Application of dynamical analyses of heart rate to rhythm classification and prognosis

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***Abstract*— We have developed numerical approaches to dynamical analysis of heart rates, measured as interbeat or RR, intervals, based on entropy and fluctuation analyses in a large data base of consecutive Holter monitor recordings. In Part I, we present a RR interval-based classifier that distinguishes normal sinus rhythm (NSR), atrial fibrillation (AF) and sinus rhythm with ectopy with an accuracy of 99%, 81% and 77%respectively, using 10-minute segments. In Part II, we present 2-year mortality estimation based on the entropy calculations. The major finding is that normal dynamics identify a very low risk group. Taken together, these results point to automated analysis of heart rate time series with important clinical applications.**

I. Introduction

Analysis of cardiac rhythm using only RR interval time series is an important goal because EKG waveforms may not always be available, especially in ambulatory monitoring. For example, while time domain methods may distinguish well between NSR and AF, the common clinical finding of SR with atrial or ventricular ectopy challenges them. In addition, rich prognostic information should be available. We reasoned that dynamical measures of RR interval time series would add benefit both in rhythm classification and in determining prognosis.

Here, we present two works developed in a large database of 2722 consecutive 24-hour ambulatory Holter monitor recordings from the University of Virginia Heart Station from 12/2004 to 10/2010. In the first, we tested whether knowledge of the dynamical measures of entropy and fluctuation analysis added to heart rate and heart rate variability in classifying rhythm into NSR, AF (only a 5% burden required for diagnosis, and we manually overread the AF labels) and SR with ectopy (a 10% burden required, and we used the Philips labels). Thus, the dataset is composed of 79% NSR, 8% AF and 13% SR with ectopy segments. The low burdens required for rhythm classification are consistent with clinical practice. In the second, we obtained two-mortality and tested whether the entropy measures gave prognostic information.

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II. Rhythm Classification: Materials and Methods

A. Parameters

The means and standard deviations of RR series were computed over the 10 minute segments. The Coefficient of Sample entropy (COSEn) was assessed on 30 second segments. COSEn is derived from the sample entropy and was developed specifically for the detection of AF in very short RR interval time series [1]. For those recordings with an AF burden lower than 90% we analyzed only the segments where each beat was labeled as AF. Local Dynamics score (LDs) is a new index that was also developed for very short series, here 12-beat segments [2] The familiar Detrended Fluctuation Analysis (DFA) detects long-range correlations in non-stationary signals [3]. Although the original calculation of the DFA was proposed for a 24-hours signal, several studies demonstrated the applicability to shorter time series. The DFA scaling exponent was computed on 10-minute segments by limiting the box size to 12 beats. The statistical analyses were performed on single 10-minute averages, one from each patient.

B. Methods and Statistical Analysis.

Univariate comparisons among the three groups were performed for each index with the Kruskal–Wallis one-way analysis of variance; post-hoc comparison were performed by Wilcoxon rank-sum test using the Bonferroni correction. For this statistical analysis only a single 10-minute segment for each patient was taken. A rhythm classification scheme was developed based on three logistic regression models, each using predictor variables to discriminate one rhythm classification group from the other two. Models were validated using a 10-fold cross-validation procedure. The final classification model classified RR series by using the highest output among the three models. A comparison between two multi-label models was carried out: a first model, called standard factors model, created using only linear parameters such as HR, HRV and age, was compared to a second one where the dynamical parameters, described in the previous section, were added.

III. Rhythm Classification: Results

Table I shows the median and (25°, 75°) percentile values for each group and for each parameter. Significant differences were obtained for all the parameters except mean and the standard deviations of RR series. SR with ectopy has the slowest average heart rate, AF and SR with ectopy has similar high variability (S.D.), AF occurred mainly in the

oldest patients and showed the highest COSEn values, finally SR with ectopy had the lowest DFA slope values.

Table II shows the accuracy of labeling 10-minute records using the standard factors model. The columns give the correct classification; the rows give the classification from the model-based scheme. The label-based accuracy is 88.4%.

Table III shows the accuracy of labeling 10-minute records considering the other model, when also non-linear indices are taken into account. The accuracy of the classification is 94.1%.

