phases of the fibrillation episode. It should be noted that the rate of adaptation of ρ to changes of signal complexity is inversely related to the number of LAWs ($N = 10$ in this case) included in the analyzed epoch. Thus, the selection of the length of the analysis window, which is beat by beat moved during the dynamic analysis, influences the ability of the algorithm to capture rapid changes in AF regularity.

The evaluation of regularity index was spatially extended by mapping the index over the whole atrial surface. In Fig. 6, the regularity index was simultaneously measured ($\varepsilon = \pi/3$ rad) in 26 sites in the right atrium. The spatial distribution of ρ was evaluated for a 30-s recording. Values of the regularity index were color coded according to gray scale, with the lightest shades of gray representing the lowest regularity index and the darkest shades of gray representing the highest regularity index. Each of the three regularity intervals demarcated by the two optimal thresholds found in the classification analysis was divided in two subintervals, thus determining six levels of gray for coding the regularity values at each site. The analysis evidenced as AF organization is spatially distributed, with a high regularity index

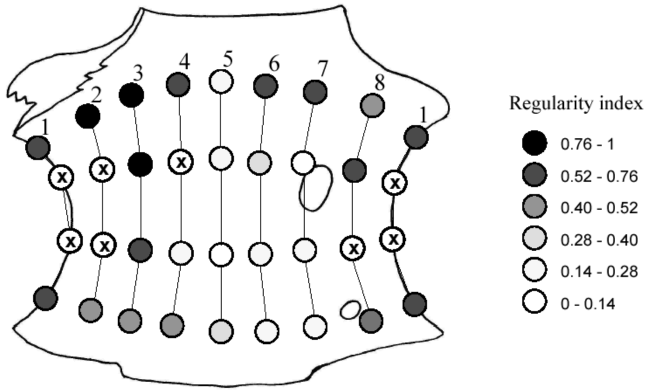

Fig. 6. Spatial mapping of the regularity index during an AF episode. The figure shows a sketch of the opened right atrium with the position of the bipolar electrodes on the endocardial wall represented by the circles. The splines of the basket catheter, each one supporting four bipolar electrodes vertically connected, are numbered according to their position: 1—Anterior; 2—Antero-Lateral; 3—Lateral; 4—Postero–Lateral; 5—Posterior; 6—Postero–Septal; 7)—Septal; 8)—Antero–Septal. The Anterior spline is reported on both sides of the scheme. The color inside each circle represents the value of the regularity index, evaluated on a window lasting 30 s and coded in accordance with the gray scale reported on the right. Circles containing a cross correspond to sites not acquired.

in the lateral and anterior walls and a more disorganized electrical activity of the posterior and septal regions of the right atrium.

IV. Discussion

A. Measuring the Organization of AF

This paper proposes a new method for quantifying the organization of the intracardiac electrograms recorded in the human atrium during AF. The algorithm is sensitive to the morphological variations of the consecutive atrial depolarization waves. Due to the regularity of the activation sequence in the atrium, electrograms acquired during organized atrial rhythms (e.g., atrial flutter or type I AF) present LAWs with well-defined and repetitive characteristics. As a consequence, most of LAW pairs resulted to be similar and the regularity index approaches to one. On the contrary, highly disorganized electrograms showing fragmented activation waves with complex morphology contain more dissimilar LAWs, thus, leading toward zero the probability to find similar depolarizations. From a methodological point of view, these observations lead to a new perspective in the definition and quantification of AF organization. Indeed, most of the previous efforts to describe the "state of organization" of AF, either analyzing the correlation between two electrograms [11]–[13] or the dynamic of a single recording [14], [15], were implemented on the whole atrial signals, including also parts of the electrogram not interested by the depolarizing wave front. Since the analyzed signals are in large part constituted by data with low informative content concerning the depolarizing wave front and with worst SNR, such methods can be sensitive to changes in signal organization which are not completely related to changes in the underlying AF activation pattern. Our algorithm, analyzing electrogram characteristics during a time window centered in the detected activation times, focuses on the part of the signal more representative of the activation wave front and less sensitive to noise.

The morphological similarity of the atrial activations could be quantified by means of simpler measures than the regularity index, thus reducing computational times. Indeed, while our method requires $N(N-1)/2$ distance calculations and as many LAWs comparisons, measuring the average distance of the LAWs to their average or the average distance between pairs of LAWs takes, respectively, N and $N(N-1)/2$ distance calculations. However, comparative analysis demonstrated that these alternative similarity measures have a lower discriminative power than the adopted regularity index. Particularly, they failed in discriminating the two AF classes with higher morphological complexity, i.e., type II and type III AF. The better performance of regularity index calculation can be explained by considering that the algorithm processes the distance between LAWs by means of a nonlinear transformation [see (4)].

