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

**Ainara Garde · Leif Sörnmo · Pablo Laguna ·
Raimon Jané · Salvador Benito ·
Antoni Bayes-Genis · Beatriz F. Giraldo***

Abstract 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). The differences between these parameters are assessed considering the following three classification: CHF patients with periodic breathing (PB) vs CHF patients 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

A. Garde
Institut de Bioenginyeria de Catalunya (IBEC), Barcelona, Spain
E-mail: agarde@ibecbarcelona.eu

L. Sörnmo
Department of Biomedical Engineering and Center of Integrative Electrocardiology, Lund University, Lund, Sweden. E-mail: leif.sornmo@eit.lth.se

P. Laguna
Biomedical Signal Interpretation and Computational Simulation Group (BSICoS), Aragón Institute of Engineering Research (I3A), Instituto de Investigación Sanitaria (IIS), University of Zaragoza, and also with the CIBER de BioengenierÃŋa, Biomateriales y Nanomedicina (CIBER-BBN), Spain. E-mail: laguna@unizar.es

R. Jané
Institut de Bioenginyeria de Catalunya (IBEC), Dept. ESAII, Universitat PolitÃĺcnica de Catalunya, Barcelona, Spain and also with the CIBER de BioengenierÃŋa, Biomateriales y Nanomedicina (CIBER-BBN). E-mail: rjane@ibecbarcelona.eu

S. Benito
Dept. of Emergency Medicine, Hospital de la Santa Creu i Sant Pau, Dept. of Medicine, Universitat Autónoma de Barcelona, Spain. E-mail: SBenito@santpau.cat

A. Bayes-Genis
Cardiology Dep., Hospital Universitari Germans Trias i Pujol, Dept. of Medicine, Universitat Autónoma de Barcelona, Spain. E-mail: abayesgenis@gmail.com

*Corresponding author
B.F. Giraldo
Dept. ESAII, EUETIB, Universitat PolitÃĺcnica de Catalunya, Barcelona; Institut de Bioenginyeria de Catalunya (IBEC), Barcelona, Spain and also with the CIBER de BioengenierÃŋa, Biomateriales y Nanomedicina (CIBER-BBN), Spain. E-mail: Beatriz.Giraldo@upc.edu

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], [19], [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 [22], [18]. 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 [12], especially in patients with Cheyne–Stokes respiration [30], [4].

Various parameters have been suggested for the characterization and identification of different breathing patterns [16], [31], [32], [35]. For example, the sleep-disordered breathing index is associated with an accelerated decline in cardiac function and increased morbidity and mortality [13], [14]. 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 conditions 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 [17].

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 [15], [23].

We have previously characterized the respiratory pattern in CHF patients and healthy subjects using spectral parameters computed from the envelope of the respiratory flow signal [10]. In a subsequent study [11], we found that the correntropy function, using parameters based on the correntropy spectral density (CSD), was better suited for classification of respiratory patterns since this technique can be used to detect nonlinearities in the respiratory flow signal, which conventional techniques based on second-order statistics are unable to do [33], [20].

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.

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. The accuracy of the proposed time domain parameters is evaluated for different signal lengths, and compared to CSD-based parameters [8].

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 obtained to compare these results with those obtained with the morphology parameters. Finally, a statistical analysis is applied.

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 [10] 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).

The characteristics of the CHF patients and healthy subjects are shown in Table 1. Figure 1 illustrates respiratory flow 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.

