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Comparison of time-domain, frequency-domain and non-linear analysis for distinguishing congestive heart failure patients from normal sinus rhythm subjects

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Abstract: It is known that patients with congestive heart failure have reduced ability to modulate heart rate in comparison with normal subjects. However, the characteristics of these changes is not well understood. This study therefore investigated the characteristic features of heart rate changes to assess how they differed between both groups. Fifty-two normal sinus rhythm subjects and 18 congestive heart failure patients from the PhysioNet database were studied. Nine common heart rate indices were studied: three time-domain indices (MEAN RR interval, standard deviation of successive RR SDNN, and square root of mean squared differences of successive RR RMSSD), three frequency-domain indices (normalized low-frequency power LF_n, normalized high-frequency power HF_n, and their ratio LF/HF), and three non-linear indices (vector length index VLI, vector angle index VAI and sample entropy SampEn). Two 5-min segments from every subject, neither of which had any ectopic beat, were analyzed. The statistical differences between the two clinical groups for the first and second segments, and their average were determined for all nine indices. Results showed that there was no significant difference between the two 5-min RR interval segments for any technique. All frequency-domain and non-linear indices, but only one time-domain index (SDNN), were significantly different between subject groups. However, some indices were much more sensitive to the clinical differences than others; with the best performing techniques, one non-linear index VLI and one time domain index SDNN, followed by all three frequency indices of LF_n, HF_n and LF/HF, and finally two of the other non-linear indices VAI and SampEn. A simple RBF SVM-based classification algorithm gave a good performance for classifying the CHF and NSR subjects. And the mean Se, Sp and Acc of SVM classifier from 10 folds were 91.31%, 90.04% and 90.95% respectively. We have shown that there are characteristic differences in heart rate changes between congestive heart failure and normal sinus rhythm, suggesting characteristic rhythm differences.
Key words: Heart rate variability (HRV), congestive heart failure (CHF), normal sinus rhythm (NSR), HRV analysis, RR time series.

1. Introduction

Heart rate variability (HRV) analysis is a non-invasive method for assessing the function of the cardiovascular autonomic nervous system (ANS) [1; 2]. Depressed HRV has been used as a predictor of risk after acute myocardial infarction [3], and as an early warning sign of diabetic neuropathy [4]. In addition, low HRV has been observed in patients suffering from dilated cardiomyopathy [5], fetal distress conditions, and obstructive sleep apnea [6; 7], as well as congestive heart failure (CHF) [8-11]. CHF is a typical degeneration of the heart

function featured by the reduced ability for the heart to pump blood efficiently [7]. It is a difficult condition to manage in clinical practice, and the mortality from CHF is high [12-16].

For healthy subjects, it has been proven that the increased sympathetic and the decreased parasympathetic activity results in the decrease of mean RR interval, as well as the decrease of indices of the standard deviation of beat-to-beat intervals (SDNN), low frequency content (LF), and also non-linear indices VAI and VLI [17]. Moreover, the increased parasympathetic activity has been proven to be a the major contributor to the increase in the index for high frequency (HF) content [18]. HRV analysis has also given an insight into understanding the abnormalities of CHF, and can also be used to identify the higher-risk CHF patients. Depressed HRV has been used as a risk predictor in CHF [9; 11; 19; 20]. CHF patients usually have a higher sympathetic and a lower parasympathetic activity [9; 20]. Typical HRV analysis for CHF patients include the following publications: Nolan *et al*. performed a prospective study on recruited 433 CHF patients and found that SDNN was the most powerful predictor of the risk of death for CHF disease [13]. Binkley *et al.* studied 15 healthy subjects and 10 CHF patients, and reported that parasympathetic withdrawal, in addition to the augmentation of sympathetic drive, is an integral component of the autonomic imbalance characteristic for CHF patients and can be detected noninvasively by HRV spectral analysis [9]. Rovere *et al*. studied 202 CHF patients and reported that the LF component was a powerful predictor of sudden death in CHF patients [21]. Hadase *et al*. also confirmed that the very low frequency (VLF) content was a powerful predictor from a 54 CHF patient study [2]. Woo *et al.* studied 21 patients with heart failure and demonstrated that Poincare plot analysis is associated with marked sympathetic activation for heart failure patients and may provide additional prognostic information and an insight into autonomic alterations and sudden cardiac death [20]. Guzzetti *et al*. (2000) studied 200 CHF patients and found significantly lower normalized LF power and lower 1/*f* slope in CHF patients compared with controls. Moreover, the patients who died during the follow-up period presented further reduced LF power and steeper 1/*f* slope than the survivors [22]. Makikallio *et al.* studied 499 CHF patients and showed that a short-term fractal scaling exponent was the strongest predictor of mortality of CHF [23]. Poon and Merrill studied 8 healthy subjects and 11 CHF patients, and found that the short-term variations of beat-to-beat interval exhibited strongly and consistently chaotic behaviour in all healthy subjects but were frequently interrupted by periods of seemingly non-chaotic fluctuations in patients with CHF [19]. Peng *et al.* used FDA analysis and confirmed a reduction in HR complexity in CHF patients [24]. Liu *et al.* studied 60 CHF patients and 60 healthy control subjects, and reported decrease of ApEn values in CHF group [25]. Costa *et al.* used the multiscale entropy method for classifying CHF patients and healthy subjects, and reported that the best discrimination between CHF and healthy HR signals with the scale 5 in the multiscale entropy calculation [26].

