Breathing Pattern Estimation using Wearable Bioimpedance for Assessing COPD Severity

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***Abstract*— Breathing pattern has been shown to be different in chronic obstructive pulmonary disease (COPD) patients compared to healthy controls during rest and walking. In this study we evaluated respiratory parameters and the breathing variability of COPD patients as a function of their severity. Thoracic bioimpedance was acquired on 66 COPD patients during the performance of the six-minute walk test (6MWT), as well as 5 minutes before and after the test while the patients were seated, i.e. resting and recovery phases. The patients were classified by their level of airflow limitation into moderate and severe groups. We characterized the breathing patterns by evaluating common respiratory parameters using only wearable bioimpedance. Specifically, we computed the median and the coefficient of variation of the parameters during the three phases of the protocol, and evaluated the statistical differences between the two COPD severity groups. We observed significant differences between the COPD severity groups only during the sitting phases, whereas the behavior during the 6MWT was similar. Particularly, we observed an inverse relationship between breathing pattern variability and COPD severity, which may indicate that the most severely diseased patients had a more restricted breathing compared to the moderate patients.**

***Index Terms*— bioimpedance, chronic obstructive pulmonary disease, 6MWT, breathing pattern, wearables**

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I. Introduction

THE assessment of chronic obstructive pulmonary disease (COPD) requires the confirmation and evaluation of the airflow limitation of the patient [1]. To achieve this, the pulmonary function is measured by performing a spirometry test [2]. The assessment is complemented with questionnaires, that are commonly used to assess the symptoms of COPD patients. These tests and questionnaires make the assessment of COPD complex since it includes different sources of information and requires medical equipment as well as clinical experts. As a result, COPD assessment results in a big socioeconomic burden, in particular considering that it is one of the leading causes of death worldwide [3], [4]. Therefore, simplifying COPD monitoring is an important challenge for the healthcare systems. To address this need, other non-invasive techniques have been investigated as complementary methods for respiratory disease monitoring. Examples include thoracic bioimpedance [5]–[8] or electromyography [9]–[11] which have been shown to have a good performance in capturing respiratory information. Nevertheless, the use of these techniques in healthcare applications needs to be further validated to confirm the clinical benefit. This validation implies technical and regulatory certification of wearable sensors as well as user trust in the proposed techniques (i.e. clinical experts and patients) to be accepted for the clinical practice [12].

Thoracic bioimpedance has been suggested to provide respiratory information related to ventilation due to its linear relationship with respiratory volume [5]–[7], having the advantage of being a less intrusive technique compared to spirometry. Most of the previous studies, however, focused on static measurements in which the breathing of the subjects was controlled. At the same time, an important aspect of the applicability of bioimpedance for breathing monitoring is its use in common activities like walking. This will allow the evaluation of breathing and its adaptability under different activities with different metabolic demands. Therefore, future studies that evaluate the use of bioimpedance should include other breathing evaluation in free conditions to confirm its usability for respiratory monitoring.

Breathing pattern is regulated in rhythm and depth by the central nervous system to adapt ventilation to different metabolic demands. Consequently, breathing pattern shows variability in nature. Alterations in the variability have been associated with pathological states such as restrictive lung

disease [13], vegetative states [14], postoperative patients [15], and COPD [16], [17]. Therefore, the monitoring of breathing pattern variability is a potential source of information on respiratory control in different diseases. Furthermore, previous studies have shown that thoracic bioimpedance can be used for detecting respiratory cycles and for estimating breathing pattern parameters [18]–[21]. Hence, monitoring breathing patterns using wearable bioimpedance is an interesting unobtrusive approach for evaluating respiration in health and disease.

The present study aims to evaluate the breathing patterns of COPD patients during sitting and walking, which are activities that require different metabolic demands. The characterization of the breathing pattern included the estimation of respiratory parameters as well as studying their variability, using only wearable bioimpedance. The evolution of the breathing pattern was investigated across the different activities but also depending on COPD severity. The novelty of this study lies in two relevant factors: the use of wearable bioimpedance for estimating breathing pattern in COPD patients and the evaluation of breathing pattern depending on the COPD severity. The results of the present analysis support the applicability of wearable bioimpedance for pulmonary disease monitoring, in particular, evaluating COPD disease progression and exacerbation.

II. Materials and Methods

A. Study population

Sixty-six patients previously diagnosed with COPD were recruited at Ziekenhuis Oost-Limburg (ZOL) (Genk, Belgium) during their consultation or rehabilitation session. The study followed the Declaration of Helsinki and was approved by the institutional medical ethics committee (reference 18/0047U). All patients gave written consent prior their study participation.

The population was divided into two groups depending on the patients' forced expiratory volume in one second (FEV_1) *% pred* obtained from the spirometry test. The FEV_1 parameter assesses the airflow limitation and is useful to predict health status in COPD patients [1]. Patients with FEV_1 *% pred* higher than 50 % were classified as moderate, whereas, patients with FEV_1 *% pred* lower than 50 were classified as severe.

B. Protocol and physiological acquisition

The protocol consisted of three consecutive phases:

1) a 5-minute resting phase,
2) a standard six-minute walk test (6MWT) [22],
3) a 5-minute recovery phase.

During the resting and recovery phases, the patients were seated in a wheelchair. Note that the metabolic demand is different for the sitting and walking phases, being higher during walking. The distance walked by the patients during the 6MWT was annotated for the clinical record.

