Discrimination power of short-term heart rate variability measures for CHF assessment

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***Abstract*— In this study, we investigated the discrimination power of short-term Heart Rate Variability (HRV) for discriminating normal subjects versus Chronic Heart Failure (CHF) patients. We analyzed 1,914.40 hours of ECG of 83 patients of which 54 are normal and 29 are suffering from CHF with New York Heart Classification (NYHA) I, II, III, extracted by public databases. Following guidelines, we performed time and frequency analysis in order to measure HRV features. To assess the discrimination power of HRV features we designed a classifier based on the Classification and Regression Tree (CART) method, which is a non-parametric statistical technique, strongly effective on non-normal medical data mining. The best subset of features for subject classification includes RMSSD, total power, high frequencies power and the ratio between low and high Frequencies power (LF/HF). The classifier we developed achieved specificity and sensitivity values of 79.31% and 100% respectively. Moreover, we demonstrated that it is possible to achieve specificity and sensitivity of 89.7% and 100% respectively, by introducing two non-standard features ΔAVNN and ΔLF/HF, which account respectively for variation over the 24 hours of the average of consecutive normal intervals (AVNN) and LF/HF. Our results are comparable with other similar studies, but the method we used is particularly valuable because it allows a fully human-understandable description of classification procedures, in terms of intelligible "if … then …" rules.**

***Index Terms*— HRV, CHF, CART, NYHA classification**

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I. Introduction

HEART rate variability is a non-invasive measure commonly used to assess the influence of autonomic nervous system (ANS) on the heart [1]. HRV is widely studied in patients suffering from Chronic Heart Failure (CHF) [2-16]. CHF is a patho-physiological condition in which an abnormal cardiac function is responsible for the failure of the heart to pump blood as required by the body. CHF is chronic, degenerative and age related [17] [18]. Therefore, the growing number of elderly people in western countries could be one of the reasons that the number of patients with CHF is increasing [19]. Moreover, heart failure (HF) is asymptomatic in its first stages. Therefore, early detection is crucial to avoid the condition worsening and to prevent complication of clinical conditions, which may cause higher social costs. Therefore, new non-invasive and low-cost techniques for early assessment of HF severity, could contribute to containing the number of patients and related costs.

One of the most diffused measurements of the severity of CHF is the New York Heart Association (NYHA) classification, which is a symptomatic functional scale [20]. Nonetheless, this scale is criticized because, being based on subjective evaluation, it is amenable to inter-observer variability [21]. For an objective assessment of HF, international guidelines [22] suggest that the most effective diagnostic test is the comprehensive 2-dimensional echocardiogram coupled with Doppler flow studies to determine whether abnormalities of myocardium, heart valves, or pericardium are present and in which chamber. As far as electrocardiography is concerned, the same guidelines evidenced that conventional 12-lead electrocardiogram (ECG) should not form the primary basis for determining the specific cardiac abnormality responsible for the development of CHF, because of low sensitivity and specificity.

Therefore, an interesting question is whether HRV analysis may improve both sensitivity and specificity of ECG examination, thus providing a robust independent tool for HF assessment.

The majority of literature studies used HRV measures for the prognosis of the disease, in particular as predictor of the risk of

mortality [5, 7, 10, 12-15]. A small number of studies focused on using HRV measures for CHF diagnosis. Asyali [23] studied the discrimination power of long-term HRV measures (time-domain and FFT-based frequency domain) and, using linear discriminant analysis and a Bayesian Classifier, obtained sensitivity and specificity rate of 81,82% and 98,08% respectively. Isler et al. [24] investigated the discrimination power of short-term HRV measures, including wavelet entropy. In their studies, they achieved the best performance using Genetic Algorithms and k-Nearest Neighbor Classifier, resulting in a sensitivity rate of 100.00% and specificity rate of 94.74%. Although these studies reached interesting results, they all use difficult methods, which could be too complex for the daily activity of clinicians.

