International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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ORIGINAL RESEARCH

Acoustic Monitoring of Night-Time Respiratory Symptoms in 14 Patients with Exacerbated COPD Over a 3- Week Period

Tobias Boeselt[1], Johannes Kroenig[1], Theresa-Sophie Lueders[1], Niklas Koehler[2], Bjoern Beutel[1], Olaf Hildebrandt[1], Ulrich Koehler[1], Regina Conradt[1]

[1]Department of Internal Medicine, Division of Pneumology, Intensive Care and Sleep Medicine, Philipps-University Marburg, Marburg, Germany; [2]Thora Tech GmbH, Clinical Research Department, Gießen, Germany

Correspondence: Tobias Boeselt, Department of Internal Medicine, Division of Pneumology, Intensive Care and Sleep Medicine, Philipps-University Marburg, Baldingerstrasse 1, Marburg, 35033, Germany, Email tobias.boeselt@uni-marburg.de

Introduction: In clinical practice, wheezing and coughing represent a worsening of the respiratory situation of COPD patients and should be monitored long-term during and after an Acute Exacerbation of COPD (AECOPD) to observe the therapy. We investigated if overnight monitoring of wheezing and coughing is feasible during AECOPD and whether automatic long - term monitoring enables an objective assessment during and after an AECOPD.

Methods: In 14 patients (age: 56–80 years) with pre-existing COPD (stages B-D) nighttime wheezing and coughing events were monitored for a period of three weeks. The portable LEOSound® monitor recorded three nights into AECOPD (nights 1, 3 and 6) during the hospital stay, and the 20th night post- AECOPD ambulatory. Before each recording the subjective symptom severity was assessed by a COPD Assessment Test (CAT) and a Modified British Medical Research Council (MMRC) dyspnoea index questionnaire.

Results: In all 14 patients, lung sounds were recorded in good quality during each of the 4 recording nights. Wheezing ranged between 5% and 90% (79 −539.5 minutes) of the recording time on the first night. All patients showed some coughs, in four patients coughing was particularly pronounced and largely receding over the total investigation period. As group, the percentages of wheezing and the number of coughs did not show significant differences between the four recording times. The CAT scores ($p<0.001$) declined over the course of investigation period, suggesting a subjective improvement of symptoms.

Conclusion: The observational study showed that standardized long-term recording can be performed in high-quality during acute COPD exacerbation as it does not require the patient's cooperation. The good-quality data of coughs and wheezing were analyzed qualitatively and quantitatively. The long-term presentation of respiratory symptoms during an AECOPD offers the opportunity to evaluate factors that influence exacerbations and therapeutic approaches.

Keywords: COPD, wheezing, cough, long term monitoring of respiratory sounds, CAT, exacerbation

Introduction

Chronic obstructive pulmonary disease (COPD) shows characteristic symptoms like dyspnea, coughing, wheezing and sputum. The symptoms vary in terms of their intensity and occur more frequently at night.[1]

An acute COPD exacerbation represents a crucial phase in terms of mortality and disease progression.[2–5] During an AECOPD there is an increased occurrence of respiratory wheezing[5] and coughing.[4,6] Wheezing should always be considered as an expression of bronchial obstruction.[7] Cough, especially when productive, is associated with increased mortality and may describe the course of an exacerbation.[8] Cough and wheezing were subjectively the most bothersome symptoms during night in severe COPD patients.[9] Therefore, it seems reasonable to represent these parameters by valid long-term recordings. A response to therapy for bronchial obstruction could be monitored and adapted if necessary.

So far, there is no suitable method to monitor the course of primary COPD symptoms in a standardized and objective way and to present them in the time course. Seemungal and co-workers demonstrated that patients with moderate to

Received: 5 July 2022
Accepted: 5 October 2022
Published: 18 November 2022

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severe COPD exacerbations took a median of 8 days to recover subjectively.[5] Questionnaires are currently a valid means of recording symptoms. However, the use of questionnaires shows limitations. The general subjectivity of the questionnaires does not allow an objective statement to be made about the severity and frequency of nocturnal symptoms in the course of an acute exacerbation.