All those studies have verified that decreased HRV was associated with the increased mortality in CHF patients. However, detailed analysis of the power of the indices to distinguishing CHF from normal cardiac function is lacking. Existing studies included the work of Pecchia *et al.* that compared a limited number of time-domain and frequency-domain indices [27], the work from Mietus *et al.* comparing the performance of a family of pNNx indices, defined as the mean number of times per hour in which the change in consecutive normal sinus intervals exceeds x ms, [28], and the work from Isler *et al.* using a wavelet entropy method [7]. However, investigations comparing a wide range of indices is missing. Evaluating how well the common HRV indices can separate CHF patients from normal subjects could lead to an important clinical tool. This study therefore investigated the commonly used short-term HRV indices, subdivided into three groups: time-domain, frequency-domain and non-linear, to compare their abilities to differentiate normal sinus rhythm (NSR) subjects and CHF patients.

2. Method

2.1. Data

RR interval time series data were from a free-access, on-line archive database in http://www.physionet.org [29]. The original ECG signals were digitized at 128 Hz, and the

beat annotations were obtained by automated analysis with manual review and correction. Fifty-two NSR subjects and 18 CHF patients were studied. Two 5-min RR segments from every subject/patient, neither of which had any ectopic beat, were analyzed. Figure 1 shows the examples of 5-min RR segments from NSR subjects and CHF patients respectively.

