Telemedicine Assisted Secondary Prevention with Individual Forecasting based on ECG Monitoring

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Abstract

The aim of our study was to apply two HRV methods (PD2i and wavelet-CART) for the individual forecasting of ventricular tachycardia (VT) and death in telemedicine setting during the cardiac rehabilitation of postinfarction patients. Eighty-eight postinfarction patients were ECG monitored monthly during 36 months. The predictive accuracy of time-frequency HRV variables for ventricular tachycardia (VT), wavelet (W;Daub-4) decomposition parameters from level 2 (W2) to level 256 (W256)) analyzed. The best variable was W32 (W 0.799, p<0.0001). Th eCART's decision sensitivity and specificity reaching 84.5% and 91.9% respectively. The role of telemedicine management (TM+), and 94 age-matched control group without it (TM-) were also studied. Nine deaths in the TM+, and 21 death in the TM- group were observed (p<0.01). The sensitivity, specificity, positive and negative predictive accuracy of the PD2i values (cutoff 1.9) was 66.4, 79.5, 64. and 83.7% respectively.

1. Introduction

The official guideline (and the standards) about heart rate variability [1] is dated by 1996, and stated:

"The parameters which have been used to measure non-linear properties of HRV include 1/f scaling of Fourier spectra, H scaling exponent, and Coarse Graining Spectral Analysis (CGSA)…for data representation, Poincarè sections, low-dimension attractor plots, singular value decomposition, and attractor trajectories have been used…for other quantitative descriptions, the D2 correlation dimension, Lyapunov exponents, and Kolmogorov entropy have been employed. Although in principle these techniques have been shown to be powerful tools for characterization of various complex systems, no major breakthrough has yet been achieved by their application to bio-medical data including HRV analysis. .. However, no systematic study has been conducted to investigate large patient populations using these methods. At present, the non-linear methods represent potentially promising tools for HRV assessment, but standards are lacking and the full scope of these methods cannot be assessed. Advances in technology and the interpretation of the results of non-linear methods are needed before these methods are ready for physiological and clinical studies." Several methods have been developed during the last 20 years (correlation dimension,) [2-6] , but these were not approved to the standard-of-care.

Telemedicine can be divided into three areas: aids to decision-making, remote sensing, and collaborative arrangements for the real-time management of patients at a distance. As an aid to decision-making, telemedicine includes areas such as remote expert systems that contribute to patient diagnosis or the use of online databases in the actual practice of medicine. Our work demonstrates how to integrate into a telemedicine network the non-linear heart rate variability analysis for the everyday clinical practice.

2. Method

For the prospective, internet based HRV analysis studies, a telemedicine network have been developed some years ago. The mobile equipment was changed (from the on-line, GPRS communication route ("HeartSpy") to the store-and-forward, SD card solution ("HeartKeeper"), but some technical features remained. The sampling rate is 1000 Hz, the ECG recordings did not compressed, the filtering did not change the determination of the R wave, and the baseline and trend removal minimally affect the lower components in the spectrum. The automated R wave detection based on a training and test set of 1200-1200 patients with normal and abnormal ECGs. The proper interpolation on preceding/successive beats on the HRV signals is essential (the influence of the ectopic beats on non-linear HRV analysis). Our clinical database collects the relevant clinical data with the 24h ambulatory electrocardiograms (AECG). The telemedicine decision support system splits the analysis into two parts. The first is named "direct ECG analysis", where the standard AECG analysis is

performed within 2-4 hours after the registration (supervised by the telemedicine cardiologist far from the patient), and the standard non-linear HRV calculations are also performed. After the first analysis of the patients ECG in the prospective, follow-up study, an individual, non-linear HRV "fingerprint" is determined. During the repeated examinations of the given patient, the change could be determined "dirt on the fingerprint". In this case the patient and his doctor get a message about the possible disease worsening. One of the presented two studies (PD2i) shows an example about it.

