Telemedicine Application for Predicting Ventricular Arrhythmia and Sudden Cardiac Death by the Analysis of Phase Synchronization in Heart Failure Patients

S Khoor[2], T Szuszai[1], N Balogh[1] I Kecskes[1],
K Fugedi[2], I Kovacs[2], I Simon[1], S Rubicsek[1]

[1]Medartintech Ltd, Budapest, Hungary
[2]Szent Istvan Hospital, Budapest, Hungary

Abstract

The approach consists of an application of the Hilbert-Huang transform to decompose an empirical time series into a number of intrinsic mode functions (IMFs), calculation of instantaneous phase of the resultant IMFs, and the statistics of synchronization. Our telemedicine server collected the 24-hour ambulatory ECGs (RhythmPattern, SzivLeso) and analyzed the data. The study population (age 67.3±8.2 years) consists of 97 heart failure patients with EF < 0.35, where frequent (> 4000/24 hours) ventricular ectopic beats were found. The ECG monitoring was repeated in every month with a mean follow-up was 36.4 months. The number of synchronization (NSy), its length (ASy), were compared in patients with and without ventricular tachycardia (VT+: number of patients 21, VT-: 76); with and without sudden cardiac death (SCD+: 11, SCD-: 86). The dichotomization cutoff points that maximized the hazard ratio obtained from the Cox regression model were: NSy: 18.4/24hour; ASy: 69.3 minute; SI: 0.39.

1. Introduction

The concept of synchronization is used to reveal interaction between two or more systems from experimental data. Only the phase locking is important, while no restriction on the amplitudes is imposed. Thus, the phase synchronization of coupled systems is defined as the appearance of certain relation between their phases, while the amplitudes can remain non-correlated. The synchronization properties were analyzed in the medical field [1-11]. Prediction or forecasting the sudden cardiac death (SCD) with or without ventricular tachycardia (VT) or ventricular fibrillation is an unsolved problem.

We decided to analyze the relation of the intrinsic heart rate (iHR) and the ventricular premature beat time-series (VPB_TS) using the math calculations of synchronization – we did not find in the literature such a solution. Figure 1. shows an example of frequent VPB. We have no method to forecast the possible VT, VF, or SCD in this (and any other) patient.

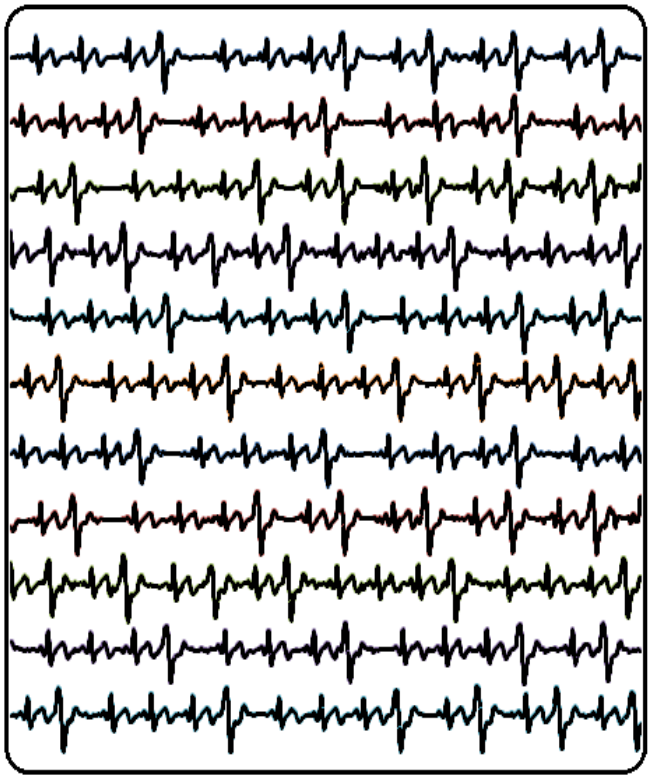

Figure 1. Frequent VPB in a study patient without any serious endpoints during our study.

