Assessment of Respiratory Flow Cycle Morphology in Patients with Chronic Heart Failure

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Abstract

Breathing pattern as periodic breathing (PB) in chronic heart failure (CHF) is associated with poor prognosis and high mortality risk. This work investigates the significance of a number of time domain parameters for characterizing respiratory flow cycle morphology in patients with chronic heart failure (CHF). Thus, our primary goal is to detect PB pattern and identify patients at higher risk. In addition, differences in respiratory flow cycle morphology between CHF patients (with and without PB) and healthy subjects are studied. Differences between these parameters are assessed by investigating the following three classification issues: CHF patients with PB vs. with non-periodic breathing (nPB), CHF patients (both PB and nPB) vs. healthy subjects, and nPB patients vs. healthy subjects. 26 CHF patients (8/18 with PB/nPB) and 35 healthy subjects are studied. The results show that the maximal expiratory flow interval is shorter and with lower dispersion in CHF patients than in healthy subjects. The flow slopes are much steeper in CHF patients, especially for PB. Both inspiration and expiration durations are reduced in CHF patients, mostly for PB. Using the classification and regression tree technique, the most discriminant parameters are selected. For signals shorter than 1 min, the time domain parameters produce better results than the spectral parameters, with accuracies for each classification of 82/78%, 89/85% and 91/89%, respectively. It is concluded that morphologic analysis in the time domain is useful, especially when short signals are analyzed.

Keywords

Chronic heart failure, respiratory pattern, periodic and non-periodic breathing, ensemble average.

1. Introduction

Chronic heart failure (CHF) is a growing epidemic in Western countries with increasing incidence and prevalence [5]. Despite important progress in recent decades, mortality remains high for patients with CHF. Moreover, established indexes such as New York Heart association (NYHA) functional class and the left ventricular ejection fraction (LVEF), associated with the laboratory values and medication use do not fully explain the mortality risk of patients with CHF and do not estimate an individual's prognosis [29], [18], [3]. CHF is associated with major abnormalities in the autonomic cardiovascular control, characterized by enhanced sympathetic nerve activity and cardiorespiratory disorder.

Breathing disorders are very common in CHF patients, usually manifested as a centrally-driven, rhythmic rise and fall in ventilation [26]. This type of breathing pattern, referred to as periodic breathing (PB), can be classified into ventilation with apnea, known as Cheyne–Stokes respiration, or without apnea [20], [17]. With a prevalence as high as 70% in CHF patients [27], the PB pattern has been established as a powerful predictor of poor prognosis in these patients [7] and increased mortality [11], especially in patients with Cheyne–Stokes respiration [30], [4].

Various parameters have been suggested for the characterization and identification of different breathing patterns [15], [31], [32], [35]. For example, the sleep-disordered breathing index is associated with an accelerated decline in cardiac function and in- creased morbidity and mortality [12], [13]. Sympathetic activity was found to increase with faster breathing rates and to decrease with higher tidal volumes in CHF patients. Some reports shown that the baroreflex sensitivity in CHF patients under basal con- ditions was lower than that of healthy subjects [1]. Short-term analysis of HRV has independent prognostic value of CHF patients: reduced low-frequency power during controlled breathing is a predictor of sudden death [16].

Several studies have reported that central sleep apnea is highly prevalent among patients with CHF [36], [34]. The continuous positive airway pressure treatment of obstructive sleep apnea in CHF patients demonstrated significant improvements in cardiac function and left ventricular systolic function, and attenuation of sympathetic nerve activity [14], [21]. We have previously characterized the respiratory pattern in CHF patients and healthy subjects using spectral parameters computed from

the enve- lope of the respiratory flow signal [9]. In a subsequent study, we used the correntropy function, extracting parameters based on the correntropy spectral density (CSD) to detect nonlinearities in the respiratory flow signal [10].

The aim of this work is to study the morphology of the respiratory flow cycle in CHF patients with PB and non-periodic breathing (nPB). We analyze the evolution of morphology over time using a novel template-based technique. In general, differences in the spectral domain between CHF and healthy subjects are related to the modulation of the respiratory signal. The modulation may be characterized in the time domain by quantifying morphologic changes in the respiratory cycle, potentially offering the advantage of requiring shorter signals for analysis than required for computing the correntropy function.

2. Methods

The study of respiratory flow cycle morphology involves the following processing steps: segmentation and time alignment, computation of a respiratory cycle template from which a set of time domain parameters are extracted. On the other hand, CSD- based parameters are computed so that these results can be compared with those of the morphologic parameters. Finally, statistical analysis and respiratory pattern classification are performed.

