Quantitative Assessment of Synchronization during Atrial Fibrillation by Shannon Entropy Characterization of Propagation Delays

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Abstract

This study introduced a new method for the quantification of the synchronization (S) and the causal verse of activation (S12) in couples of atrial electrograms recorded during atrial fibrillation (AF). The synchronization indexes S and S12 relied on the measure of the propagation delays between coupled activation times in two atrial signals and on the characterization of their dispersion by Shannon-Entropy (SE). S and S12 were validated both on simulated activation time series and endocavitary signals in patients. In simulation, S and S12 were equal to 1 for propagation of one single wavefront in a fully excitable tissue, while they decreased for reentries in partially excitable tissue (S = 0.70 ± 0.05, S12 = 0.66 ± 0.05) and multiple wavelet propagation (S = 0.46 ± 0.06, S12 = 0.39 ± 0.08). In patients S, was equal to 1 during atrial flutter (AFl) and decreased with increasing complexity of AF (AF1: S = 0.76 ± 0.05; AF2: S = 0.56 ± 0.06; AF3: S = 0.39 ± 0.03). Moreover S12 evidenced the preservation of a correct activation sequence during AFl and AF1 (S12 = S) and its loss during AF2 (S12 = 0.41 ± 0.12 < S) and AF3 (S12 = 0.26 ± 0.03 < S). As indirect markers of the electrophysiological properties of atrial tissue, indexes S and S12 may provide a new insight in understanding the mechanisms initiating and maintaining AF and support new clinical treatments for its interruption.

1.   Introduction

Although AF has been referred as a totally disorganized rhythm, a growing body of work has demonstrated that, also during this arrhythmia, the activation of the atrial chambers is affected by a certain number of factors (as anatomy, refractoriness etc), which may play an important role in limiting the randomness of propagation and giving "organization" to AF. As the interest in AF has grown in the scientific community, many methods to quantify this aspect have been proposed [1]. These followed different philosophical and methodological ways, due to the lack of an universally recognized definition of "organization". In this study we focus on a specific aspect of organization, namely the synchronization, which concerns the relationship between the electrical activities of couples of atrial sites. To quantify this aspect we introduce two different measures of the level of synchronization: the indexes of synchronization (S) and of causal coupling (S12). S and S12 rely on a Shannon Entropy measure of the dispersion of the propagation delays between coupled activations in two atrial sites. In fact they are based on the assumption that, if two atrial sites are repeatedly interested by the passage of the same stable activation-wave (i.e. are synchronized), the consecutive propagation delays between coupled activations recorded in the sites should have a small dispersion. On the contrary, when the sites are activated by the same but unstable wave or by different wavelets [2], the values of the delays should present a higher variability. The two indexes S and S12 were validated and compared on cellular automaton (CA) simulated activation time series and on endocavitary signals in patients.

2.   Methods

2.1.   Index of synchronization S

The level of synchronization in the electrical activity of two atrial sites was defined by a Shannon Entropy-characterization of the distribution of the propagation delays between coupled activations in the two sites.

Once the activation time series had been estimated for both signals by a morphology-based algorithm [3], the propagation delays were defined as the absolute value of the differences between coupled activations in the two signals. Couples were obtained by associating each activation in one series with the closest in the other series.

Then the propagation delay values were organized in a histogram and their spreading was characterized by a measure of Shannon Entropy (SE):

$$SE = -\sum_{i=1}^{N} p(i) \cdot \ln p(i) \qquad (1)$$

where p(i) was the probability for the i-th bin, estimated as the ratio of the number of delays in the bin to their total number in the series, and N the total number of bins.

Starting from SE, the synchronization index S was defined as follows:

$$S = \left(1 - \frac{SE}{\ln(ndelays)}\right) \qquad (2)$$

where *ndelays* was the number of delays (couples of activations) from the signals and its logarithm represented the higher value of SE obtainable from a delay series of length *ndelays* (with all the delays in different bins).

Owing to this definition, S presented values ranging from 0 to 1 and increasing with increasing degree of synchronization. It reached its maximum value 1, when it was computed on completely synchronous signals (i.e. signals which had delays less different than the bin size, resulting in a null SE), while it took its minimum value 0, when the spreading of values in the histogram was maximal (SE = *ln(ndelays)*). The last condition was rarely satisfied even by independent series: in fact, also for random propagation delays there was a non-null probability to find at least two delays in the same bin, resulting in a value of S greater than zero. This bias imposed a case-by-case assessment of significance of S values to ensure a correct interpretation of the level of synchronization obtained. This task was performed by surrogate data analysis. For each original pair of activation time series, a set of surrogate pairs (35 surrogate series from each original series) was obtained by randomly permuting the order of the FF intervals (i.e., the intervals between two consecutive activation times in the same series). In this way the statistical properties of the original series were preserved, while any linear coupling between the two series was destroyed. The 95th percentile (p<0.05 in refusing the null hypothesis of S arising from independent series) of each S distribution obtained from surrogate data was assumed as threshold of significance for the correspondent original value of S.

