

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

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18

1 **Abstract**

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

6 **Objective:** To evaluate computerised ARS changes during AECOPD.

7 **Methods:** 25 non-hospitalised patients with AECOPD (16♂, 70[62.5-77.0]yrs, FEV₁ 59[31.5-
8 73.0]%predicted) and 34 healthy volunteers (17♂, 63.5[57.7-72.3]yrs, FEV₁ 103.0[88.8-
9 125.3]%predicted) were enrolled. ARS at anterior and posterior right and left chest were
10 recorded at hospital presentation (T1), 15 days (T2) and 45 days (T3) after hospital
11 presentation from patients with AECOPD and only once from healthy participants. A
12 subsample of 9 patients (7♂; 66[60.0-76.0]yrs; FEV₁ 62[26.5-74.0]%predicted) was also
13 included to study ARS pre-AECOPD (T0). Number of crackles and wheeze occupation rate
14 (%Wh) were processed using validated algorithms.

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

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

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

27

1 **Introduction**

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

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

15 Physiologically, AECOPD are characterised by an increase in airway inflammation and
16 obstruction, abnormal bronchial mucus production and marked air trapping [2], which results
17 in changes in lung acoustics. As respiratory sounds are directly related to the movement of
18 air within the tracheobronchial tree [9], the changes in respiratory mechanics related with
19 AECOPD may be primarily detected by changes in respiratory sounds, namely adventitious
20 respiratory sounds (ARS, crackles and wheezes). Recent studies have shown respiratory
21 sounds ability to differentiate between groups of patients with stable and exacerbated COPD
22 [10] and to characterise AECOPD into two phenotypes, based on computerised analysis
23 [11].

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

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

1 **Material and methods**

2 Study design and participants

3 A longitudinal observational study was conducted in non-hospitalised patients with AECOPD
4 recruited from the urgent care of a Central hospital between January 2016 and February
5 2017. Inclusion criteria were diagnosis of AECOPD according to the Global Initiative for
6 Chronic Obstructive Lung Disease (GOLD) criteria [2]. A subsample of stable patients with
7 COPD was recruited from routine pulmonology appointments of a Central hospital and asked
8 to contact the researchers if an episode of exacerbation requiring hospital visit occurred.
9 Patients were included if they were diagnosed with COPD according to the GOLD criteria
10 and were clinically stable for 1 month prior to the study (no hospital admissions,
11 exacerbations or changes in medication for the respiratory system) [2]. Exclusion criteria for
12 both samples were hospitalisation or presence of severe co-existing respiratory,
13 neurological, cardiac, musculoskeletal (e.g., kyphoscoliosis), or psychiatric impairments.
14 Eligible patients were identified by clinicians and contacted by the researchers, who
15 explained the purpose of the study and asked about their willingness to participate. When
16 subjects agreed to participate, an appointment with the researchers was scheduled.

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

23 Approval for this study was obtained from the ethics committee of the Central Hospital
24 (13NOV'1514:40065682) and of the University of (omitted for blinded purposes) (8/2015)
25 and from the National Data Protection Committee (8828/2016). Written informed consent
26 was obtained before data collection.

27

28 Sample size

29 A sample size estimation with 95% power at 5% significance determined that a significant
30 difference in the inspiratory mean number of crackles obtained through repeated measures
31 from patients with COPD at exacerbated (2.97 ± 1.98) and stable (1.20 ± 0.80) phases of their
32 disease would be detected with a minimum of 23 participants [10]. A high statistical power
33 was chosen due to the great amount of inter and intra subject variability presented by ARS
34 [14, 15], which could potentially cause type II errors if the study was underpowered [16]. In

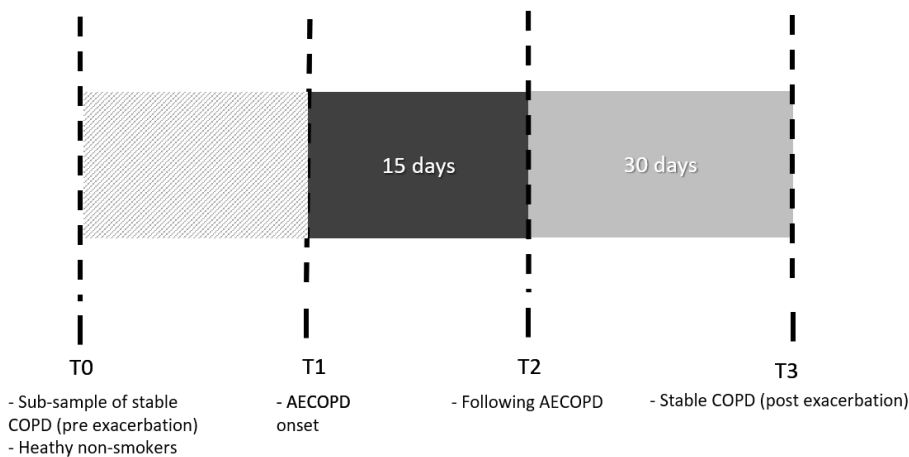
1 health-related longitudinal studies, dropout rates are of approximately 20 to 45% [17, 18]
2 thus, 36 participants with AECOPD were aimed to be recruited. Sample size estimation was
3 performed using the G*Power 3.1 software (University Düsseldorf, Germany).