As a standard method, auscultation represents an important part of the basic diagnostics. However, this can only reflect the actual state of the bronchial obstruction at one point in time and is also very dependent on the examiner.[10,11] Computer-assisted long-term auscultation procedures overcome the natural limitations of manual auscultation by minimizing the investigator-dependent variability, recording long periods of time and ensuring a qualitative and quantitative consistent data analysis.

The Lung sound Monitor (LEOSound) enables objective measurements and analyses of COPD symptoms over a longer period of time (up to 24 hours). The system allows the severity of the nocturnal COPD symptoms to be assessed precisely and, in comparison to lung function diagnostics, does not require active cooperation on the part of the patient.[12] This enables the qualitative and quantitative assessment of lung sounds in the course of acute exacerbated COPD. Kroenig et al have already been able to objectify nocturnal breath sounds in stable COPD patients using the technique.[13] The LEOSound has been validated for coughs and wheezings.[14–16]

The aim of the study was to depict the course of AECOPD and to objectify its development by automatic long - term monitoring of pulmonary symptoms (wheezing and cough) in the course of AECOPD.

Methods

Patients

All patients were recruited in the period from March 2017 to January 2019 in the department of pneumology of St. Christophorus Hospital GmbH Werne, Germany. The inclusion criteria were an age between 40 and 80 years and a diagnosis of COPD stage between B and D. All patients were admitted to hospital immediately after an acute worsening of respiratory symptoms.

Consecutive patient acquisition took place if the study criteria were met. Exclusion criteria were the patient's refusal to participate in the study, limited or non-existent ability to consent, the presence of other serious infectious diseases such as tuberculosis or the necessity of temporary ventilation (eg in intensive care). The protocol received full approval by the Marburg and Munster Ethics Committees before the start of the study. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained in all cases.

Study Design

The study was a non-interventional observational study. Over a period of three weeks, wheezing and cough events were recorded overnight for a total of 4 nights. The first three nights (nights 1, 3 and 6) immediately followed the onset of AECOPD and were conducted during hospitalization to reveal short-term changes during the acute phase of exacerbated COPD. An additional recording took place in a more stable phase of the AECOPD course three weeks (night 20) after the AECOPD onset.

This recording was performed at the patient's home. The LEOSound® recorder (Löwenstein medical, Bad Ems, Germany) was used for computer-assisted long-term auscultation.

The four recording times were chosen to reflect the acute exacerbation phase (measurement night 1 to measurement night 6) and the bronchopulmonary status of the patients in the continued recovery (measurement night 20). The recording was initiated by the patient at the normal bedtime and stopped by the patient the following morning.

In addition, the objective measurement method was compared with standardized questionnaires (mMRC and CAT score).

Longterm Recording of Respiratory Sounds - LEOSound

The LEOSound Lung-Sound-Monitor is a mobile device validated for automatic long-term recording and analysis of normal and adventitious respiratory sounds such as cough and wheezing in adults and children.[14,16–18] The system automatically detects cough and wheezing for up to 24h and can be used either in the hospital or at the patient's home. Sound is recorded by three bio-acoustical sensors (see Figure 1A) which are placed at the trachea and on the back of the patients (see Figure 1B). In

