Title: Enhancing our understanding of computerised adventitious respiratory sounds in different COPD phases and healthy people.

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Abstract

Background: Timely diagnosis of acute exacerbations of COPD (AECOPD) is challenging as it depends on patients' reports. AECOPD are characterised by increased airway obstruction, mucus and air trapping, which results in changes in lung acoustics. Thus, adventitious respiratory sounds (ARS) may be useful to detect/monitor AECOPD.

Objective: To evaluate computerised ARS changes during AECOPD.

Methods: 25 non-hospitalised patients with AECOPD (16♂, 70[62.5-77.0]yrs, FEV_1 59[31.5-73.0]%predicted) and 34 healthy volunteers (17♂, 63.5[57.7-72.3]yrs, FEV_1 103.0[88.8-125.3]%predicted) were enrolled. ARS at anterior and posterior right and left chest were recorded at hospital presentation (T1), 15 days (T2) and 45 days (T3) after hospital presentation from patients with AECOPD and only once from healthy participants. A subsample of 9 patients (7♂; 66[60.0-76.0]yrs; FEV_1 62[26.5-74.0]%predicted) was also included to study ARS pre-AECOPD (T0). Number of crackles and wheeze occupation rate (%Wh) were processed using validated algorithms.

Results: During AECOPD, patients presented more inspiratory crackles at T1 than T3 ($p=0.013$) and more inspiratory %Wh at T1 than T2 ($p=0.006$), at posterior chest. Patients with stable COPD presented more inspiratory crackles ($p=0.012$), at posterior chest, and more expiratory %Wh, both at anterior ($p<0.001$) and posterior ($p=0.001$) chest, than healthy participants. No differences were observed for the remaining ARS parameters or subsamples ($p>0.05$).

Conclusions: Inspiratory crackles seem to persist until 15 days post exacerbation whilst inspiratory %Wh decreased after this period. ARS seem to be sensitive to monitor AECOPD. This information may allow advances in monitoring the recovery time of patients with AECOPD across all clinical and non-clinical settings.

Key-Words: chronic obstructive pulmonary disease; acute exacerbations; crackles; wheezes; computerised respiratory sounds

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory disease frequently punctuated by acute exacerbations (AECOPD) [1], i.e., “acute worsening of respiratory symptoms that result in additional therapy” [2]. These events account for half of the total respiratory admissions for COPD [3] and are closely related with increases in healthcare costs (AECOPD related costs vary approximately from $88 to $7.757 per exacerbation worldwide) [4]. Furthermore, AECOPD are responsible for accelerating lung function decline, decrease quality of life and increase mortality [5].

The early identification and timely management of AECOPD has been shown to reduce hospital admissions and recovery time, while improving quality of life [6]. Nevertheless, most exacerbations are still not timely treated as the diagnosis/monitoring relies exclusively on patients’ reports of symptoms worsening [2]. Such reports require patients’ collaboration and judgment, which are frequently affected by their pronounced dyspnoea and anxiety associated with these events [7, 8].

Physiologically, AECOPD are characterised by an increase in airway inflammation and obstruction, abnormal bronchial mucus production and marked air trapping [2], which results in changes in lung acoustics. As respiratory sounds are directly related to the movement of air within the tracheobronchial tree [9], the changes in respiratory mechanics related with AECOPD may be primarily detected by changes in respiratory sounds, namely adventitious respiratory sounds (ARS, crackles and wheezes). Recent studies have shown respiratory sounds ability to differentiate between groups of patients with stable and exacerbated COPD [10] and to characterise AECOPD into two phenotypes, based on computerised analysis [11].

Nevertheless, there is little information available on the time course of respiratory sounds changes during recovery from AECOPD, within the same group of patients. This information may advance the monitoring of patients with COPD across all clinical and non-clinical settings, as respiratory sounds are non-invasive, population-specific and nearly universally available by simple means [12]. Additionally, improved knowledge on ARS behaviour preceding, during and after an exacerbation may aid to standardise and optimise the length of treatment, and to plan appropriate follow-up and clinical studies involving AECOPD.