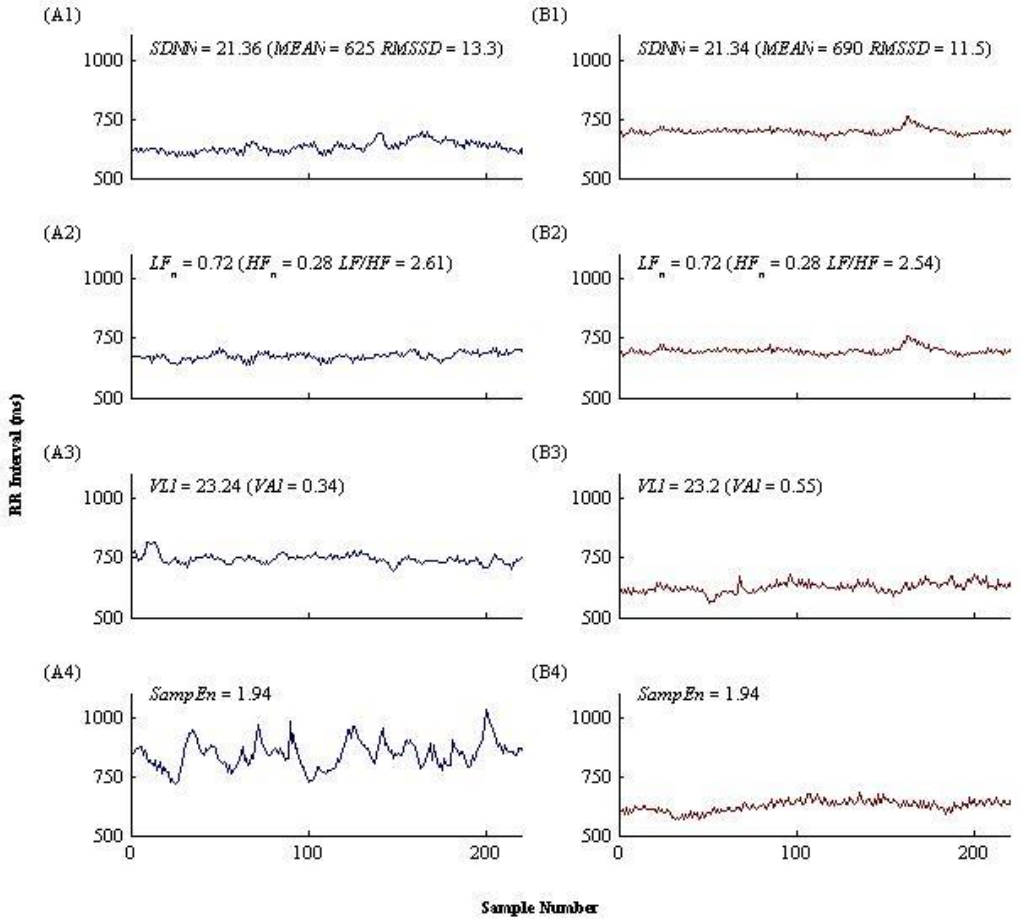

Figure 1. (A1-A4) Examples of 5-min RR segments from NSR subjects. (B1-B4) Examples of 5-min RR segments from CHF patients.

2.2. HRV index calculations

Time-domain indices. The mean value (MEAN) of RR intervals, the standard deviation (SDNN) of RR intervals and the square root of mean squared differences of successive RR intervals (RMSSD) were used as time-domain indices [30; 31], defined as:

$$\mathrm{MEAN} = \frac{\sum_{\mathrm{n}=1}^{\mathrm{N}} RR_n}{N} \tag{1}$$

$$\mathrm{SDNN} = \sqrt{E\left[\left(RR_n - E\left(RR_n\right)\right)^2\right]} \tag{2}$$

$$\mathrm{RMSSD} = \sqrt{\mathrm{E}\left[\left(\mathrm{RR_n} - RR_{n+1}\right)^2\right]} \tag{3}$$

where RR_n denotes the n^{th} RR interval.

Frequency-domain indices. The AR method can be used for the analysis of frequency domain. AR method of order p is expressed as the following equation [32]:

$$\mathrm{x}[\mathrm{n}] = -\sum_{\mathrm{k}=1}^{\mathrm{p}} a(k)\, x[n-k] + w[n] \tag{4}$$

where $a(k)$ are the AR coefficients and $w[n]$ is white noise of variance equal to σ^2. The Burg method is used to get the AR model parameter. The power spectrum of a p^{th} order AR process is [32]:

$$\mathrm{P}^{\mathrm{BU}}(f)=\frac{E_p}{\left|1+\sum_{k=1}^{p}a_p(k)e^{-j2\pi fk}\right|^2} \tag{5}$$

where E_p is total least square error.

Burg's method with an order of 16 was used to produce the HRV frequency spectrum, which was integrated across the low-frequency power (0.04 to 0.15 Hz) and high-frequency power (0.15 to 0.40 Hz) spectra. The normalized low-frequency power (LF_n) and normalized high-frequency power (HF_n), and their ratio (LF/HF) were used as the frequency-domain indices [30].

Non-linear indices. The vector length index (VLI) and vector angle index (VAI) from Poincare scatter plots were studied as two non-linear indices. They are defined by [33]:

$$\mathrm{VLI}=\sqrt{\sum_{i=1}^{N}(l_i-L)^2}\Big/N \tag{6}$$

$$\mathrm{VAI}=\sum_{i=1}^{N}|\theta_i-45|\Big/N \tag{7}$$

where, l_i is the vector length of each point in the Poincare scatter plot of the RR interval time series, L is the mean vector length, θ_i is the angle of each point, and N is the point number of the Poincare scatter plot.