The second part of our telemedicine system is called "indirect clinical ECG analysis", which is an integrated database and calculation system for research purpose. Using our telemedicine system some prospective AECG studies have been performed [6-9], the ECG recordings and the relevant clinical data are collected in the database. The complex math/statistical models were calculated in the special disease population (general population, subjects with high cardiovascular risk, postinfarction or heart failure patients and/or with various arrhythmias (atrial fibrillation, ventricular malignant arrhythmias). The correlation dimension (CD or named D2) of heart rate intervals could be determined by three methods: pointwise method of Grassberger, the method of Farmer and the "point" estimate (PD2i) method by Skinner. In this study we used the Skinner method (PD2i) [10]. In general, all methods determine the logC(r,n)/log r slopes (C(r,n) is the cumulative number of all vector difference lengths within a range (r), and n is the number of vector difference lengths), and the linear slope represents the scaling feature. The PD2i method does not use all possible vector lengths, the nref value is fixed. The PD2i is a rough estimate of the CD, the slope in the linear scaling region is less precise, but this loss is compensated for by its lack of sensitivity to data nonstationarities and size.

The correlation dimension (D2) is defined as C(r) =rD , where C(r) is the cumulative number of all rank-ordered vector differences within a range, r, that begins with the smallest and ends with the largest vector difference. Vectors of varying time steps, that is, embedding dimensions (m), are made; when increasing m no longer increases D2 (i.e., convergence occurs), then D2=log C(r)/log r. PD2i has the advantage of requiring a small data set for analysis of nonstationary signals compared with the classic Grasberger-Procaccia determination of correlation dimension (D2). Each PD2i reference vector (i.e., the vector for a given R-R interval for a given epoch size of m RR intervals) remains fixed, whereas each of the j vectors (the vector from a given beat to subsequent non-neighboring beats) runs through the entire data series. The point-D2 uses a fixed beginning point, nref, and calculates the vector differences (for a given m) relative only to the reference vector anchored at nref. Then the cumulative number of this subset of rank-ordered vector differences, N, within a range, R, is determined for the convergent values of m, and the point-D2=logN/log R. Because nref is chosen sequentially for each digitized point in the time series, the point-D2 can be estimated as a function of time. For the PD2i algorithm the log N versus log R plot for each m was required to show large linear ranges of slope. Once tau was selected, the vector differences for each m were made and rank ordered, and then the cumulative number of vector differences, N, within a range, R, were counted, beginning with the smallest vector difference. Then the log N versus log R plot was made for that embedding dimension and tested by the linearity and convergence criteria described below. For the linearity criterion, the most linear segment in each log N versus log R plot was determined by the first derivative of the log N versus log R plot was within + 15% of that of an initial slope, which had, beginning from the smallest log R value, a minimum of 10 points. The new points were added sequentially on the log R scale until the calculated first derivative of the slope exceeded the ± 15% level; the length of the slope then was noted (i.e., the square root of log N' plus log R2). Then a new initial slope was constructed, beginning with the next smallest log R value, and points were added to the initial 10 until again the "+ 15% rule" was exceeded. This procedure was repeated, iteratively, starting at each log R value, and a corresponding slope segment length was determined. The slope of the longest segment, if it covered at least one logl0 unit on the log R scale, then was accepted as the measure of D2 for that embedding dimension. Value of 0.4 was determined for the convergence criterion, minimizing error in the D2 estimates calculated from the 1,5000-point data samples. In our calculations, the same PD2i parameters were used as in Skinner's publications (tau = 1, LC = 0.30, convergence criterion (CC) = 0.40, PL = 0.15, PI = 4). Artifacts and arrhythmias are generally rejected from analysis by the LC and CC criteria in the PD2i algorithm. The %N Test was used for rejection of noisy data.

In the PD2i study 88 postinfarction patients were monitored weekly with our 24 hour one-channel mobile ECG equipment for 3 years. Our internet server calculated with 1-2 hours delay the correlation dimensions, comparing these data with the previous ones. In the case of lowering the CD under the cutoff value (value of 1.8), the patient was alarmed, and immediate (within 6 hours) medical visit was performed. Figure 1. shows a 1,500 point segment of the R-R tachogram of a patient having critical PD2i values.