2.1. Dataset

Respiratory flow signals were recorded from 26 CHF patients (20 males; 65 ± 9 years) and 35 healthy volunteers (12 males; 27 ± 7 years) at Santa Creu i Sant Pau Hospital, Barcelona, Spain; see [9] for more details of the dataset. The study was approved by the local Ethics Committee. The signals were originally recorded at a sampling rate of 250 Hz, for 15 min, but, given that the frequency content of interest is below 1 Hz, the signals were decimated to 10 Hz using zero-phase, antialiasing filtering. All signals were analyzed visually by an experienced physician. According to clinical criteria, the PB patterns were visually identified by analyzing the waxing and waning of the respiratory flow signal. The CHF patients were divided into two groups: 8 patients with PB pattern (7 male; 71 ± 7 years) and 18 patients with nPB pattern (13 male; 63 ± 9 years).

Figure 1 illustrates respiratory flow signals with patterns observed in CHF patients (PB and nPB) and in a healthy subject. For the entire dataset with 61 subjects, the respiratory rate was found to range from 11.5 to 29.0 breaths/min. The characteristics of the CHF patients and healthy subjects, in terms of respiratory rate and the duration of inspiratory and expiratory cycles, are shown in Table 1.

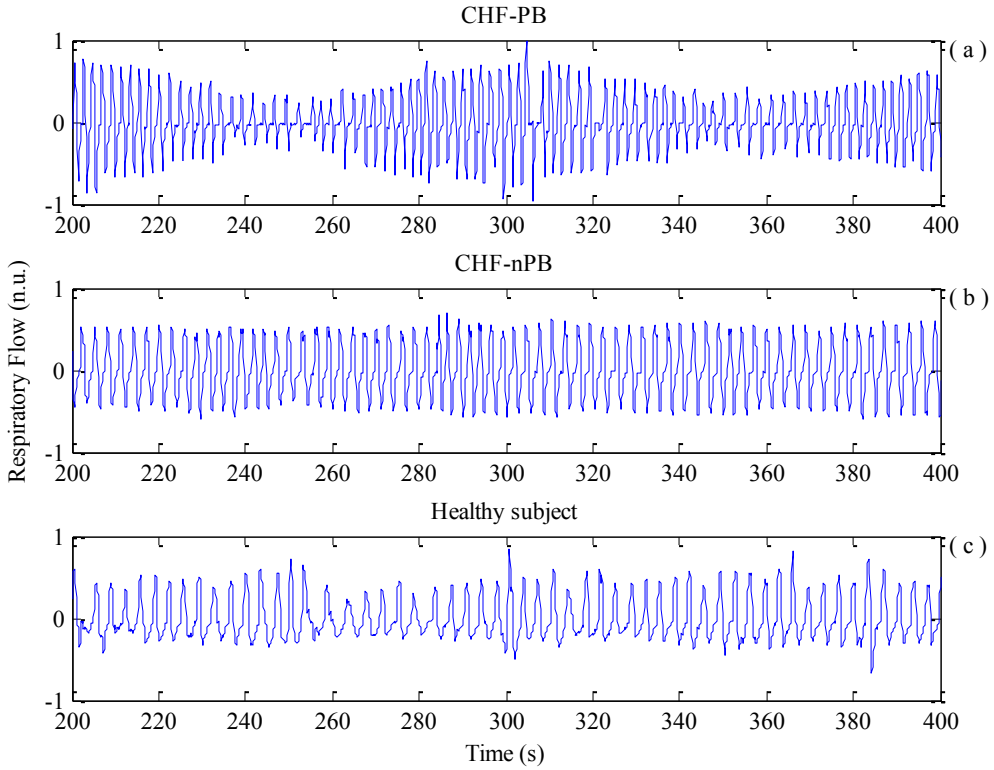

Fig. 1 Respiratory flow signals from (a) a CHF-PB patient, (b) a CHF-nPB patient, and (c) a healthy subject (n.u. denotes normalized units).

Table 1 Respiratory Rate (Mean ± Standard Deviation) in CHF Patients and Healthy Subjects

CHF	PB (n = 8)	nPB (n = 18)
R_f (breaths/min)	22.5 ± 4.3	18.4 ± 2.2
D_I (s)	0.97 ± 0.20	1.14 ± 0.18
D_E (s)	1.79 ± 0.38	2.16 ± 0.32
	CHF	Healthy subjects

	(n = 8)	(n = 18)
R_f (breaths/min)	19.6 ± 3.4	15.5± 3.7
D_I (s)	1.09 ± 0.20	1.8 ± 0.35
D_E (s)	2.05 ± 0.38	2.3± 0.64

R_f : Respiratory rate; D_I : Duration of inspiration; D_E : Duration of inspiration.

2.2. Segmentation and Time Alignment

The respiratory flow signal is analyzed using a sliding window of 30-s length (80% overlap); this choice was based on the observation that the period length of PB ranges from 25 to 100 s (i.e., 10–20 cycles) [28]. The alignment method was found to perform particularly well for small ensemble sizes.

The signal is normalized with respect to its largest absolute amplitude, and all cycles within the window are extracted using an algorithm that finds the zero-crossings of the respiratory flow signal. The resulting ensemble of successive respiratory cycles is represented by an N × M data matrix X,

$$\boldsymbol{X} = [X_1 \quad X_2 \quad \cdots \quad X_M] \ , \tag{1}$$

where each column X_i contains N samples of the i:th cycle, and M is the total number of respiratory cycles.