The regularity of AF was also previously characterized in the frequency domain by FFT estimates computed on single atrial signals [10], [24]. Since these studies made use of wide bipolar electrograms, they have been proven to be useful in the assessment of the global electrical features of AF. Conversely, our algorithm provides a *local* measure of AF complexity, as it works on single atrial recordings acquired from closely spaced bipolar electrodes. A local evaluation of AF features allows to better characterize the electrical activity of restricted atrial areas. On the other hand, the simultaneous multisite evaluation of the regularity index facilitates the introduction of an organization map in which the local measure of regularity is extended over the whole atrial surface. Even though traditional isochronal maps based on the evaluation of the activation times in multiple sites have been proven to be informative about the AF propagation pattern, the continuous spatio-temporal changes of AF waveforms suggests the extension of mapping to other parameters besides activation times [13], [25]. By evaluating the morphological changes of successive activation waves, our organization map should provide additional information respect to isochronal maps in the analysis of the complexity of AF pattern. If correlated to anatomic and structural properties of the atria, the analysis of the spatial distribution of the morphological complexity of intra-atrial signals should be useful for relating the substrate to the electrical properties of AF [6].

B. Performance of the Algorithm

The significant different values of the regularity index calculated on the distributions of atrial flutter and type I, II, and III AF (Wells' criteria [9]) demonstrate the ability of our algorithm to distinguish among various atrial arrhythmias. In addition, results of the classification analysis pointed out that it succeeds in discriminating different types of AF. The possibility to distinguish varying states of AF was previously investigated by detecting marked changes in AF spatial organization due to drug administration [12], [13]. More recently, different types of AF were analyzed by means of conditional entropy estimates, measuring a regularity of about 0.3 for normal sinus rhythm and type I AF and of about 0.1 for type II and type III AF [15]. The high performance of our method in distinguishing different AF types can be attributed mainly to the fact that it works without requiring substantial modifications of the shape of the activation wave.

Our results show the possibility to discriminate different types of AF even in presence of few atrial depolarizations, as no significant variation in the regularity index was observed by reducing the length of strips of the same AF type down to include five depolarizations. In addition, we show a reduction of the regularity index proceeding from type I to type III AF. Since the number of propagating wavefronts increases as the complexity of fibrillation increases [26], this result is consistent with Moe's hypothesis of multiple wavelets randomly propagating throughout the atrial tissue during AF [4], suggesting that the regularity of a single atrial lead depends on the number and the reciprocal orientation of the wavefronts encountering the electrode at the time of analysis.

In terms of classification analysis, comparable results were achieved in [21], where a classification rate of 93% was obtained by designing a multiparameter classifier for the automatic recognition of intraatrial electrograms in relation to the Wells' classification scheme. Nevertheless, the use of a single parameter (i.e., the regularity index) and the high sensitivity to changes in AF complexity entitles our algorithm to introduce a multilevel scale of regularity values (see, for example, Fig. 6). This allows to evaluate with high resolution the regularity of fibrillatory episodes, analyzing the recording characteristics beyond their classification into three types of AF. Theoretically, the number of levels in the regularity scale depends on the number of LAWs involved in the analysis and more precisely on the number of compared LAWs couples, with a finer scale as N increases. The resolution of the regularity index is also influenced by the choice of the threshold distance ε which determines whether two LAWs are morphologically similar or not. In the present study, the threshold value of ε was chosen in order to assure that signals exhibiting the lowest degree of morphological complexity (i.e., atrial flutter recordings) produce the highest degree of regularity ($\rho = 1$). However, this parameter can be set in accordance with the desired resolution in the distinction between different activation morphologies: the lower the value of ε, the higher the tendency of the algorithm to differentiate pairs of LAWs.