Thoracic bioimpedance was acquired using a wearable research prototype device (Stichting imec the Netherlands, Eindhoven, the Netherlands). The patients wore the device around the neck and attached to chest using adhesive stickers, causing minimal discomfort. The device is illustrated in Fig. 1. The device is equipped with cables that allow the acquisition of physiological signals such as bioimpedance. Technical information on the device and on the system-on-a-chip for biomedical signal acquisition can be found in [23] and [24], respectively.

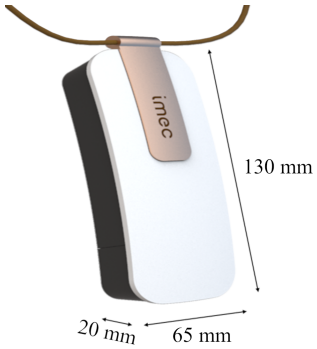

Fig. 1: Research wearable prototype device used in this study. The device was developed by Stichting imec the Netherlands. The device is attached to the chest of the patient by adhesive stickers and it was worn around the neck.

In the current study, bioimmpedance was measured using a tetrapolar electrode configuration on the midaxillary line and symmetrical from the midesternal line (Ag/AgCl electrodes, Kendall H92SG, Covidien Inc., MA, USA), as previously reported in [11]. The injection current was 110 μA P-P at 80 kHz and the sampling frequency was 16 Hz. The setup used in this study was previously tested having a high signal-to-noise ratio (SNR) and showing the linear behavior of the recorded bioimpedance signal [7], [11].

C. Breathing pattern analysis

Pre-processing: We followed the conclusions of our previous studies [20], [21] to preprocess bioimpedance signals. These previous studies focused on the evaluation of different preprocessing steps in the estimation of respiratory parameters.

In this study, the bioimpedance signal was linearly interpolated to 100 Hz to increase the time resolution. The interpolated signals were band-pass filtered with a high-pass filter (zero-phase 4^{th} order Butterworth, f_c= 0.1 Hz) and a low-pass filter (zero-phase 4^{th} order Butterworth, f_c= 2.5 Hz). A moving average filter of 250 ms was applied to the filtered signals. We followed the conclusions of our previous study [20] except for the high-pass filter which cut-off frequency was higher. This modification was made because we observed that the baseline of the signals had slightly higher frequency content compared to the ones in [20]. We think that this difference is most probably because of the differences between protocols in both studies. In [20] the signals were acquired during a static protocol in which the patients only focused on breathing following the examiner guidance, i.e. a inspiratory threshold loading protocol. However, in the current study the protocol was different and the patients walked and were seated on a wheelchair. These activities could induce movements that make the signals baseline different compared to the one

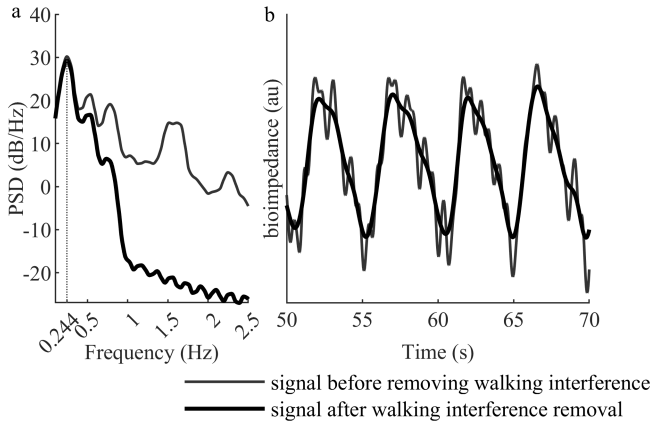

Fig. 2: Bioimpedance signal during the 6MWT. (a) power spectral density (PSD) estimation of the bioimpedance signals and (b) 20 s segment of the signals in the time domain. The grey lines correspond to the signals before the additional filtering of the walking part, whereas the bold black lines are the signals after the preprocessing.

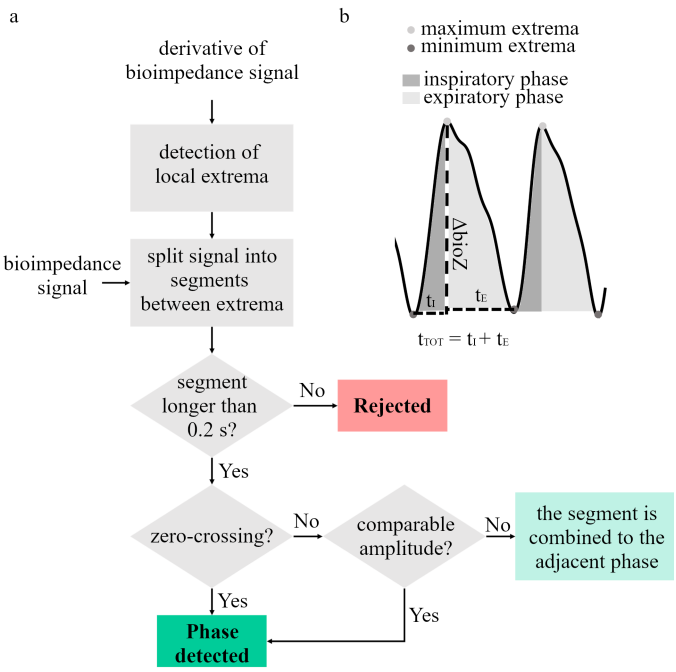

Fig. 3: (a) Representation of the respiratory phase algorithm and (b) the calculation of breathing pattern parameters using bioimpedance signal: inspiratory time (t_I), expiratory time (t_E), respiratory time (t_{TOT}), and peak-to-peak amplitude of bioimpedance (ΔbioZ).

observed in [20]. Furthermore, the selection of 0.1 Hz as low cut-off frequency is supported by previous studies [6], [19].