2.2.   Index of causal coupling S12

The definition of index S did not consider if a preferential verse in the propagation of activation was present (i.e. which site activated the other, or which site was activated before). In fact the delays were defined associating to each activation time in one series the closest in the other, independently if one activation was former or subsequent to the other. Therefore index S provided a generalized measure of the coupling between two sites, without assuming any preferential direction in wave propagation. However, provided that two atrial sites showed a high level of synchronization (index S), the existence of a preferential verse in the coupling of

activations should be tested. To obtain information about this second aspect, another index of synchronization (S12) was introduced and defined in a similar manner to S, except for the way activation times were coupled: in this case, each activation of the first series was associated with the closest subsequent activation of the second. The calculus of index S12 was repeated and the propagation delay series were determined starting from each one of the two activation series. In this way two values of the index of synchronization (S12 and S21) were obtained for each couple of signals: the higher value of the two was assumed as strength of the causal coupling and the verse of its calculus as causal verse. Aimed simulations were proposed to investigate thoroughly this point.

2.3.   Cellular automaton model

A 2D CA model, simulating propagation of excitation in the atrial tissue, was used to examine the response of index S and S12 to changes in the dynamics of impulse propagation.

The model consisted in a 100x100 lattice of individual square units, each connected with a Moore neighborhood of radius 1. Each unit was characterized by 7 electrophysiological parameters (state of activity, absolute and relative refractory periods, 4 directional latencies for the transmission of excitation). At any discrete time step nT, each unit assumed an excitation state E among rest, firing, absolute refractory and relative refractory. An unit remained at rest, unless excited by a neighbor or externally stimulated. After excitation, the unit passed through firing, absolute and relative refractory states and rest again. Excitation could be transmitted only to excitable (at rest or in relative refractory state) neighbors and after a time delay, which depended on the latency of the firing cell and on the excitation state E of the excitable neighbor. As output of the model, we considered the activation time series of each unit.

The model was used, first of all, to study the different meaning of index S and S12. Concerning this, we considered the simple case of radial propagation from a point source of excitation, firing with a constant rate in a partially excitable tissue, and associated it with two different geometrical dispositions of the recording sites. Then indexes S and S12 were tested on five different conditions of propagation, with increasing complexity: single wave in fully excitable tissue, specifically radial propagation (RP) and anatomical reentry with excitable gap (ARG), single wave in partially excitable tissue, namely anatomical reentry with no excitable gap (ARnG) and spiral wave reentry (SW), and finally multiple wavelet propagation (MW). For each condition the mean values of indexes S and S12 were calculated on 10 couples of units, randomly chosen in different parts of the lattice, but with fixed distance between paired units.

2.4. Data collection in patients

Intra-atrial electrograms were obtained from a multielectrode basket catheter in the right atrium of patients with paroxysmal or chronic AF. AF signals were subdivided by an expert cardiologist in three classes of increasing complexity (AF1, AF2, AF3, Well's criterion [4]) and for each class 10 couples of signals lasting 50 activations (time resolution of almost 10 sec) were analysed. Couples were chosen along the same spline, to allow the comparison with a normal activation sequence.

As reference case of highly synchronized activity, we chose 10 couples of bipolar signals recorded in patients during atrial flutter.
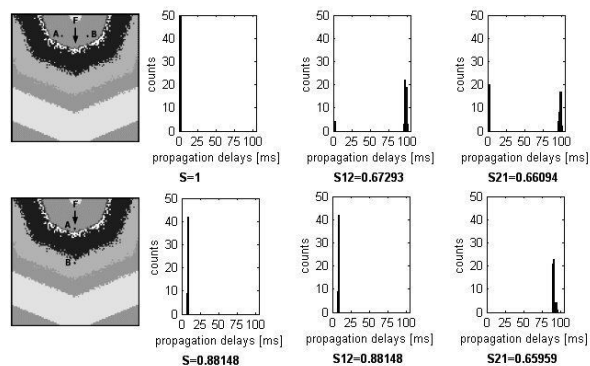

Figure 1. Synchronization and causal verse of activation for radial propagation in a partially excitable tissue. F indicates the firing source of excitation, while A and B are the recording sites (see text for details).