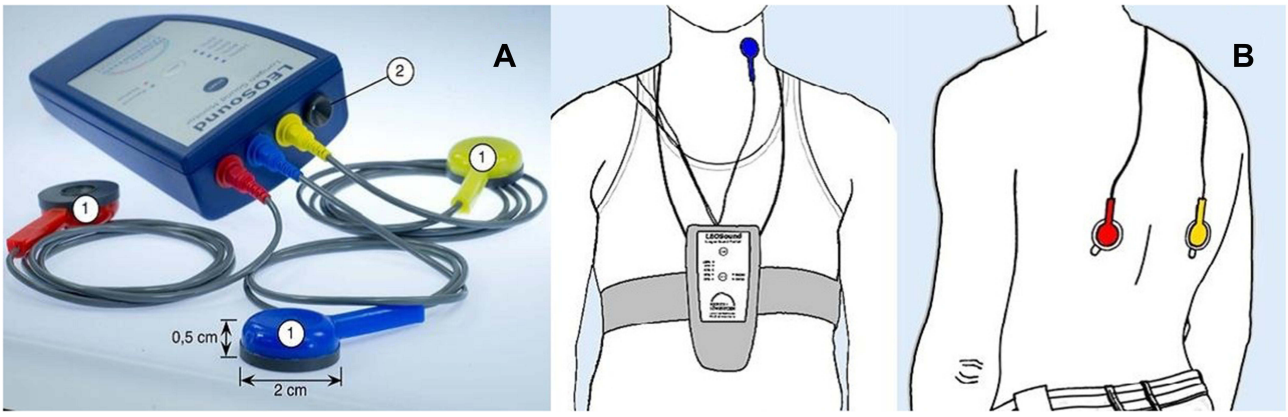

Figure 1 (**A**) LEOSound-recorder with three body microphones (1) and an integrated ambient microphone (2). The size of the body microphone has been displayed. (**B**) Illustration of how to wear the recorder during the observation. The Figure depicts the position if the tracheal microphone (blue) and the two bronchial microphones (red and yellow). The recorder was worn with one strap around the neck and one around the chest.
Note: Reproduced from Doenges J, Kuckuck E, Cassel W, et al. Disease control in patients with asthma and respiratory symptoms (wheezing, cough) during sleep. Asthma Res Pract. 2020;6:9. doi:10.1186/s40733-020-00062-w.[15]

addition, an ambient microphone is integrated in the LEOSound device to distinguish lung sounds from any environment noise (see Figure 1A). The related software "LeoSound analyzer" (Löwenstein medical, Bad Ems, Germany) contains automated algorithms for cough and wheezing detection (seeFigure 2). The LEOSound-system was tested in various clinical studies, showing a high sensitivity and specificity of 80–95% for the detection of cough and wheezing.[14] The analyses were manually checked by qualified personnel and individual false positive and false negative events were corrected. The number of resulting coughing and wheezing epochs in 30s sequences were calculated automatically.

Questionnaires

Before each LeoSound® recording the patients completed both, a COPD Assessment Test (CAT) and a Modified British Medical Research Council (MMRC) dyspnoea index questionnaire.

Modified British Medical Research Council Dyspnoea Index (mMRC)

The mMRC is a standardized questionnaire used to assess the severity of symptoms, specifically for classifying perceived dyspnea.[19] In the mMRC, grading is based on the severity of the symptoms of the dyspnea and their influence on everyday activities. Higher values indicate more pronounced perceived dyspnea.

COPD Assessment Test (CAT)

The CAT comprises 8 questions relating to current complaints and their severity.[20] Each item is scored from 0 to 5. The higher the score, the more pronounced the perceived COPD severity.

Spirometry and Body Plethysmography

All patients received a spirometry and body plethysmography, which were scheduled for the fifth day of the hospital stay. The body plethysmography was performed according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[21] Static and dynamic lung volumes, and airway resistance were assessed with a constant-volume plethysmograph (MasterScreen Body Lab 4; Jaeger, Würzburg, Germany).

Medication

A medical history was taken with regards to the use of oral and inhalative long-term medication as well as medication on demand, in particular whether a long-term anti-inflammatory medication was given orally or by inhalation. All additionally administered medications during the acute inpatient stay were recorded, in particular the systemic corticosteroids administered.