Walking interference removal: During the 6MWT, the bioimpedance signal also captured the walking interference, which clearly contains frequency components above the respiratory information, as Fig. 2 shows. We included an additional preprocessing for the walking part, in particular the one found as the best in [21] for the interference removal. This preprocessing consists of, firstly, a low-pass filter, (zero-phase 4^{th} order Butterworth, f_c= 1 Hz), and secondly, a moving average filter of 1 s [19]. An example of the signal before and after the filtering can be observed in Fig. 2.

Respiratory cycles detection: The derivative of the entire bioimpedance signal was computed using Savitzky-Golay differentiation of 250 ms followed by a moving average filter of 750 ms [6], [20].

We detected the respiratory cycles, inspiration phase and expiration phase using an algorithm based on the work presented in [20]. A representation of the algorithm is shown in Fig. 3a. It uses the derivative of the bioimpedance signal to detect the local extrema. The respiratory phases correspond to the segments between extrema longer than 0.2 s. Inspiratory phases are the segments between consecutive minimum and maximum extrema, whereas, the expiratory phases are the segments between maximum and its corresponding minimum. This definitions are based on the normal waveform of thoracic bioimpedance, as it can be observed in Fig. 3b. Note that the time restriction of 0.2 s is connected to the minimum respiratory phase duration used in previous studies [25]. After detecting the respiratory phases, the algorithm aims to reject false detections by verifying the presence of a zero-crossing within the phase. The conventional waveform of bioimpedance after the DC filtering suggests that the respiratory phase detection should include at least a zero-crossing. However, the baseline of the bioimpedance signals used in this study was not as stable compared to the signals of [20], [21] in which the subjects were in resting condition and their movement was limited. In the current study, the patients were free to move while sitting and they performed the 6MWT causing more motion artifacts compared to [20]. Therefore, the algorithm checks if the respiratory phase includes a zero-crossing and if not, the amplitude of the phase is evaluated, i.e., the maximum value minus the minimum value during the phase. If the amplitude is very low ($<$ 5 % of the mean amplitude of adjacent detections), the phase is combined with the adjacent respiratory phase. Otherwise, the segment is considered as a correct respiratory phase detection.

Signal quality index and cycle rejection: The movement artifacts can influence the detection of the respiratory cycles producing false detections. To mitigate this effect, we rejected the low quality segments applying the SQI presented in [26] in windows of 32 s with 75 % overlap. The original SQI [26] includes constraints based on the duration and morphology of the breaths. Some of the constrains on the duration of the cycles are very restrictive and can have significant effect on the breathing pattern analysis, in particular in the variability one. Consequently, we did not include all the constraints and we marked a window as of good quality if:

- the window included at least 60 % of breathing detection
- the mean correlation between the respiratory cycle waveforms and the average of all the cycle waveforms in the window was higher than 0.75

Additional to the SQI criteria we rejected respiratory cycles individually when the correlation with the window average was lower than 0.4. We added this constraint to remove individual