The aim of this study is to investigate the power of short-term HRV features in classifying CHF patients according to disease severity, by using Classification and Regression Tree (CART). We identify the subset of features achieving the highest sensitivity and specificity rate in distinguishing CHF patients from normal subject. Moreover, we evaluated the improvement in the classifier performance by introducing two non-standard HRV features, ΔAVNN and ΔLF/HF, which account respectively for variation over the 24 hours of the average of consecutive normal intervals (AVNN) and LF/HF.

CART was applied to HRV measures for other investigations, such as the diagnosis of Obstructive Sleep Apnea Syndrome [25], or the analysis of the relationship between HRV and menstrual cycle in healthy young women [26]. As far as the authors' knowledge, CART has not been applied yet to HRV analysis for CHF diagnosis.

CART [27] is a method widely used in several applications of pattern recognition for medical diagnosis [28]. This method is particularly interesting because its results are fully understandable without advanced mathematical skills: the models behind this method can easily be expressed as logic rules. Other powerful methods are not easily human-understandable [29], whilst in medical applications the intelligibility of the method is strongly appreciated especially for clinical interpretation of results [29]. Moreover, CART requires no assumptions regarding the underlying distribution of features' values [30].

The CART algorithm iteratively splits the data set, according to a criterion that maximizes the separation of the data, producing a tree-like decision structure. More details of the CART model building process can be found in Breiman et al. [27]. We used the "leave one out" cross-validation technique [31].

In order to maximize the reproducibility of our investigation, we applied this method on public databases [32], and we analyzed only standard measures [1].

II. Method

A. Data

We performed a retrospective analysis using two RR interval databases, one with normal middle-aged subjects, the other with patients suffering from CHF in NYHA I-III. The data of normal subjects was retrieved from the Normal Sinus Rhythm RR Interval Database [32]. It includes RR intervals extracted from 24-hour ECG-Holter of 30 men and 24 women, aged 29-76 years (61±11). The data for the CHF group was retrieved from the Congestive Heart Failure RR Interval Database [32]. It includes RR intervals extracted from 24-hour ECG-Holter recordings of 8 men, 2 women, and 19 unknown-gender subjects, aged 34-79 years (55±11): 4 subjects were classified as NYHA class I, 8 NYHA class II and 17 NYHA class III. The RR interval records are provided with beat annotations obtained by automated analysis with manual review and correction. The original ECG records were digitalized at 128 samples per second.

TABLE I
SELECTED HRV FEATURES

Measure	Description	Unit
AVNN	Average of all NN intervals	ms
SDNN	Standard deviation of all NN intervals.	ms
RMSSD	The square root of the mean of the sum of the squares of differences between adjacent NN intervals	ms
pNN50	Percentage of differences between adjacent NN intervals that are > 50 ms	%
TOTPWR	Total spectral power of all NN intervals 0-0.4 Hz.	ms^2
VLF	Total spectral power of all NN intervals 0-0.04 Hz	ms^2
LF	Total spectral power of all NN intervals 0.04-0.15 Hz	ms^2
HF	Total spectral power of all NN intervals 0.15-0.4 Hz	ms^2
LF/HF	Ratio of low to high frequency power	

B. Short-term HRV feature measurements

We chose to perform standard short-term HRV analysis, according to International Guidelines [1]. Therefore, we extracted 5-min RR Interval Time Series (RRITS) excerpts from the 24-hour records and processed them using PhysioNet's HRV Toolkit [32]. We chose this tool, since it is rigorously validated and open-source. This toolkit provides calculation of basic time- and frequency-domain HRV features widely used in the literature [1] and reported in Table 1.

Furthermore, this toolkit estimates frequency-domain HRV features by Lomb-Scamble periodogram (LS) [33] which can produce a more accurate estimation of the PSD than FFT-based methods for RR data [34], without pre-processing. Moreover, it calculates NN-RR ratio, which represents the fraction of total RR intervals that are classified as normal-to-normal (NN) intervals. This ratio is used as a measure of data reliability and if it is less than 80% the excerpt is excluded.

Finally, to reduce false negatives, we introduced two non-standard measurements: the difference, over the 24 hours, between the maximum and the minimum values both for AVNN and LF/HF, called respectively Δ_{AVNN} and $\Delta_{LF/HF}$. These two measurements account for AVNN and LF/HF variation in the same subject over the 24 hours and are computed by a MS Excel worksheet.

