Quantification of Phase Recurrences in Atrioventricular (AV) Conduction during Atrial Arrhythmias

M Masè[1], L Glass[2], F Ravelli[1,3]

[1]Dept of Physics, University of Trento, Trento, Italy
[2]Dept of Physiology, McGill University, Montreal, Canada
[3]ITC-irst, Trento, Italy

Abstract

In this study we propose a new method to characterize atrioventricular (AV) coupling during atrial arrhythmias, based on the quantification of the recurrences of the AV phase series, which represents the timing of atrial beats with respect to subsequent ventricular beats. Recurrences are quantified in terms of autocorrelation function maximum (R), Shannon Entropy (SE) and synchrogram features (locking ratio LR, presence p and length k of phase-locked epochs). AV phase series obtained during type I and II atrial flutter (AFL1 and AFL2) and atrial fibrillation (AF) showed the existence of significant phase-locked segments, whose presence, length and locking ratios decreased at increasing atrial frequency and complexity (AFL1: R=0.99±0.01, SE=1.13±0.52, p=99.5±0.9%, k=96.3±30.4, LR=0.37±0.15; AFL2: R=0.75±0.01, SE=2.99±0.01, p=57.3±8.8%, k=2.42± 0.54, LR=0.23±0.02; AF: R=0.77±0.06, SE=2.90±0.25, p=70.8±18.9%, k=2.24±0.29, LR=0.34±0.06). The quantification of AV phase recurrences could have basic as well as clinical applications for understanding AV node dynamics during atrial arrhythmias and characterizing AV pharmacological control.

1. Introduction

The control of ventricular response during atrial arrhythmias as atrial flutter (AFL) and fibrillation (AF) is one of the principal strategies in the therapy of these arrhythmias. Nevertheless the mechanisms responsible for AFL and AF ventricular rhythm, which involve interactions between high frequency atrial activity and AV node filtering action, are still poorly understood.

An extensive literature is present in cardiology documenting the statistical properties of ventricular activity during AF [1]. In addition more recently great attention has been devoted to the spatial mapping of atrial activity to quantify AF organization [2,3]. Conversely just a few studies, mostly in animal or computer models, have dealt with the relationship between atrial and ventricular activities in order to characterize quantitatively the AV node during arrhythmias.

In this study we present a method to quantify the coupling between atrial and ventricular activation time series during atrial arrhythmias. The method is based on the construction of the AV phase series, which represents the timing of atrial activations with respect to subsequent ventricular activations. Conditions of AV coupling are recognized in presence of phase recurrences (i.e. phase-locking patterns) and quantitatively characterized in terms of the autocorrelation function, Shannon Entropy (SE) and synchrogram features. The method is applied to atrial and ventricular signals recorded in patients with atrial arrhythmias of different complexity class, i.e. type I and II AFL (AFL1 and AFL2) and AF.

2. Methods

2.1. Data collection

Atrial and ventricular signals were recorded during an electrophysiological study in patients with AFL1, AFL2 and AF (4, 2 and 4 patients respectively). Atrial activity was recorded by a bipolar catheter in the esophagus in patients with AFL and by a quadripolar catheter in the right atrium in AF patients. In the last case the recording from the low right atrium (i.e. closer to AV node entrance) was considered. A body surface ECG (lead V1) was recorded simultaneously with the atrial electrograms (bandpass of 30-500 Hz) and digitalized at 1 kHz in both AFL and AF patients. A signal window of 60 seconds was considered in each patient for phase series construction and analysis.

2.2. Phase series construction

To investigate the presence of coupling between atrial and ventricular activity during atrial arrhythmias, we introduced the AV phase series, a mixed series constructed using both atrial and ventricular activation

time series.

For each atrial activation time ta_i a temporal phase ϕ_i was defined with respect to the closest subsequent ventricular activation time tv_f as:

$$\phi_i = ta_i - tv_f \quad (1)$$

The phase defined above (*1-phase*) was generalized to detect higher orders of coupling, referring atrial activation times to a sub-sampled set of ventricular beats, i.e. considering groups of *n* ventricular cycles (*n-phase*). The construction of the phase series starting from atrial and ventricular activation times is schematized in Figure 1 for $n = 1, 2$, which were considered in this study.

