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Computerized respiratory sounds: a comparison between patients with stable and exacerbated COPD

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Review

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3 **Computerized respiratory sounds: a comparison between patients with stable and**
4 **exacerbated COPD**
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6 Running head: Computerized respiratory sounds in COPD
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36 **Author contributions**
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38 All authors were responsible for the study conception and design. CJ and AO performed data
39 collection. CJ performed the data analysis and was responsible for drafting the manuscript. AM
40 and AO critically revised the paper for important intellectual content. CJ and AM obtained the
41 funding.
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47 **Declaration of Interest**
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49 The authors report no conflicts of interest.
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Abstract

Introduction: Diagnosis of acute exacerbations of COPD (AECOPD) is often challenging as it relies on patients' clinical presentation. Computerized respiratory sounds (CRS), namely crackles and wheezes, may have the potential to contribute for the objective diagnosis/monitoring of an AECOPD.

Objectives: This study explored if CRS differ during stable and exacerbation periods in patients with COPD.

Methods: 13 patients with stable COPD and 14 with AECOPD were enrolled. CRS were recorded simultaneously at trachea, anterior, lateral and posterior chest locations using seven stethoscopes. Airflow (0.4-0.6l/s) was recorded with a pneumotachograph. Breathing phases were detected using airflow signals; crackles and wheezes with validated algorithms.

Results: At trachea, anterior and lateral chest, no significant differences were found between the two groups in the number of inspiratory/expiratory crackles or inspiratory wheeze occupation rate. At posterior chest, the number of crackles (median 2.97-3.17 vs. 0.83-1.2, $p<0.001$) and wheeze occupation rate (median 3.28-3.8% vs. 1.12-1.77%, $p=0.014-0.016$) during both inspiration and expiration were significantly higher in patients with AECOPD than in stable patients. During expiration, wheeze occupation rate was also significantly higher in patients with AECOPD at trachea (median 3.12% vs. 0.79%, $p<0.001$) and anterior chest (median 3.55% vs. 1.28%, $p<0.001$).

Conclusion: Crackles and wheezes are more frequent in patients with AECOPD than in stable patients, particularly at posterior chest. These findings suggest that these CRS can contribute to the objective diagnosis/monitoring of AECOPD, which is especially valuable considering that they can be obtained by integrating computerized techniques with pulmonary auscultation, a non-invasive method that is a component of patients' physical examination.

Key words: computerized auscultation; computerized respiratory sounds; AECOPD; COPD; crackles; wheezes.

Introduction

Acute exacerbations constitute one of the most important causes of morbidity and mortality in patients with Chronic Obstructive Pulmonary Disease (COPD) and account for the greatest proportion of the disease burden on health care systems.(1) Therefore, methods for prevention and early diagnosis of acute exacerbations of COPD (AECOPD) are of paramount importance worldwide.(2)

According to the Global Initiative for Chronic Obstructive Lung Diseases (GOLD), diagnosis of an AECOPD relies on the clinical presentation of the patient complaining of an acute change of symptoms, that is beyond normal day-to-day variation.(3) This may affect patients' diagnosis and optimal management and ultimately increase the severity of the exacerbation, length of hospitalization and health costs.

During exacerbations there is increased hyperinflation and gas trapping, with reduced expiratory flow, thus accounting for the increased dyspnea.(4) Respiratory sounds (RS), namely crackles and wheezes, are directly related to movement of air, changes within lung morphology and presence of secretions.(5, 6) Moreover, in a recent study, it was possible to characterize AECOPD into two phenotypes based on computerized RS analysis.(7)

From the available evidence, it appears that computerized RS provide valuable information regarding the respiratory system and may have the potential to contribute for the objective diagnosis and monitoring of an AECOPD. However, to date, no studies exist exploring if computerized RS differ significantly between stable and exacerbation periods in COPD.

Thus, this study explored differences in computerized RS between patients with stable COPD and patients with AECOPD.