To ensure that the signal ensemble is well-aligned, a novel eigenvalue-based method is employed which performs joint alignment of all signals; for more information on the method and its performance, see [8]. The method is based on the eigenvalue decomposition of the N x N sample correlation matrix as

$$\widehat{\boldsymbol{R}}_{\boldsymbol{x}} = \frac{1}{M} \boldsymbol{X}\boldsymbol{X}^{\boldsymbol{T}} \ . \tag{2}$$

Interestingly, the ratio Λ_θ between the largest eigenvalue λ_1 of $\widehat{\boldsymbol{R}}_{\boldsymbol{x}}$ and the sum of the remaining $N - 1$ eigenvalues, i.e.,

$$\Lambda_\theta = \frac{\lambda_1}{\sum_{i=2}^{N} \lambda_i} \ , \tag{3}$$

can be interpreted as a signal-to-jitter-and-noise ratio [8]. Optimal alignment is obtained by finding those column shifts $\hat{\theta}_1, \cdots, \hat{\theta}_M$ which maximize the ratio Λ_θ. This is accomplished by shifting all

columns symmetrically around their initial positions (corresponding to cycles aligned to the maximal inspiration), resulting in a combinatorial optimization problem.

2.3. Respiratory flow cycle template

A respiratory flow cycle template is calculated from the sliding window by computing the ensemble average of time-aligned respiratory flow cycles. The template is then characterized by a set of time domain parameters reflecting inspiratory and expiratory time intervals, maximal inspiratory and expiratory flow values, and down-/upward inspiratory and expiratory slopes, see Table 2 for a list of the parameters, and Fig. 2 for graphical representation.

Table 2 Time Domain Parameters Extracted from the Respiratory Flow Cycle Template

Parameter	**Description**
D_I [s]	Inspiration duration
D_E [s]	Expiration duration
M_I [n.u.]	Maximal inspiratory flow
M_E [n.u.]	Maximal expiratory flow
I_I [s]	Maximal inspiratory flow interval
I_E [s]	Maximal expiratory flow interval
S_{I1} [n.u.]	Upward inspiratory slope
S_{I2} [n.u.]	Downward inspiratory slope
S_{E1} [n.u.]	Downward expiratory slope
S_{E2} [n.u.]	Upward expiratory slope

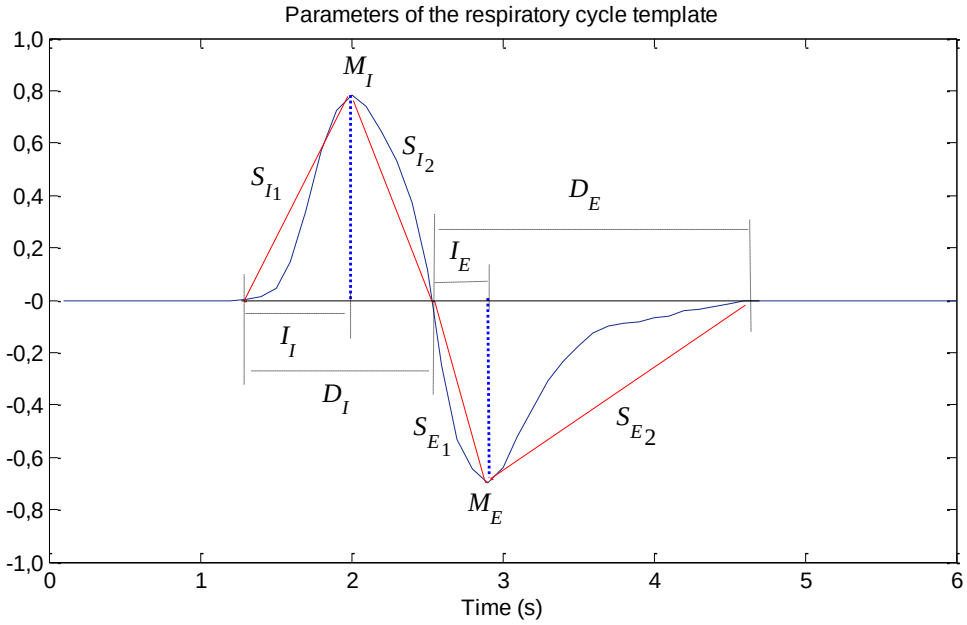

Fig. 2 Time domain parameters extracted from the respiratory flow cycle template.

2.4. Spectral parameters

We showed that the CSD was particularly well-suited for the characterization of modulated breathing patterns [10]. In this study, the same characterization is applied but with signals much shorter than the 15 min used in [10]; here, the signal length ranges from 1 to 5 min, incremented in steps of 30 s. The CSD can be viewed as a generalization of the conventional power spectral density, but with better spectral resolution. The CSD-based parameters are derived from frequency bands centered around the peaks corresponding to the respiratory frequency and the modulation frequency, see Table 3.