Figure 2. shows a short time-segment of the patient. Our system, the HeartPattern analyses the P-wave to P'-wave intervals instead of the R-wave to R'-wave intervals, because in the case of frequent VPB, the iHR could be calculated by interpolation ("hidden R-waves") – which distorts the time-series.

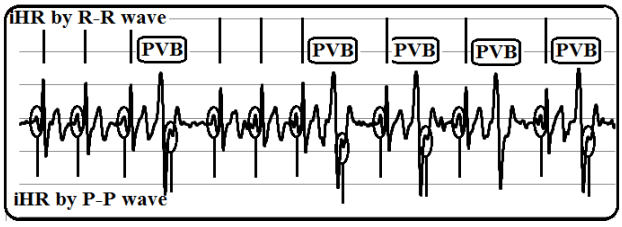

Figure 2. Signal processing based on R-R' (top) or P-P' (bottom) wave detection.

2. Methods

The study population (age 67.3±8.2) consists of 97 heart failure patients with EF < 0.35, where frequent (> 4000/24 hours) ventricular ectopic beats were found. The ECG monitoring was repeated in every month with a mean follow-up was 36.4 months. The number of synchronization (NSy), its averaged length (ASy), and the synchronization index (SI) were compared in patients with and without ventricular tachycardia (VT+: number of patients 21, VT-: 76); with and without sudden cardiac death (SCD+: 11, SCD-: 86).

The EMD method was developed [8,11] from the assumption that any time series data consist of different simple intrinsic modes of oscillation. The essence of the method is to identify the intrinsic oscillatory modes by their characteristic time scales in the data empirically, and then decompose the data. This is achieved by "sifting" data to generate IMFs. The IMFs obtained by EMD are a set of well-behaved intrinsic modes, and these functions satisfy the conditions that they are symmetric with respect to the local zero mean and have the same numbers of zero crossings and extremes. Based on this property, one can select a reasonable one from IMFs as a respiratory rhythm and simply apply the Hilbert transform on it to calculate the instantaneous phase.

The calculations were performed in our telemedicine server: the remote site (mostly the General Practitioners) sent the data into the Internet server. After retrieving the data, the virtual cardiologist and the virtual engineer check the data and perform the analysis by the following steps:

I. The ECG data are retrieving from the telemedicine server

II. Automated calculation:

1. The local extremes in the VPB-time series data are identified,

2. All the local maxima are connected by a cubic spline line U(t), forming the upper envelope of the time-series,

3. The same procedure is applied for the local minima forming the lower envelope L(t),

4. Calculate the (running) mean : $m_1(t) = (U(t)-L(t))/2$,

5. Calculate the first component: $h_1(t) = x(t)-m_1(t)$

III. Supervised telemedicine signal processing:

1. Decision about $h_1(t)$ (IMF or not): if it satisfies the following 4 criteria:

   a. $h_1(t)$ is free of riding waves,

   b. it shows symmetry of the upper and lower envelopes with respect to zero,

   c. the numbers of zero crossing and extremes are the same, or only differ by 1,

   d. analysis of intermittence (the synchronization must appear again and again in some time intervals)

2. If $h_1(t)$ is not an IMF, the shifting process has to be repeated as many times as is required to reduce the extracted signal to an IMF:

   a. $h_1(t)-m_{11}(t) = h_{11}(t)$,

   b. repeat III.1/a-b

   c. the sifting process continues up to k times untill the tolerance limit:

   $h_{1(k-1)}(t)-m_{1k}(t) = h_{1k}(t)$.

3. The first IMF ($c_1 = h_{1k}(t)$ is subtracted from the original data, and the difference r_1 is the first residue $(x(t)-c_1(t) = r_1(t)$.

