Linear and Nonlinear Heart Rate Variability Risk Stratification in Heart Failure Patients

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Abstract

Chronic heart failure (CHF) is a major and growing public health concern (~23 million people worldwide) with five-year survival rates of 25% in men and 38% in women. Objective of this study was to investigate whether linear and nonlinear heart rate variability (HRV) indices enhance risk prediction in patients with CHF. To discriminate between low risk (stable condition, N=459) and high risk (cardiac death, N=50) CHF patient groups, nonlinear indices from compression entropy (CE), detrended fluctuation analysis (DFA), symbolic dynamics (SD) and standard linear HRV analysis were calculated from 24h Holter ECG recordings. Indices from nonlinear dynamics (CE, DFA, SD: $p<0.001$) contribute together with clinical parameters NYHA and LVEF to an enhanced risk stratification in CHF patients.

1. Introduction

Chronic heart failure (CHF) is an increasingly frequent occurring clinical syndrome affecting about 23 million people worldwide, particularly in the industrialized countries with ageing populations [1,2]. Often CHF is caused by a variety of factors, such as hypertension, cardiomyopathy and coronary artery disease and is characterized by an impaired ventricular filling or a reduced ventricular ejection fraction. Results from the Framingham study [3] revealed five-year mortality rates of 75% in men and 62% in women.

The use of an implantable cardioverter-defibrillator can reduce the risk of death in CHF by 23%, but depends mainly on risk stratification [4]. In various studies [5-7] several non-invasive linear and nonlinear approaches were developed for identifying patients at high risk of cardiac death who would benefit from a preventive therapy. However, some of them could not contribute considerably to such risk stratification.

The aim of this study was to investigate whether some most promising measures from linear [8] and from nonlinear heart rate variability (HRV) analysis enhance risk prediction in patients with CHF.

2. Methods

In the scope of the Spanish multicenter study MUSIC2 (MUerte Subita en Insuficiencia Cardiaca or sudden death in heart failure) 509 CHF patients whose heart failure arises from different etiologies were enrolled. Inclusion criteria were: New York Heart Association index NYHA II or III, left ventricular ejection fraction LVEF<40%, left ventricular diastolic diameter LVDD>60mm, left ventricular hypertrophy LVH>14mm and sinus rhythm. Patients with severe valvular disease, severe hepatic, pulmonary or renal disease and other criteria influencing the autonomic regulation were excluded. All CHF patients were optimal treated with drugs as ACE inhibitors (74%), beta blockers (70%), diuretics (65%) and digitalis (21%). The investigation was conforming to the recommendations of the Declaration of Helsinki, the ethical committee of the respective institutions approved the study protocol and all patients gave their written informed consent before participation.

From 24h Holter ECG records (sampling frequency = 200Hz, ELA Medical) the beat-to-beat interval (BBI) time series (tachograms) were extracted. Afterwards, ectopic beats and artifacts within the tachograms were detected and corrected by an adaptive filter.

The following indices were obtained from time domain and frequency domain (estimation of power spectra by Fast Fourier transform applying a Blackman Harris window) according the Task Force recommendations [8]: meanNN, sdNN, rmssd, LF, HF, LFn, HFn and LF/HF.

Nonlinear dynamic behavior within BBI time series can be characterized by measures from nonlinear symbolic dynamics (SD). According to Voss et al. [9], BBI time series were transformed into time series consisting of either four or two different symbols. From these symbol strings time series of words consisting of 3 or 6 successive symbols were estimated and from these word sequences different single word type probabilities (pW000-pW333, plvar5) were calculated.

In a further SD approach [10] a sliding window w consisting of five BBIs is shifted (here τ=1) over the whole BBI time series (equation 1). Within every window k (L - number of total shifts), the number of consecutive BBI differences that are decreased in comparison to the a-scaled (in this study a=1) standard deviation sd(k) of the current window is determined and coded as symbol S_k resulting in a symbol string with a range of five possible symbols {0,1,2,3,4}. Amongst others, the measure tau1_p001 was obtained by counting the number of symbol types which exceed a probability of occurrence of 1%.

$$S_k = \sum_{i=1}^{4} \begin{cases} 0 : \left| BBI_i^k - BBI_{i+1}^k \right| \geq a * sd(k) \\ 1 : \left| BBI_i^k - BBI_{i+1}^k \right| < a * sd(k) \end{cases} \quad with\ k = 1 : L \tag{1}$$

Detrended fluctuation analysis (DFA) [11] was applied to quantify the absence or presence of fractal correlation properties in the non-stationary BBI time series. The DFA calculation was performed as described in [12]. In this study, two DFA indices were calculated: a short-term scaling exponent α_1 (box size n=4-16) and a long-term scaling exponent α_2 (n=16-64).