4

5 Data collection

6 Participants with AECOPD recruited from the urgent care were asked to attend to 3
7 assessment sessions: at the exacerbation onset (T1 – 24 to 48 hours of the hospital visit),
8 15 days (T2 – following exacerbation) [19, 20] and 45 days after the hospital visit (T3 – at
9 stability post exacerbation). The subsample of patients recruited from routine pulmonology
10 appointments were asked to attend to 4 assessment sessions: 24 to 48 hours after the
11 pulmonology routine appointment (T0 – at stability pre exacerbation), at the exacerbation
12 onset (T1 – 24 to 48 hours of the hospital visit), 15 days (T2 – following exacerbation) [19,
13 20] and 45 days after the hospital visit (T3 – at stability post exacerbation). Data from
14 healthy non-smokers was only collected once (T0) (Figure 1). Data collection occurred at the
15 urgent care, in the facilities of the University of (omitted for blinded purposes) or at patients'
16 home.

17



18

19 *Figure 1 – Time points of data collection.*

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

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

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

7 *Respiratory sound recordings*

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

23 *Signal processing*

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

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

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

7

8 Statistical Analysis

9 All statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM
10 Corporation, Armonk, NY, USA) and plots created using GraphPad Prism version 5.01
11 (GraphPad Software, Inc., La Jolla, CA, USA). The level of significance was set at 0.05.

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

18

19 Computerised ARS data were explored for each of the five analysed locations; however, no
20 significant differences were found between right and left chest of the same region (i.e.,
21 anterior, lateral or posterior), thus, to simplify the interpretability of the findings, data from
22 right and left were pooled for each chest region [32]. Then, the number of participants with
23 crackles and wheezes in each chest region was calculated and the Cochran test with
24 Bonferroni corrections was used to compare number of participants presenting crackles and
25 wheezes among T1, T2 and T3. Fisher's exact test was used to investigate differences
26 between healthy non-smokers and patients with COPD at stable phases (T3) on the number
27 of participants presenting crackles and wheezes. Comparisons of number of crackles and
28 %Wh among T1, T2 and T3 in patients with COPD were performed with the Friedman test,
29 and multiple comparisons with the Wilcoxon sign-rank test. Multiple comparisons were
30 corrected for number of comparisons using Bonferroni corrections. Comparisons between
31 healthy non-smokers and patients with COPD at stable phases regarding mean number of
32 crackles and %Wh was performed with Mann-Whitney U test. When statistically significant
33 differences were found for the number of crackles or %Wh, a comparison of the type of
34 crackles or wheezes was also performed.

1 An additional analysis, similar to the described previously for patients recruited at the onset
 2 of the AECOPD, was conducted with the subsample of patients presenting data collected
 3 prior to the exacerbation.
 4

5 **Results**

7 Participants

8 Seventy-four non-hospitalised patients with AECOPD were referred for possible inclusion in
 9 the study. Of these, 34 patients referred with AECOPD were excluded because at T1 they
 10 had pulmonary function test not compatible with a diagnosis of COPD (n=22), did not meet
 11 the definition for AECOPD (n=1), presented lung neoplasia (n=2), severe heart failure (n=1),
 12 were unable to comply with data collection (n=3), or declined to participate in the study
 13 (n=5). Fifteen patients were further excluded from the analysis because failed to complete all
 14 time points of data collection (i.e., T1, T2 and T3) (n=6) and their respiratory sounds
 15 (collected at the urgent care) had a significant amount of background noise hindering the
 16 use of the algorithms described in the *Signal processing* section (n=9). Thirty-four healthy
 17 non-smokers were also contacted and invited to participate. Thus, twenty-five participants
 18 with AECOPD (16 males; 70 [62.5-77.0] years old; FEV₁ 59 [31.5-73.0]% predicted) and
 19 thirty-four healthy non-smokers (17 male; 63.5 [57.7-72.3] years old; FEV₁ 103.0 [88.8-
 20 125.3]% predicted) were enrolled in the study. Participants' characteristics are summarised
 21 in Table 1.
 22

23 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/m², 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)	-	
FEV₁, L	1.2 [0.8-1.7]	2.6 [2.1-3.0]	<0.001*
FEV₁, %predicted	59 [31.5-73.0]	103.0 [88.8-125.3]	<0.001*
FEV₁/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*

1 *p<0.05

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

3 Legend: BMI, body mass index; FEV₁, forced expiratory volume in one second (at stability); FVC, forced vital
4 capacity (at stability); GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, Modified British
5 Medical Research Council questionnaire; SD, standard deviation.