The proper alignment of the LAWs represents a crucial step for similarity evaluation. Although other techniques for wave alignment could be used (i.e., the time of maximum cross-correlation between LAWs), a procedure based on a physiological criterion was utilized. From a physiological point of view, the reference point for locating a LAW is the activation time, which represents the instant of wave front passage beyond the electrode. Since for bipolar electrograms an objective way to set the activation times has not been yet established [23], we developed an estimate based on calculation of the local barycenter. Comparison with the manual measurement of activation times performed by expert cardiologist indicates that barycenter calculation is more reliable than the traditional maximum peak or maximum slope estimates when fibrillation is characterized by fragmented LAWs with complex morphology (type II and III AF). On the other hand, the better performance of morphological algorithms with respect to methods based on slope or amplitude in presence of fragmented waves has been previously addressed [16], [22], [23]. Moreover, the goodness of barycenter detector for similarity evaluation is evidenced by the fact that the regularity index did not change significantly when based on manual rather than on automatic activation time measurement. Even for type III AF, where discrepancies between automatic and manual LAWs location were greater, the index did not show significant variations. While in type I and II AF this result is due to the good LAWs detection, for type III AF the good agreement can be explained by the great morphological heterogeneity of the atrial waves which mask the possible influences of detection errors on the regularity value.

The ability of our algorithm to distinguish different levels of regularity can also be used to follow dynamic changes of AF organization. Indeed, by limiting the analysis to short epochs it is possible to quantify the variations of regularity corresponding to subtle and/or rapid changes in rhythm. By moving the epochs over the time and updating beat-to-beat the regularity index it is possible to follow the time evolution of AF local organization (see Fig. 5). The beat-to-beat evaluation of the index is allowed by the fact that our method is based on the comparison between depolarization waves and not on the analysis of the complete signal.

C. *Clinical and Physiological Implications*

A measure of organization of AF electrograms which is highly sensitive to changes in wave morphology should be useful to investigate disturbances in the conduction pattern. Indeed, the complex waveforms of AF electrograms have been shown to depend on the local features of the conduction pattern such as areas of slow conduction, arcs of intra-atrial conduction blocks and pivot points turning wavelets [6]. Moreover, the ability of the proposed index to evaluate beat-by-beat changes in AF complexity indicates the possibility to follow both spontaneous and induced dynamic changes of AF pattern. For instance, the regularity index should be able to reflect changes in the electrophysiological features due to pharmacological intervention or electrical remodeling of the atria. In fact, it is now firmly established that AF itself causes progressive electrophysiological and/or structural changes to the atria, which promote the initiation or perpetuation of AF [27]. The study of the dynamic evolution of remodeling is important to determine the optimal moment for pharmacological or electrical cardioversion of AF.

The evaluation of the regularity of intraatrial electrograms recorded during AF may also play an important role in the new strategies developed for the treatment of AF, such as electrical cardioversion, overdrive pacing, and catheter ablation [28]. In defibrillation, it has been recently demonstrated that the shock efficacy is improved during periods of plain AF organization [10]. In AF pacing, it is now well established that atrial fibrillation has a small excitable gap and, thus, can be entrained by overdrive stimulation [29]. The determination of AF organization can be used to optimize both the time and the site of pacing leading to AF termination. In electrophysiological studies, the manual classification of atrial electrograms, usually performed according to Wells' criteria [9], is widely used to give a morphological characterization of AF and has been related to the anatomic location and to the results of radiofrequency catheter ablation [7], [8]. In fact, it has been firmly established that during AF different regions of the atria exhibit different patterns of electrical activation [6], [30], [31]. The utilization of multipolar basket catheters in the clinical practice [32] prompts the development of automatic algorithms allowing the online quantification of the organization of the electrograms simultaneously acquired in multiple atrial sites. Thus, the introduction of regularity maps like the one reported in Fig. 6 should constitute an effective support to the treatment of AF. Indeed, the real-time evaluation of the spatial distribution of AF regularity may guide the definition of the optimal ablative pathway.

V. Conclusion

We introduced a new method for the evaluation of the organization of intraatrial bipolar electrograms recorded in the human atria during AF. Organization was defined as the repetitiveness in time of the morphology of atrial activation waves detected in a single atrial lead during AF. Our results demonstrated that the proposed regularity index is suitable to characterize changes in atrial signals when passing from atrial flutter to AF and when increasing the complexity of AF episodes from type I to type III [9]. Moreover, the high sensitivity of the algorithm to the morphological variations of the consecutive atrial activations suggested its implementation for typifying the complexity of AF in more than three level of regularity. The beat-to-beat evaluation of the regularity index and the spatial mapping of AF organization allowed to follow the temporal evolution of the AF organization and to point out regional differences in the degree of organization. These potentialities may provide new insights on the study of the physiological mechanisms ruling the perpetuation of AF, and may open new perspectives in the treating of AF performed either by radiofrequency catheter ablation or by electrical cardioversion.

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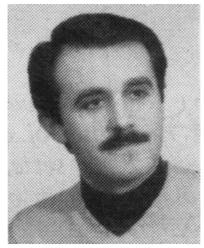

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