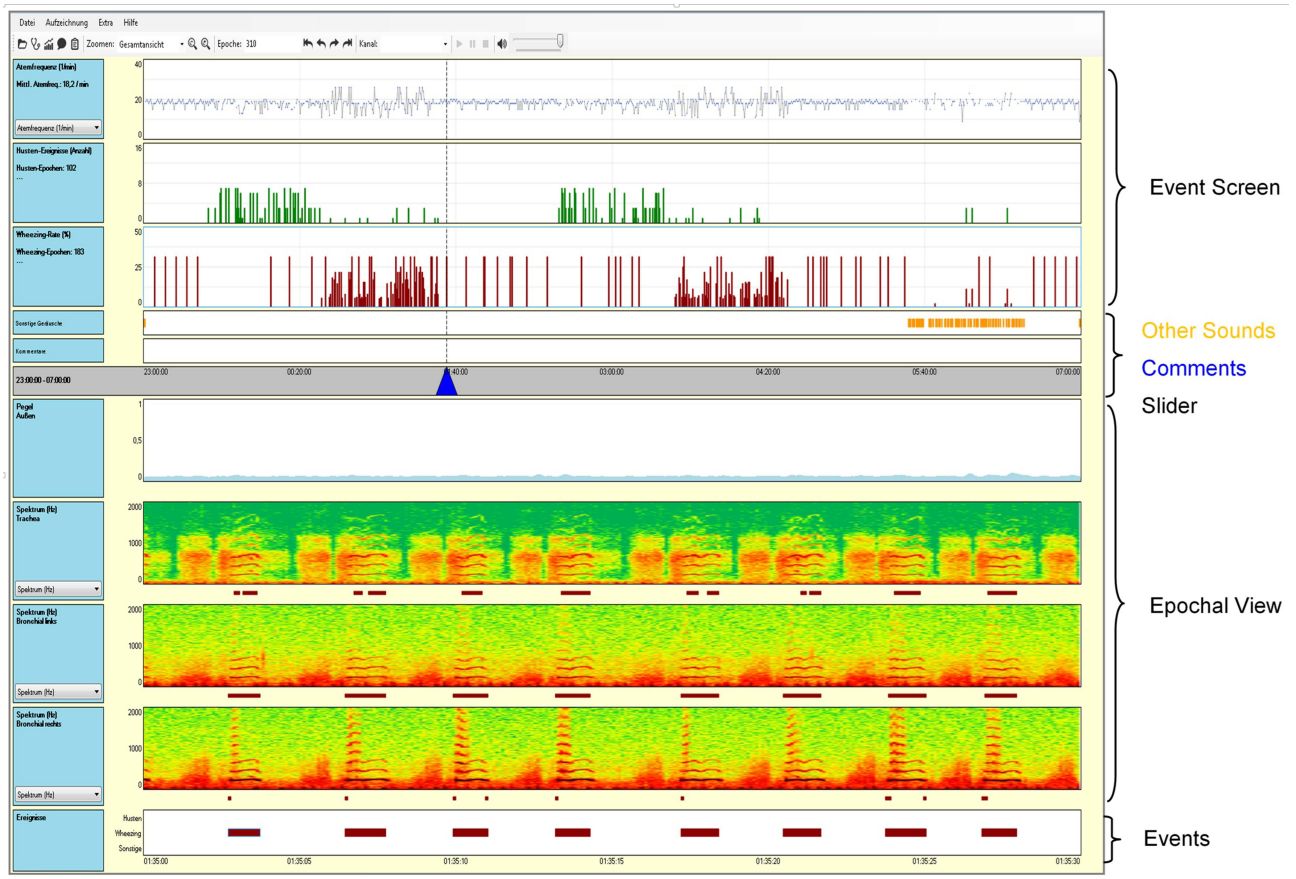

Figure 2 The user interface of the LEOSound-Analyzer is divided into two major fields - shown as Event Screen and Epochal View. The Event Screen displays the breathing rate (blue line), the detected coughing events (shown in green) and the wheezing rate of the associated epoch (shown in red). In the Epochal View the selected epochs in this example. The Event Screen is displayed as a spectrogram. Optionally, the epochs can also be represented as a loudness level.
Note: Reproduced from Doenges J, Kuckuck E, Cassel W, et al. Disease control in patients with asthma and respiratory symptoms (wheezing, cough) during sleep. Asthma Res Pract. 2020;6:9. doi:10.1186/s40733-020-00062-w.[15]

Statistical Methods

The study was conducted as an observational study because no previous scientific studies on computer-assisted long-term auscultation for such a long observation period were available. All statistical calculations were performed using SPSS 25 IBM GmbH Germany. For a descriptive analysis of the collected data, frequency, minimum, maximum, median, lower quartile (Q25) and upper quartile (Q75) were determined. All variables were checked for deviations from a normal distribution by the Kolmogorov–Smirnov test. Since the sample was small and no normal distribution could be confirmed, the Mann–Whitney *U*-test was used. Correlations between variables were explored using the nonparametric ranked Spearman rank test. Differences with an error probability of less than 5% ($p < 0.05$) were considered significant for all tests.