Table 1 Respiratory Rate (Mean $\pm$ 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 (n = 26)	Healthy subjects (n = 35)
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

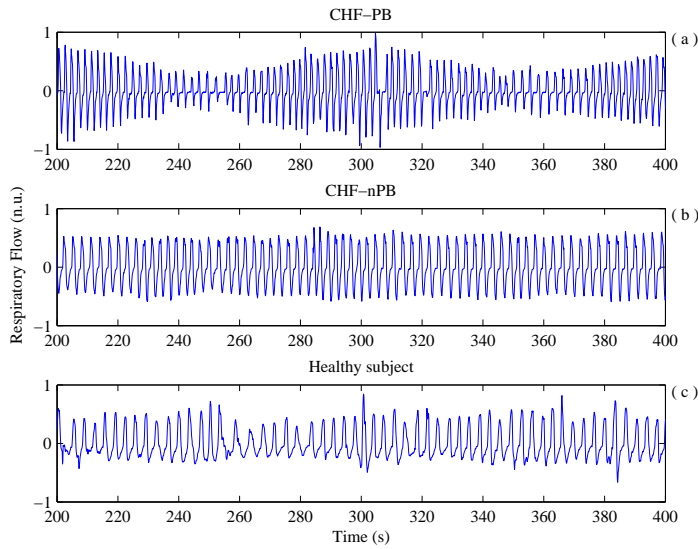R_f: Respiratory rate; D_I: Duration of inspiration; D_E: Duration of expiration.

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).

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 [28]. 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 $N \times M$ data matrix $\mathbf{X}$,

$$\mathbf{X} = \begin{bmatrix} \mathbf{x}_1 \ \mathbf{x}_2 \ \cdots \ \mathbf{x}_M \end{bmatrix}, \tag{1}$$

where each column $\mathbf{x}_i$ 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 [9]. The method is based on the eigenvalue decomposition of the $N \times N$ sample correlation matrix as

$$\hat{\mathbf{R}}_x = \frac{1}{M} \mathbf{X} \mathbf{X}^T.$$

(2)

Interestingly, the ratio $\Lambda_{\boldsymbol{\theta}}$ between the largest eigenvalue λ_1 of $\hat{\mathbf{R}}_x$ and the sum of the remaining $N - 1$ eigenvalues, i.e.,

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

(3)

can be interpreted as a signal-to-jitter-and-noise ratio [9]. Optimal alignment is obtained by finding those column shifts $\hat{\theta}_1, \dots, \hat{\theta}_M$ which maximize the ratio $\Lambda_{\boldsymbol{\theta}}$. 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. The alignment method was found to perform particularly well for small ensemble sizes, i.e., 10–20 cycles, which are analyzed in the present study.

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

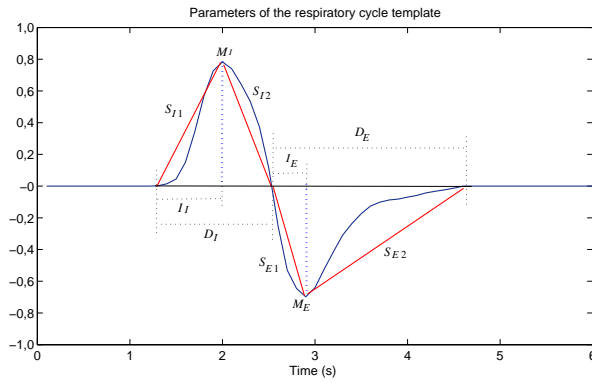| Parameter	Description
D_I [s]	Inspiration duration
D_E [s]	Expiration duration
M_I [n.u.]	Maximal inspiratory flow
M_E [n.u.]	Maximal expiratory flow
I_I [s]	Maximal inspiratory flow interval
I_E [s]	Maximal expiratory flow interval
S_{I1} [n.u.]	Upward inspiratory slope
S_{I2} [n.u.]	Downward inspiratory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

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
$\overline{V}$	Correntropy mean

2.4 Spectral Parameters

We showed that the CSD was particularly well-suited for the characterization of modulated breathing patterns [11]. In this study, the same characterization is applied but with signals much shorter than the 15 min used in [11]; 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 were derived in frequency bands centered around the peaks corresponding to the respiratory frequency and the modulation frequency, see Table 3.