Table 3 Parameters based on the Correntropy Spectral Density

Parameter	**Description**
P_m	Power of the modulation frequency band
P_r	Power of the respiratory frequency band
R	P_m / P_r
V	Correntropy mean

2.5. Data Analysis

In order to analyze the dynamics of the respiratory flow cycle morphology over different signal lengths, the mean and standard deviation of each time domain parameter are computed. Statistical analysis is carried out using IBM SPSS software (v19). Differences between groups are tested by the Mann–Whitney U test and a p-value < 0.05 was considered statistically significant. The classification and regression tree technique is used to select the most discriminant parameters and classify, in a binary way, the different breathing patterns using leave-one-out crossvalidation. To allow for comparison with previous studies, the same classification framework is employed: 1) PB vs. nPB patients, 2) CHF patients vs. healthy subjects, and 3) nPB patients vs. healthy subjects. To avoid overfitting, we followed the ten events per parameter rule and consequently used only one parameter for each classification [25]. Parameters offering the best discriminatory power are presented in terms of accuracy, sensitivity, and specificity.

3. Results

3.1. Illustration of the Method

Examples of respiratory flow signals, respiratory cycle templates, and parameter trends are presented in Figs. 3, 4, and 5, for a patient with PB, a patient with nPB, and a healthy subject, respectively. It is noted from Fig. 3 that PB periodicity is well reflected by the trends of maximal inspiratory (M_I), expiratory (M_E) flow value, and duration of expiration (D_E).

The upward and downward slopes of inspiration and expiration are represented by their respective mean values for each of the four groups, i.e., PB, nPB, CHF, and healthy, see Fig. 6. The respiratory flow cycle in CHF patients is compressed, especially for those with PB who exhibit the steepest slopes. Conversely, healthy subjects exhibit the least steep slopes, especially with respect to the upward expiratory slope (S_{E2}).

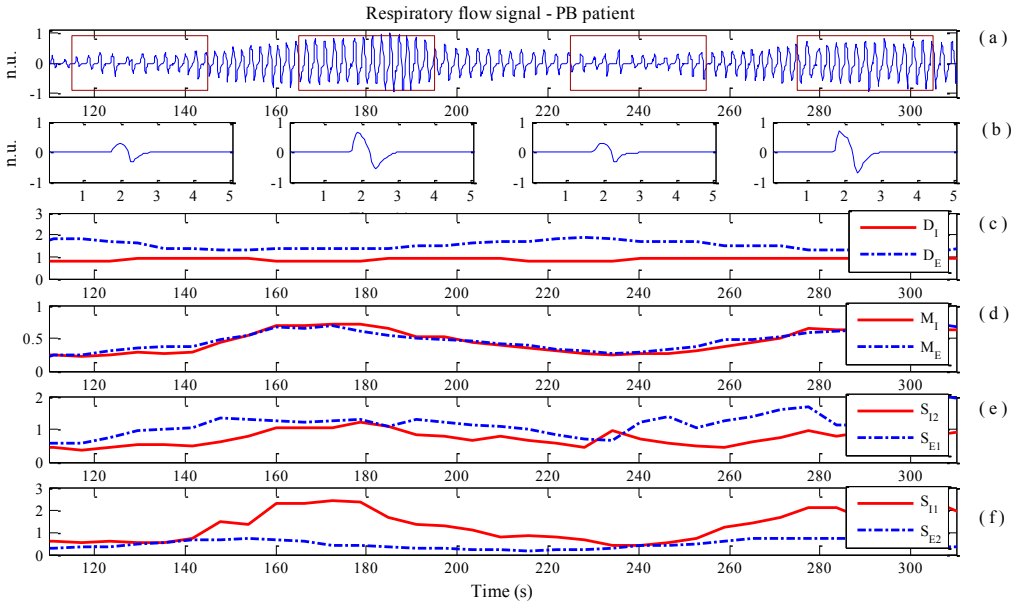

Fig. 3 Signals of a CHF patient with PB: (a) The respiratory flow signal and (b) related templates calculated in the four windows indicated in (a). The following trends, resulting from sliding window analysis, are displayed: (c) duration of inspiration (D_I) and expiration (D_E), (d) maximal inspiratory (M_I) and expiratory (M_E) flow value, (c) downward inspiratory (S_{I2}) and expiratory (S_{E2}) slope, and (f) upward inspiratory (S_{I1}) and expiratory (S_{E2}) slope.