All statistical models used were primarily for exploring differences between groups and not for formal hypothesis testing. Therefore, no corrections for multiple testing were made in this study. Statistical differences between groups (p-values) should be interpreted as indications and not as evidence of differences.

Results

In all, 14 patients aged between 56 and 80 years took part in the study. Three women and 11 men were included with a median age of 65.5 years and a median BMI of 23.5 kg/m^2.

Table 1 summarizes the patients' characteristics. There was no restriction in medication. All patients had a positive history of smoking. Seven patients (50%) were smokers at the time of the study. In 12 patients (85.7%), a respiratory

Table 1 Anthropometric Data of Study Cohort (n=14)

	Gold Status	FEV1/VC 1	Active Smoker	PY	Month of Admission	BMI (kg/m^2)	Gender
Patient 1	D	0.21	Yes	35	03	23.7	M
Patient 2	D	0.29	Yes	40	03	27.0	M
Patient 3	C	0.31	No	40	03	28.4	M
Patient 4	C	0.62	Yes	40	04	18.5	M
Patient 5	C	0.27	Yes	40	04	17.9	M
Patient 6	C	0.65	Yes	40	08	39.2	F
Patient 7	D	0.4	No	40	10	21.5	F
Patient 8	C	0.38	Yes	30	01	20.3	F
Patient 9	C	0.36	No	40	01	21.8	M
Patient 10	C	0.51	No	40	04	23.4	M
Patient 11	D	0.35	No	45	04	19.9	M
Patient 12	B	0.42	No	42	10	24.0	M
Patient 13	C	0.32	Yes	52	10	23.7	M
Patient 14	B	0.42	No	25	01	35.7	M

infection was the cause of the exacerbation. The majority of patients had taken an ICS/LABA combination and used a SABA as emergency medication.

Medication

In 11 patients (78.5%), the medication plan was adjusted as part of the acute inpatient stay due to a COPD exacerbation. On admission to hospital, LABA and LAMA were taken regularly by 12 patients (85.7%) and ICS by 8 patients (57.1%). As on-demand medication, 11 patients (78.5%) received SABA and 13 patients (92.8%) SAMA.

As discharge medication 14 patients (100%) received LABA, 13 patients (92.8%) LAMA and 10 patients (71.4%) ICS as long-term medication. As an on-demand medication, 13 patients (92.8%) received SABA and 13 patients (92.8%) received SAMA. During the acute inpatient stay, 10 patients (71.4%) received cortisone shock therapy. In 12 patients (85.7%) antibiotics were administered. All patients with wet inhalations inhaled bronchodilatory drugs. A diagnostic and / or therapeutic bronchoscopy was performed in 6 patients (42.8%) during their hospital stay.

Lung Function Test Results

All patients underwent a body plethysmography usually on day 5 of the hospital stay. The lung function test showed airway resistances ranging from normal (0.2 kPa*sec/l; min) to a 6-fold increase (669.9% of target, max). The obstruction was between FEV1 = 570mL (16.6% of target, min) and 2300mL (67% of target, max). The Tiffeneau index ranged between 21% (min) and 65% (max).

Questionnaires

During the acute exacerbation phase (night 1, 3 and 6), each participant reported a subjective improvement in symptom severity in the CAT questionnaire. The CAT scores of night 6 were 2–20 points lower than the initial values obtained in night 1. On the ambulatory assessment (on night 20), 12 out of the 14 patients reported a lower symptom severity compared to night 1. For the measurement period (from night 1 to 20), the CAT scores presented a statistically significant decrease (p=0.000013).

The Dyspnoea symptoms, as reported by the MMRC had improved from night 1 compared to night 6 in six patients. Seven patients reported in night 20 less dyspnea than at night 1. In four patients, shortness of breath remained unchanged over the three weeks study period. Two patients reported more dyspnea in night 3. For the measurement period (from night 1 to 20), the mMRC scores did not present a statistically significant decrease (p=0.065).

Nocturnal Lung Sound Analysis

In all 14 patients, lung sounds were recorded in good quality during each of the 4 measurement nights. On average, the evaluated measurement time per night was 593 minutes ±11 minutes.