This study aimed to evaluate ARS changes during the course of AECOPD. A secondary aim was to explore prospectively the influence of exacerbations in ARS in a subsample of patients with stable COPD followed by an AECOPD.

Material and methods

Study design and participants

A longitudinal observational study was conducted in non-hospitalised patients with AECOPD recruited from the urgent care of a Central hospital between January 2016 and February 2017. Inclusion criteria were diagnosis of AECOPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [2]. A subsample of stable patients with COPD was recruited from routine pulmonology appointments of a Central hospital and asked to contact the researchers if an episode of exacerbation requiring hospital visit occurred. Patients were included if they were diagnosed with COPD according to the GOLD criteria and were clinically stable for 1 month prior to the study (no hospital admissions, exacerbations or changes in medication for the respiratory system) [2]. Exclusion criteria for both samples were hospitalisation or presence of severe co-existing respiratory, neurological, cardiac, musculoskeletal (e.g., kyphoscoliosis), or psychiatric impairments. Eligible patients were identified by clinicians and contacted by the researchers, who explained the purpose of the study and asked about their willingness to participate. When subjects agreed to participate, an appointment with the researchers was scheduled.

A group of healthy non-smokers, matched for gender, age and body mass index (BMI), were also recruited to serve as control, as currently there are no established reference values for ARS [13]. Healthy non-smokers were recruited from the university campus and surrounding community and excluded if they presented one or more of the following conditions: acute (within the past month) or chronic respiratory disease, cardiac disease, musculoskeletal or signs of psychiatric impairments.

Approval for this study was obtained from the ethics committee of the Central Hospital (13NOV'1514:40065682) and of the University of (omitted for blinded purposes) (8/2015) and from the National Data Protection Committee (8828/2016). Written informed consent was obtained before data collection.

Sample size

A sample size estimation with 95% power at 5% significance determined that a significant difference in the inspiratory mean number of crackles obtained through repeated measures from patients with COPD at exacerbated (2.97±1.98) and stable (1.20±0.80) phases of their disease would be detected with a minimum of 23 participants [10]. A high statistical power was chosen due to the great amount of inter and intra subject variability presented by ARS [14, 15], which could potentially cause type II errors if the study was underpowered [16]. In

health-related longitudinal studies, dropout rates are of approximately 20 to 45% [17, 18] thus, 36 participants with AECOPD were aimed to be recruited. Sample size estimation was performed using the G*Power 3.1 software (University Düsseldorf, Germany).

Data collection

Participants with AECOPD recruited from the urgent care were asked to attend to 3 assessment sessions: at the exacerbation onset (T1 – 24 to 48 hours of the hospital visit), 15 days (T2 – following exacerbation) [19, 20] and 45 days after the hospital visit (T3 – at stability post exacerbation). The subsample of patients recruited from routine pulmonology appointments were asked to attend to 4 assessment sessions: 24 to 48 hours after the pulmonology routine appointment (T0 – at stability pre exacerbation), at the exacerbation onset (T1 – 24 to 48 hours of the hospital visit), 15 days (T2 – following exacerbation) [19, 20] and 45 days after the hospital visit (T3 – at stability post exacerbation). Data from healthy non-smokers was only collected once (T0) (Figure 1). Data collection occurred at the urgent care, in the facilities of the University of (omitted for blinded purposes) or at patients' home.