C. Classification

In order to find the best subset of features, we adopted the so-called exhaustive search method, investigating the predictive value of all the possible combinations, without repetitions, of K out-of-N features [35]. Then we chose as best combination the one that maximizes specificity and sensitivity. Since the number of features is N=9, we used 2^9=512 subsets of features to train and test the same number of classification trees. The classification process is subdivided into two steps: *excerpts classification* and *subject classification*. With the first, each excerpt from a subject is classified as normal or abnormal. With the latter, the subject is classified as normal or CHF, according to the percentage of excerpts classified as CHF. Finally, we tried to enhance the second step by introducing the two non-standard HRV measurements defined above (section 2.2). Figure 1 shows the whole process of classification.

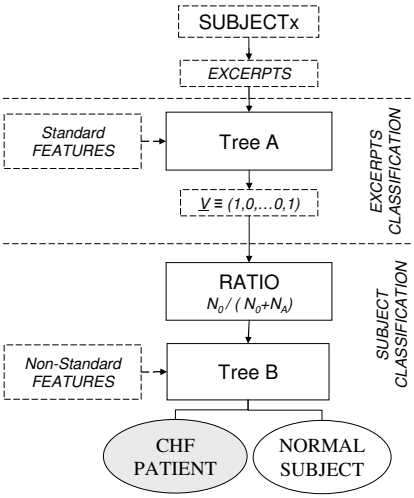

Figure 1: Workflow of Classification

1) Excerpts classification

The excerpts of each subject were labeled with a binary index, according to the status of the subject (0=normal; 1=NYHA I-II-III). Excerpts extracted from the same subject cannot be assumed to be uncorrelated: therefore, if some excerpts from one subject are used to train a tree, then none of his excerpts can be used to test the same tree, otherwise the specificity and sensitivity of the tree would be higher. Therefore, we divided the training- and testing-set according to subjects and not to their excerpts.

Afterwards, for each combination of features, leaving out one of the subjects, we used the excerpts of the others to train a CART, using as splitting criterion the Gini index [27]. It is a measure of the impurity of each node t, which, for binary classification, can be computed as follows:

$$Gini\ \ index\ \ (t) = 1 - \sum_{i=1,2} p^2(i|t); \qquad (1)$$

where "t" is the considered node, "i" is the class label, p(ilt) is the conditional probability that a subject fallen in the node "t" belongs to the class "i".

We repeated this step for each subject left out and for each combination of features. Then we tested each tree with the excerpts of the subject left out during its training. Via binary classification of excerpts, we associated to each subject a vector ($\underline{V}$) containing a 1 for each excerpt classified as abnormal and 0 for each excerpt classified as normal.

2) Subject classification

From the vector $\underline{V}$, we computed the number of excerpts classified as normal (N_0) and the number of excerpts classified as abnormal (N_A). We tried two different models for the Tree B (Fig.1): "Tree B1" and "Tree B2". The former classifies subjects on the base of the ratio $R=N_0/(N_0+N_A)$: if R is greater than a threshold (α), the subject is considered normal. The latter uses the ratio R and the two non-standard variables introduced above (section 2.2): ΔAVNN and ΔLF/HF. In both cases, to choose the optimal threshold α, we considered all its possible values between 0 and 1, with a step of 0.01. Then, studying the ROC curve [36], we choose the value of α maximizing the sensitivity and specificity of the classifier (Figure 3).

3) Validation

As discussed above excerpts extracted from the same subject cannot be assumed to be uncorrelated, therefore we divided the data into training-set and test-set for subjects and not for excerpts, although this reduces the datasets. Therefore, we used the leave-one-out cross-validation method [31]. In this method, the classifier is trained using the whole dataset except the data of one subject and then tested on the excerpts of the excluded subject. This process is repeated for all the subjects in the dataset.