4. Repeat the processes of III. until the final residue will be a constant or a monotonic function, and get:

$$x(t) = \sum_{i=1}^{n} c_i(t)+r_n(t) \quad \text{and}$$

$$r_{i-1}(t) - c_i(t) = r_i(t)$$

5. Applying Hilbert transform:

   a. calculation of the conjugate pair of $c_r(t)$: $y_r(t) = 1/\pi * P\int(c_r(t')/t-t')dt'$ (P indicates the Cauchy principal value)

   b. $c_r(t)$ and $y_r(t)$ form a complex conjugate pair of an analytic signal $(z_r(t)\varphi$, where the instantaneous phase $\varphi_r(t) = \arctan(y_r(t)/ c_r(t)$ with amplitude $A_r(t) = (c_r^2(t) + y_r^2(t))^{1/2}$

IV. Constructing the synchrogram:

   a. Denote the phase of PVB time series φ_{PB} and of heart rate φ_{HR}

   b. the condition of phase locking: $|n\ \varphi_{PB} - m\ \varphi_{HR}| = const$,

   c. the condition of fequency locking: $|n\ \varphi_{PB} - m\ \varphi_{HR}| < const$,

   d. Defining $\psi_m(t_k) = 1/2\pi\ (\varphi_{PB}(t_k) \mathrm{mod}\ 2\pi n$,

   e. Plotting $\psi_m(t_k)$ versus t_k (t_k is the heart rate event time and $\varphi_{PB}(t_{k+m}) - \varphi_{PB}(t_k) = 2\ \pi n$)

V. Calculate the quantitative parameters of the synchronization.

The number of synchronization (NSy) and the average length of these episodes (ASy) were determined during 24 hours. The third parameter, the Synchronization Index (SI) can be constructed, which exhibits small and large values for non-phase-locked and phase-locked groups, respectively, as SI = σ ((r1)+r2)/2;

where σ is a measure of phase synchrony between the two time series, and σ =1-S/Smax, where S is the Shannon entropy (S=-∑_(i=0)^n pilnpi of the cyclic phase distribution and Smax is the maximal entropy. (The cyclic phase distribution is the distribution of 2π modulated difference ΔΨ(t) between the phases of the two groups: the distribution is divided into M bins, and pk is the probability that ΔΨ is in bin k; Smax = ln M.) The value σ exhibits a large (approximately unity) value for phase-locked groups and low (close to zero) value for phase-drifting. For perfect phase-locking, SI has a value of the mean of the group orders (same as Rmod); however, for lack of phase-locking, SI is zero (because σ is zero) as opposed to the small but fluctuating values of Rmod. The normalized value of SI (0<SI<1.0) was used in the analysis.

Figure 3 shows the synchronogram of the same patient (short time-segment), with the parallel lines.

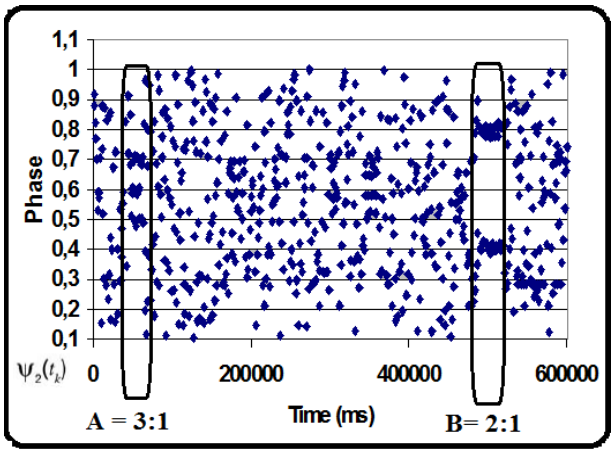

Figure 3. Synchronogram with 3:1 and 2:1 synchronization.

The statistical calculation was performed with SPSS V 15.0.

3. Results

The telemedicine assisted patients were divided into 3 groups: G1 (N=76) = Group 1 (pts without VT and/or SCD), G2 (N=21) = Group 2 (pts with VT), G3 (N=11) = Group 3 (pts with SCD).
Table 1. shows the descriptive statistics of the 3 synchronization parameters (NSy/h: the number of synchronization episodes/hour; ASy: the averaged time-duration of the synchronization; SI: the synchronization index.