3. Results and discussion

3.1. Validation of S and S12 by simulations

The performances of S and S12 were compared in the simple case of a radial propagation in a partially recovered tissue (Figure 1). Two different dispositions of the recording sites A and B were considered: sites at the same distance from the firing source F (top) and at increasing distance (bottom). In the first case we obtained a high value of S (histogram with single bin), but smaller values of S12 and S21 (higher spreading of values). This reflected the existence of a high synchronization between the sites, but the absence of a causal verse in excitation: in fact the sites were repeatedly activated by the same wave, but almost simultaneously. On the contrary, with sites at increasing distance from the source, S and S12 presented the same high value, which indicated the existence of a causal verse in addition to a high synchronization level. The smaller value of S21 respect to S12 identified the causal verse as going from A to B. Concerning the calculation of S and S12 on the five simulated propagation types (Table 1), both indexes were able to distinguish different levels of complexity in propagation. In fact S and S12 were maximal in the case of single wave propagation in a fully excitable tissue (RP and ARG), while decreased progressively and significantly from reentry without excitable gap (ARnG) to spiral wave (SW) and multiple wavelet (MW) propagation (p<0.001, Kruskall-Wallis and Wilcoxon-Mann-Whitney test). Moreover in multiple wavelet propagation S and S12 presented different values, which evidenced the difficulty of identifying a clear causal verse. Finally, according to surrogate data analysis, all coupling resulted significant for the first four classes of propagation. Instead in MW the number of significant coupling was significantly reduced (to 30% for S, to 40% for S12). This could be expected considering that the activation time series were likely behaving as independent during multiple wavelet propagation.

Table 1. Synchronization (S) and causal coupling (S12) indexes for different kinds of propagation. All data are expressed as mean ± SD.

Propagation	S	S12
RP	1	1
ARG	1	1
ARnG	0.92±0.05	0.92±0.05
SW	0.70±0.05	0.66±0.05
MW	0.48±0.08	0.39±0.08

3.2. Validation of S and S12 by endocavitary signal analysis

Synchronization index S and causal coupling index S12 were calculated as a function of the bin size (ranging from 1 to 100, step 1) on the 4 classes of atrial rhythm considered. Both S and S12 presented a high dependence from this parameter: for each of the rhythms there was a foreseeable increase in the values of S and S12 as the bin size increased (Figure 2). However, for a large range of bin sizes the four distributions resulted significantly different: for index S, Kruskal-Wallis test was significant (p<0.001) for bin sizes < 87 ms, while Wilcoxon-Mann-Whitney tests between pairs of distributions were all significant for bin sizes < 15 ms. Similarly, for index S12, Kruskal-Wallis test was significant for bin sizes < 163 ms, while Wilcoxon-Mann-Whitney for bin sizes < 20 ms.
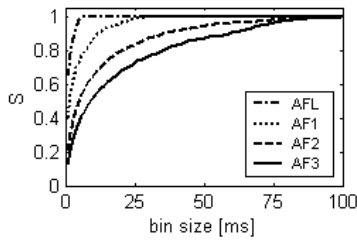
Figure 2. Dependence of the index S on the bin size in the four atrial rhythms considered.

Table 2. Synchronization indexes S and S12 for different atrial rhythms (bin size = 6 ms). All data are expressed as mean ± SD.

Class	S	S12
AFl	1	1
AF1	0.76±0.05	0.76±0.05
AF2	0.56±0.06	0.41±0.12
AF3	0.39±0.03	0.26±0.03

The values of indexes S and S12 for the four classes of atrial rhythms were compared (Table 2) for a bin size of 6 ms. This value was chosen to have S and S12 equal to 1 in AFl signals, which represented our maximally synchronized reference case. Both indexes decreased progressively and significantly (p<0.001) from AFl to AF of increasing complexity class. This accounted for the fact that the complexity and irregularity in the morphology of the signals reflected complex underlying mechanisms in the propagation of the excitation wavelets [5]. Moreover, in the case of AFl and AF1 both indexes presented the same values, indicating the presence of a causal verse in excitation and thus the preservation of a correct activation sequence (from the upper to the lower part of the atrium). On the contrary the former condition was not observed in Type II and Type III AF, where, even if a certain level of synchronization could be present, the correct activation path was not preserved (index S12 was lower than S) and the activation waves followed different and abnormal paths.

In accordance with simulation results, the percentage of significant synchronization (S) obtained by surrogate data analysis was 100% for AFl and Type I and II AF, while reduced to 50% for Type III AF. Similarly the percentage of significant causal coupling (S12) was 100% in AFl and Type I AF, 70% in Type II AF and decreased to 10% in Type III AF. This low percentage confirmed the absence of a regular, causal activation sequence in the last two rhythms.

4.   Conclusions

In this study two measures for the quantification of synchronization (S and S12) in the electrical activities of couples of atrial sites during AF were proposed. Both indexes were defined starting from the simple concept of propagation delays between coupled activation time series and tested by experiments realized with a cellular automaton model, before application to real data. The clear electrophysiological meaning of our indexes and the keen testing technique, consisting in simulating plausible propagation abnormalities, were the most distinctive features of our study. Moreover this work made a distinction between two definitions of synchronization, one generalized (S), which could be applied to every couple of chosen electrodes regardless the direction of the activation wave, the other (S12), more specific, which provided information about the causal verse of activation between the two sites. This last allowed to distinguish normal and abnormal activation sequences and gave hints about the direction of activation waves. Therefore the completing information provided by the use of both indexes could help outlining the abnormal paths of propagation involved in AF, differentiating zones with different values of synchronization, and evaluating the extent of space synchronization. These features stood S and S12 as useful tools both in the understanding of AF mechanisms and guiding therapy approaches, as catheter ablation or overdrive pacing.

References

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