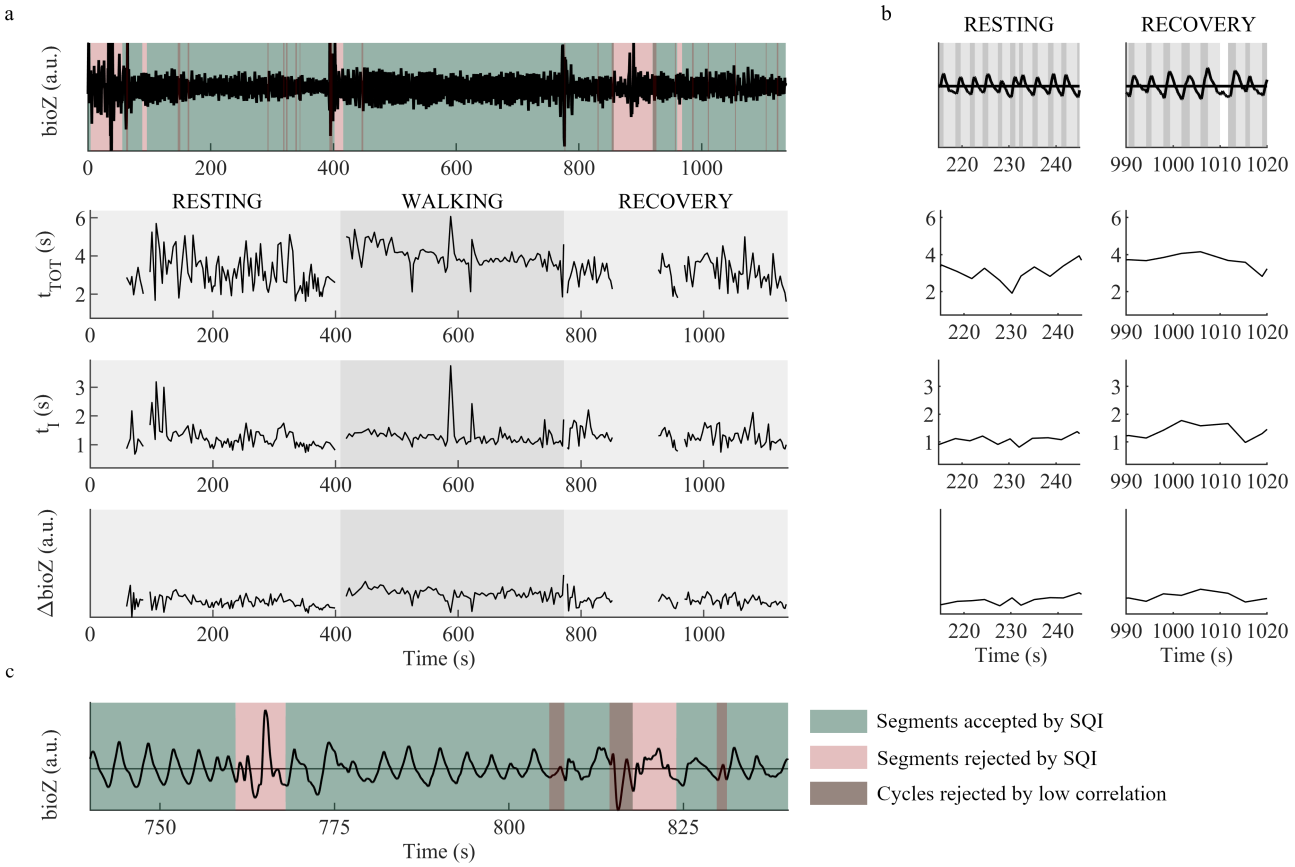

Fig. 4: Example of respiratory cycle detections from bioimpedance signal (a) during the three parts of the protocol, and the corresponding estimation of the respiratory time (t_{TOT}), inspiratory time (t_I) and peak-to-peak amplitude of bioimpedance (ΔbioZ). In the first graph, the bioimpedance signal is represented after applying the preprocessing techniques described in section II. The green background represents the segments used for the analysis, and the red one represents segments rejected because of bad signal quality. (b) shows 30 s of bioimpedance signal and the corresponding estimation of breathing parameters for the sitting parts, resting and recovery respectively. (c) illustrates an example of segments accepted or rejected by signal quality index (SQI) as well as cycles rejected due to the low correlation with the window average cycle waveform.

cycles with very different waveforms which most probably were false detections. We observed that using these constraints on the signals of the present study was sufficient to detect the good quality segments.

Breathing pattern parameters: In the case of the walking and recovery part of the 6MWT recordings, we rejected the first 90 s. We chose this time window based on visual inspection. We observed that it was enough to mitigate the effect of the noise periods originated by the transition from one protocol phase to the other.

Common breathing pattern parameters were extracted from the detected respiratory cycles. In particular, we computed inspiratory time (t_I), expiratory time (t_E), total respiratory time (t_{TOT}), duty cycle (t_I/t_{TOT}), and respiratory rate (RR). The t_I and t_E were computed as the duration of the inspiratory and expiratory phases, respectively. t_{TOT} was calculated as the duration of the complete respiratory cycle ($t_I + t_E$), and respiratory rate (RR) was calculated as the inverse of t_{TOT} for each respiratory phase detection. We also computed the peak-to-peak amplitude of bioimpedance (ΔbioZ) for each respiratory cycle as the difference between the value of the signal at the end and the beginning of each inspiration (see Fig. 3b). The median of the aforementioned parameters derived from the last 30 respiratory cycles of each phase of the experiment was calculated. The variability of each parameter was also analyzed by computing the coefficient of variation (CV) of the 30 cycles of each phase, i.e. the standard deviation over the mean.

Statistical analysis: Significant differences of the anthropometric and pulmonary parameters between the moderate and severe groups were tested with a Willcoxon test, considering a p-value < 0.05 as significant.

The parameter and variability values were statistically analyzed using linear mixed-effect models. We computed two models per breathing pattern parameter, one using the value parameter and another one with the CVs. For the $\Delta bioZ$, only the CV was analyzed because inter-subject comparisons are not possible. The fixed and random effects were defined in the same way for each model. We included the group (moderate and severe), the phase of the protocol (resting, walking and recovery), and the interaction between group and phase as fixed-effects for the models. Regarding the subject random-effect, we defined a random intercept for the model. We detect and reject outliers using the standardized Pearson

TABLE I: Demographic and anthropometric data for COPD patients

	Moderate n = 27	Severe n=28
Male (Female)	17 (10)	24 (4)
Age yr	65.0 (58.8 - 69.8)	65.0 (59.0 - 69.5)
BMI kg/m^2	24.6 (23.1 - 29.5)	24.5 (21.5 - 27.6)
MIP cm^{2}H$_2$O	47.0 (32.0 - 62.0)	53.5 (38.0 - 61.0)
FVC % pred	93.7 (83.6 - 118.2)**	74.8 (54.5 - 97.6)**
FEV$_1$ % pred	69.5 (58.0 - 77.8)***	41.3 (32.8 - 45.5)***
FEV$_1$/FVC %	60.5 (48.0 - 67.9)***	40.0 (34.3 - 47.5)***
6MWD m	465 (376 - 520)	425 (361 - 492)

The data are presented as median (first - third quartile) values. BMI: body mass index; MIP: maximum inspiratory pressure; FVC: forced vital capacity; FEV$_1$: forced expiratory volume in one second. The p-values were obtained from Willcoxon test. Asterisks denote statistically significant differences (** for p-value < 0.01 and *** for p-value < 0.001).

residuals. We applied F-tests to evaluate the statistical significance for the fixed-effects. The interactions between group and phase with statistical significance were tested using a multiple pairwise F-test with Benjamini-Hochberg-adjusted p-values to determine group differences across the three protocol phases. We considered a p-value < 0.05 as significant

We assessed the relationship between the FEV$_1$ and the breathing parameter values and CV using the Spearman correlation which indicates the monotonic relationship between two variables.