Table 1. Descriptive statistics of 3 parameters in the 3 groups.

	G1	G2	G3
Mean_NSy/h	11.57	22.21	28.27
SD_NSy/h	4.50	7.26	8.15
Mean_ASy	43.12	53.28	59.77
SD_ASy	16.88	11.72	45.65
Mean_SI	0.29	0.34	0.44
SD_SI	0.13	0.09	0.12

Abbr.: G1 (N=76) = Group 1 (pts without VT and/or SCD), G2 (N=21) = Group 2 (pts with VT), G3 (N=11) = Group 3 (pts with SCD), NSy/h = number of synchronization/hour, ASy = average duration of synchronization, SI = synchronization index.

Table 2 shows the t-test significance levels (p<0.01)

between the 3 groups.

Table 2. Inter-group significance based on the 3 synchronization parameters.

	NSy/h	ASy	SI
G1 vs G2	0.00	0.01	0.00
G1 vs G3	0.00	NS	0.00
G2 vs G3	NS	NS	NS

The synchronization episodes were also analyzed: the factor analysis model selected the 2:1, 3:1, 5:1, 8:1, 3:2, 5:2, 8:2, 5:3, 7:3, 8:3, 7:4, and 11:4 episodes. All of this showed $p<0.001$ significance between G1 vs G2 and G1 vs G3 and only 5:3 and 8:3 of G2 vs G3of NSy/h; in the ASy parameter : G1 vs G2: 2:1, 8:2, 5:3, 7:3, 11:4; G1 vs G3: 3:2 and 11:4; G2 vs G3: all parameter were insignificant, in the SI parameter: there are not any significant parameter between the 3 groups.

The multivariate discriminant analysis (stepwise method of Wilks) showed an excellent result predicting the 3 groups. The model selected only three parameters (Asy, ASy_7:3 and ASy_11:4), the prediction Wilks' lambda was 0.03 ($p<0.0001$). The classification results G1 to G1: 98.6%, G2 to G2 and G3 to G3 were: 100.0%.

The univariable predictors of SCD: NSy: >18.4/24hour: relative risk 3.07, 95% CI: 1.77-5.46, $p<0.0001$; ASy: >69.3 minute: 1.77, 1.18-2.59, $p<0.01$. Using multivariate discriminant analysis, the separation of the groups was very good: VT+ vs. VT- : Wilks' lambda: 0.236, $p<0.001$; SCD+ vs. SCD-: 0.319, $p<0.001$.

4. Discussion and conclusions

Our data show the forecasting possibility of malignant cardiac arrhythmias and/or the sudden cardiac death using the new methods in calculation of synchronization. The other unique solution to embedding the complex math calculations into a telemedicine system, where the remote part (generally the GPs, not the cardiologists) sends the ECG recordings, the telemedicine center analyze the data in two forms. The telemedicine doctor analyses the ECG registrations according the standard-of-care. The telemedicine engineer supervises and leads the math calculation, as it seen in the previous ("Decision about $h_1(t)$: IMF or not") chapters.

In the case of frequent PVB, the R-R tachogram determined by the R-waves does not represent the real R-R interval because the use of any form of interpolation. Our HeartPattern software can detect the p-waves (it is impossible for the commercial Holter equipments), thus the real intrinsic heart rate time-series could be detected.

Our heart rhythm monitor measures the one-lead electrocardiogram, processes the signal (filtering, QRS detection, QRS-clustering), calculates the non-linear parameters of the intrinsic heart rate variability, determines the interactions of the intrinsic heart rate and the ventricular ectopy. These several parameters are used as input parameters for the multivariate discriminant analysis (MDA), where the 3 output parameters are: normal, moderate risk, and high risk (for cardiovascular events). The system could be used for either primary, or secondary cardiovascular prevention and directly useable by the general practitioners.

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Address for correspondence
Sandor Khoor, Szent István Hospital, Dept of Cardiology, Nagyvárad tér 1, Budapest, Hungary. H-1097
email: skhoor@gmail.com
nandor.balogh@mkardio.hu