TABLE I. MEDIAN AND(25°,75°) PERCENTILE VALUES OF THE PARAMETERS FOR EACH GROUP

Parameters	*AF*	*NRS*	*SR with ectopy*	*KW test p-value*
Mean RR (sec)	763 (660,884)[b]	795 (676,928)[b]	820 (707,942)	< 0.001
Std RR (sec^2)	149 (116,186)	38 (24,58)[a,b]	152 (108,208)	< 0.001
COSEn	-0.5 (-0.8,-0.3)[b]	-2.1 (-2.3,-1.8)[a,b]	-1.7(-2,-1.4)	< 0.001
LDs	1.92 (1.5,2.36)[b]	0.84 (0.52,1.33)[a,b]	1.28 (1.01,1.62)	< 0.001
DFA	0.61 (0.56,0.66)[b]	0.98 (0.66,1.26)[a,b]	0.32 (0.21,0.5)	< 0.001
Age	71.9 (64.9,78.8)[b]	47 (22.5,65.6)[a,b]	58.4 (20.1,73.5)	< 0.001

Post-hoc comparisons p-value<0.05: [a] vs AF, [b]vs SR with ectopy

TABLE II. CONTINGENCY MATRIX OF MULTI-LABEL MODEL WITH LINEAR MEASURES

	AF	**NSR**	**SR with ectopy**
AF	34%	0%	10%
NSR	13%	99%	31%
SR with ectopy	53%	1%	59%

TABLE III. CONTINGENCY MATRIX OF MULTI-LABEL MODEL WITH DYNAMICAL MEASURES

	AF	**NSR**	**SR with ectopy**
AF	81%	0%	4%
NSR	10%	99%	19%
SR with ectopy	9%	1%	77%

We tested the accuracy of the new model by varying the threshold on ectopy burden required to relabel NSR as SR with ectopy. The threshold was varied from 4% to 20% with an increasing step of 2%. An improvement of the exact match of signals classified as SR with ectopy was observed as the value was increased from 55% (4% burden) to 90% (20% burden). The overall accuracy rose from 88.9% to 93.7% and peaked at 94.4% for 14% burden.

By comparing the results in Table II and Table III this improvement is evident: the exact match percentage for both AF and SR with ectopy increased, without losing accuracy of NSR detection. The biggest improvement in the performance was reduction in SR with ectopy segments misclassified as AF, from 53% to 9%. The total accuracy increased from 88.4% to 94.1%. Moreover, we can fairly assume that the exact match percentage of 81% for AF could be higher if atrial flutter segments were discarded from the analysis.

IV. RHYTHM CLASSIFICATION: APPLICATION

The worth and effectiveness of this classifier are represented by its ability to work on segments of 10 minutes only, allowing it to be a useful adjunct in a real time contest. An example could be the Intensive Care Unit where a continuous monitoring is very important since changes in the cardiac rhythm are very abrupt and can be life-threatening. Fig. 1 shows two examples of continuous monitoring with a 24-hour Holter recording, where an update of the model output is performed every two minutes. As figure shows, the proposed model can track sudden changes in heart rhythm.

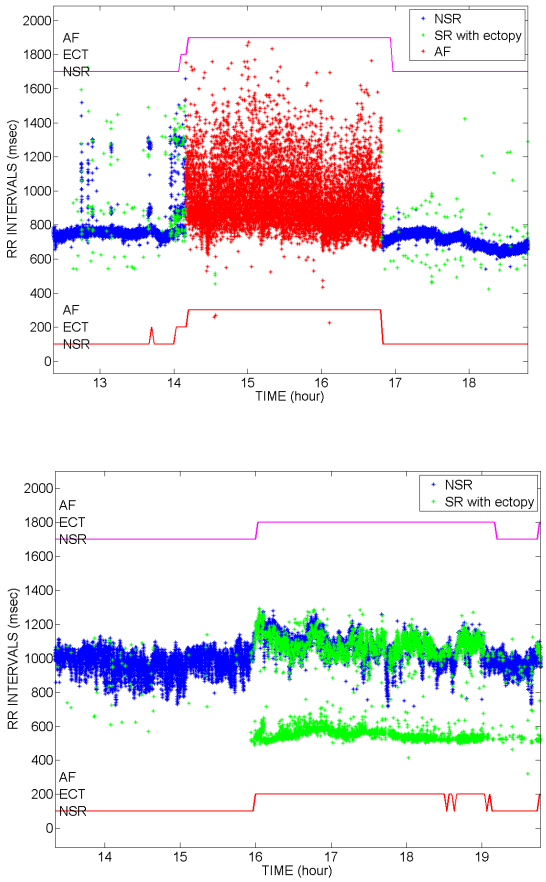

Figura 1. In the upper and lower panel the figures show two 5-hr RR interval series from two distinct patients of the UVa Holter database. Each beat is classified according to Philips beat label and the dot markers are colored accordingly (red=AF, blue=NSR, green=SR with ectopy). The purple upper line indicates the classification performed every 2-minute according to the highest percentage of one of the three class beat labels. The lower red line indicates the output of the classifier proposed in this work.