III. Results

The study included 66 COPD, 48 males and 18 females. We excluded 11 patients from the final analysis: 3 patients due to technical device problems, 3 patients because of the low SNR of bioimpedance signal, and 5 patients because of the detection of less than 30 respiratory cycles in any of the 3 phases of the protocol. Note that we only used the cycles from signal segments in which the SQI indicated good quality.

The COPD patients were classified into two groups depending on their airflow limitation level. We classified the patients with FEV$_1$ % pred $\geq$ 50 % as moderate (27 patients) and the ones with FEV$_1$ % pred $<$ 50 as severe (28 patients). Table I shows the demographic and anthropometric data of the patients. As expected, significant differences were only found between the groups in parameters related to the pulmonary function, forced vital capacity (FVC) % pred, FEV$_1$ % pred and FEV$_1$/FVC %.

The study consisted of three sequential phases, 5 minutes of resting, the 6MWT, and 5 minutes of recovery. During the three phases, we acquired thoracic bioimpedance which was used to characterize the breathing pattern of the patients. The characterization included the estimation of typical temporal breathing parameters as well as the peak-to-peak amplitude of bioimpedance computed for each respiratory cycle. The bioimpedance amplitude parameter is related to respiratory ventilation because of the relationship between bioimpedance and respiratory volume [5]–[7], [18], [19]. Fig. 4a illustrates an example of the detection of the respiratory cycles. Rejected segments with low signal quality are highlighted in red. Fig. 4 also shows the evolution of the t_{TOT}, t_I and ΔbioZ estimated from the detections. The evolution shown in the figure points to a lower variability during the walking phase than during the resting and recovery phases.

Table II shows the mean and CV of the breathing pattern parameters for the moderate and severe groups during the three phases. The distributions of these values for the three phases of the protocol are shown in Fig. 5. We computed linear mixed-effect models to test the statistical differences between severity level and phase, and the interaction between these factors. Regarding the severity level, we found significant differences in t_I in both the parameter and the CV values, in t_I/t_{TOT} values and in the CV of ΔbioZ. These differences were only significant for the static measures, i.e. the resting and recovery phases. Both, t_I and t_I/t_{TOT} values were significantly lower for the severe group than for the moderate. On the other hand, we observed lower variability for the t_I and ΔbioZ in the severe patients compared to the moderate ones. Furthermore, we found significantly lower variability of RR for the group of severe patients compared to the moderate one across the three phases of the protocol but not in the interaction between group and phase (Fig. 5b). We analyzed the relationships between the parameters and airflow limitation of the patients (by means of FEV$_1$ % pred). Fig. 6 demonstrates these relationships, but only for the parameters that showed statistical significant differences between severity groups. The correlation coefficients between FEV$_1$ % pred and t_I, CV t_I and CV ΔbioZ were moderate. The relationship between CV ΔbioZ and FEV$_1$ % pred showed the strongest correlation. All correlation coefficients were statistically significant, $p < 0.05$.

We analyzed the evolution of the parameters and the variability between the three phases of the protocol for each group of severity, the results are shown in Table II. In the moderate group, we observed significant differences in all the parameters between the resting and walking phases. These differences were maintained between the walking and the recovery phases except for the t_E and RR. Particularly, t_I, t_{TOT} and t_I/t_{TOT} were significantly lower during the sitting phases, whereas RR was higher. On the other hand, the severe group only showed significant differences in t_{TOT} between the sitting and walking phases. Regarding the variability of the parameters, the CV was significantly lower during the walking compared to the resting and recovery phases. This behavior was observed for all the parameters and for the two severity groups. About the sitting phases, we noticed that for the severe group the variability was lower during the recovery phase compared to the resting phase for all the parameters, except t_I. The moderate patients showed significant differences in fewer parameters, specifically, lower variability for t_I, RR and ΔbioZ during the recovery than during the resting phase.

IV. Discussion

The main objective of the present study was to evaluate the breathing patterns of COPD patients obtained using only wearable bioimpedance. Breathing is constantly adapting, e.g., by rhythm and depth, to the activities being carried out. Therefore, the variability of breathing patterns and its characterization is important since it reflects how the respiratory