Materials and Methods

Study design and participants

A cross-sectional study with 15 outpatients with stable COPD, recruited from one primary care center, and 15 outpatients with AECOPD, recruited from one emergency department of a general hospital, was conducted between January and October 2013. Patients were included if they had a diagnosis of COPD according to the GOLD.(3) Patients with regular appointments with their general practitioner and clinically stable for 1 month prior to the study (no hospital admissions, exacerbations or changes in medication for the respiratory system) were eligible for the group of stable COPD. Diagnosis of an AECOPD according to the GOLD,(3) clinical presentation compatible with mild to moderate AECOPD(8) (no need for hospital admission) were inclusion criteria for the group of patients with AECOPD. Exclusion criteria for both groups were presence of co-existing respiratory diseases or severe neurological, musculoskeletal or psychiatric impairments. Approval for this study was obtained from the ethics committees. Eligible patients were identified via clinicians and were then contacted by researchers, who explained the purpose of the study. When patients agreed to participate, an appointment with the researchers was scheduled in a room at the University of Aveiro. In patients with AECOPD, this appointment was scheduled within 24-48 hours of hospital presentation. Written informed consent was obtained prior to any data collection.

Data collection procedures

Socio-demographic (age, gender) and clinical (body mass index and medication) data were first recorded. Dyspnea was assessed with the modified British Medical Research Council questionnaire.(3) The questionnaire comprises five grades in a scale from 0 to 4, with higher grades indicating greater perceived dyspnea. Then, RS and lung function were collected. Severity of COPD was collected from patients' records. All assessments were performed by two physiotherapists in a standardized order.

Airflow and RS were acquired simultaneously for 20-seconds.(9) Patients were in a seated-upright position, wearing a nose clip and breathing through a mouthpiece at a typical tidal airflow (0.4-0.6L/s)(10) into a heated pneumotachograph (3830, Hans Rudolph, Inc., Shawnee, KS, USA). RS were shown to be reliable at this selected airflow.(11) Visual biofeedback of the

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3 flow signal was presented to patients (RSS 100R Research Pneumotach System, Hans
4 Rudolph, Shawnee, KS, USA) to standardize the airflow during recordings.

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6 RS recordings followed Computerized respiratory sound analysis (CORSA) guidelines for short-
7 term acquisitions.(12) Data were acquired simultaneously at seven chest locations (trachea;
8 right and left: anterior, lateral and posterior)(12) using the LungSounds@UA interface.(13)
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10 Seven chest pieces (Classic II S.E., Littmann®, 3M, St. Paul, MN, USA), with a microphone (flat
11 response between 20Hz and 19kHz - TOM-1545P-R, Projects Unlimited, Inc.®, Dayton, OH,
12 USA) and preamplifier circuit (Intelligent Sensing Anywhere®, Coimbra, PT) in the main tube,
13 were attached to the patient's skin with adhesive tape (Soft Cloth Surgical Tape, 3M, St. Paul,
14 MN, USA). The resulting analogue sound signals were further amplified and converted to digital
15 by a multi-channel audio interface (M-Audio® ProFire 2626, Irwindale, CA, USA). The signal
16 was converted with a 24-bit resolution at a sampling rate of 44.1 KHz and recorded in wav.
17 format.

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19 A spirometric test (MicroLab 3500, CareFusion, Kent, UK) was last performed according to
20 standardized guidelines.(14)

21 Signal processing

22 All files were processed using algorithms written in Matlab®R2009a (Mathworks, Natick, MA,
23 USA). Breathing phases were automatically detected using the flow signals. Signals were timed
24 synchronized to combine the detected breathing phases with sound signals.

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26 Crackles are adventitious, discontinuous and explosive sounds that can be classified as fine or
27 coarse.(15) Fine crackles are high pitch, low amplitude and short duration (two cycle duration
28 <10ms), while coarse crackles are low pitch, high amplitude and long duration (two cycle
29 duration >10ms).(15) As CORSA guidelines do not endorse a specific method to detect
30 crackles, a multi-algorithm agreement method was used.(16-18) This multi-algorithm technique
31 was based on the implementation of established algorithms, i.e., i) the time-domain waveform
32 identification approach of Vannuccini, Rossi et al.,(16) ii) the fractal dimension filtering
33 technique of Hadjileontiadis and Rekanos,(17) and iii) the fractal dimension filtering technique
34 with variations inspired in the work of Lu and Bahoura.(18) This multi-algorithm technique was
35 found to have high sensitivity (91.4%) and precision (83.7%) and a 7% improvement over the

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3 performance of the individual algorithms.(19) The total number of crackles, as well as the
4 number of coarse and fine crackles, were extracted per breathing phase.(15)

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7 Wheezes are adventitious, continuous (≥ 100 ms) sounds with a musical character (dominant
8 frequency usually over 100 Hz).(15) Wheezes were classified as monophonic, when containing
9 essentially a single frequency, or as polyphonic, when containing several frequencies.(15)