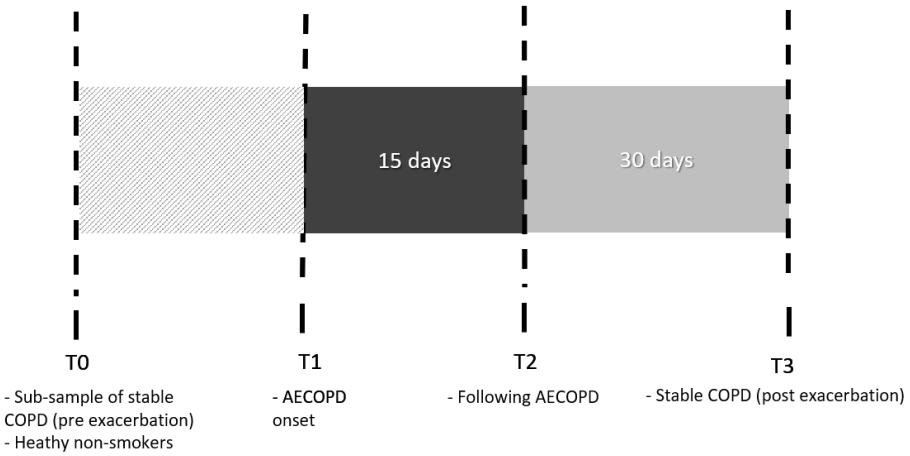

Figure 1 – Time points of data collection.

Sociodemographic (age, gender), anthropometric (height, weight and BMI) and general clinical data (smoking habits, number of exacerbations in the past year, medication and dyspnoea) were first collected. Dyspnoea was assessed with the modified British Medical Research Council questionnaire [21]. The questionnaire comprises five grades in a scale from 0 to 4, with higher grades indicating greater perceived dyspnoea. Then, computerised respiratory sounds (recorded as described below) and lung function, assessed with a

portable spirometer (MicroLab 3535, CareFusion, Kent, UK) according to standardised guidelines were collected [22]. Respiratory sounds were collected in all data collection moments and spirometry was also performed at T3, during the stable phase, post exacerbation.

All assessments were performed by a physiotherapist following the described standardised order.

Respiratory sound recordings

Respiratory sound recordings followed computerised respiratory sound analysis guidelines for short-term acquisitions [23] (i.e., participants were in a seated-upright position, wearing a nose clip and were asked to breathe deeper than normal through the mouth). Recordings were performed simultaneously at 7 anatomic locations (trachea and right and left anterior, lateral, and posterior chest). The system for respiratory sound recordings included eight air-coupled electret microphones with 20-20kHz frequency bandwidth (C 417 PP, AKG Acoustics GmbH, Vienna, Austria) [24]. a multi-channel audio interface (AudioBox 1818 VSL, PreSonus, Florida, USA), and a laptop computer running LungSounds@UA software [25]. Seven microphones, mounted in capsules made of Teflon [26, 27], were attached on the participant's skin with double-faced adhesive tapes (Double Stick Discs, 3M Littmann, Cheshire, UK). The eighth microphone was placed close to the patient to record background noise. The analog sound signals acquired were amplified and converted to digital by the audio interface with a 24-bit resolution and a sampling rate of 44.1 kHz. Each data acquisition session lasted for 20-s [28] and the recorded data were later converted to WAV format.

Signal processing

All sound files were analysed using automatic algorithms implemented in Matlab R2009a (MathWorks, Natick, Massachusetts).

Breathing cycles were semi-automatically detected using the algorithm developed by Huq and Moussavi (95.5% sensitivity and 95.6% specificity) [29]. Crackles were detected using a validated algorithm based on the combination of fractal dimension and box filtering techniques [30]. Wheezes were detected using an algorithm based on time-frequency analysis [31]. The mean number of crackles (total, fine and coarse) and wheeze occupation rate (%Wh – total, monophonic and polyphonic), per breathing phase (inspiration and expiration) and per chest location was extracted. Normal respiratory sounds were also analysed but were only slightly louder than the superimposed background sound so these data were excluded from further analyses (please see supplementary material 1). The

average spectra of normal respiratory sounds at trachea, anterior and posterior chest can be found in the supplementary material 1 and a detailed description of the signal processing is provided elsewhere [32]. Lateral locations were also excluded from the analysis, as previous literature as shown that this anatomical location presents a great number of artefacts and is poorly reliable [15]. All analyses were checked by two respiratory experts to ensure the quality of the sound recordings.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 24.0 (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.