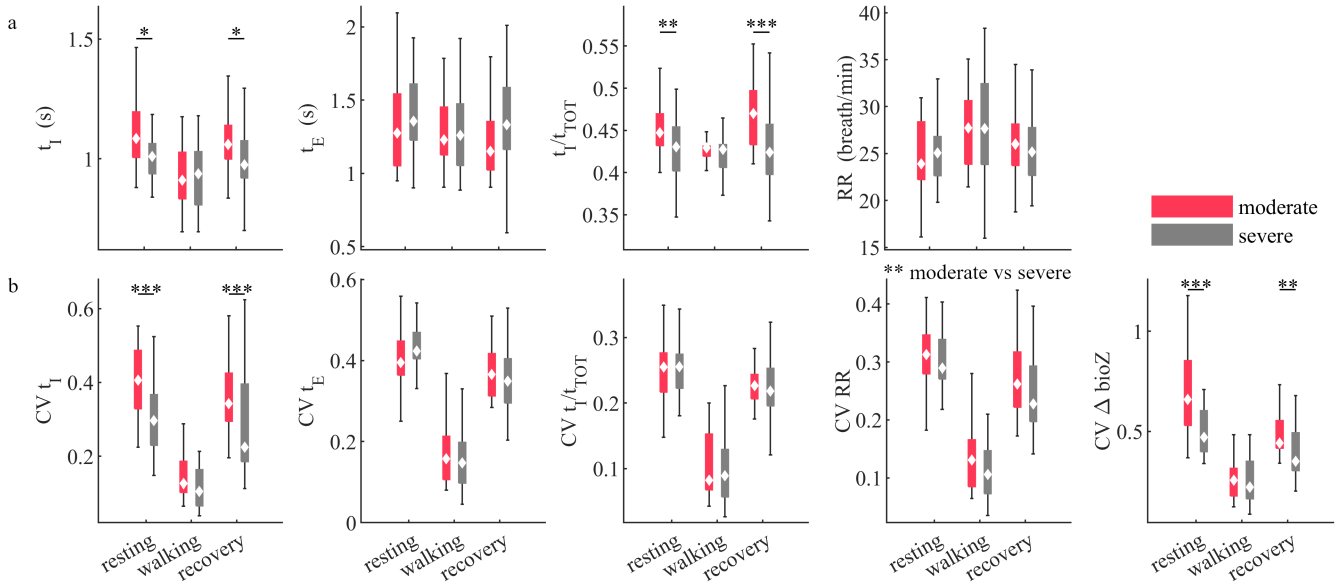

Fig. 5: Breathing pattern characterization during the six-minute walk test measured by (a) the median of 30 respiratory cycles and (b) the coefficient of variation (CV) of the parameters. The peak-to-peak amplitude of bioimpedance (ΔbioZ) magnitude is only used in the analysis of the variability since its values are not comparable inter-subject. Asterisks denote statistically significant differences between moderate and severe groups (* for p-value < 0.05, ** for p-value < 0.01 and *** for p-value < 0.001). The statistical analysis was performed using linear mixed-effect models. The significant differences are shown in the protocol phases when the interaction between phase and severity resulted significant (inspiratory time (t_I), duty cycle (t_I/t_{TOT}), CV t_I and CV ΔbioZ), or across the protocol when only the differences were significant for severity (CV respiratory rate (RR)).

TABLE II: Breathing pattern characterization during resting, walking and recovery

	Moderate n=27						Severe n=28					
	resting		walking		recovery		resting		walking		recovery	
	μ	CV	μ	CV	μ	CV	μ	CV	μ	CV	μ	CV
t_I s	1.12*	0.41*†	0.92*#	0.13*#	1.06#	0.34†#	1.03	0.30*	0.93	0.10*#	0.98	0.22#
t_E s	1.32*	0.40*	1.27*	0.16*#	1.24	0.37#	1.42	0.42*†	1.37	0.15*#	1.34	0.35†#
t_{TOT} s	2.48*	0.31*	2.21*#	0.14*#	2.36#	0.29#	2.47*	0.30*†	2.30*#	0.12*#	2.35#	0.25†#
t_I/t_{TOT}	0.46*†	0.25*	0.42*#	0.08*#	0.47†#	0.23#	0.43	0.26*†	0.41	0.09*#	0.40*	0.22†#
RR breaths/min	24.74*	0.31*†	27.76*	0.13*#	26.03	0.26†#	24.98	0.29*†	27.44	0.11*#	26.77	0.23†#
ΔbioZ	-	0.71*†	-	0.26*#	-	0.51†#	-	0.53*†	-	0.25*#	-	0.41†#

t_I: inspiratory time; t_E: expiratory time; t_{TOT}: respiratory time; t_I/t_{TOT}: duty cycle; RR: respiratory rate; ΔbioZ: peak-to-peak amplitude of bioimpedance. The statistical analysis was performed using linear mixed-effect models. The * denote the statistical significant differences between resting and walking phases, the † between resting and recovery phases, and the # between walking and recovery phases. No significance levels are shown, only $p < 0.05$.

system works in different scenarios. Accordingly, we evaluated the changes in breathing parameters during common activities, like sitting and walking. The objective is to investigate if the differences in breathing pattern are related to COPD severity. The protocol consisted of three consecutive phases, namely, a resting phase, a 6MWT, and a recovery phase. During the entire protocol thoracic bioimpedance was acquired using a wearable device. The bioimpedance signals were used to detect the respiratory cycles and extract breathing parameters for two severity groups. Our results showed that breathing pattern was different depending on the COPD severity and the evolution during the protocol was also different.

In this study we used thoracic bioimpedance to measure respiration due to its linear relationship with respiratory volume [5]–[7] and thus, its capability to provide respiratory ventilation information [6], [27]. Accordingly, bioimpedance has been suggested as a tool to evaluate respiratory status during different activities such as sitting or walking, by extracting different breathing parameters from those [18], [19], [21]. Recent studies reported an accurate detection of respiratory cycles and estimation of breathing parameters using wearable bioimpedance during resting and walking conditions [19]–[21].

We applied the methods and conclusions of previous studies to analyze the breathing pattern of COPD patients. Thus, we expected similar performances as in [20], [21]. In these studies, the accuracy was above 93 % and we reported errors of 2.8 % and 3.2 % for the estimation of RR and errors of 8.7 % and 15.5 % for t_I estimations, for sitting and walking measurements, respectively [21]. Note that the aim of the

current work is focused only on the evaluation of breathing pattern which differs from the previous studies. The main novelty of the presented approach is the analysis of breathing parameters depending on COPD severity using only wearable bioimpedance.