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12 Wheezes were detected using an algorithm based on time-frequency analysis, which was found
13 to have high sensitivity (95.5%) and specificity (93.7%).(20) In the implemented algorithm, the
14 signal was digitally filtered (band pass 60–2100Hz, order-8 Butterworth) and resampled (to
15 5512s-1) before the Short-time Fourier transform calculation.(20), A smoothing procedure
16 based on box filtering was also applied to remove noise from the signal. Peaks higher than a
17 specific magnitude threshold were then selected and classified as wheezes or non-wheezes,
18 according to a set of criteria that includes: local maxima, peak coexistence and continuity in
19 time.(20) The total wheeze occupation rate, and the monophonic and polyphonic wheeze
20 occupation rates were extracted per breathing phase.(15)

21 22 23 24 25 26 27 28 29 30 Statistical analysis

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32 A power calculation was not performed since the expected sample variance in crackle or
33 wheeze parameters were unknown in stable and exacerbated patients with COPD. Descriptive
34 statistics were used to describe the sample. Independent t-tests for continuous, Mann-Whitney
35 U-tests for ordinal and chi-square tests for categorical data were used to compare the socio-
36 demographic and clinical characteristics between groups.

37
38 RS data were explored per each one of the 7 recorded locations, however, no significant
39 differences were found between right and left locations. To simplify the interpretability of the
40 findings, data from right and left were pooled for each chest region. Median and interquartile
41 range were used to describe RS parameters. Mann-Whitney U tests were used to compare RS
42 parameters between groups at trachea, anterior, lateral and posterior chest. When statistically
43 significant differences were found for the number of crackles or wheeze occupation rate, a
44 comparison of the type of crackles or wheezes was also performed.

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47 Statistical analyzes were completed with the estimation of effect size. The r , interpreted as small
48 ($r \geq 0.2$), medium ($r \geq 0.3$) or large ($r \geq 0.5$),(21) was used as this is the effect size estimate
49 recommended for Mann-Whitney U tests.(22) Statistical analyzes were performed using IBM
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SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA) and plots created using GraphPad Prism version 5.01 (GraphPad Software, Inc., La Jolla, CA, USA). The level of significance was set at 0.05.

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Results

Participants

Of the 30 patients eligible, 2 declined to participate as they did not perceive the study as relevant and 1 failed to **keep** the appointment. Twenty-seven participants were enrolled, 13 with stable COPD and 14 with mild/moderate AECOPD. All participants were medicated with long-acting inhaled bronchodilators. Patients with AECOPD were additionally medicated with systemic corticosteroids and antibiotics. No significant differences were noted between groups, with the exception of perceived dyspnea ($p=0.010$).

(Table 1)

Computerized respiratory sounds

Crackles

Figure 1 presents the number of crackles at each chest region in patients with stable and AECOPD. There were no significant differences between the two groups in number of inspiratory and expiratory crackles at trachea, anterior and lateral chest (Figure 1). However, at posterior chest, patients with AECOPD had significantly more inspiratory ($2.97[2.15-4.13]$ vs. $1.20[0.72-1.62]$, $p<0.001$, $r=-0.701$) and expiratory ($3.17[2.73-4.05]$ vs. $0.83[0.53-1.55]$, $p<0.001$, $r=-0.819$) crackles than stable patients (Figure 1). Figure 2 shows a respiratory sound file at posterior chest from a stable and an exacerbated patient with COPD.

(Figure 1 and 2)

When analyzing differences regarding type of crackles at posterior chest (Figure 3), coarse crackles were significantly more frequent in patients with AECOPD at inspiration ($2.73[2.02-3.8]$ vs. $0.93[0.6-1.33]$, $p<0.001$, $r=-0.736$) and expiration ($3.07[2.48-3.8]$ vs. $0.73[0.47-1.22]$, $p<0.001$, $r=-0.827$). Fine crackles were almost absent in both groups, with no significant differences between them (inspiration $0.2[0.07-0.4]$ vs. $0.2[0.07-0.28]$, $p=0.638$, $r=-0.064$; expiration $0.17[0.07-0.33]$ vs. $0.13[0.07-0.22]$, $p=0.362$, $r=-0.124$).