V. Prognosis: Material and Methods

A. Study Population

To relate the work to clinical practice, we analyzed only the 1518 recordings in patients over the age of 40 based on the low incidence of AF in younger patients. The average (S.D.) age was 65 (13) years. The mortality rate in two years was 5%. As noted above, the recordings were classified as AF if the burden was greater than 5%, as normal sinus rhythm (NSR) if the RR series had more than 90% of normal beats, as sinus rhythm (SR) with ectopy if the burden was more than 10%. Thus, the dataset is composed of 71% NSR, 13% AF and 16% SR with ectopy recordings. The categories are mutually exclusive and reflect clinical practice.

B. Parameters

The Coefficient of Sample entropy (COSEn) was assessed on 30 second segments and we averaged all results over 24 hours. COSEn is derived from the sample entropy and it is developed specifically for the detection of AF in very short heart beat interval time series [1].

Local Dynamics score (LDs) is a new index to investigate the local dynamics of short RR series [2]. The new idea is to examine how often individual templates match each other. Given a 12-beat segment, the algorithm consists mainly into counting the number of times each sample matches with the others within a certain tolerance. A histogram of the count of templates as a function of the number of matches is constructed. The LDs is computed as a linear combination of the values in bin 0, bin 10 and bin 11; the coefficients were normalized so as to sum to 1. A uniform distribution of matches, i.e. the counts in all bins are equal to 1, leads to LD score of 1. Lower scores imply a bell-shape histogram distribution, and higher scores imply a distribution concentrated on either or both extremes of the histogram.

This index was developed to detect the abnormal phenotype of reduced HRV with premature VE, a condition where other common metrics fail [2] and it is elevated even when only reduced HRV is present. The prognostic importance of this index has been evaluated by Moss et al, who introduce LDs as a significant independent predictor factor of mortality in ambulatory patient undergoing 24hr Holter, in addition to standard risk factors for death such as age, hypertension, diabetes, hyperlipidemia, history of tobacco use and history of congestive heart failure. Results show that patients with higher local abnormalities, i.e. higher values of the index, were subject to higher mortality during a follow-up of 8 years. High values can be reached with both situations of high irregularity, such as AF or ectopy, or very low variability, such as conditions of reduced HRV.

C. Methods

Histograms of joint distributions of COSEn and LDs were derived by means of a multivariate kernel density approach. The kernel chosen is a bivariate Gaussian with a diagonal bandwidth matrix. The two bandwidth parameters are chosen optimally without assuming a parametric model.

VI. Prognosis: Results

Fig. 2. shows the distribution of the 24-hour average values of LDs and COSEn for the entire population. The three groups AF, SR with ectopy and NSR are distinguishable labeled by their colors. The red dots represent the AF patients: it is noticeable that the majority of them has the highest values of COSEn and LDS, and that they are gathered in an upper corner separated from all the rest of the population. Blue dots denote patients in NSR, which have the lowest averaged value of COSEn, but they are scattered over a wide range of LDs values, from 0.5 to 2. Finally the patients in SR with ectopy denoted by green dots, have intermediate values of both COSEn and LDs.

Fig. 3 plots the joint distributions of COSEn and LDs of the population with a color map of the 2-year mortality risk. over 2 years computed as the ratio of the joint distributions of COSEn and LDs of the patients who died and the whole population.High values of COSEn are diagnostic of AF, accounting for the group at the top of the plot.

The color bar defines the different levels of mortality risk. The light blue, i.e. the color associated with the value 1, indicates regions that have a risk equal to the average mortality rate of the dataset. Cooler colors indicate areas associated with a lower risk, whereas regions marked with warmer colors denote higher risk. For example, patients in regions with a royal blue color value of 0.5 have a mortality risk equal to half of the average, whereas orange regions hold patients with a 2 times higher risk than the average.