Breathing pattern characterization

Walking and resting conditions: The control of respiration is a mechanism that helps to deal with metabolic needs by regulating breathing. Therefore, breathing is constantly fluctuating in frequency and depth [28], [29] which results in variations in breathing parameters like RR, respiratory times and volumes. The present study characterized breathing patterns during the three phases of the protocol as a representation of activities with different metabolic demands. Our results showed statistically significant differences between the sitting parts and the walking in both, moderate and severe patients. These differences were conclusive in terms of CV, showing significantly lower variability during the walking phase in all parameters under study. These results agree with a recent study from Yentes *et al.* who compared breathing patterns of COPD patients and controls while they were seated and while performing the 6MWT [30]. Yentes *et al.* reported lower variability during walking compared to sitting in both groups. Moreover, they reported lower variability in COPD patients compared to healthy controls. In the current work, we analyzed breathing pattern for moderate and severe COPD patients and we did not observe differences during walking. The lack of differences during the walking suggests that the regulation of breathing during an increase in metabolic need did not depend on COPD severity.

For sitting phases, both severity groups showed lower variability during recovery compared to the resting phase. However, the differences were more conclusive in the more severe patients showing differences in more breathing parameters compared to the moderate ones. These findings suggest that 5 minutes of recovery after the walking was not enough for the respiratory system to return to baseline, especially for the more severe patients.

COPD severity levels: We observed statistically significant differences in respiratory timings between the two severity groups only during the sitting phases (i.e., resting and recovery). Particularly, we observed lower inspiratory time in the severe group compared to the moderate one. This decrease in inspiratory time may indicate more breathing work which is related to the demand of increased ventilation commonly suffered by COPD patients [31]. Furthermore, the airflow limitation in COPD patients causes longer expiratory times [32], which is reflected in the duty cycle that was significantly lower in the severe group. Accordingly, these findings suggest that significant differences found in t_I and duty cycle are related to the airflow limitation and the need of ventilation of COPD patients. However, these differences were not observed in the walking phase, which may mean that the ventilation needs are comparable between the two COPD groups during walking.

Previous studies evaluated breathing patterns of COPD patients compared to healthy controls during rest and peak

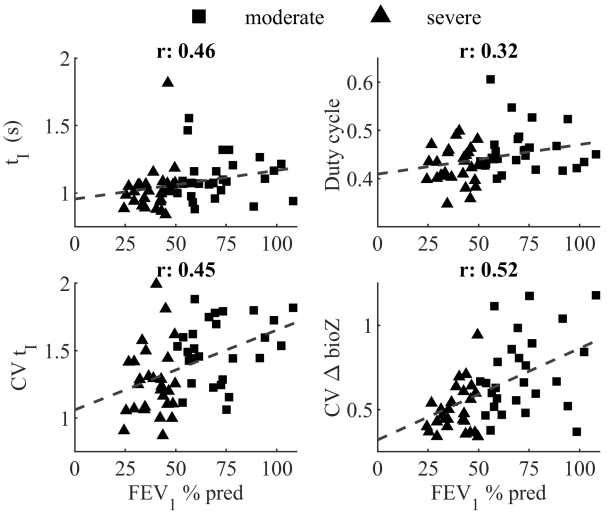

Fig. 6: Relationship between forced expiratory volume in one second and breathing pattern parameters and coefficient of variation (CV) during the resting phase. Only the parameters and CV that showed significant differences between severity are shown. Spearman correlation was performed for each relationship, all coefficients showed in this figure resulted significant.

exercise [33], [34]. These studies reported similar results, that is significantly lower duty cycle in COPD than in healthy controls. However, the differences between studies are considerable. Firstly, [33], [34] focused on breathing patterns during a maximal exercise test, whereas the 6MWT is a sub-maximal test to evaluate the functional exercise capacity, a case in which patients rarely reach their exercise limit [22]. Secondly, the patients of [33], [34] had more severe COPD compared to the ones in the present study, according to the reported FEV$_1$ % pred values. These differences may explain why the reported values were substantially lower than our results. Moreover, they compared COPD patients with controls, without grouping them by COPD severity. These results are in line with our rationale and despite these differences between studies, the findings in both literature and in the present work suggest a negative correlation between t_I and t_I/t_{TOT} with the airflow limitation (FEV$_1$ % pred) and thus, with COPD disease severity.

The increase or decrease of the variability of breathing patterns has been hypothesized to be related to different pathological conditions such as restrictive lung disease [13], weaning success in postoperative patients [15], or COPD [16], [17]. The previous studies focusing on COPD compared the variability between patients and healthy controls [16], [17], [30], showing lower breathing pattern variability in the patients compared to healthy controls. Loveridge *et al.* explained that alteration of breathing pattern variability reflected changes in neural control due to COPD [16]. Similarly, Wrigge *et al.* reported in a more recent study a decreased variability in tidal volume when the subjects breathed with proportional assist ventilation [17]. They explained this behavior as an incapacity of the COPD patients to regulate their respiratory

volume to adapt to different breathing demands. Therefore, these previous results suggest that COPD has a direct effect on the mechanism involved in the respiratory control, making it more difficult for the patients to adapt to different breathing demands. Jaworski et al. developed a computational model to evaluate the sources of breathing pattern variability [35]. The model evidenced that the main changes in variability of breathing pattern were caused by an increase in lung resistance and impairments in gas exchange, which are known to be commonly caused by pulmonary diseases. These results suggested that pulmonary diseases like COPD affect the patients' control of breathing.