Sample entropy (SampEn) was also studied as a non-linear index. The detailed calculation can refer to [34]. Because SampEn values are influenced by the parameters of embedding dimension m and tolerance threshold r [35], we used the different parameter combinations as follows: m was set as 1, 2 and 3 and r set as 0.10, 0.15, 0.20 and 0.25, to determine the parameter combination giving the best distinguishing performance for CHF patients and NSR subjects.

Figure 1 also shows the output values of the aforementioned HRV indices, which reports similar results between the two groups.

2.3. Statistical analysis

Normal distributions of all HRV indices for the two groups were confirmed by the Kolmogorov-Smirnov test and Q-Q plot. All HRV indices meet the normal distribution. The paired differences between the first and second segments for the NSR and CHF group, as well as for the first, second and average calculated values for the nine HRV indices. The Student *t*-test was used to test the statistical difference between the two groups for all calculations. All statistical analyses were performed using the SPSS software (Ver. 20, IBM, USA). A statistical significance was accepted at $P<0.05$.

2.4. Classification algorithm

In order to verify the effectiveness of those HRV indices, we used a simple SVM-based classification algorithm for classifying the CHF and NSR subjects. As one of the most popular classifiers, SVM aims at minimizing an upper bound of the generalization error through maximizing the margin between the separating hyperplane and the data, and it has been successfully applied to many situations [36]. In this study, 10-fold cross-validation method was used for training and testing of SVM. The smaller the 10-fold cross-validation error, the better the classification effect. There are totally 52×3 5-min RR segments from NSR group and 18×3 5-min RR segments from CHF group. The 5-min RR segments were randomly divided into 10 folds. The division was performed separately for the two groups to keep each fold has similar amount 5-min RR segments for both two groups. Then the SVM was trained using the HRV index results on the nine folds and was tested on the remaining one fold. The indices of *Se*, *Sp* and *Acc* were calculated to evaluate the SVM model.

3. Results

First, we tested the group difference results (mean ± standard error of mean SEM) between the NSR and CHF groups when using SampEn index under different parameter combinations as described in the Methods section. Table 1 shows the lower and upper bounds of normalized 95% confidence interval (CI) of mean group difference of SampEn values by averaging the results from the two 5-min segments. The parameter combination of embedding dimension m=1 and tolerance threshold r=0.10 reported the best distinguishing performance for CHF patients and NSR subjects. Thus this parameter combination was used in the following analysis.

Table 1. Lower and upper bounds of normalized 95% CI of mean group difference for SampEn index when using different parameter combinations of m and r. * means P<0.05.

Parameter value		Normalized mean group difference	Normalized 95% CI of mean group difference		P value between two groups
r	m		Lower	Upper	
0.10	1	1	0.25	1.75	0.010*
	2	1	0.10	1.90	0.030*
	3	1	-1.86	3.86	0.488
0.15	1	1	-0.69	2.69	0.243
	2	1	-1.03	3.03	0.331
	3	1	-9.33	11.33	0.847
0.20	1	1	-1.81	3.81	0.481
	2	1	-1.67	3.67	0.459
	3	1	-1.78	3.78	0.475
0.25	1	1	-0.88	2.88	0.293
	2	1	-0.75	2.75	0.259
	3	1	-0.59	2.59	0.215

Table 2 shows the paired difference results (mean ± SEM) of all HRV indices between the first and second segments for the NSR and CHF groups separately, and for all subjects combined. The lower and upper boundaries of 95% CI of segment difference are also show. Table 2 shows that there was no significant difference between the two 5-min RR interval segments for any technique (all P>0.05) in both NSR and CHF groups, and in all subjects combined.

Table 2. Statistical results for paired differences of the first and second segments.

Group	Type	Indices	Segment difference ± SEM	95% CI of segment difference		P value between two segments
				Lower	Upper	
NSR	Time-domain	MEAN (ms)	-5.12 ± 9.02	-23.23	12.98	0.57
		SDNN (ms)	0.84 ± 2.81	-4.80	6.48	0.77
		RMSSD (ms)	1.64 ± 1.58	-1.53	4.81	0.30
	Frequency-domain	LF_n	-0.006 ± 0.02	-0.05	0.03	0.76
		HF_n	0.006 ± 0.02	-0.03	0.05	0.76
		LF/HF	-0.17 ± 0.42	-1.02	0.67	0.68
	Nonlinear	VAI	0.02 ±0.02	-0.02	0.07	0.37
		VLI	1.06 ± 3.56	-6.10	8.21	0.77