The severity of coughs and wheeze over the course of AECOPD was represented by single case plots to visually demonstrate the feasibility of long-term recordings of symptom progression.

Wheezing

Wheezing was detected in all patients on each measurement night (see Figure 3). On night 1, the percentage of wheezing ranged between 5% and 90% of the total measurement time (79.0–539.5 minutes). Seven patients showed a continuous decrease in wheezing from night 1 to night 2. In 3 patients the wheezing periods first increased and then decreased again.

In nine patients, fewer wheezing was recorded during night 6 compared to the beginning of exacerbation (night 1). In three patients, the reverse was true and more wheezing was recorded. In the measurement after acute exacerbation, which was carried out at home (night 20), in terms of percentage of the total measurement time (≙ 5–550 minutes) wheezing lay between 1% and 92%).

Neither age, gender, smoking, GOLD status nor the Tiffeneau Index could account for the different wheezing dynamics or the wheezing rates.

Cough

Cough events were recorded in all nights but in night 1 of patient 14 (s. Figure 4). Four patients showed a high number of coughing events (>20/hour on the first night of measurement), which decreased distinctly in all four patients on the third and sixth night. The remaining ten patients showed fewer coughing symptoms, which resulted in a heterogeneous picture overall. The number of coughs per hour decreased in six patients from night 1 to night 6 or to night 20.

The age, gender, smoking status, GOLD status or the Tiffeneau Index did not correspond to the different courses in the number of coughs in the individual patients.

Correlation Between Subjective and Objective Assessment

There was no significant correlation between the mMRC scores and the automatically recorded wheezing or cough rate.

The CAT questionnaire showed a significant correlation to the objectively measured number of cough/hour (r=0.559; p=0.038) on recording night 3.

On recording night 20 (ambulatory recording) the CAT scores were correlated with the number of coughs per hour (r=0.678; p=0.008), and wheezing percentage of the total night (r=0.581; p=0.029).

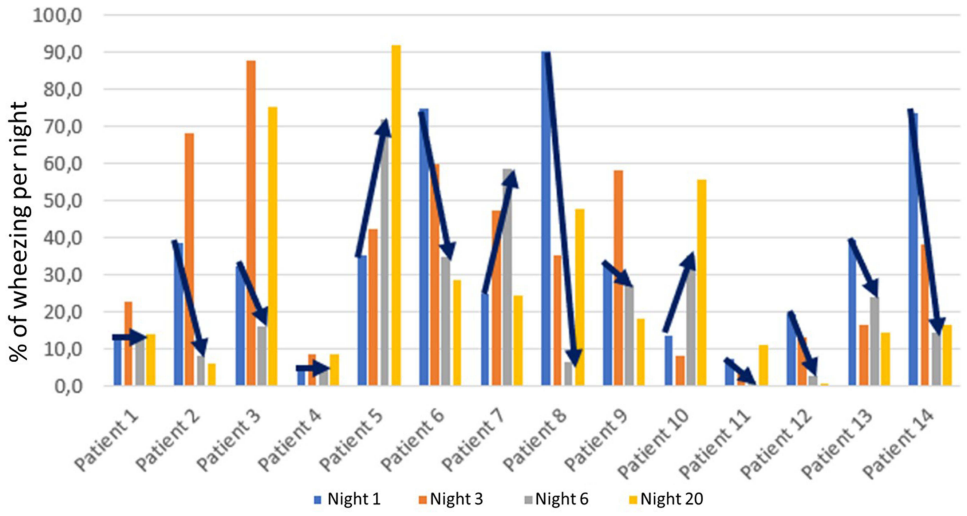

Figure 3 Percentage of wheezing during the 4 measurement nights. Percentages of wheezing on the 4 recording nights. Nights 1 to 6 correspond to the in-hospital nights following an AECOPD; night 20 describes an ambulatory overnight recording post-AECOPD. The trend of the acute phase (night 1 to night 6) was shown with an arrow.