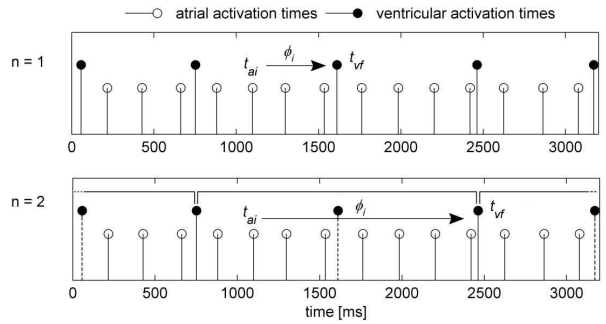

Figure1. Construction of the AV phase series, which represents the timing of atrial activation times in *n*-ventricular cycles.

Atrial and ventricular time series used in the calculation of ϕ series were automatically estimated from the recorded signals. After a preprocessing step to reduce ventricular interference, atrial activation times were detected in correspondence of the maximum positive signal slope in AFL, while in AF a morphology-based approach was used to allow a consistent estimation of activation times even in presence of fragmented electrograms [4]. Ventricular activation times were set in correspondence of the QRS complex maximums.

2.3. Quantification of phase recurrences

The condition of AV coupling was identified with the presence of recurrent structures in the AV phase series. Recurrences were identified and quantified by calculation of autocorrelation function maximum (*R*), Shannon Entropy (*SE*) and synchrogram [5] features.

The presence of periodicities in the AV phase series was tested by calculation of the autocorrelation function, which is defined for a generic lag *m* by:

$$R_{\phi\phi}(m) = \sum_{n=0}^{N-m-1} \phi_{n+m}\phi_n \qquad m \geq 0 \quad (2)$$

where *N* is the number of elements in the series.

$R_{\phi\phi}$ was normalized to obtain values identically equal to 1.0 at lag zero and was calculated for lags *m* over the range [0,50]. The maximum *R* (for $m \neq 0$) of $R_{\phi\phi}$ was used to quantify AV coupling.

The presence of recurrent values in the AV phase series was assessed by constructing phase histograms and quantifying their dispersion by SE, defined by:

$$SE = -\sum_{i=1}^{M} p_i \cdot ln\, p_i \quad (3)$$

where *M* is the number of bins (fixing a bin size of 50 ms) and p_i the maximum likelihood estimate of the i^{th} bin probability (i.e. ratio of number of phases in the i^{th} bin to the total number of phases). *SE* is minimal (*ln(m)*) in presence of *m* minimally dispersed peaks (i.e. perfect *m:n* coupling), while is maximal (*ln(M)*) for a uniform distribution (i.e. absence of coupling).

The presence of phase-locked epochs in the AV phase series was evaluated by constructing synchrograms [5], which display the sequence of phase values as a function of time. Phase-locked conditions result in the appearance of horizontal line structures in the synchrogram, which were automatically identified and classified [6]. To identify a *m:n* phase-locked segment, the *n-phase* series values were divided alternatively into *m* subgroups, starting from one phase and including *k* (with $k \geq 2$, $k \in \mathbf{N}$) elements in each subgroup. The mean value of each subgroup was calculated and subtracted from each element of the subgroup, thus eliminating the vertical distance between lines. The dispersion of the resulting line was compared to a defined threshold ε. In case of line dispersion smaller than ε, a phase-locked segment was recognized, the number of elements in each subgroup increased by one ($k=k+1$) and the previous steps repeated to test the presence of longer locked segments. Otherwise, the window of the analysis was forwarded by one phase element and the grouping repeated from $k=2$.

The analysis was performed for phase-locking ratios equal to: $n = 1$, $m = 2, \ldots, 8$; and $n = 2$, $m = 3, 5, 7, 9, 11, 13, 15$. The threshold ε was set to 50 ms to match visual inspection criteria. Identified phase-locking patterns were characterized by their locking ratio (i.e. $LR = n/m$), their presence *p* on the 60 s window (i.e. number of *m:n* phase-locked beats over total number of beats) and their mean length (i.e. mean *k* value).

2.4. Surrogate data analysis

The significance of the three measurements performed was assessed on a case-by-case basis by surrogate data analysis.