TABLE II
BINARY CLASSIFICATION PERFORMANCE MEASURES

Measure (Abbreviation)	Formula
Accuracy (Acc)	$\frac{TP+TN}{TP+TN+FP+FN}$
Precision (Pre)	$\frac{TP}{TP+FP}$
Sensitivity (Sen)	$\frac{TP}{TP+FN}$
Specificity (Spe)	$\frac{TN}{FP+TN}$
Area Under the Curve (AUC)	$AUC=\frac{1}{2}\left(\frac{TP}{TP+FN}+\frac{TN}{TN+FP}\right)$;

TP: the number of CHF patients detected. TN: number of normal subject detected. FP: number of normal subject incorrectly labeled as CHF. FN: number of CHF patients incorrectly labeled as normal.

D. Performance measurements

To measure the performance of each classifier, we used the confusion matrixes [37] From these matrices, we computed the widely used measures reported in table II for binary classification in order to enable the comparison of our method with others.

We selected the subset of features which obtained the best sensitivity. The final model was obtained by pruning the trees at the first six levels in order to improve the intelligibleness.

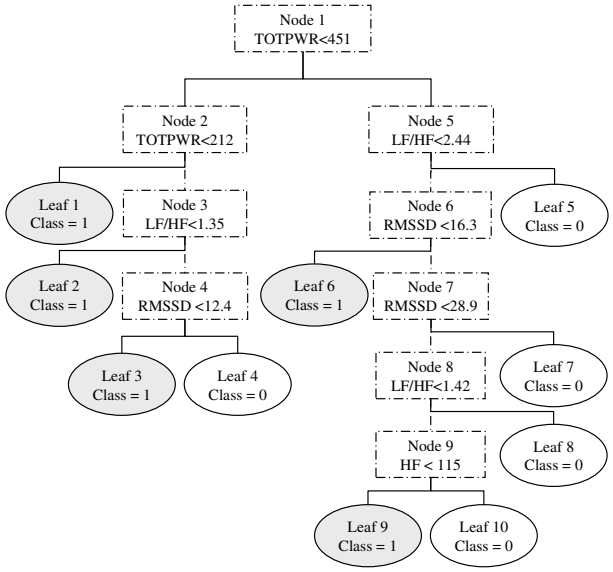

Figure 2: excerpt classification decision tree. The 5-mins RR intervals labeled as class 1, are considered abnormal, class 0 normal

Results obtained with this tree are presented and discussed here.

III. RESULTS

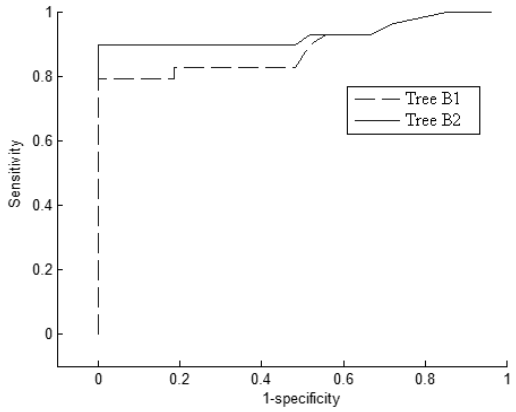

Figure 3: ROC curve, representing how sensitivity and specificity vary for α changing from 0 to 1

The subset of features achieving the best results in classifying the excerpts is constituted by: RMSSD, TOTPWR, HF and LF/HF. Figure 2 shows the final model of the Tree A, for

TABLE III
CONFUSION MATRIX USING THE TREE B1

	Classified Normal	*Classified CHF*
Normal	54	0
CHF	6	23

excerpts classification with the best subset of features. At each node, if condition expressed in the node is true then, the excerpt goes in the left sub-node (or leaf). For instance, if TOTPWR is less than 212.168 ms^2, the excerpt is labeled as 1 (CHF), if not, the LF/HF ratio is considered, and so on. All the terminal nodes for CHF class are on the left of their parent nodes. This reflects the fact that CHF subjects have a depressed HRV.

Figure 3 shows the ROC curve for all the possible value of α, for both trees. The best thresholds α was assessed to 0.68±1 and to 0.65±4, respectively with the Tree B-1 or B2.

Table III, shows the confusion matrix of the classifier with the tree B1, while Table IV reports the confusion matrix per NYHA classes for the same tree.