The present study focused exclusively on COPD patients evaluating differences between airflow limitation levels. To the best of our knowledge, this work is the first study evaluating breathing patterns between different COPD severity levels. Our results show significantly lower CV values on the patients with severe COPD patients compared to the moderate ones using the t_I, ΔbioZ and RR parameters (see Fig. 5 and Table II). The results of previous studies indicate that COPD patients had a restricted breathing pattern due to the disease [16], [17], [35]. This hypothesis together with our results suggest that the breathing pattern variability decreases with COPD severity, reflecting the impairment of the breathing control mechanisms.

COPD patients commonly suffer from respiratory muscle dysfunction [36]–[38], in which a lower mechanical efficiency in the very severe patients is observed compared to the severe ones [39]. This muscle weakness contributes to the feeling of dyspnea in the patients. In a previous study, we introduced the combination of bioimpedance and myographic indices for COPD assessment [11]. We found that patients with more severe COPD needed more levels of inspiratory muscle activation to get similar ventilation than the mild subjects. These alterations in muscle activation and efficiency may contribute to the lower variability of breathing patterns reported in the present and previous studies.

Potential use in clinical application

Thoracic bioimpedance can be easily acquired using wearable devices avoiding cumbersome setups, as previous studies proposed [19], [23], [40]. This feature is a clear advantage compared to the classical methods to assess breathing. Some proposed applications of wearable bioimpedance include monitoring of infants [40] or sleep monitoring [23]. Furthermore, the estimation of breathing pattern parameters and the variability analysis provide information about several respiratory conditions, such as COPD [16], [17] as this study and previous ones have shown. Therefore, the use of bioimpedance to estimate breathing pattern parameters has a lot of potential to monitor respiratory conditions.

The novelty of the present study was the analysis of breathing patterns for different levels of COPD which resulted in statistically significant differences between severity groups. Our results reinforce the potential application of wearable bioimpedance for breathing pattern monitoring and disease progression. Nevertheless, the objective of the presented analysis differs from the objective of the spirometry test, which is to estimate the pulmonary function and is used as the gold standard for diagnosing and assessing COPD [1]. The reported results in the current study can potentially be applied to monitor breathing pattern in home and health center environment. In both scenarios the patient will perform different activities, e.g., sitting and walking, while wearing the device for bioimpedance measurement. In the health center scenario, bioimpedance can be recorded during the periodic 6MWT causing minimal discomfort for the patient and workload for the clinicians. Accordingly, further studies should focus on the validation of tracking breathing patterns over time as a complementary tool to assess and monitor COPD condition and exacerbation, particularly, the ability of the patients to control breathing.

Focus and target application domain of the study

The study initially included 66 COPD patients from which 11 were discarded due to technical device problems and low signal quality. We acknowledge that the sample size is a limitation in terms of generalization. However, the sample size was large enough to get conclusive results from the statistical analysis. Further studies should evaluate the reported results on broader populations.

There are many parameters to evaluate variability, and the selection of one of them depends on the data, especially the length, and the purpose of the study. In our case, we selected the coefficient of variation because it measures the degree of variability related to the mean of the values, which is useful to compare data with different means, as is the case for the bioimpedance amplitude. Moreover, CV can be used for short-term variations [41]. The recordings length was at least 5 min for each phase, and we used 30 respiratory cycles to estimate breathing parameters and compute the corresponding CV. On the other hand, we acknowledge that the segments we used in the analysis can include missing respiratory cycles, e.g., due to the discarded low quality segments. However, the presence of missing cycles is not expected to influence the results since we selected cycles from stationary segments for which the statistical properties were stable. Accordingly, we consider that the selection of CV and the number of cycles is enough to get accurate results. Nevertheless, complementary studies, including longer recordings, can provide other insights on variability and its relation with daily-life activities and thus, with different levels of metabolic needs.

The use of bioimpedance for respiratory applications has been the subject of many research studies in recent years, however, its application in activities that imply movement has been limited. In this study we acquired bioimpedance during walking, and we reduced the interference due to the activity based on the results of [21]. The specific preprocessing for the walking part of the recording allowed us to get better performance in the detection of respiratory cycles and the estimation of breathing pattern parameters. Nevertheless, we acknowledge that further studies, including measurements with movement, are needed to broaden the scope of the application of bioimpedance for breathing monitoring. Consequently, next research studies on bioimpedance for respiratory monitoring should focus on daily-life activities.

V. Conclusions

The presented study evaluated the breathing pattern of COPD patients with different disease severity using only wearable bioimpedance. Our results showed that breathing pattern was different depending on the COPD severity level during the sitting measurements but not during the walking phase. In particular, the severe COPD patients showed lower variability than the moderate ones. However, we found differences in breathing patterns between the sitting phases and walking. These findings suggest that the control of breathing has a relationship with the COPD severity during the sitting phases. Particularly, we observed an inverse relationship between breathing pattern variability and the level of airflow limitation. Both groups showed similar behavior during walking which may indicate a lack of relation between the regulation of breathing and COPD severity during an increase in metabolic need. Consequently, our study reinforces the use of wearable bioimpedance as a noninvasive tool for assessing and monitoring COPD condition and exacerbation, particularly, the ability of the patients to control breathing.

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