2.5 Statistical Analysis

Statistical analysis was carried out using IBM SPSS software (v19). Differences between groups were tested by the Mann–Whitney U test. The mean and standard deviation of each time domain parameter computed every 30-seconds were evaluated as predictors for periodic breathing. The Classification and Regression Tree (CART) technique was used, together with leave-one-out cross-validation to identify the different breathing patterns. A p-value < 0.05 was considered statistically significant. Parameters offering the best discriminatory power are presented in terms of accuracy, sensitivity, and specificity.
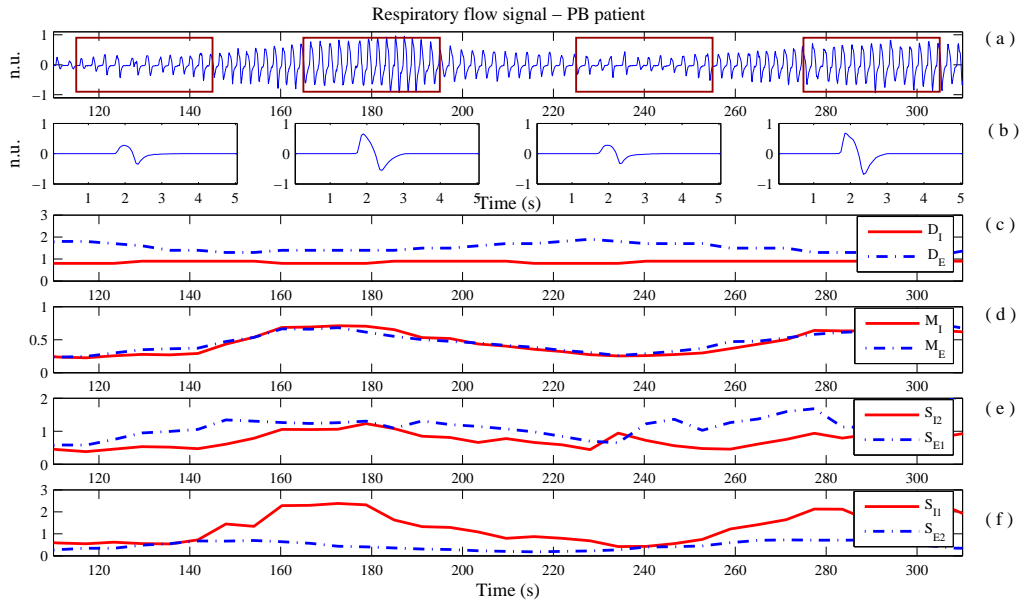
Fig. 3 Signals and trends of a CHF patient with PB: (a) The respiratory flow signal and (b) related templates determined in the four windows indicated in (a). The following trends, resulting from sliding window analysis, are displayed: (c) duration of inspiration (D_I) and expiration (D_E), (d) maximal inspiratory (M_I) and expiratory (M_E) flow value, (e) downward inspiratory (S_{I2}) and expiratory (S_{E1}) slope, and (f) upward inspiratory (S_{I1}) and expiratory (S_{E2}) slope.