(Figure 3)

Wheezes

During inspiration, wheeze occupation rate was found to be significantly different between groups only at posterior chest ($3.28[1.02-7.31]\%$ vs. $1.12[0.66-2.29]\%$, $p=0.014$, $r=-0.333$) (Figure 4). During expiration, wheeze occupation rate was significantly higher in patients with

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3 AECOPD at the trachea (3.12[2.43-6.74]% vs. 0.79[0-1.99]%, $p < 0.001$, $r = -0.637$), anterior
4 (3.55[1.9-10.19]% vs. 1.28[0-4.18]%, $p < 0.001$, $r = -0.388$) and posterior (3.80[2-10.24]% vs.
5 1.77[0.58-4.17]%, $p = 0.016$, $r = -0.330$) chest (Figure 4).
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8 *(Figure 4)*
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10 Regarding wheeze type, significant differences between groups were only observed on
11 monophonic wheeze occupation rate at trachea (expiration 2.94[1.88-5.71]% vs. 0.79[0-1.55]%;
12 $p < 0.001$; $r = -0.646$), anterior (expiration 3.43[1.9-9.49]% vs. 1.28[0-4.18]; $p = 0.004$; $r = -0.386$)
13 and posterior (inspiration 15.98[5.12-28.41]% vs. 5.58[3.31-11.45]%, $p = 0.014$, $r = -0.333$;
14 expiration 3.80[1.77-8.76]% vs. 1.68[0.58-4]%, $p = 0.015$, $r = -0.332$) chest (Figure 5). Figure 6
15 shows spectrograms of respiratory sounds recorded at posterior chest from a stable and an
16 exacerbated patient with COPD.
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Discussion

The main findings indicated that crackles and wheezes are significantly more frequent in patients with AECOPD, especially at posterior chest.

It has been generally accepted that crackles are generated when an airway opens during inspiration or closes during expiration.(24, 25) In patients with stable COPD, a median of 1.20 inspiratory and of 0.83 expiratory crackles were found at posterior chest, which is slightly lower than the results of Piirila et al. (inspiratory 2.9; expiratory 0.73).(26) Patients with AECOPD had significantly more inspiratory and expiratory crackles (2.97-3.17), with large effect sizes. This may be related to the excessive production of secretions in AECOPD,(27) which alter airway diameter and characteristics,(28, 29) possibly causing more sudden airway opening/closing events. Therefore, the occurrence of more coarse and fine crackles in patients with AECOPD than in stable patients was expected.(26, 30) In fact, more crackles, especially fine, have been identified in lower respiratory tract infections.(31) However, in the present study only more coarse crackles were observed and fine crackles were almost absent in both groups. This may be due to the use of stethoscopes to record RS, which tend to amplify low frequencies and attenuate high frequencies.(28, 32) Future research should therefore focus in developing technologies to acquire RS with higher quality. The posterior chest was found to be the most informative. The posterior chest is a gravity-dependent region, where greater volume changes occur during inspiration.(33) As crackles genesis is related with critical transitions in the airway volume this chest region might be the most useful to assess and monitor patients with COPD.(25, 34) Additionally, anterior and lateral regions are normally characterized by recordings with lower quality,(31) which may also have limited crackles' algorithm performance. Inspiratory and expiratory wheeze occupation rates at the posterior chest were found to be around 1-2% in stable patients. A previous study from Murphy presented higher wheeze occupation rates (inspiratory 2% and expiratory 12%).(35) These differences may be due to distinct procedures used to record and analyze RS. In the present study, RS were recorded with a standardized airflow, at seven locations and wheeze occupation rate was computed for 4 chest regions (trachea, anterior, lateral and posterior chest). In Murphy's study, RS were recorded with an unstandardized airflow, at sixteen locations and wheeze occupation rate was the average of all locations.(35) Inspiratory and expiratory wheeze occupation rates at posterior

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3 chest were significantly higher in patients with AECOPD (median differences 1.67 and 2.26),
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5 with medium effect sizes. At trachea and anterior chest significant differences were also
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7 observed during expiration (median differences 2.6 and 2.12). Increased wheezing has long
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9 been described as a commonly observed sign of an AECOPD.(36-38) During exacerbation
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11 periods, the increased airway inflammation induces edema, bronchospasm and sputum
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13 production.(27) These airway changes will probably reduce the critical flutter velocity, producing
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15 oscillations of the airway walls more easily.(39) The differences were only statistically significant
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17 for monophonic wheeze occupation rate. Polyphonic wheeze occupation rate tended to be
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19 higher in patients with AECOPD, which was anticipated as the presence of polyphonic wheezes
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21 indicates a more serious obstruction.(40)