Descriptive statistics were used to describe the sample. Characteristics were compared between healthy non-smokers and patients with COPD at stable phases (T3) using independent t-tests for normally distributed data (i.e., BMI), Mann-Whitney U-tests for non-normally distributed data (i.e., age, lung function, packs-year) and ordinal data (i.e., mMRC), and Chi-square tests for categorical data (i.e., gender, smoking status, exacerbations/year and GOLD stages).

Computerised ARS data were explored for each of the five analysed locations; however, no significant differences were found between right and left chest of the same region (i.e., anterior, lateral or posterior), thus, to simplify the interpretability of the findings, data from right and left were pooled for each chest region [32]. Then, the number of participants with crackles and wheezes in each chest region was calculated and the Cochran test with Bonferroni corrections was used to compare number of participants presenting crackles and wheezes among T1, T2 and T3. Fisher's exact test was used to investigate differences between healthy non-smokers and patients with COPD at stable phases (T3) on the number of participants presenting crackles and wheezes. Comparisons of number of crackles and %Wh among T1, T2 and T3 in patients with COPD were performed with the Friedman test, and multiple comparisons with the Wilcoxon sign-rank test. Multiple comparisons were corrected for number of comparisons using Bonferroni corrections. Comparisons between healthy non-smokers and patients with COPD at stable phases regarding mean number of crackles and %Wh was performed with Mann–Whitney U test. When statistically significant differences were found for the number of crackles or %Wh, a comparison of the type of crackles or wheezes was also performed.

An additional analysis, similar to the described previously for patients recruited at the onset of the AECOPD, was conducted with the subsample of patients presenting data collected prior to the exacerbation.

Results

Participants

Seventy-four non-hospitalised patients with AECOPD were referred for possible inclusion in the study. Of these, 34 patients refereed with AECOPD were excluded because at T1 they had pulmonary function test not compatible with a diagnosis of COPD (n=22), did not meet the definition for AECOPD (n=1), presented lung neoplasia (n=2), severe heart failure (n=1), were unable to comply with data collection (n=3), or declined to participate in the study (n=5). Fifteen patients were further excluded from the analysis because failed to complete all time points of data collection (i.e., T1, T2 and T3) (n=6) and their respiratory sounds (collected at the urgent care) had a significant amount of background noise hindering the use of the algorithms described in the *Signal processing* section (n=9). Thirty-four healthy non-smokers were also contacted and invited to participate. Thus, twenty-five participants with AECOPD (16 males; 70 [62.5-77.0] years old; FEV_1 59 [31.5-73.0]% predicted) and thirty-four healthy non-smokers (17 male; 63.5 [57.7-72.3] years old; FEV_1 103.0 [88.8-125.3]% predicted) were enrolled in the study. Participants' characteristics are summarised in Table 1.

Table 1. Sample characterization.

Characteristics	**Patients with AECOPD (n=25)**	**Healthy non-smokers (n=34)**	**p-value**
Age, **years**	70 [62.5-77.0]	63.5 [57.7-72.3]	0.061
Gender (male), n(%)	16 (47.1)	17 (68.0)	0.090
BMI, **kg/m^2, mean±SD**	26.7±4.9	27.4±4.7	0.568
Smoking status, n(%)			0.002*
Current	4 (16.0)	-	
Former	11 (44.0)	6 (17.6)	
Never	10 (40.0)	28 (82.4)	
Packs/year	30.0 [15.0-70.0]	6.5 [1.8-18.8]	0.010*
Exacerbations/year, n(%)			<0.001*