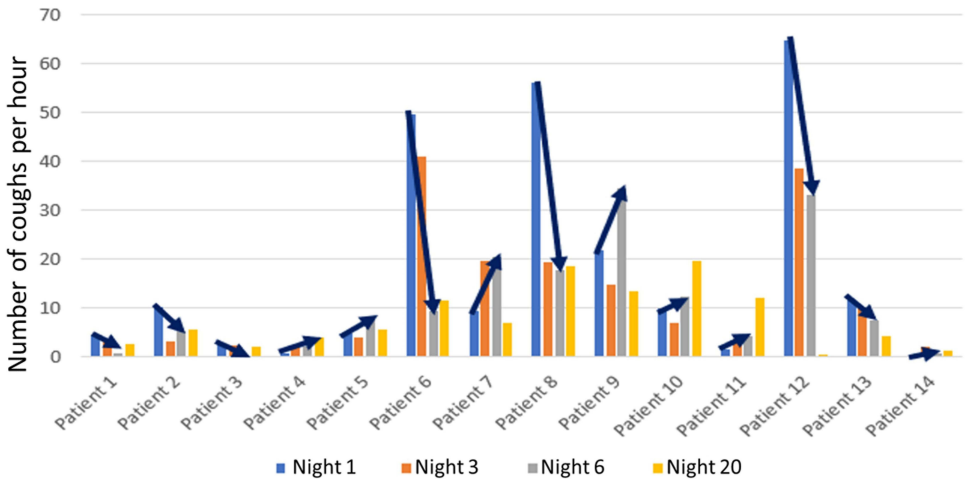

Figure 4 Number of coughs during the 4 measurement nights. Number of coughs on the 4 recording nights. Nights 1 to 6 correspond to the in-hospital nights following an AECOPD; night 20 describes an ambulatory overnight recording post-AECOPD. The trend of the acute phase (night 1 to night 6) was shown with an arrow.

The intra-individual courses of symptoms showed changes tin 5 out of the 14 patients in the CAT score and paralleled the changes in the automatically recorded coughs. In 6 out of the 14 patients the CAT score showed a similar course compared to the objectively measured changes in wheezing.

The two subjective assessments (CAT score and mMRC questionnaire) correlated in three of the four measurement nights: recording night 1 (r= 0.583; p=0.029), recording night 3: (r=0.669; p=0.009) and recording night 6 (r=0.784; p=0.001).

Discussion

There are still a relatively small number of clinical studies looking at the dynamics of COPD exacerbations, although AECOPD has a central role in disease progression and mortality rates. Our study showed that the objective symptoms like coughs and wheezing can persist for more than three weeks after the exacerbations of COPD, even if the patients perceived themselves as improved.

The night-time is a vulnerable phase for COPD patients but is rarely objectively monitored.

Physician usually rely on patient´s perception of their overnight symptoms, which can be provided with great uncertainty only, as events during sleep cannot perceived by patients. The main measurable pulmonary symptoms experienced by patients during an exacerbation are an increase in breathlessness, wheezing, and cough.[5,6] Up to now, the course of symptoms has mostly been described by means of diary cards or selective examinations.[22]

To our knowledge, this was the first time, that long-term overnight recordings of lung sounds were achieved to objectively analyze the course of AECOPD. In this study, the nocturnal respiratory symptoms of COPD patients during an acute exacerbation were recorded using a valid method to detect wheezing and coughs.[16,23] The method made it possible to assess respiratory symptoms objectively over time.[23]

Circadian variations usually worsen respiratory problems during sleep.[24] This may be caused by changes in vagal tone, a reduction in muscle tone during REM sleep and mechanical factors during supine sleep.[25] Braghiroli et al recently alluded to the lack of research in this area and the absence of established 24hr clinical monitoring of respiratory symptoms that would lead to better suited drug therapy.[25]

A key advantage of overnight recordings is an improved recording environment, as noise and patient distress was minimized. In our study we performed recordings with a consistently high quality, both overnight during the hospital stay (night 1 to 6) as well as at the patient's own home (night 20).