22 Findings from the present study suggest that the detection of increased or decreased number of
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24 crackles and/or wheeze occupation rate may have the potential to contribute to the objective
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26 diagnosis and/or monitoring of AECOPD. This is in line with recent research stating that
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28 computerized RS can support the diagnosis of pneumonia and characterize acute
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30 exacerbations in patients with COPD.(7, 41) Furthermore, the findings also indicate that, in the
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32 absence of time to perform a complete pulmonary auscultation, computerized auscultation of
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34 the posterior chest can provide the most relevant clinical information. Nevertheless, similar to
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36 other biosignals that support clinical decisions (e.g., heart rate variability,
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38 electromyography),(42, 43) computerized RS have high inter-subject variability,(11) and thus, a
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40 change in RS may indicate the onset of an AECOPD for one patient, but not for another. To
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42 overcome this limitation it is fundamental to record computerized RS of each individual during
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44 routine appointments or via telemedicine applications. This would facilitate the definition of
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46 individual RS profiles and alert thresholds indicating the onset/recovery of acute exacerbations.
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48 This study has a number of limitations that need to be acknowledged. RS in patients with
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50 AECOPD were recorded within 24-48 hours of hospital presentation, at a timing where the
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52 medication prescribed (systemic corticosteroids and antibiotics) had presumably some
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54 beneficial effects on lung function. Moreover, the inclusion of patients with mild to moderate
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56 AECOPD may have also influenced the results. Probably, more remarkable differences would
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58 have been found if patients with stable COPD were compared to patients with AECOPD at the
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60 moment of hospital presentation or with severe exacerbations. In addition, an analysis of the RS

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3 in patients with AECOPD after recovery could have been performed to see if their RS became
4 similar to those from patients with stable COPD. This would clarify if patients with AECOPD
5 have indeed more adventitious RS than stable patients, or instead if patients with COPD more
6 predisposed to exacerbations have already more adventitious RS during stable periods than
7 patients with lower exacerbation rates. Moreover, in future research, it would also be interesting
8 to compare computerized RS at stable and exacerbation periods within the same subjects. This
9 would eliminate the bias due to the high inter-subject variability of RS.(11) It could be
10 hypothesized that the detection of crackles and wheezes may have been influenced by the
11 airflow selected. Nevertheless, in a recent study with patients with COPD, these computerized
12 RS were not significantly different across distinct airflows.(11) This study was conducted with a
13 small sample of each COPD grade, therefore it was not possible to determine whether the
14 severity of the disease impacted on the results. Further research with larger samples is
15 necessary to investigate the RS differences on each COPD grade. The complex set up used to
16 record RS and airflow can also be seen as a limitation of the study and restricts the application
17 of computerized RS in more severe patients and particularly in acute clinical settings. As
18 computerized RS shows promise, research should focus in developing technological solutions
19 to acquire RS and airflow with minimal setup.

Conclusion

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21 Using computerized auscultation, it was found that crackles and wheezes are more frequent in
22 patients with an AECOPD than in patients with stable COPD. Furthermore, the findings also
23 indicate that, in the absence of time to perform a complete pulmonary auscultation,
24 computerized auscultation of the posterior chest provides the most relevant clinical information.
25 These findings suggest that computerized RS can contribute to the objective diagnosis and/or
26 monitoring of AECOPD, which is especially valuable considering that this information can be
27 obtained by integrating computerized techniques with pulmonary auscultation, a quickly, easily
28 and non-invasive method, that is a routine component of the patients' physical examination.

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Table 1 - Socio-demographic and clinical characteristics of participants (n=27).

Characteristics	Stable	Acute	p-value
	(n=13)	Exacerbation (n=14)	
Age (years), M±SD	69 ± 9	67 ± 12	0.512
Sex (male), n	10	9	0.275
mMRC, M[IQR]	1 [1, 2]	2 [1, 3]	0.010
BMI (kg/m ²), M±SD	27 ± 4	25 ± 5	0.322
FEV ₁ (L), M±SD	1.85 ± 0.61	1.47 ± 0.54	0.090
FEV ₁ (% predicted(23)), M±SD	71 ± 21	59 ± 20	0.799
FEV ₁ /FVC (%), M±SD	66 ± 9	56 ± 16	0.119
GOLD classification, n			
Mild	4	3	0.410
Moderate	6	7	
Severe-to-very-severe	3	4	

Values are shown as mean±standard deviation unless otherwise indicated. mMRC, modified British Medical Research Council questionnaire; M, median; IQR, interquartile range; BMI, body mass index; FEV₁, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Figure legends

Fig. 1 – Number of crackles at trachea, anterior, lateral and posterior chest in patients with stable COPD and AECOPD. Data are presented as median and interquartile range. Significant differences are identified with * ($p<0.05$).