A well-defined dark blue region, i.e., with very low mortality risk, is characterized by low values of LDs, whereas high risk zones are related to higher values of the index. A mutual increase of LDs values and mortality risk is thus observable. In particular, starting from the low risk region (left lower edge), it is possible to distinguish two different directions along which the risk becomes higher: the first, marked by the lower arrow, evolves toward increased values of LDs independently of COSEn values, whereas the second one, highlighted by the upper arrow, points toward both higher values of LDs and COSEn, reaching the maximum for both the indices.

The AF group had higher mortality. This is expected [4] given its increased occurrence in patients with heart disease. The arrows draw attention to two trends of HR dynamics in higher-risk patients. The lower arrow follows a group with high LDs and low COSEn: these are patients with SR with reduced HRV and little or no ectopy. The upper arrow follows a group with high LDs and intermediate COSEn, not high enough to signify AF: these patients have SR and a high burden of ectopy.

The most important finding is the greatly reduced mortality risk in the patients with lowest values of both of the dynamical measures. However a blue region is also observable in the upper right corner, where the AF patients place. This is related to limit number of patients and high percentage of survivors. When computing the ratio between the joint distributions of the people who died and the whole population, this situation generates a low risk region, which is not consistent with the value of risk of the rest of AF patients.

VII. Conclusion

Dynamical analyses of RR interval time series can be effective in assigning rhythm classification, including detection of SR with frequent ectopy, even when we use strict clinical thinking about how low burdens of AF or ectopy color the clinical assessment and dictate management. Thus atrial flutter is classed as atrial fibrillation even though the dynamics are vastly different, and only 5 to 10% presence of AF or ectopy was dominant in classification.

Moreover, normal dynamics implying SR without a high burden of ectopy identify a group of patients at low risk of 2-year mortaltiy. Situations related to higher risk are SR with reduced HRV, SR with an increasing amount of ectopy and AF. These are clinically sensible findings.

This analysis was performed using averaged values over 24 hours, but the possibility to have measures of COSEn and LDs every 30 seconds allows this risk stratification analysis to be carried out in Intensive Care Unit and hospital patients, where a continuous monitoring may be lifesaving, as it is in premature infants [5]. It will be interesting to study how watching trends of dynamical measures in real time might improve patient outcomes.

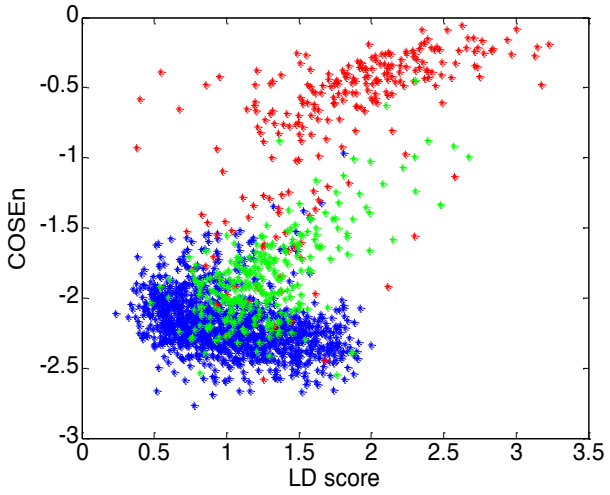

Figure 2. Distribution of the average values over 24 hours of LDs and COSEn for the UVa Holter population. The three categories of AF, NSR and SR with ectopy are displayed with different colors: red for AF, blue for NSR, green for SR with ectopy.

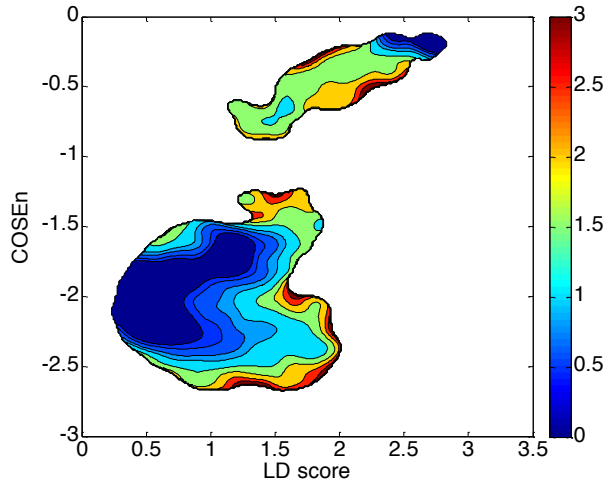

Figure 3. Color map showing the mortality risk in the UVa Holter population. The color bar indicates the fold-increased risk. The arrows mark an increasing risk path from a region of very low risk to areas with higher risk.

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