0	5 (20)		34 (100)	
1	5 (20)		-	
≥2	15 (60)		-	
FEV_1, L	1.2 [0.8-1.7]		2.6 [2.1-3.0]	<0.001*
FEV_1, %predicted	59 [31.5-73.0]		103.0 [88.8-125.3]	<0.001*
FEV_1/FVC, %	52 [40.0-62.0]		83 [79.5-88.3]	<0.001*
GOLD stages, n(%)				
A	4 (6.8)		-	
B	3 (5.1)		-	
C	5 (8.5)		-	
D	13 (22.0)		-	
Medication use, n(%)	**Stability**	**AECOPD (extra)**		
Antibiotics	1 (4)	15 (60)	-	
Bronchodilators			-	
Beta-adrenergic agonists	7 (28)	0 (0)	0	
Cholinergic antagonists	15 (60)	3 (12)	0	
Anti-inflammatory	4 (16)	1 (4)	0	
Xanthines	8 (32)	0	0	
Associations of bronchodilators with cholinergic antagonists	17 (68)	5 (20)	0	
Expectorants	4 (16)	6 (24)	0	
mMRC	1 [0.5-2.0]		0.0 [0.0-1.0]	<0.001*

*p<0.05

Values are presented as median [interquartile range], unless otherwise stated.

Legend: BMI, body mass index; FEV_1, forced expiratory volume in one second (at stability); FVC, forced vital capacity (at stability); GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, Modified British Medical Research Council questionnaire; SD, standard deviation.

A subsample of 9 participants with stable COPD *a priori* was also included and followed up until an AECOPD occurred and during its recovery. This sub-group of participants (7 males; 66 [60.0-76.0] years old; FEV_1 62 [26.5-74.0]% predicted) was slightly overweight (27.9±4.46 Kg/m^2), presented a median number of packs/year of 21.2 [10.0-30.0] and were mainly former smokers (n=5; 55.6%; current smokers: n=2; 22.2%; never smokers: n=2; 22.2%). Most participants were classified as being in a stage D of the GOLD classification (n=5; 55.6%; GOLD B: n=2; 22.2%; GOLD C: n=2; 22.2%), presented more than 2 AECOPD in the past year (n=6; 66.7%; 1 AECOPD: n=2; 22.2%; 0 AECOPD: n=1; 11.1%) and were treated for their AECOPD with antibiotics (n=5; 56%), cholinergic antagonist bronchodilators (n=2; 22%), anti-inflammatory bronchodilators (n=1; 11%) and expectorants (n=3; 33%). Patients presented a median mMRC of 2 [1-3]. Median time to exacerbation was 23 [18-146] days.

Computerised Respiratory Sounds

Crackles

Significant differences were found in the total number of inspiratory (p=0.008) and coarse (p=0.003) crackles within patients with AECOPD at T1, T2 and T3 at the posterior chest. Patients presented significantly more inspiratory (p=0.013) and coarse (p=0.013) crackles at T1 than at T3. Figure 2 presents the number of crackles at each chest region in healthy participants and patients with AECOPD. A detailed characterisation of crackles can be found in the supplementary material 2.

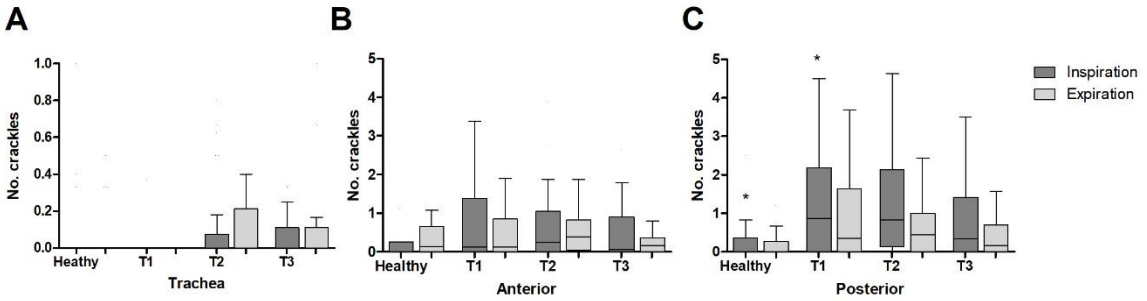

Figure 2 – Number of inspiratory and expiratory crackles in healthy participants and participants with COPD (T1, T2, T3) at A) trachea, B) anterior and C) posterior chest regions.
* significantly different from T3.

Patients with stable COPD presented significantly more inspiratory crackles (p=0.012), both fine (p=0.003) and coarse (p=0.013) crackles, at the posterior chest than healthy participants. No significant differences were found regarding the remaining variables, locations or respiratory phases (p>0.05).