In the case of autocorrelation function $R_{\phi\phi}$ and synchrogram index *k*, 100 surrogate series were obtained

by shuffling the temporal order of each original phase series and surrogate index values were calculated. Significance thresholds for R (R_s) and k (k_s) were defined as the 95th percentile of the correspondent surrogate distribution. Index values higher than surrogate counterparts were considered significant ($p<0.05$).

In the case of *SE*, 100 surrogate data series were generated for each original series as realizations of processes (i.e. white noise) uniformly distributed between min (ϕ) – 0. A significant threshold for *SE* (SE_s) was defined as the 95th percentile of the surrogate distribution. Index values smaller than surrogate counterparts were considered significant ($p<0.05$).

3. Results

Representative examples of the study of AV coupling by phase recurrences are displayed in Figure 2 and 3 for patients with AFL1 and AF respectively.

In the first case a stable 4:1 phase-locking pattern was identified by the three methods proposed. In fact the autocorrelation function (upper panel, left) showed high, significant values for lags equal to 4 (R=0.99 vs R_s=0.81) and multiples. The phase distribution (upper panel, right) presented four minimally dispersed peaks, corresponding to the four recurrent values of the phase. The small dispersion of phase values resulted in a small value of *SE*, significantly different from its surrogate counterpart (*SE* =1.43 vs SE_s=2.84). Finally the phase looking condition was visually evident in the synchrogram (lower panel), which displayed a clear four line structure, maintained along the quite whole analysed window (p=98.1%, k=65).

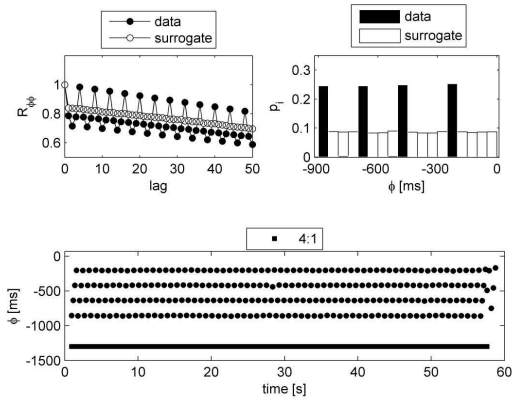

Figure 2. Phase-locking patterns in a patient with AFL1. Autocorrelation function (left upper panel), AV phase distribution (right upper panel) and synchrogram (lower panel). The three methods identified a stable 4:1 phase-locking.

A different situation was observed in AF patients, as exemplified in Figure 3. In this case phase-looking conditions were still observed, although transient and less stable. The synchrogram (bottom panel) showed the presence of a prevalent (p=40.7%), but unstable (short length k=3.0±1.0) 4:1 phase-locking pattern, together with 7:2 and 5:1 phase-locking ratios, which presented limited presence and length (p=4.38% and 6.02% respectively, k=2.00). This condition resulted in a fast decrease of the autocorrelation function (upper panel, left), which grew above surrogate threshold just at lag 4 (R=0.81 vs R_s=0.75). A broadening of the 4 peaks in the phase distribution (upper panel right) was likewise observed, which produced an increase in *SE*=2.94 towards surrogate threshold (SE_s=3.31). Thus, with respect to synchrogram method, R and *SE* methods identified clearly only the prevalent and more stable locking patterns.

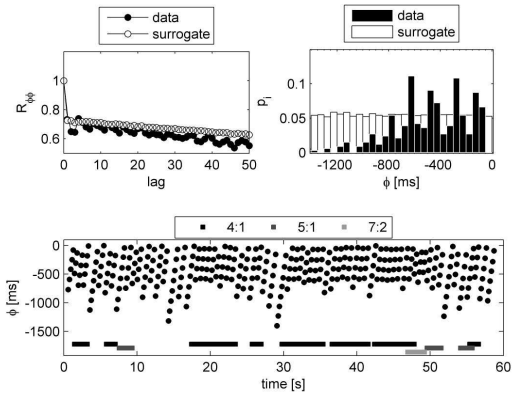

Figure 3. Phase-locking patterns in a patient with AF. Autocorrelation function (left upper panel), AV phase distribution (right upper panel) and synchrogram (lower panel). Different phase-locking patterns can be observed, although transient and less stable.