		SampEn	0.02 ± 0.05	-0.07	0.11	0.681
CHF	Time-domain	MEAN (ms)	-0.66 ± 6.48	-14.32	13.00	0.92
		SDNN (ms)	1.64 ± 3.03	-4.74	8.03	0.59
		RMSSD (ms)	0.12 ± 5.58	-11.66	11.90	0.98
	Frequency-domain	LF_n	0.02 ± 0.04	-0.07	0.12	0.58
		HF_n	-0.02 ± 0.04	-0.12	0.07	0.58
		LF/HF	-0.11 ± 0.38	-0.92	0.69	0.77
	Nonlinear	VAI	-0.05 ± 0.05	-0.16	0.05	0.32
		VLI	2.92 ± 2.04	-1.38	7.22	0.17
		SampEn	-0.03 ± 0.04	-0.12	0.06	0.53
All	Time-domain	MEAN (ms)	-3.98 ± 6.88	-17.71	9.76	0.57
		SDNN (ms)	1.05 ±2.22	-3.37	5.47	0.64
		RMSSD (ms)	1.25 ± 1.83	-2.40	4.90	0.50
	Frequency-domain	LF_n	0.002 ± 0.02	-0.04	0.04	0.93
		HF_n	-0.002 ± 0.02	-0.04	0.04	0.93
		LF/HF	-0.16 ± 0.33	-0.81	0.49	0.63
	Nonlinear	VAI	0.002 ± 0.02	-0.04	0.04	0.92
		VLI	1.53 ± 2.69	-3.84	6.91	0.57
		SampEn	0.004 ± 0.04	-0.06	0.08	0.85

Table 3 shows the group difference results (mean ± SEM) of all HRV indices between the NSR and CHF groups. Table 3 shows that the group differences between the NSR and CHF groups were similar when comparing the results from the first and second 5-min RR segments, as well as from the average of the two 5-min segments. For the average segment results, all frequency-domain and non-linear indices, but only one time-domain index (SDNN), showed significant differences (all $P<0.05$) between NSR and CHF groups. The best performing techniques were VLI ($P=0.001$) and SDNN ($P=0.003$), followed by all three frequency indices LF_n, HF_n and LF/HF (all $P=0.006$), VAI ($P=0.009$) and SampEn ($P=0.010$).

Figure 2 shows the lower and upper boundaries of normalized (mean group difference equals to 1) 95% CI of mean group difference for nine HRV indices, ordered for increasing discrimination power (top to bottom) for the average results of the two 5-min RR interval segments. The lower confidence interval is shown on the right with an expended scale, where results for RMSSD are off scale and not shown. When the lower boundary of the normalized CI lies above zero this indicates statistical significance with *P* value given in Table 3. For the average of the two segments, it shows the order of HRV indices for discriminating NSR and CHF groups was in the following order: VLI, SDNN, LF_n & HF_n & LF/HF, VAI, SampEn, with Mean abs RMSSD indicating no significant discriminating power.

Table 3. Statistical results for group differences between NSR and CHF groups. * means $P<0.05$ and ** means $P<0.01$.

Signal	Type	Indices	NSR	CHF	*P* value
First 5-min segment	Time-domain	MEAN (ms)	707± 16	669± 16	0.109
		SDNN (ms)	42± 3	28± 5	0.016*
		RMSSD (ms)	22 ± 2	19± 5	0.456
	Frequency-domain	LF_n	0.73 ± 0.03	0.56± 0.06	0.003**
		HF_n	0.27 ± 0.03	0.44± 0.06	0.003**
		LF/HF	4.67 ± 0.46	2.34± 0.60	0.009**
	Nonlinear	VAI (º)	0.63 ± 0.03	0.45 ± 0.04	0.005**