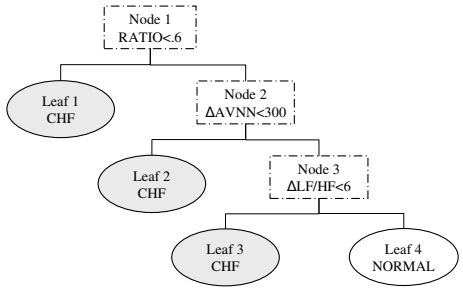

Figure 4 Tree B2: subjects classification according to non-standard features ΔAVNN and ΔLF/HF

It is possible to significantly reduce the false negatives, improving the sensitivity of the classifier, enhancing the subject classifier with the tree B1, which bases on the two non-standard measures, Δ_{AVNN} and $\Delta_{LF/HF,}$ introduced at the end of section 2.2. Figure 4 shows the final model of the tree B2.

TABLE V
CONFUSION MATRIX USING THE TREE B2

	Classified Normal	*Classified CHF*
Normal	54	0
CHF	3	26

TABLE VI
CONFUSION MATRIX PER NYHA USING THE TREE B2

	Classified Normal	*Classified CHF*
Normal	54	0
NYHA I	1	3
NYHA II	1	7
NYHA III	1	16

TABLE VII
CLASSIFICATION PERFORMANCE MEASUREMENTS

	TP	FP	TN	FN	ACC	PRE	SEN	SPE	AUC
Tree B1	23	0	54	6	92.8	100.0	79.3	100.0	89.7
Tree B2	26	0	54	3	96.4	100.0	89.7	100.0	94.8

Tree B1: obtained using: RMSSD, TOTPWR, HF, LF/HF
Tree B2: Tree B1 + features ΔAVNN and ΔLF/HF

The confusion matrixes of the classifier enhanced with the tree B2 are reported in Tables V and VI.

The performances of the classifier with the trees B1 and B2 are reported in the table VII.

The results indicate that 4 standard short-term features are sufficient to distinguish between normal subjects and CHF patients achieving a specificity and sensitivity of 79.31% and 100% respectively. Moreover, by introducing two more non-standard features it is possible to achieve specificity and sensitivity of 89.7% and 100% respectively.

IV. Discussion

In this study, we investigated the class discrimination power of 9 standard short-term HRV measures using classification and regression tree (CART). Moreover, we demonstrated that it is possible to enhance the discriminative power of these measures by adding a few non-standard measures of HRV. The results show that it is possible to discriminate normal subjects from CHF ones by using short-term HRV measures, extracted from h24 Holter registrations.

As regards the discriminative power of the features, the best subset of features includes three frequency domain measures, confirming the importance of power spectral density analysis in investigating short-term excerpts [1]. RMSDD is the only time-domain measure selected, this may be because pNN50 and SDNN are strongly correlated with RMSDD and TOTPWR, respectively [1]. It is worth to notice that SDNN does not appear in the best subset of features, even if it has been recognized as having the highest class discrimination power [23], among long term HRV features, and as a strong univariate predictor of mortality [38]. In fact, Asyali [23] showed that a depressed SDNN (<91.82 ms) is significant to identify CHF, while Bilchick [38] reported that a depressed SDNN (<70 ms and <30ms, respectively for long-term and 5-min records) is significantly associated with increased mortality. However, the predominant position of TOTPWR in nodes 1 and 2 (see Figure 2) confirms indirectly the importance of SDNN for two reasons: TOTPWR and SDNN are strongly correlated [1, 16, 38]; in our dataset all the subjects with TOTPOW<451ms^2 presented an SDNN<30ms, consistently with Bilchick's conclusions [38]. Nonetheless, when using CART, TOTPWR seems to be more effective than SDNN in detecting CHF patients.

The set of rules, reported in figure 2, is clinically consistent, even if the classifier did not use any a priori clinical knowledge. In fact, the main clinical results of this study is that the leafs containing abnormal excerpts are on "left", which reflects a depressed value of all the involved features. This is consistent with our previous research [16] and with the results showed by Bigger [3], Musialik-Lydka [11] and Arbolishvili [13], who stated that standard HRV measures were significantly lower in CHF patients than in normal subjects. However, Arbolishvili [13] showed that high frequency power (HF) was not lowered and this exception is apparently in contrast with our results (see node 9 figure 2). This inconsistency may be explained by considering that HF may have a discriminative power only for the subgroups of excerpts which had relative high value of TOTPWR (TOTPWR> 451) and intermediate values of LF/HF and RMSDD (1.42<LF/HF<2.44; 16.3<RMSSD <28.9).