In the second study (wavelet_CART) the predictive accuracy of time-frequency HRV variables for ventricular tachycardia (VT), wavelet (W) decomposition parameters from level 2 (W2) to level 256 (W256)) obtained from the 24-hour ECG monitoring were analyzed. The method was similar to other two studies [11-12]. The Daubechies-4 W transform was used.

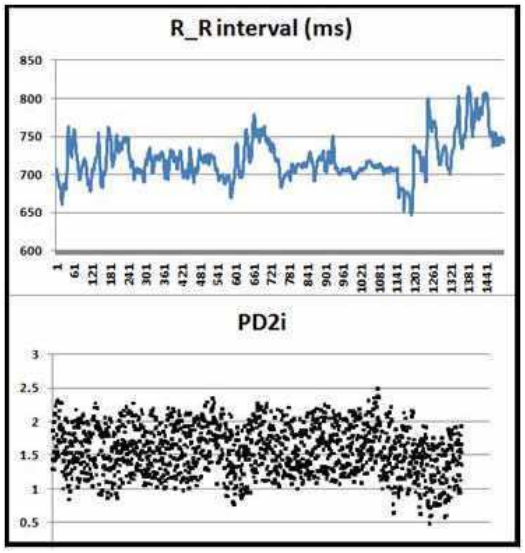

Figure 1. R-R intervals tachogram and the PD2i values of a 1,500 data segment.

For each record, the W coefficients were calculated on sets of 512 RR intervals, giving eight separate levels of analysis named W2, W4, W8, W16, W32, W64, W128 and W256; and, the variability power, level by level, was calculated as the sum of squares of the coefficients (Figure 2).

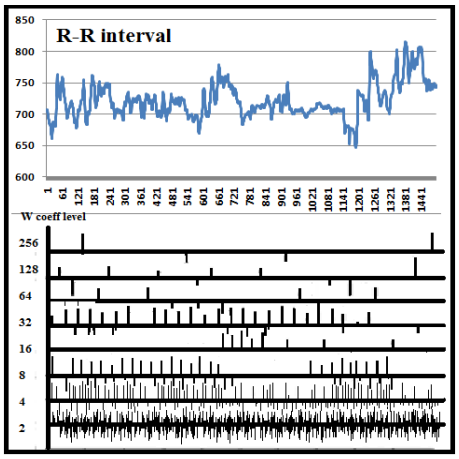

Figure 2. Wavelet coefficients level-by-level

Receiver-operating curve (ROC) analysis was used with the areas under the curves (W_area); if W_area = 0.5 the distributions of the variables are similar, if W_area = 1.0 there is not overlapping. The classification tree was built using the discriminant variables of stepwise regression analysis. The first variable shows the best separation between the two groups (VT+ or VT-), the other variables were then introduced according to a descending order of discriminative capacity. For each continuous variable, the cut-off value acting as a separator offering the smallest number of misclassification (minimizes the sum of false-positive and false-negative results). Sensitivity, specificity and percentage of agreement were calculated on learning. The Classification and Regression Trees (CART) method looks at all possible splits for all variables included in the analysis. The results are in the form of an inverted tree. CART begins with a root node and, through a process of yes/no questions, generates descendant nodes. Some nodes are terminal, meaning that a final determination for classification is reached while other nodes continue to be split until terminal nodes are reached. Once a best split is found, CART repeats the search process for each child node, continuing recursively until further splitting is impossible or stopped. Then, CART proceeds by growing trees until it is not possible to grow them any further. It generates a maximal tree and a set of subtrees.