6

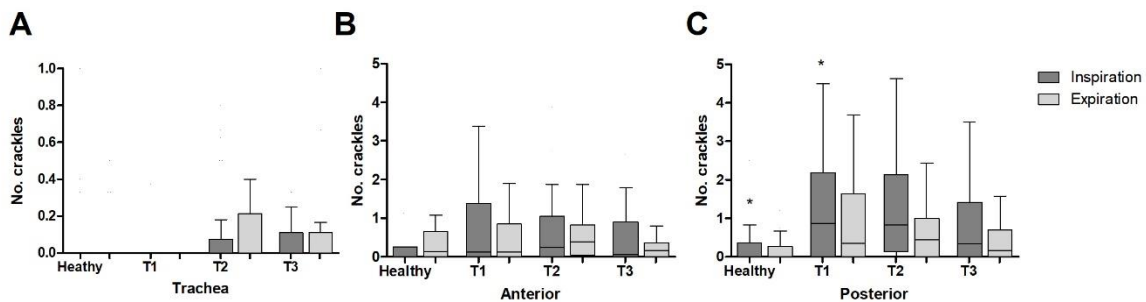
7 A subsample of 9 participants with stable COPD *a priori* was also included and followed up
8 until an AECOPD occurred and during its recovery. This sub-group of participants (7 males;
9 66 [60.0-76.0] years old; FEV₁ 62 [26.5-74.0]% predicted) was slightly overweight (27.9±4.46
10 Kg/m²), presented a median number of packs/year of 21.2 [10.0-30.0] and were mainly
11 former smokers (n=5; 55.6%; current smokers: n=2; 22.2%; never smokers: n=2; 22.2%).
12 Most participants were classified as being in a stage D of the GOLD classification (n=5;
13 55.6%; GOLD B: n=2; 22.2%; GOLD C: n=2; 22.2%), presented more than 2 AECOPD in the
14 past year (n=6; 66.7%; 1 AECOPD: n=2; 22.2%; 0 AECOPD: n=1; 11.1%) and were treated
15 for their AECOPD with antibiotics (n=5; 56%), cholinergic antagonist bronchodilators (n=2;
16 22%), anti-inflammatory bronchodilators (n=1; 11%) and expectorants (n=3; 33%). Patients
17 presented a median mMRC of 2 [1-3]. Median time to exacerbation was 23 [18-146] days.

1 Computerised Respiratory Sounds

2

3 *Crackles*

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



10

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.

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

15

16 *Wheezes*

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

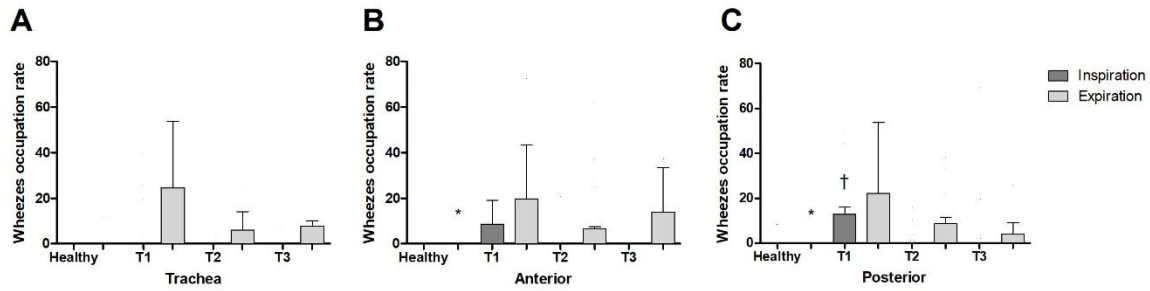


Figure 3 –Inspiratory and expiratory wheeze occupation rate in healthy participants and participants with COPD (T1, T2, T3) at A) trachea, B) anterior and C) posterior chest regions.

* 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

1 [33], might lead us to confidently identify the posterior chest region as the preferred location
2 of auscultation to monitor patients with COPD.

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

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

31 Considering the changes in ARS during the course of AECOPD, %Wh, specifically
32 monophonic, significantly decreased after 15 days of treatment (i.e., approximate time
33 needed to resolve an AECOPD [19]), whilst crackles, specifically coarse crackles, only
34 decreased significantly after 45 days post-exacerbation. Previous studies conducted during
35 an AECOPD have shown an improvement in air-flow limitation (assessed by FEV₁ and peak

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

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

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

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

1 different protocols used to collect and analyse ARS. In this study, ARS were collected using
2 AKG air-coupled electret microphones (response rate 20-20000Hz) mounted in capsules
3 made of Teflon to minimize noise and increase sound transmission [26, 27]. Additionally, all
4 participants, independently of having ARS or not, were included in the analysis to potentiate
5 the comprehensiveness and generalization of our findings. Previous studies have used
6 sensors with different frequency responses (e.g., 40-15000 [32]; 50-1800Hz; 4-20000Hz; 65-
7 20000Hz [42]), diverse set ups of data collection (e.g., electret microphones imbedded in a
8 soft foam mat and electret condenser microphones connected to the diaphragm or main tube
9 of conventional stethoscopes [10, 42, 43]) and analysis (have only included in their analysis
10 people presenting ARS [32]). Such variety of procedures may produce recordings of different
11 quality and range of sound spectrum, influencing the results achieved and thus impairing
12 comparisons among studies.

13 **Limitations**

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

36

1 **Conclusion**

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

12

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