Wheezing

Wheezing is seen as closely related to airway obstruction. Without wheezing, airway obstruction cannot be detected through routine clinical examination. The extent of the obstruction does not correlate with the loudness of wheezing, but it does, however, correlate with the number of wheezing episodes.[26]

In our study it became clear that wheezing is an important clinical symptom to describe the course of an exacerbation. The study population showed an inconsistent time-course of wheezing symptoms. In the first recording night, long-lasting episodes of wheezing were observed in some patients, they accounted for more than 90% of the total measurement time. The increased occurrence of wheezing could be due to, among other things, the increased secretion production caused by the inflammatory process. In addition, during inpatient therapy with intensified medication and inhalative therapy, there is increased mucus production and secretolysis. The mucus can lead to an additional obstruction of the airways and thus to increased wheezing. In the patients who showed more episodes of wheezing on individual nights but fewer pulmonary respiratory symptoms on measurement night 6, the increased wheezing was interpreted as part of the recovery process.

Interestingly 3 patients showed an increase of wheezing between the hospital stay and the last measurement (night 20). In patients with marked emphysema, lung sounds, like wheezing, are reduced due to pulmonary hyperinflation.[27] Schwarz and co-workers did not find any significant relation to the lung function results in exacerbated vs stable COPD patients.[28] They considered this a sign of the complexity of wheezing as a clinical feature in COPD patients, which needs further insights.

Regular long-term recordings could provide information on whether the wheezing symptoms after AECOPD persist for a longer period than our observation period or are in fact a chronic feature of COPD.

Coughing

The individual time-course was very heterogeneous, with some patients showing pronounced cough symptoms and others showing only isolated coughs.

Crooks et al conducted all-day monitoring of cough events in 16 patients with AECOPD, who documented the subjective symptoms daily.[29] The recorded number of coughs dropped significantly from day 1 to day 9 before plateauing. In our study population, declining trends were only reflected by six out of 14 patients from night 1 to night 6. From night 6 to night 20, there was no sign of plateauing, in four patients the coughs deteriorated and in four others the coughs improved compared to night 6.

Schwarz et al found with their objective recording an increase of wheezing but not of coughing during exacerbated COPD compared to stable COPD. This result clearly reflects our interindividual heterogeneous cough results, which did not show a clear pattern throughout the study period.[28] Schwarz et al and our result seem to indicate that wheezing, far more than cough, is a promising parameter to gain insight into the clinical pathophysiology of AECOPD.

Questionnaires

In the study of Crooks and colleagues the patients showed a subjective improvement over the first 9 days of observation, which we also found as perceived improvement between night 1 to night 6 in our patients.[29] Crooks' group reported a significant correlation of objective cough counts and subjective cough scores, which we, however, could not establish.

Husebø et al could show in a very large cohort of 350 patients that the self-reported AECOPD duration increased with severity, during winter, and in patients with obesity and/or chronic cough.[22] In our study we could not show relevant correlation of wheezing or coughing with age, BMI, Tiffeneau Index, GOLD status or smoking status or the month of AECOPD admission in our small cohort.

Limitations

Primarily because of the small patient collective the results can only be evaluated clinically to a limited extent. However, there is already evidence that the heterogeneity of clinical presentations and disease courses in COPD patients could be explained by different phenotypes and that the different phenotypes require different treatment strategies.[30,31] Among other things, exacerbation frequency also appears to be indicative.[32] Symptomatology but coughed less or vice versa. Due to the size of the study population, it was not possible to identify statistically significant commonalities between the subgroups.

In view of the numerous remaining open questions further studies should be conducted to clarify the key questions among them. We were able to show that a methodical implementation is possible. Good quality overnight recordings were achieved both, in a busy university hospital setting as well as in the patient's home.

Take Home Message

Computer-assisted long-term auscultation and standardized automated analysis of night-time symptoms enables an objective assessment of the course of AECOPD events.

Long-term imaging of respiratory symptoms during AECOPD provides the opportunity to assess factors influencing exacerbations and therapeutic approaches.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

UK has received fees for consultancy, lectures and support for research projects from the companies Löwenstein Medical, IfM, AstraZeneca, GlaxoSmithKline, Berlin Chemie, Resmed, Weinmann and UCB Biosciences.

RC has received scientific advisory fees from Spiromedical Norway and GDS Medtech UK and accepted consultancy fees from Löwenstein Medical. The other authors declared no conflict of interests.

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