Finally, compression entropy (CE) of the BBI time series was estimated according to a modified LZ77 data compression algorithm that is described in detail in [13]. The CE approach allows a lossless data compression of the time series based on string matching applying a lookahead buffer of length b and sliding window of length w (in this study w=7 and b=3). The CE was estimated as ratio of compressed time series length and original time series length.

After a follow-up period of 24 month, CHF patients could be separated into an age and gender matched low risk (LR: stable condition, N=415, ♂=317, ♀=98) and high risk group (HR: cardiac death, N=50, ♂=38, ♀=12) (Table 1). Furthermore, a low risk (N=221, ♂=180, ♀=41) and a high risk (N=35, ♂=30, ♀=5) subgroup consisting of only ischemic CHF patients were considered.

Univariate statistical analyses (SPSS) based on Mann-Whitney U-test ($p<0.05$) and descriptive statistics (mean values, standard deviations) were determined for all estimated parameters. Multivariate analysis on the basis of step-wise discriminant function analysis with cross-validation was applied on uncorrelated parameters (Pearson correlation coefficient). Three optimal parameter sets each consisting of 5 univariate significant parameters were determined: a clinical parameter set, a non-clinical parameter set and a mixed set (of both clinical and non-clinical indices).

3. Results

Besides clinical indices, several non-clinical parameters, especially from nonlinear SD, DFA and CE, revealed significant ($p<0.05$) differences between the LR and HR group of CHF patients (Table 1). As expected, the HR group was characterized by a significantly increased NYHA index ($p<0.01$) and decreased LVEF ($p<0.05$). The mean heart rate was slightly higher (lower meanNN, $p<0.05$) within HR. From the frequency domain of standard HRV analysis, the normalized low frequency power (LFn) reflecting predominantly sympathetic modulation and LF/HF as index of sympathovagal balance were appreciably decreased in HR patients in comparison to LR patients ($p<0.05$). The normalized high frequency component (HFn) as measure of vagal activity was significantly higher ($p<0.05$) within the HR group. From SD, plvar5 quantifying the portion of low-variability within BBI time series was clearly increased ($p<0.01$) within HR. In contrast to the LR group, the index pW333 that classifies dynamic changes within a time series was slightly decreased ($p<0.05$) within the HR group. However, tau1_p001 as a further parameter of SD was considerably decreased within HR ($p<0.01$) compared to LR. The amount of short-term correlations represented by the short-term scaling exponent α_1 from DFA was significantly decreased ($p<0.01$) within the BBI time series of HR patients. Finally, CE was also clearly decreased in HR.

Similar results were obtained considering the discrimination of the ischemic CHF patient groups. With the exception of plvar5 (not significant) from SD, the same parameters could differentiate between LR and HR.

For risk stratification in differentiating the groups LR and HR the best clinical parameter set (Figure 1) includes the following indices: gender, age, LVEF, NYHA and LVDD. This parameter combination results (Table 2) to a sensitivity (SENS) of 44%, specificity (SPEC) of 80%, area under ROC curve (AUC) of 67%, positive predictive value (PPV) of 22% and a negative predictive value (NPV) of 92%. The optimal non-clinical parameter set (tau1_p001, plvar5, α_1, CE, LFn) reached 50% SENS, 72% SPEC, 67% AUC, 50% PPV and 72% NPV. The mixed optimal parameter set consists of two clinical measures (NYHA, LVEF) and three non-clinical indices (α_1, CE, plvar5) and leads to a SENS of 54%, SPEC of 77%, AUC of 72%, PPV of 54% and a NPV of 77%.

Table 1. Univariate significances ($p<0.05$) for discrimination between low risk (LR) and high risk (HR) heart failure patients; mean value ± standard deviation, significance: n.s. - not significant, * - $p<0.05$, ** - $p<0.01$, applied analysis methods: a - clinical indices, b - standard HRV indices according to Task Force, c, d, e – indices from symbolic dynamic, detrended fluctuation analysis and compression entropy.

	parameter	LR	HR	P
	gender [♂/♀]	317/98	38/12	n.s.
	age [years]	63.64 ± 10.39	65.24 ± 12.50	n.s.
a	*LVEF [%]*	37.71 ± 14.44	33.34 ± 12.98	*
	NYHA	2.16 ± 0.37	2.40 ± 0.50	**
	LVDD [mm]	60.92 ± 10.17	62.18 ± 10.65	n.s.
	meanNN [ms]	854 ± 132	813 ± 123	*
	sdNN [ms]	110 ± 39	99 ± 43	n.s.
b	*LFn*	0.69 ± 0.13	0.64 ± 0.14	*
	HFn	0.31 ± 0.13	0.36 ± 0.14	*
	LF/HF	2.91 ± 2.07	2.21 ± 1.44	*
	plvar5	0.001 ± 0.005	0.004 ± 0.012	**
c	*pW333*	0.30± 0.08	0.27 ± 0.10	*
	tau1_p001	4.82 ± 0.38	4.60 ± 0.49	**
d	α_1	1.17 ± 0.21	1.05 ± 0.24	**
e	*CE*	0.52 ± 0.09	0.48 ± 0.10	**

4. Discussion and conclusions

From the applied linear and nonlinear methods, four parameters with a significance level $p<0.01$ as CE, α_1 (from DFA), plvar5, tau1_p001 (both from SD) and four standard HRV measures (meanNN, LFn, HFn, LF/HF) and one SD parameter (pW333) with a significance level $p<0.05$ showed a principal ability for an enhanced risk classification in CHF patients.