TABLE IV
Confusion Matrix per NYHA using the tree B1

	Classified Normal	*Classified CHF*
Normal	54	0
NYHA I	2	2
NYHA II	1	7
NYHA III	3	14

It should be underlined that comparisons with the results of other authors have some limitations: heterogeneity between lengths of analyzed recordings (5 minutes versus 24 hours) and differences in the methods for estimating power spectral density. The performance of the proposed classification could be compared with a few previously published studies, which used the same databases, as reported in Table VIII.

Compared to the other studies, we obtained higher precision and specificity values, but lower sensitivity. The performance measures of our classifiers are higher than or comparable with those of Asyali's classifier, which considered HRV long term measures. Moreover, we considered all the subjects, even those rejected by Asyali because of their low quality (24-hour NN/RR less than 90%). The performance measures of our classifier are lower than those of Isler's classifier, which considered HRV short-term measures, including wavelet entropy measures. Perhaps this is because of the discrimination power of wavelet entropy measures, which have not been considered in this study because they are complex non-standard short-term measures, presumably complex for most clinicians. In this regard, in comparison with other studies, we provided a set of rules, which are fully understandable by cardiologists.

As regards classification results and the NYHA classes, as shown in Table IV, the tree B1 achieves low performance, especially on the NYHA I patients. This result could be justified because these patients could have an HRV not so different from normal subjects. Nonetheless, this result could be due to the small number of patients in this class in the dataset. In both cases the tree B2, although in small numbers, enhances the classifier also for NYHA I patients. In this regard, Table VI shows that it is possible to further improve the performance of the classifier by adding few new variables, Δ_{AVNN} and $\Delta_{LF/HF}$, which take into account features variation over the 24h in the same subject.

Finally, a limitation of our study could be the small dataset. For instance, the value chosen for the threshold α could depend by the dataset we used, which was unbalanced. In fact, the ratio of the number of normal subjects on the total number of subjects in the dataset is 0.65 (54 normal subjects and 29 CHF patients)

V. Conclusion

In this study, we showed that standard short-term HRV measures such as RMSSD, TOTPWR, HF and LF/HF allow discriminating normal subjects from CHF patients, with a specificity and sensitivity of 79.3% and 100% respectively. Specificity is higher for the patients with NYHA II and III, rising up to the 87.5% and the 82.3% respectively. This result can be enhanced, using two additional non-standard measures

over the 24h, ΔAVNN and ΔLF/HF, which account respectively for variation over the 24 hours of AVNN and LF/HF, reflecting the variation of HRV in the day. In this case, with the same sensitivity, the specificity increases to 89.7%.

Moreover, as shown in figure 2, all the terminal nodes for CHF class are on the left of their parent nodes, reflecting the fact that CHF subjects have a depressed HRV.

Performance results are better if compared to other studies using standard measures, although in 24 hours, and are comparable with previous studies using complex measures as wavelet entropy ones. In both cases, it should be pointed out that we did not use complex methods, providing a fully understandable set of rules easily expressed as '*if … then*', which can be fully understood by a greater number of clinicians.

Finally, the proposed method meets all our requirements because it is: fully understandable; non-invasive and low-cost; provides an objective classification; improves sensitivity and specificity of ECG examinations for diagnosis of CHF.

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TABLE VIII
CLASSIFICATION PERFORMANCE MEASUREMENTS OF DIFFERENT CLASSIFIERS

	TP	FP	TN	FN	ACC	PRE	SEN	SPE	AUC
Tree B1	23	0	54	6	93	100	79	100	90
Tree B2	26	0	54	3	96	100	90	100	95
Asyali[35]	18	1	51	4	93	95	82	98	90
Isler [36]	29	3	51	0	96	91	100	94	97

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