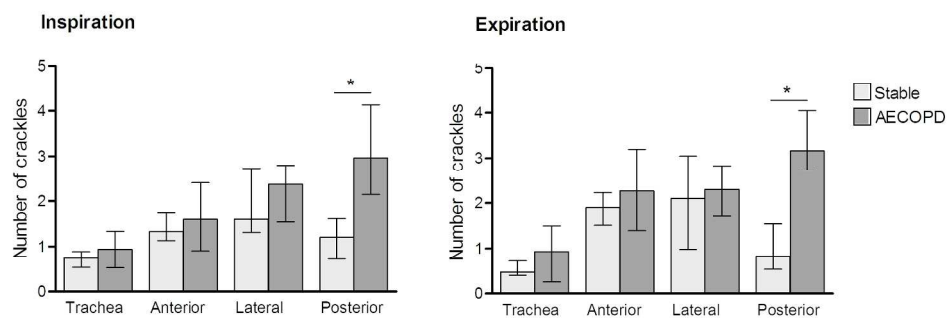
Fig. 2 – Time amplitude plots of respiratory sounds recorded at posterior chest from (a) a patient with stable COPD and (b) a patient with acute exacerbation of COPD. A respiratory sound file of 20 seconds and a breathing cycle is represented for each patient, inspiration is represented by the line above zero, while expiration corresponds to the line below zero. Each black border indicates a crackle.

Fig. 3 – Number of coarse and fine crackles at posterior chest in patients with stable COPD and AECOPD. Data are presented as median and interquartile range. Significant differences are identified with * ($p<0.05$).

Fig. 4 – Wheeze occupation rate at trachea, anterior, lateral and posterior chest in patients with stable COPD and AECOPD. Data are presented as median and interquartile range. Significant differences are identified with * ($p<0.05$).

Fig. 5 – Monophonic and polyphonic wheeze occupation rate at trachea, anterior and posterior chest in patients with stable COPD and AECOPD. Data are presented as median and interquartile range. Significant differences are identified with * ($p<0.05$).

Fig. 6 - Spectrogram of respiratory sounds recorded at posterior chest from (a) a patient with stable COPD and (b) a patient with acute exacerbation of COPD presenting expiratory wheezes.



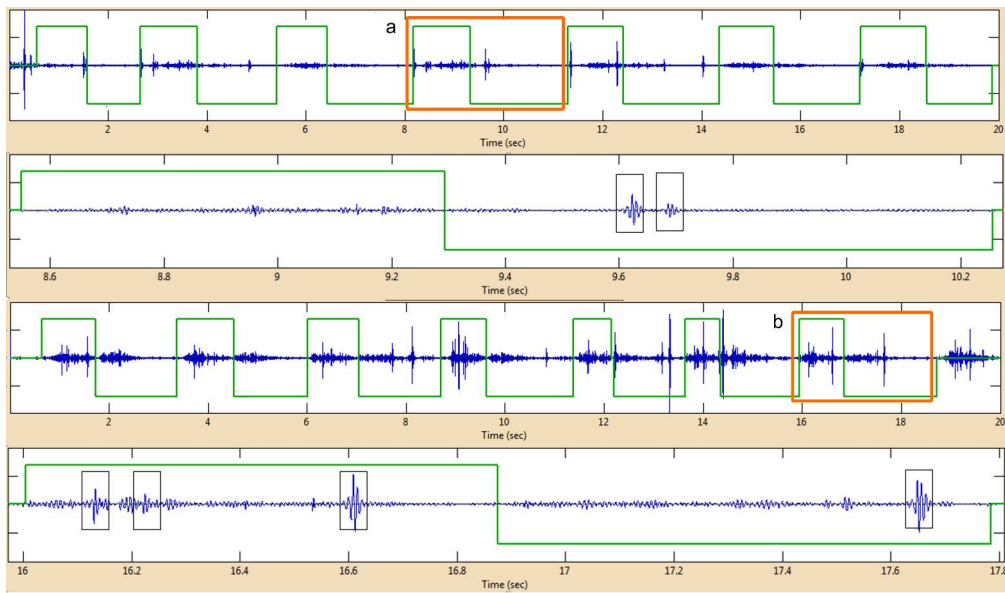
Number of crackles at trachea, anterior, lateral and posterior chest in patients with stable COPD and AECOPD. Data are presented as median and interquartile range. Significant differences are identified with * ($p < 0.05$).