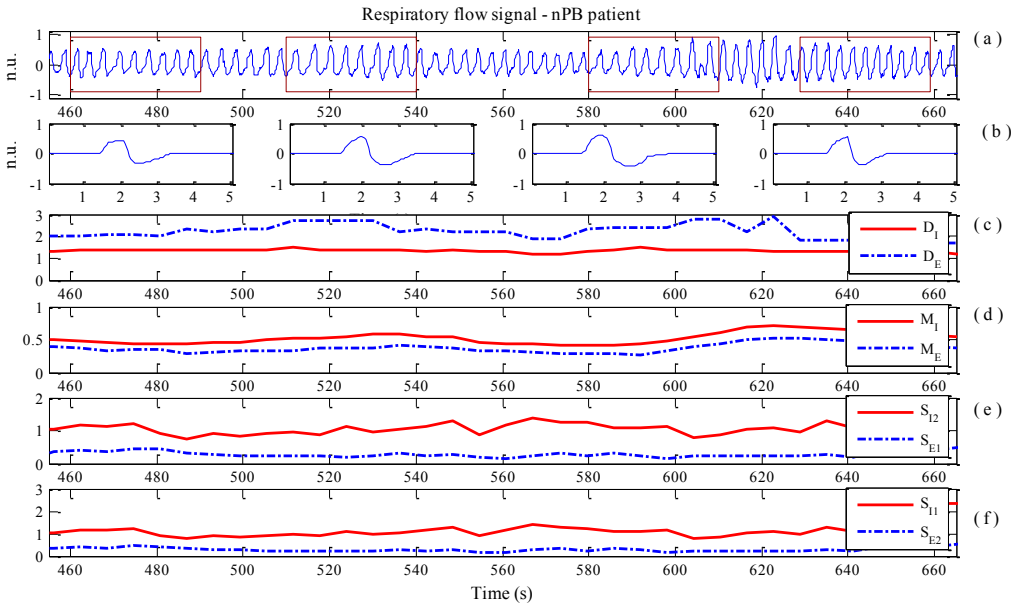

Fig. 4 Signals of a CHF patient with nPB; see Fig. 3 for an explanation of (a)-(f).

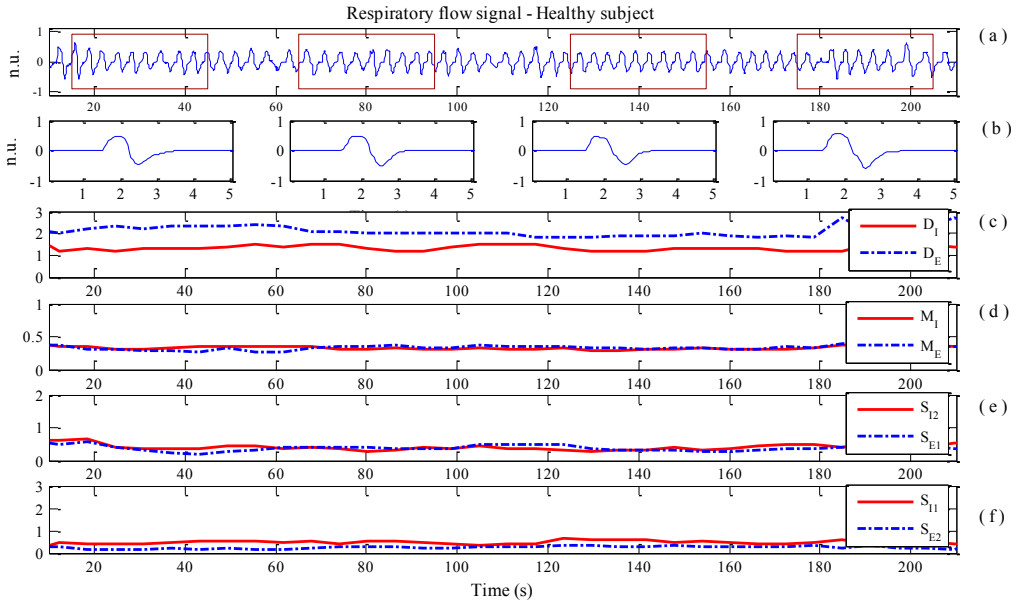

Fig. 5 Signals of a healthy subject see Fig. 3 for an explanation of (a)-(f).

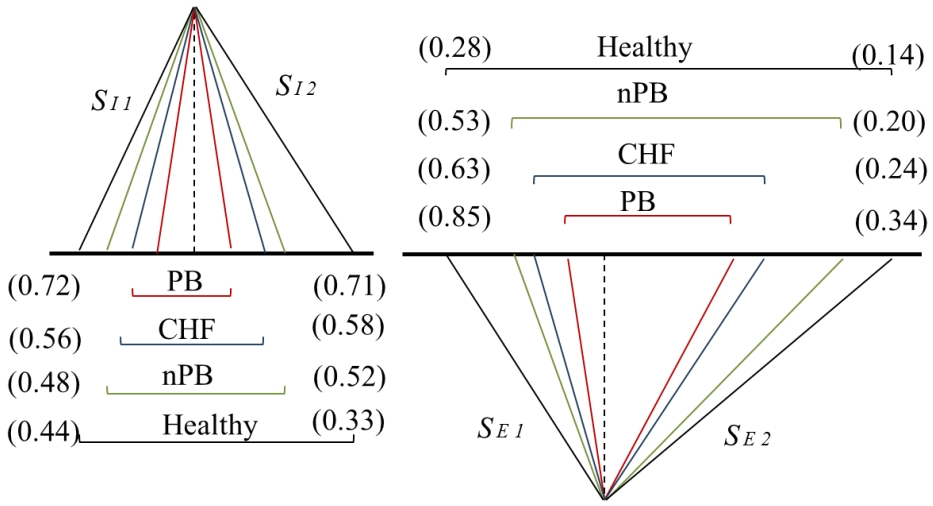

Fig. 6 Schematic representation of different slopes of the respiratory flow template cycle and their mean values.