Wheezes

Significant differences were found in the inspiratory %Wh (p=0.019) and inspiratory monophonic %Wh (p=0.012), within patients with AECOPD at T1, T2 and T3 at posterior chest. Namely, patients presented significantly more inspiratory %Wh (p=0.006) and monophonic %Wh (p=0.045) at T1 than at T2. A higher number of patients presenting inspiratory wheezes and monophonic wheezes were found at T1 than at T2 at trachea (p=0.037) and anterior chest region (p=0.014). The number of patients with expiratory monophonic wheezes was also higher at T1 than at T3 at the anterior chest (p=0.029). No significant differences were found regarding the remaining variables, locations and respiratory phases (p>0.05). Figure 3 presents the %Wh at each chest region in healthy participants and patients with AECOPD. A detailed characterisation of wheezes can be found in the supplementary material 3.

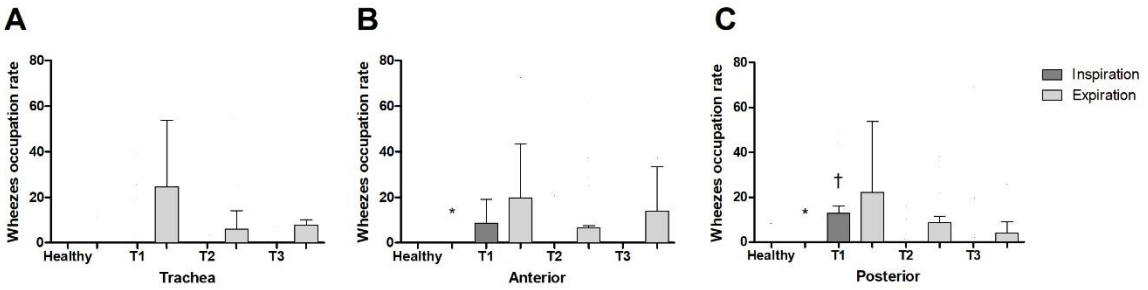

Figure 3 –Inspiratory and expiratory wheeze occupation rate in healthy participants and participants with COPD (T1, T2, T3) at A) trachea, B) anterior and C) posterior chest regions.
* significantly different from T3.
† significantly different from T2.

Patients with stable COPD presented significantly more expiratory and monophonic %Wh, both at anterior (total %Wh: $p<0.001$; monophonic %Wh: $p=0.007$) and posterior (total %Wh: $p=0.001$; monophonic %Wh: $p<0.001$) chest regions than healthy participants. No differences were found regarding the number of healthy participants and stable patients with wheezes ($p>0.05$).

Sub-analysis

No differences were found among the four-time points of data collection for inspiratory and expiratory crackles and wheezes at all anatomical locations ($p>0.05$), in the subsample of patients with stable COPD *a priori*. A detailed characterisation of the respiratory sounds of this subsample can be found in the supporting information 4 and 5.

Discussion

The main findings of this study were that inspiratory crackles and wheezes change significantly during the course of AECOPD and patients with stable COPD presented significantly more inspiratory crackles and expiratory wheezes than healthy peers.

Differences in ARS found during the course of AECOPD and between stable patients with COPD and healthy peers were mainly observed at posterior and more peripheral chest locations, both for crackles and wheezes. In previous studies, the posterior region has been indicated as the most reliable and valid chest location for auscultation in patients with COPD [14, 15]. These findings, added to physiological and epidemiological data showing that COPD is primarily targeted by smaller airway and/or alveolar abnormalities [2] and that approximately 70-80% of AECOPD are due to infections, especially of the small airways

[33], might lead us to confidently identify the posterior chest region as the preferred location of auscultation to monitor patients with COPD.