Comparable results with only slightly changed significant values were achieved considering only the subgroups of ischemic heart failure. The higher mean value of the clinical NYHA class indicates a decreasing of the physical performance within the HR group but depends on the subjective assessment of experienced cardiologists.

According to Bethany et al. [14], it could be shown that CHF patients with a high risk of cardiac death exhibit a decreased LVEF compared to LR patients. Within the group of HR patients a decreased sympathetic drive (decreased LFn and LF/HF) and an enhanced vagal activity (increased HFn) was observed in comparison to the LR group. Galinier et al. [15] presented also a close relationship between decreased LF power and sudden cardiac death of CHF patients. From SD two measures plvar5 and tau1_p001 achieved clear significances and thus they could be suitable for classification of CHF patients with high risk of mortality.

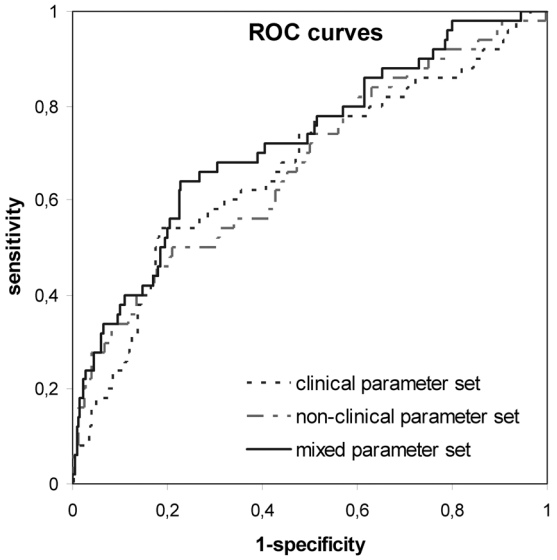

Figure 1. Comparison of the receiver operator (ROC) curves of the three different parameter sets for risk stratification in heart failure patients at high risk for cardiac death.

Table 2. Classification results of the three different parameter sets (discriminant function analysis) consisting each of 5 indices; SENS - sensitivity, SPEC - specificity, AUC - area under curve, PPV - positive predictive value, NPV - negative predictive value, PPA - positive predictive accuracy, NPA - negative predictive accuracy.

Parameter	Clinical Set	Non-clinical Set	Mixed Set
SENS	44%	50%	54%
SPEC	80%	72%	77%
AUC	67%	67%	72%
PPV	22%	50%	54%
NPV	92%	72%	77%
PPA	76%	70%	75%
NPA	24%	30%	25%

A reduction of dynamics within the BBI time series of HR patients was characterized by an increasing value of plvar5. The parameter tau1_p001 was diminished within the HR group indicating a reduced mean short-term variability associated with a lower level of complexity. A reduced complexity of the heart rate in HR patients was also approved by a decreased CE in the HR group. The SD parameter pW333 was reduced in the HR group indicating a lower probability of the occurrence of three consecutive shortened BBIs. [16] Mäkikallio et al. [16], showed that α_1 from DFA is a powerful independent predictor of mortality in CHF which could be confirmed by this study. Thereby, a reduced short-term scaling exponent within the HR group indicates a lower amount

of short-term correlations and an increased randomness of heart rate patterns within the BBI time series compared to the LR group.

Considering the results of the discriminant function analysis it could be demonstrated that the determined optimal non-clinical parameter set is comparable to the clinical parameter set. It should be noted that the clinical indices NYHA, LVEF and LVDD were diagnosed by very experienced specialists leading to enhanced results of risk stratification compared to more inexperienced general practitioners. In comparison to clinical indices the linear and nonlinear parameters are easy to apply and independent on subjective influences.

Interestingly, in addition to the clinical indices (NYHA, LVEF) only nonlinear measures were automatically chosen by the step-wise discriminant analysis (α_1, CE, plvar5) for inclusion in the mixed optimal parameter set. The mixed parameter set leads to an enhanced risk stratification (increasing accuracy from AUC=67% to AUC=72%).

In conclusion, the results of this study show that HRV measures especially from nonlinear dynamics together with clinical parameters contribute to an enhanced risk stratification in heart failure patients independent from the origin of heart failure which has to be verified by additional studies.

Acknowledgements

This study was partly supported by grants from the DAAD program "Acciones Integradas Hispano-Alemanas 2006-2007".

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