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}).
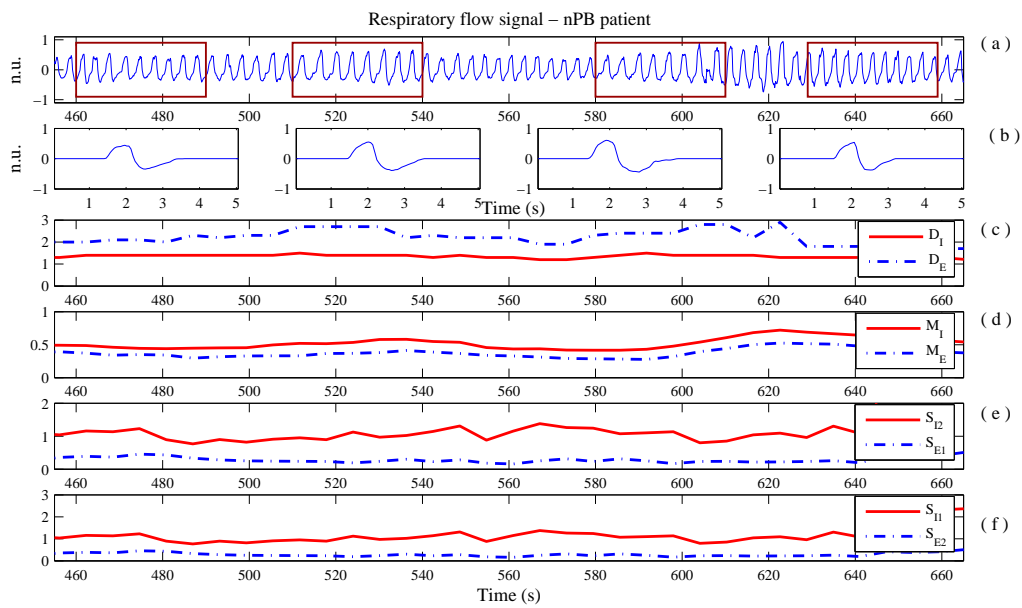
Fig. 4 Signals and trends of a CHF patient with nPB; see Fig. 3 for an explanation of (a)–(f).
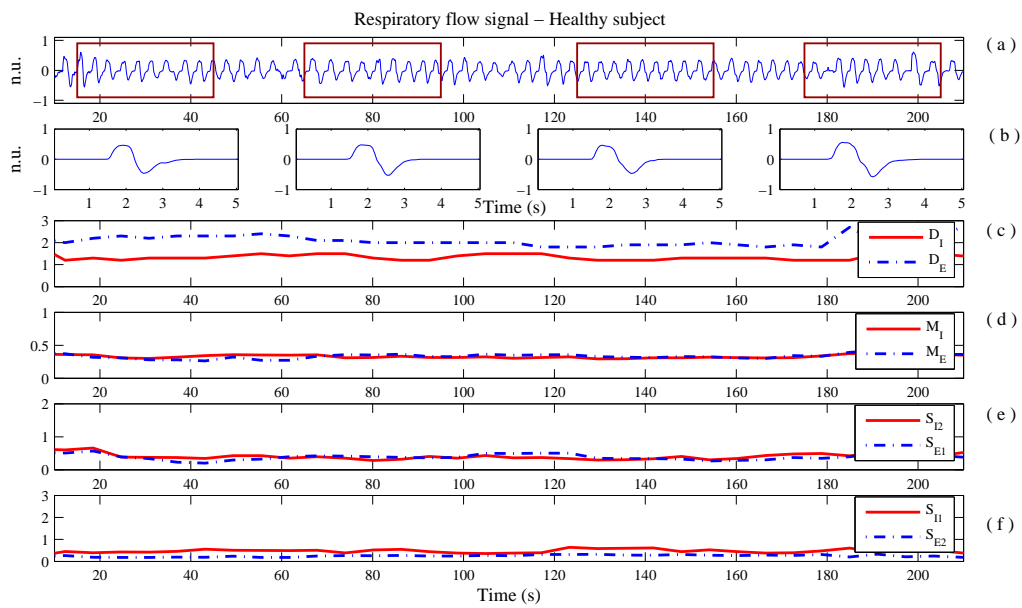

Fig. 5 Signals and trends of a healthy subject; see Fig. 3 for an explanation of (a)–(f).
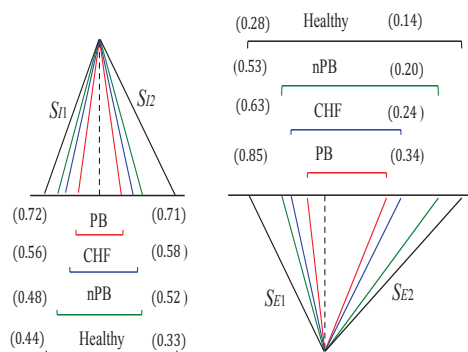
Fig. 6 Schematic representation of different slopes of the respiratory flow template cycle and their mean values.

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.