		VLI (ms)	46 ± 4	28 ± 4	0.002**
		SampEn	1.87± 0.05	1.61± 0.07	0.012*
Second 5-min segment	Time-domain	MEAN (ms)	712± 17	670± 15	0.068
		SDNN (ms)	41± 3	26± 4	0.003**
		RMSSD (ms)	20 ± 1	18± 3	0.621
	Frequency-domain	LF_n	0.74 ± 0.03	0.54± 0.07	0.009**
		HF_n	0.26 ± 0.03	0.46± 0.07	0.009**
		LF/HF	4.84 ± 0.52	2.45± 0.60	0.014*
	Nonlinear	VAI (º)	0.61 ± 0.03	0.50 ± 0.06	0.057
		VLI (ms)	45 ± 3	25 ± 4	0.001**
		SampEn	1.85± 0.05	1.64± 0.08	0.028*
Average of the two 5-min segments	Time-domain	MEAN (ms)	710± 16	670± 15	0.078
		SDNN (ms)	42± 2	27± 4	0.003**
		RMSSD (ms)	21 ± 1	19± 4	0.509
	Frequency-domain	LF_n	0.74 ± 0.02	0.55± 0.06	0.006**
		HF_n	0.26 ± 0.02	0.45± 0.06	0.006**
		LF/HF	4.75 ± 0.44	2.40± 0.57	0.006**
	Nonlinear	VAI (º)	0.62 ± 0.03	0.47 ± 0.04	0.009**
		VLI (ms)	46 ± 3	27 ± 4	0.001**
		SampEn	1.86± 0.05	1.62± 0.07	0.010*

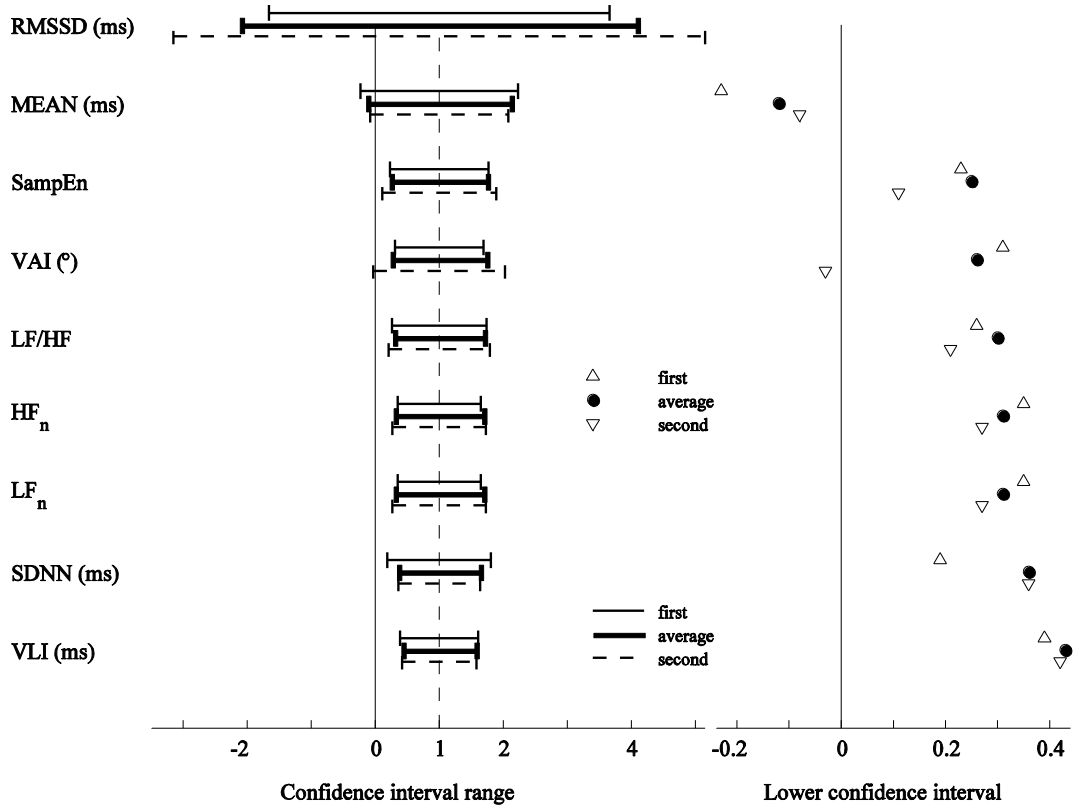

Figure 2. Lower and upper boundaries of normalized (mean group difference equals 1) 95% CI of mean group difference for all nine HRV indices. The axis scale for the lower CI boundary is expanded on the right to better illustrate differences.