223x78mm (300 x 300 DPI)

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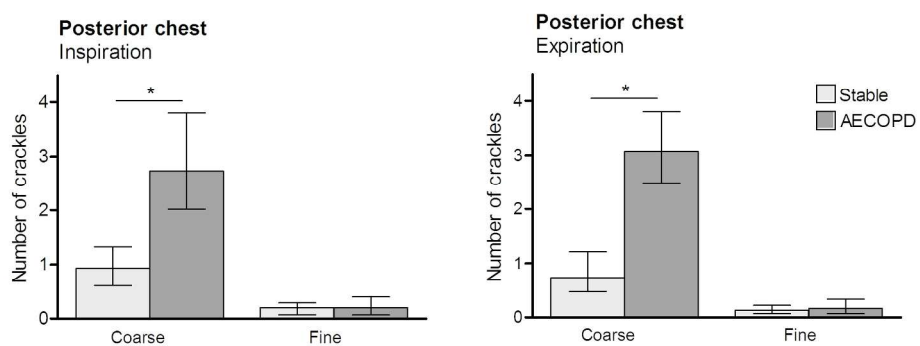
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Time amplitude plots of respiratory sounds recorded at posterior chest from (a) a patient with stable COPD and (b) a patient with acute exacerbation of COPD. A respiratory sound file of 20 seconds and a breathing cycle is represented for each patient, inspiration is represented by the line above zero, while expiration corresponds to the line below zero. Each black border indicates a crackle.
423x248mm (300 x 300 DPI)

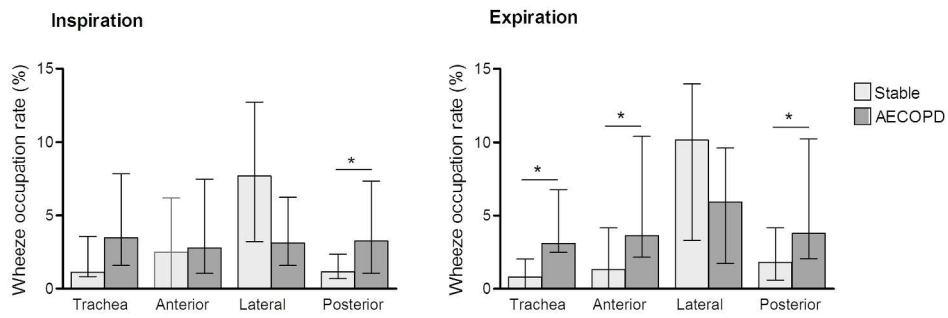
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Number of coarse and fine crackles at posterior chest in patients with stable COPD and AECOPD. Data are presented as median and interquartile range. Significant differences are identified with * ($p < 0.05$).
207x78mm (300 x 300 DPI)

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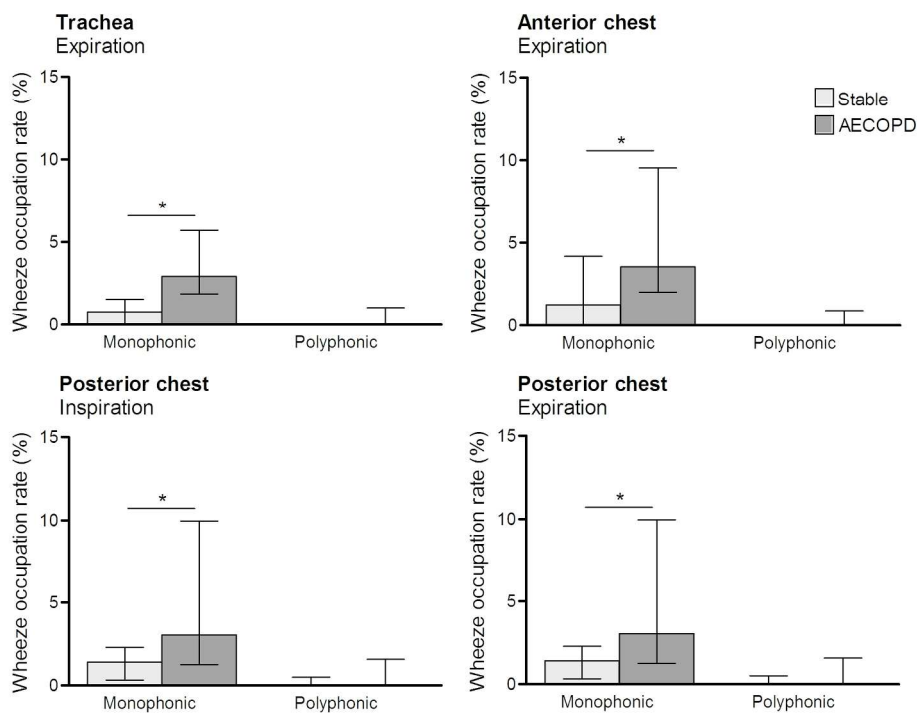
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Wheeze occupation rate at trachea, anterior, lateral and posterior chest in patients with stable COPD and AECOPD. Data are presented as median and interquartile range. Significant differences are identified with * (p<0.05).