Coarse crackles and monophonic wheezes during inspiration were the respiratory sounds parameters presenting significant degrees of change. Previous research, conducted in independent samples of stable and exacerbated patients with COPD, has shown equivalent results for the number of coarse crackles [10], despite acknowledging that respiratory tract infections, the main cause of AECOPD, are mainly characterised by fine crackles. Such results have been attributed to the frequency response of stethoscopes used which might be cutting high frequencies of interest, and consequently affect fine crackles detection [34]. Thus, a deeper understanding of this matter is yet needed. Respiratory tract infections define a wide range of infectious diseases, including pneumonia, acute bronchitis, AECOPD and acute infective exacerbations of asthma [35]. Pneumonia is the respiratory infection most studied for ARS [36]. It should be emphasised that AECOPD and pneumonia differ greatly in their pathophysiology [2, 36]. AECOPD is characterised by an increase in airway inflammation and obstruction, abnormal bronchial mucus and marked air trapping [2], whilst pneumonia usually presents lung consolidation and a filling of the alveolar air spaces with exudate, inflammatory cells, and fibrin [36]. Accordingly, AECOPD are more prompt to develop hypersecretions than pneumonia and thus, generate more coarse crackles, which "indicates intermittent airway opening related to secretions", than fine crackles that are "unrelated to secretions" [12].

Contrary to what has been reported in previous literature [10], only inspiratory wheezes presented significant changes during the course of AECOPD. Compared to crackles, wheezes usually present higher inter subject variability [14] and, in patients with more severe airway obstruction, expiratory wheezes have been indicated as a poorly reliable parameter, as they are strongly influenced by air-flow and respiratory manoeuvres [15]. Because previous research has been conducted using independent samples of patients with stable and AECOPD, variability might be increased, explaining the differences found. Also, previous studies have included mainly mild to moderate patients with COPD [10, 37], whilst our sample included mostly severe patients, where inspiratory wheezes might be more representative.

Considering the changes in ARS during the course of AECOPD, %Wh, specifically monophonic, significantly decreased after 15 days of treatment (i.e., approximate time needed to resolve an AECOPD [19]), whilst crackles, specifically coarse crackles, only decreased significantly after 45 days post-exacerbation. Previous studies conducted during an AECOPD have shown an improvement in air-flow limitation (assessed by FEV_1 and peak

expiratory flow - PEF) approximately 15-days post exacerbation [7, 19]. Knowing that %Wh is highly associated with the degree of bronchial obstruction [38, 39], this was an expected result and enhances the role of wheezes auscultation to monitor AECOPD. Crackles are more related to changes (i.e., inflammation and/or infection) in more peripheral airways which usually take longer to resolve [40, 41].

No differences were observed in the subsample of patients with stable COPD studied *a priori* and during AECOPD across any time points. Thus, it was not possible to demonstrate if ARS recovered to baseline characteristics after an exacerbation, or if AECOPD have a cumulative effect in ARS similar to other outcomes, such as muscle strength and lung function [5]. It is known that ARS present high inter and intra subject variability [14] and thus, the sample size included in this sub-analysis might have been insufficient to detect significant changes. Nevertheless, if ARS are to be used clinically, knowing their evolution before and after exacerbations is essential to better interpret and manage treatment. This sub-analysis was therefore a needed first step towards ARS use in the monitoring of AECOPD and can be used as a pilot study to compute sample sizes in future studies (data are in supporting information 4 and 5).

Patients with COPD presented significantly more inspiratory crackles and expiratory wheezes than healthy peers. It is known that COPD is mainly characterized by inspiratory and coarse crackles and expiratory wheezes [42], when compared with other chronic diseases, such as fibrosis, asthma, pneumonia, bronchiectasis and heart failure. Thus, this was an expected result. However, few studies have compared ARS in healthy people and patients with COPD, even though the presence of ARS has been recognized in healthy people [13]. Although differences in ARS were found between patients with COPD and healthy people the number of people with ARS in both groups was not significantly different. Therefore, our results further enhance the recommendation of not using the presence of ARS as an indicator of pathology [15], but instead investigate ARS characteristics (i.e., number, type, position in the respiratory cycle) and place it together with other clinical findings.