Table 4 shows the 10-fold cross validation of SVM classifier results on all 210 5-min RR segments used in this study. The mean Se, Sp and Acc of SVM classifier from 10 folds are 91.31%, 90.04% and 90.95% respectively. The SD values of Se, Sp and Acc indices are 11.75%, 6.19% and 4.74% respectively.

Table 4. Results of 10-fold cross validation for classifying NSR and CHF groups using the default SVM parameter setting.

Fold	MSE_RR (original RR segment)		
	Se (%)	Sp (%)	Acc (%)
1	75	94.12	90.48
2	83.33	93.33	90.48
3	83.33	93.33	90.48
4	100	100	100
5	100	85.71	90.48
6	100	94.12	95.24
7	100	94.44	95.24
8	71.43	92.86	85.71
9	100	81.25	85.71
10	100	81.25	85.71
Mean	**91.31**	**90.04**	**90.95**
SD	11.75	6.19	4.74

4. Discussion

Previous studies have shown that HRV indices can predict of CHF incidents. Nolan *et al.* found that SDNN was a predictor of the death risk for CHF disease [13]. Rovere *et al.* reported that the LF component was a predictor of sudden death in CHF patients [37]. Hadase *et al.* also confirmed that VLF was a predictor [2]. All those studies verified that the decreased HRV was associated with increased mortality in CHF patients. For discriminating CHF patients from normal subjects, Pecchia *et al.* designed a classifier based on the regression tree method and selected RMSSD, total power, HF, and LF/HF as useful classification features [27]. Previous studies have also described two abnormal Poincare plot patterns in CHF patients: a torpedo pattern with reduced beat to beat variability and a complex pattern with clustering of points [20]. Isler *et al.* designed a 7-nearest neighbor classifier, and found that the best subset of classification features were MEAN, RMSSD, VLI, LF/HF, VLF (0 to 0.04 Hz), LF_n and HF_n [7]. Liu *et al*. proposed three nonstandard HRV measures. With the combination of SVM, they reported a perfect CHF classification accuracy, sensitivity and specificity of 100%, 100%, 100%, respectively [38]. Kazmi *et al*. used human and animal data to demonstrate the inverse correlation between HRV and HR, and thus to suggest the common NSR/CHF classification using HRV method should considering the HR effect [39].

In this study, we found that all frequency-domain and nonlinear indices, as well as time-domain index SDNN, had discrimination power for CHF patients and NSR subjects. Importantly, we compared the discrimination power of the common HRV indices and found that some indices were much more sensitive to the clinical differences than others, with the best performing techniques VLI and SDNN, followed by all three frequency indices LF_n, HF_n and LF/HF, and non-linear index SampEn. We have shown that some analysis techniques are much more effective in separating the two clinical groups than others, providing both useful analysis tools and suggesting possible differences between the rhythms. For performance validation of the employed HRV indices, we performed a classification method using the common SVM toolbox and achieved a classification accuracy of 90.95% when using 10-fold cross validation on the MIT-BIH NSR and CHF RR interval databases.

ANS has sympathetic and parasympathetic components. Sympathetic stimulation causes an increase in HR by increasing the firing rate of pacemaker cells in the heart's sino-atrial node. Parasympathetic activity decreases the firing rate of pacemaker cells and the HR. Sympathetic activity is associated with the low frequency range (0.04-0.15 Hz) while

parasympathetic activity is associated with the higher frequency range (0.15-0.4 Hz) of modulation frequencies of the HR [32]. Reference [40] demonstrated that the activation of the sympathetic nervous system, the decreased activity of the parasympathetic nervous system, as well as the depressed baroreceptor function, are early features that may precede the onset of clinically obvious symptoms and signs of heart failure. The difference between the two groups can be partly explained by the ANS balance. The CHF patients usually have a lower parasympathetic activity and a higher sympathetic activity [8; 9; 20; 41]. Decreased parasympathetic and increased sympathetic activity results in the decrease of mean RR interval, as well as the decreases of indices of SDNN [32], LF_n [30; 42], VAI and VLI [17], whereas increased parasympathetic activity is the major contributor to the increase of index of HF_n [18; 42; 43].

Conflict of Interest

The authors declared that they do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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