3.2. Performance of the time domain parameters

Table 4 presents median, interquartile range, and p-value of the most statistically significant parameters when analyzing 15-min signals. The parameters corresponding to mean and standard deviation of characteristics are shown in Table 1.

Table 4 Median and interquartile range of the most statistically significant parameters of the respiratory template cycle when comparing CHF patients, PB and nPB patients, and healthy subjects

	CHF	**PB**	**nPB**	**Healthy**	***p*-value** *CHF vs. H*	***p*-value** *PB vs. nPB*	***p*-value** *nPB vs. H*
M_D_I	1.20 (0.30)	1.11 (0.28)	1.23 (0.30)	1.5 (0.36)	0.0002	n.s.	0.005
M_D_E	2.04 (0.45)	1.74 (0.41)	2.12 (0.45)	2.56 (1.27)	0.0003	0.016	0.009
M_I_E	0.54 (0.12)	0.54 (0.11)	0.54 (0.11)	0.87 (0.35)	0.0004	n.s.	0.0003
M_S_{I2}	-0.68 (0.41)	-0.83 (0.33)	-0.66 (0.27)	-0.36 (0.22)	0.0004	0.041	0.004
M_S_{E1}	0.59 (0.37)	0.78 (0.23)	0.48 (0.35)	0.21 (0.16)	0.0005	0.009	0.0002
SD_D_I	0.18 (0.07)	0.18 (0.04)	0.19 (0.07)	0.33 (0.22)	0.0004	n.s.	0.0005
SD_D_E	0.27 (0.15)	0.21 (0.09)	0.30 (0.20)	0.47 (0.46)	0.0002	n.s.	0.008
SD_I_E	0.10 (0.04)	0.10 (0.02)	0.09 (0.05)	0.21 (0.15)	0.0003	n.s.	0.0005
SD_S_{I2}	-0.28 (0.23)	-0.31 (0.22)	-0.27 (0.24)	-0.11 (0.11)	0.0005	0.026	0.006
SD_S_{E1}	-0.16 (0.16)	-0.26 (0.18)	-0.14 (0.11)	-0.08 (0.06)	0.0004	0.035	0.004
SD_S_{E2}	0.06 (0.06)	0.11 (0.04)	0.05 (0.03)	0.04 (0.02)	0.02	0.001	n.s.

M_{XX} : Mean value of each parameter, of each patient, during 15 min of signal; SD_{XX} : Standard deviation of each parameter; n.s.: not significant (p-value > 0.05)

PB vs nPB: The mean value of D_E is lower in PB than in nPB patients (p = 0.009). All slopes (S_{I1}, S_{I2}, S_{E1}, and S_{E2}) are steeper in PB patients than in nPB patients.

CHF patients vs healthy subjects: The mean values of D_I and D_E are lower in CHF patients than in healthy subjects. The maximal expiratory flow interval I_E is shorter and with a lower dispersion in CHF patients than in healthy subjects. CHF patients present much steeper slopes (S_{I2} and S_{E1}) with a higher dispersion when compared to healthy subjects. All parameters are significantly different with a $p < 0.0005$, except the standard deviation of S_{E2} with p = 0.02.

nPB patients vs healthy subjects: The results show that I_E is shorter and with a lower dispersion in nPB patients than in healthy subjects (both $p < 0.0005$). Furthermore, it is shown that S_{I2} ($p = 0.004$) and S_{E1} ($p < 0.0005$) are steeper and with higher dispersion in nPB patients.

3.3. Performance using different signal lengths

The performance of the most discriminatory parameters ($p < 0.01$) is studied with respect to signal length, for ranges from 1 to 5 min, being SD_S_{E2} and SD_I_E in time domain and R and $\bar{V}$ in the correntropy spectral domain. The accuracy, sensitivity, and specificity of these parameters are presented in Table 5 for 1-min signals (the minimal signal length used to calculate CSD values). When classifying PB vs nPB patients, the standard deviation of the upward expiratory slope (SD_S_{E2}) has an accuracy of 82%, and R an accuracy of 78%. When comparing CHF patients vs healthy subjects, SD_I_E has an accuracy of 89%, whereas $\bar{V}$ has an accuracy of 85%. When classifying nPB patients and healthy subjects, the mean of the maximal expiratory flow interval (M_I_E) correctly identifies the 91% of the subjects, and $\bar{V}$ the 89%.