228x79mm (300 x 300 DPI)

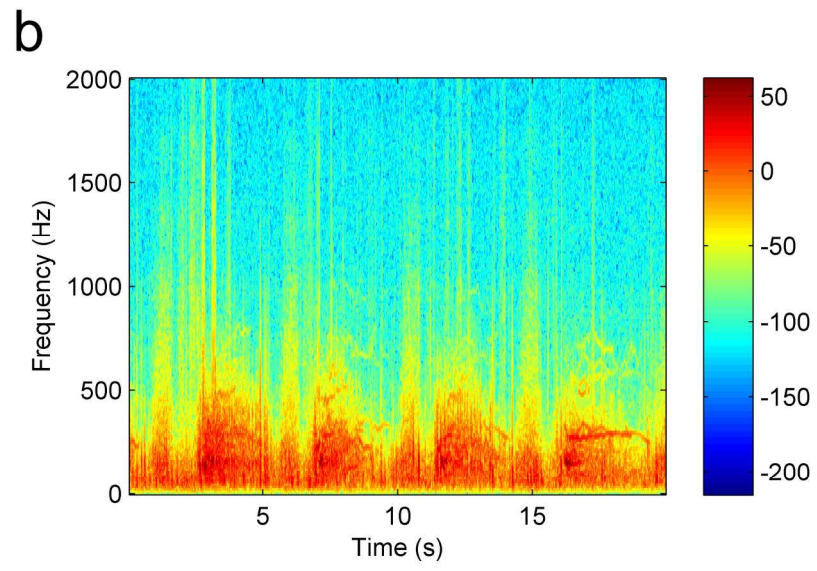
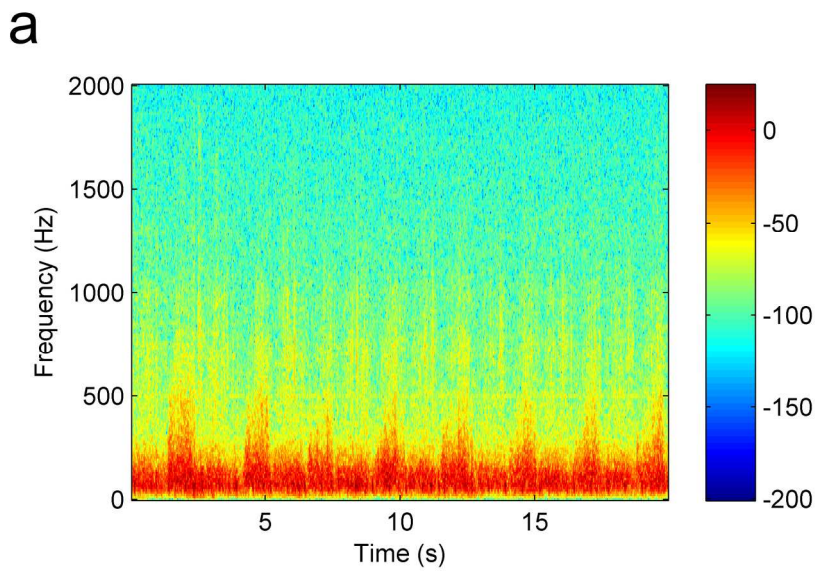
Peer Review



Monophonic and polyphonic wheeze occupation rate at trachea, anterior and posterior chest in patients with stable COPD and AECOPD. Data are presented as median and interquartile range. Significant differences are identified with * ($p < 0.05$).

204x152mm (300 x 300 DPI)

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Spectrogram of respiratory sounds recorded at posterior chest from (a) a patient with stable COPD and (b) a patient with acute exacerbation of COPD presenting expiratory wheezes.
170x239mm (300 x 300 DPI)