3. Results

Eighty-eight postinfarction patients were monitored monthly with our mobile 24 hour, one-channel mobile ECG equipment with a store-and-forward technique. In the case of lowering the PD2i under the cutoff value (1.8), an immediate medical visit was performed. During the 3 years follow-up 88 patients (age 67+-9.4 m/f 48/40, ejection fraction >0.35) with telemedicine management (TM+), and 94 age-matched postinfarction control group (age 65+-8.3 m/f 50/44, ejection fraction >0.35) without it (TM-) were studied. 9 deaths in the TM+, and 21 in the TM- group were observed ($p<0.01$). The sensitivity, specificity, positive and negative predictive accuracy of the CD values was 66.4, 79.5, 64.1, 83.7%. The CD cutoff value of 1.8 showed significant difference (< 0,001) by the Kaplan-Meier survival curves.

In the same patient group, the predictive accuracy of time-frequency HRV variables for ventricular tachycardia (VT), wavelet (W) decomposition parameters from level 2 (W2) to level 256 (W256)) obtained from 24-hour ECG monitoring were analyzed. During the 3 years 11786 recordings were made and VT of 379 patients were observed. The analysis was performed in the time-segment before 2 hours of the VT. The Daubechies-4 W transform was used. For each record, the W coefficients were calculated on sets of 512 RR intervals (the 2-hour segment was divided into the 512 R-R intervals, giving eight separate levels of analysis named W2, W4, W8, W16, W32, W64, W128 and W256. The variability power, level by level, was calculated as the sum of squares of the coefficients. Using ROC curves analysis, the best variable was W32 (W 0.799, $p<0.0001$), followed by W16 (W 0.722, $p<0.0001$).

Table 1. The result of ROC analysis of the wavelets' variability power and their value of importance.

Variable	W-value	p-value	Rel.imp.%
W_002	0.498	0.025	44.56
W_004	0.511	0.033	47.94
W_008	0.623	0.048	66.78
W_016	0.727	<0.001	74.92
W_032	0.794	<0.001	81.34
W_064	0.612	0.034	56.83
W_128	0.801	<0.001	100.00
W_256	0.373	0.042	39.42

The CART methodology generated a decision tree for VT prediction including all levels of W coefficients, from W2 to W256 with a sensitivity reaching 84.5% and a specificity of 91.9%.

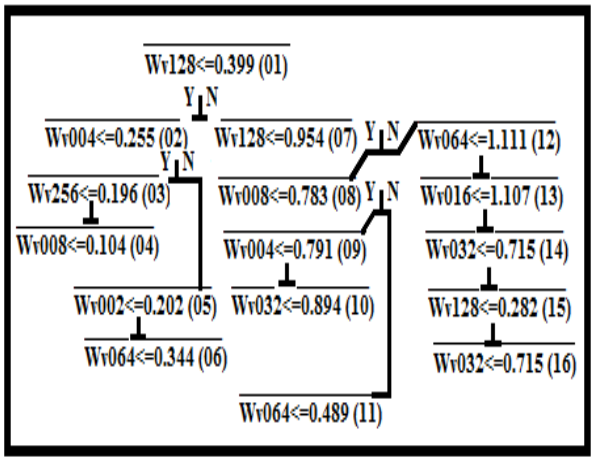

Figure 3. CART decision tree (abbr.: WvNNN the wavelet coefficients; Y=yes, N=no splitting rule; the node-number in bracket from (01 to (16)).

4. Conclusion

The major finding of the study is that the frequent internet monitoring of heart rate is capable of predicting fatal outcomes not only in statistically, but as an individual forecasting. Our result confirms the importance of non-linear analysis of heart beat intervals. The correlation dimension analysis would have better prognostic value in the postinfarction population than the alpha1 (short-term scaling exponent), determined by detrended fluctuation analysis, and the approximate entropy values. Using the internet is a valuable tool in arrhythmia detection. The ECG registrations during night are sent to the internet server in the morning, where the math calculations for the more sophisticated arrhythmia analysis are performed. At this time, our solution is situated between the online ECG monitoring (with 1-3 leads) and the offline 12 lead ECG monitoring methods. In high risk patients, few hours interpretation delay is sufficient in case of frequent monitoring. In case of significant ECG changes, the patients get a message to attend the cardiologist.

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