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; 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

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	$\overline{V}$	85%	100%	74%
nPB vs. H	$\overline{V}$	89%	100%	68%

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 $\overline{V}$ 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 $\overline{V}$ 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 $\overline{V}$ the 89%.

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% ($\overline{V}$) vs 94% (SD_I_E) in the first case, and 98% ($\overline{V}$) vs 94% (M_I_E) in the second case.
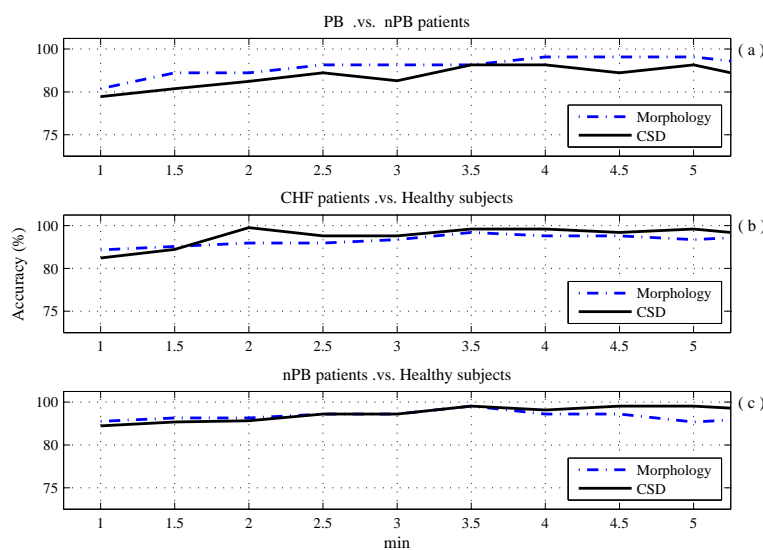
Fig. 7 Accuracy as a function of signal length, using the best parameters (see Table 5), when classifying (a) PB vs nPB patients, (b) CHF patients vs healthy subjects, and (c) nPB patients vs healthy subjects.

4 Discussion

In this study we have proposed a number of time domain parameters for morphologic characterization of the respiratory flow cycle in CHF patients with different conditions. 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.

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 had been analyzed, mostly in relation with the sleep disorders [24], [35]; in healthy subjects, analyzing the relationship between the blood pressure and heart rate oscillations, through the tidal volume [21], and in the acclimatization to high altitude in healthy mountaineers [25], [6]. 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 information about the condition of the patient, using respiratory flow signal, could support the clinical decision and optimize the 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 [10], or the correntropy of the respiratory flow signal [11]. Correntropy was found to be particularly well-suited to characterize different breathing patterns in CHF patients and identify patientsâĂŹ 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 5-min signals, shorter signals are needed for morphologic characterization to get significant parameters that identify CHF (PB and nPB) patients and healthy subjects. According to these results, 1-min signals could provide relevant information about patientâĂŹs condition (see Fig. 7). Thus, a promising advantage of the present morphologic characterization is its ability to provide parameters in time domain, with a prognostic value using short respiratory flow signals.

An interesting conclusion is, that the dispersion of expiratory respiration evaluated through the upward slope and the maximal expiratory flow interval make the highest difference in the morphology of the respiratory flow cycle. These results are in concordance with the different slopes that describe the different groups of patients (Fig. 6).

In the clinical practice, the respiratory rate together with the peripheral pulse oximetry values are altered quickly with respiratory and cardiac diseases. CHF patient status is chronic and, the treatment every so often need to be reviewed and re-adapted. Changes in the respiratory flow cycle morphology can be a clear indicator of decompensation of these patients. The results of this study introduce parameters that can be very relevant in the decompensation of the patient, using shorter signals.

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. Once these results are clinically validated, the incorporation of the respiratory patterns into clinical practice for the prediction of death could be accomplished.

Limitations of the study. A limitation of this study is that the number of patients studied is small, especially the group of patients with periodic breathing. Another limitation is the difference between ages of the healthy group and CHF patients group.

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 in CHF patients, especially when dealing with short length signals.

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