Table 5 Accuracy (*Acc*), Sensitivity (S_E) and Specificity (S_p) obtained with the best parameter for each classification of 1-min signal length

Classification	Parameter	*Acc*	S_E	S_p
Morphology parameters				
PB vs. nPB	SD_S_{E2}	82%	75%	94%
CHF vs. H	SD_I_E	89%	85%	91%
nPB vs. H	M_I_E	91%	84%	91%
CSD parameters				
PB vs. nPB	R	78%	88%	74%
CHF vs. H	$\bar{V}$	85%	100%	74%
nPB vs. H	$\bar{V}$	89%	100%	68%

The accuracy of the most discriminatory parameters is evaluated for different signal lengths, see Figure 7. These results show that the time domain parameters perform slightly better than the CSD-based parameters for signals shorter than 1.5- min. This difference is maintained for 5-min signals when classifying PB vs nPB patients with an accuracy of 96% (SD_S_{E2}) vs. 93% (R). The CSD-based parameters perform slightly better than the time domain parameters for most signal lengths, when comparing CHF patients vs. healthy subjects, and nPB patients vs. healthy subjects. In these cases, the accuracies obtained with 5-min signals are 97% ($\bar{V}$) vs 94% (SD_I_E) in the first case, and 98% ($\bar{V}$) vs 94% (M_I_E) in the second case.

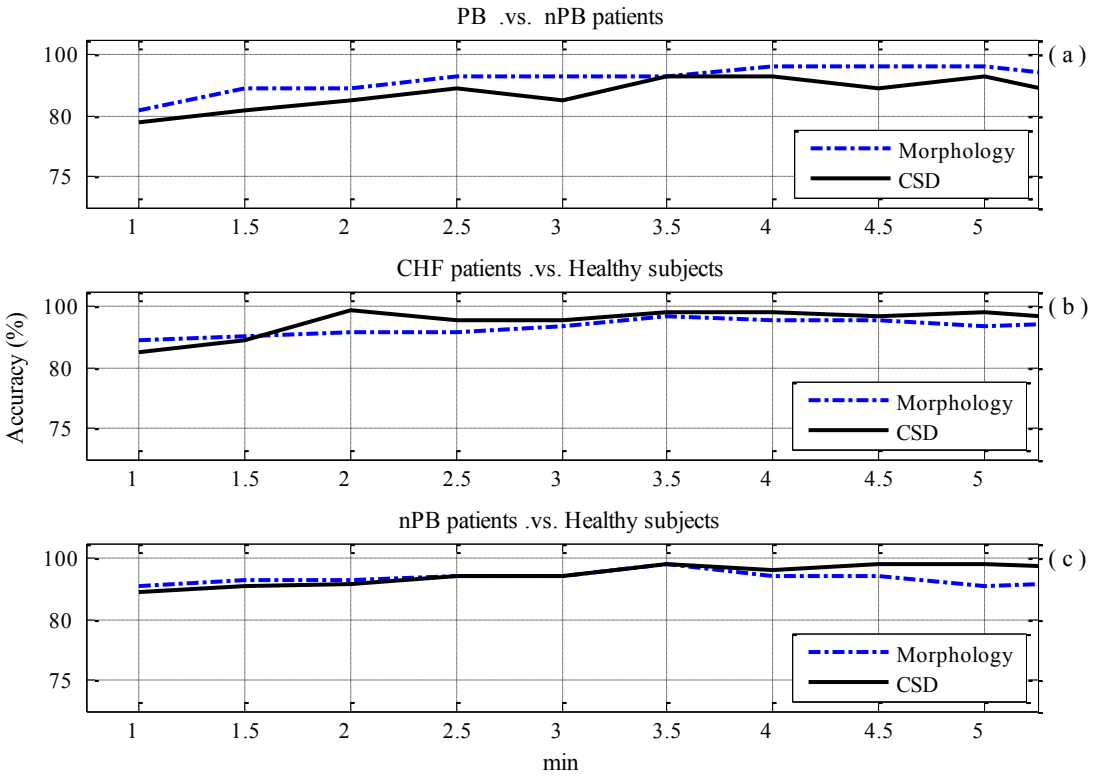

Fig. 7 Accuracy as a function of signal length, using the best parameters (see Table 5), when classifying (a) PB vs. nPB patients, (b) CHF patients vs. healthy subjects, and (c) nPB patients vs. healthy subjects.

4. Discussion

In this study, we have proposed a number of time domain parameters to characterize the respiratory flow cycle morphology in CHF patients, a method that is advantageous as it provides clinically relevant information even when only short-length signals are available. We have successfully used respiratory flow cycle morphology to detect PB in CHF patients, information which represents a strong predictor of poor prognosis. A respiratory template cycle is calculated for every 30-s respiratory flow signal segment. The time domain parameters, extracted from the template, provide statistically significant differences when comparing CHF patients (PB and nPB) and healthy subjects.

Selecting the length of the sliding window was a trade-off between providing a reliable respiratory flow cycle template and the capability to track changes in the respiratory cycle morphology during PB. Longer windows provide larger ensemble sizes and permit the estimation of a more reliable respiratory flow cycle template. On the other hand, shorter window lengths provide better monitoring of changes in the respiratory cycle morphology. A sliding window of 30 s (80% overlap) moving forward in steps of 6 s allowed us to extract a robust cycle template (with ensemble sizes ranging from 4-30 cycles) and monitor changes in its morphology over the PB period (ranging from 25-100 s).