The phase recurrences analysis conducted on the overall population of patients showed the existence of a wide spectrum of phase-locking patterns in different types of atrial arrhythmias. The results of the analysis reported in Table 1 evidence a dependence of the presence and length of patterns on atrial cycle length (i.e. FF mean) and complexity (i.e. FF std). Indeed single, highly stable 2:1 and 4:1 phase-locking patterns were observed in AFL1 patients, who were characterized by lower atrial rates and very regular activity. The presence of stable patterns was reflected by high values of R, p and k and low values of *SE*. Conversely in AFL2 patients, characterized by regular but high atrial rates, phase locking patterns were still observed but as transient, less stable epochs. This situation was reflected by lower values of R, p and k and higher values of *SE*. Finally in AF patients, characterized by high atrial rates and high complexity, the least stable (smaller k values) patterns were observed. With regards to

the mean *LR* of the patterns, it decreased progressively at increasing atrial rates, meaning a higher number of blocked beats for higher atrial rates.

Regarding the significance of AV coupling, surrogate data analysis showed all coupled epochs to be significant in patients with AFL1 and AFL2. Differently in AF, just the 68±23% of phase-locked epochs detected in synchrograms presented lengths *k* longer than surrogate threshold.

Table 1. Autocorrelation maximum (*R*), Shannon Entropy (*SE*) of AV phase series, total presence (*p*), mean length (*k*) and mean locking ratio (*LR*) of phase-locked segments in patients with type I and II atrial flutter (AFL1 and AFL2) and atrial fibrillation (AF). All data are expressed as mean ± std.

	AFL1	AFL2	AF
FF mean (ms)	240±48	167±11	190±33
FF std (ms)	3.8±2.2	7.5±0.7	20.2±9.7
R	0.99±0.01	0.75±0.01	0.77±0.06
SE	1.13±0.52	2.99±0.01	2.90±0.25
p	99.5±0.9	57.3±8.8	70.8±18.9
k	96.3±30.4	2.42±0.54	2.24±0.29
LR	0.37±0.15	0.23±0.02	0.34±0.06

4. Discussion and conclusions

In the present work a quantitative method for the characterization of AV coupling in terms of phase recurrences was introduced and applied to atrial arrhythmias of different complexity class.

From the methodological point of view, our technique is based on the construction of a mixed phase series and thus has the advantage of providing information on both atrial and ventricular activation processes and their relationship by characterizing a single time series. The quantification of AV coupling is obtained by three analysis tools already described in literature, but applied for the first time to the problem of AV coupling. Other linear and non linear methods in time series analysis could be used as well to characterize recurrences in AV phase series. Nevertheless, due to the transient nature of the phase-locking pattern especially during AF, methods with high time resolution should be preferred. In our study, while autocorrelation function and SE methods evidenced only sufficiently stable locked segments, synchrogram analysis allowed us to detect and characterize even short segments of locked activity. Finally the application of a test based on surrogate data provided a case-by-case assessment of the significance of the locked patterns to exclude background couplings.

From the electrophysiological point of view, our study showed the existence of a wide spectrum of AV coupling patterns during atrial arrhythmias of different complexity class. An original result of the study is the effect of atrial rate, in addition to atrial activity complexity, in the determination of pattern stability. Indeed the presence of unstable patterns, even during regular rhythms as in AFL2 patients, evidenced a direct involvement of AV node properties in the determination of the patterns. The observed decrease of pattern *LR* and stability with increasing atrial rates and complexity is consistent with the hypothesis of concealed conduction [7], according to which non-conducted beats affect AV nodal properties and thus the conduction of subsequent beats.

In consideration of the importance of ventricular rate control in the treatment of atrial arrhythmias, especially AF, and of the still limited knowledge of AV node conduction properties during arrhythmias, the method proposed could have applications at the basic research level, providing new insights on the investigation of AV node conduction, but also at a clinical level for the characterization of the efficacy of pharmacological treatment.

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Address for correspondence

Michela Masè, PhD
Dept. of Physics, University of Trento
Via Sommarive 14, 38050 Povo (TN), Italy
E-mail address: mase@science.unitn.it