Comparing to previous studies, a small number of crackles and low %Wh were found in patients with COPD (median no. of crackles per respiratory phase between 0.3 in stable patients to 0.6 in AECOPD; median %Wh of approximately 0) and healthy people (median no. of crackles and %Wh of approximately 0). Studies have been indicating a mean number of crackles between 0.8 to 5 per respiratory phase and a mean %Wh of 0.79% to approximately 10% in patients with COPD [10, 42, 43] and approximately 1.5 crackles and 35% %Wh in healthy people [32]. Reasons for these differences might be explained by the

different protocols used to collect and analyse ARS. In this study, ARS were collected using AKG air-coupled electret microphones (response rate 20-20000Hz) mounted in capsules made of Teflon to minimize noise and increase sound transmission [26, 27]. Additionally, all participants, independently of having ARS or not, were included in the analysis to potentiate the comprehensiveness and generalization of our findings. Previous studies have used sensors with different frequency responses (e.g., 40-15000 [32]; 50-1800Hz; 4-20000Hz; 65-20000Hz [42]), diverse set ups of data collection (e.g., electret microphones imbedded in a soft foam mat and electret condenser microphones connected to the diaphragm or main tube of conventional stethoscopes [10, 42, 43]) and analysis (have only included in their analysis people presenting ARS [32]). Such variety of procedures may produce recordings of different quality and range of sound spectrum, influencing the results achieved and thus impairing comparisons among studies.

Limitations

This study has some limitations that need to be acknowledged. Firstly, treatment of exacerbations during this study was not standardised, but rather prescribed according to the physician best judgment and clinical indication. Although for the purpose of this study the effects of therapies used were not of interest, it has to be acknowledge that different combination of drugs might have influenced the recovery times and outcomes of individual patients. Secondly, flows and/or volumes were not controlled during ARS recordings, which might have affected the results, since ARS characteristics depend on the rate and volume of the respiratory manoeuvres [44]. However, patients with AECOPD often present severe dyspnoea and anxiety [7, 8] which causes the use of a mouthpiece or facemask (necessary to assess flows and/or volumes) to be highly uncomfortable or even not tolerated. Furthermore, the primary purpose of this study was to assess computerised ARS utility in a community-based clinical setting, where control of airflow is often not practical. Thirdly, the complex set up used to record ARS may be perceived as a limitation to the use of computerised respiratory sounds in the clinical practice. Future research should focus in developing technologies for acquiring high quality data at bedside with minimal setup. Finally, although statistically significant differences were found for inspiratory number of crackles and %Wh at posterior regions, the absolute differences among data collection times were small and possibly not detected by health professionals with standard auscultation. Thus, it is imperative that future studies explore the minimal clinical important difference of ARS to enhance the clinical meaning of this measure and potentiate the development and implementation of friendly used computerised auscultation systems that can be translated into clinical practice.

Conclusion

Inspiratory crackles and wheezes changed significantly during the course of AECOPD, and patients with stable COPD presented significantly more inspiratory crackles and expiratory wheezes than healthy peers. Inspiratory crackles seem to persist until 15 days after the exacerbations (i.e., approximate time needed to resolve AECOPD) whilst inspiratory %Wh significantly decreased after this period. Crackles and wheezes seem to be sensitive to monitor the course of AECOPD. This information may allow further advances in the monitoring of patients with COPD across all clinical and non-clinical settings, as respiratory sounds are non-invasive, population-specific and nearly universally available by simple means. Further studies with larger samples and including data collected before the AECOPD are needed to confirm these findings.

Acknowledgments

The authors would like to acknowledge to Hélder Melro, Ana Machado and Sara Miranda for their assistance in data collection and to all patients and physicians from the (omitted for blinded purposes) for their collaboration in this study.

Funding: This work was supported by Fundo Europeu de Desenvolvimento Regional (FEDER) through Programa Operacional Competitividade e Internacionalização (COMPETE) and Fundação para a Ciência e Tecnologia (FCT) under the projects UID/BIM/04501/2013 and SFRH/BD/101951/2014.

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