The highest difference in the morphology of the respiratory flow cycle, among the different breathing patterns, is presented in the expiration through the upward expiratory slope and the maximal expiratory flow. The estimated maximal expiratory flow interval is shorter and with a lower dispersion in CHF patients than in healthy subjects. CHF patients and foremost PB patients present a more compressed respiratory cycle. They show steeper slopes and lower inspiratory and expiratory times than healthy subjects. When classifying PB and nPB patients, all the slopes are steeper, and the standard deviation of the maximal inspiratory and expiratory flow value is much higher in PB than in nPB patients. This could be related to the periodicity of the respiratory pattern.

Periodic breathing pattern, frequently observed in patients with chronic heart failure, has been associated with increased risk of mortality. This pattern has been analyzed, mostly in relation with

the sleep disorders [23], [35]; in healthy subjects, analyzing the relationship between the blood pressure and heart rate oscillations, through the tidal volume [19], and in the acclimatization to high altitude in healthy mountaineers [6], [24]. Despite advances in treatments of cardiovascular disease, the incidence and prevalence of heart failure continues to increase, which can be directly related to an increase in life span. In clinical practice, the CHF patients evolution is treated assessing indicators such as New York Heart Association (NYHA) classification, the percentage left ventricular ejection fraction (LVEF), and the level of natriuretic peptide (NT-proBNP) [2]. CHF patients normally have higher NYHA and ProBNP values, and lower LVEF percentages. Their diagnosis is based on tests whose results sometimes takes several days.

Introducing additional and more immediate information about the condition of the patient through the analysis of respiratory cycle morphology is expected to sup- port clinical decision and to prompt earlier treatment. The respiratory flow signal is commonly recorded in patients with cardiac and respiratory diseases, facilitating the implementation of the proposed analysis in clinical practice. CHF patients are regularly assessed in clinical practice and their treatment is adjusted based on their condition. Changes in the respiratory flow cycle morphology can indicate decompensation or poor prognosis for these patients, which can be useful to monitor and adjust their treatment.

In our previous studies, we characterized the respiratory pattern of CHF patients in the spectral domain using either the envelope of the respiratory flow signal [9], or the correntropy of the respiratory flow signal [10]. Correntropy was found to be particularly well-suited to characterize different breathing patterns in CHF patients and identify patients' condition. It was tested with 15-min of respiratory flow signals and provided an accuracy of 88.9% classifying PB vs nPB patients, and 95.2% classifying CHF patients vs healthy subjects.

Although CSD-based parameters perform slightly better with longer signals, shorter signals are needed for morphologic characterization to get significant parame- ters that identify CHF (PB and nPB) patients and healthy subjects. According to these results, 1-min signals could provide relevant

information about patient's condition (see Fig. 7). Thus, a promising advantage of the present morphologic characterization is its capability to provide clinically relevant information even from short-length respiratory flow signals, which are much easier to acquire in clinical practice.

A better risk assessment, which includes breathing patterns in heart failure, is clinically of great value as it more accurately identifies patients with CHF at increased risk of re-hospitalization and/or death who could then be targeted for more intensive monitoring and personalized treatment. Moreover, the characterization of the respiratory cycle morphology provides information that is easily interpretable by clinicians, which facilitates its introduction in clinical practice.

Limitations and Future Research: A study limitation is that the proposed method was developed and tested with leave-one-out crossvalidation using the same dataset. Thus, further validation of the method on a larger dataset is needed before it can be considered for clinical adoption. Despite the promising results obtained with simple statistical measures (median and interquartile range) of the morphologic parameters, it is of interest to pursue trend analysis and/or individual waveform analysis in future studies. Another limitation of this study is that age is not matched between CHF patients and healthy subjects. However, it has been reported that the respiratory rate does exhibit significant differences with respect to age [33], [22].

5. Conclusions

Based on a respiratory template cycle, obtained with a novel time alignment method, various parameters such as inspiratory and expiratory durations, maximal expiratory flow interval and slopes are found to offer good discrimination between respiratory patterns in CHF patients (PB and nPB) and healthy subjects. Maximal expiratory flow interval occurs earlier with higher slopes, and reduced inspiratory and expiratory duration, in CHF patients and foremost in PB patients than in healthy subjects. The results suggest that the analysis of the respiratory flow cycle morphology is a promising approach to study respiratory patterns and provide clinically relevant and interpretable information about CHF patients' condition, especially when dealing with short length signals.

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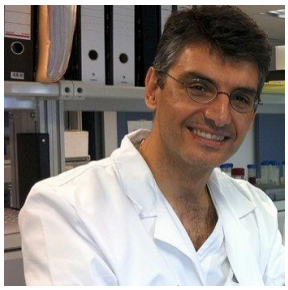

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