Respiration

Clinical Investigations

Respiration 2021;100:201–208
DOI: 10.1159/000513439

Received: May 19, 2020
Accepted: November 25, 2020
Published online: February 5, 2021

Long-Term Auscultation in Chronic Obstructive Pulmonary Disease: Renaissance of an Ideograph of Medical Care

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Keywords
Chronic obstructive pulmonary disease · Auscultation · Wheezing · Exacerbation · Cough

Abstract
Background: Electronic auscultation technology has advanced dramatically in the last few years. Therefore, long-term pulmonary auscultation could provide additional information about respiratory system by monitoring acute chronic obstructive pulmonary disease (AECOPD) exacerbations or by identifying wheezing phenotypes amongst stable COPD patients. ***Objectives:*** Comparison of respiratory sounds in stable versus AECOPD patients recorded with a portable respiratory sound monitor over a period of 24 h. ***Methods:*** This prospective trial evaluated cough and wheezing events using an auscultation monitor specially developed for this purpose with 4 integrated highly sensitive microphones, in stable and severely AECOPD patients for a period of 24 h in an inpatient setting. ***Results:*** Twenty stable COPD patients (12 male, 60%) and 20 severely exacerbated COPD patients (14 male, 70%) were analyzed. In AECOPD patients, long-term auscultation revealed a significantly higher number of wheezing epochs than stable COPD patients (591 [IQR: 145–1,645] vs. 152 [IQR: 90–400]; $p = 0.021$). Conversely, cough epochs did not differ between AECOPD and stable COPD patients (213 [IQR: 140–327] vs. 162 [IQR: 123–243]; $p = 0.256$). The Borg-dyspnea scale, CAT score, and total CCQ score each showed no correlation with wheezing frequency, while CAT and CCQ scores did correlate with coughing frequency. ***Conclusion:*** Wheezing, but not coughing, occurs more frequently in AECOPD patients than in stable COPD patients, indicating that severe wheezing is an important clinical sign of exacerbation, while coughing is not. Therefore, the patterns of wheezing and coughing, as assessed by long-term auscultation, differ in stable versus exacerbated COPD patients.

Background

Manual pulmonary auscultation is a commonly used tool for diagnosing and evaluating respiratory diseases, particularly in the case of chronic obstructive pulmonary disease (COPD). Nevertheless, the most recent edition of

The present study was presented at 2 national congresses: the German Pneumology Society (DGP), Stuttgart, March 2018; German Society of Sleep Medicine (DGSM), Münster, November 2017.

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the “Global Initiative for Chronic Obstructive Lung Disease” (GOLD) report does not call for mandatory pulmonary auscultation in the diagnosis and evaluation of COPD and instead recommends spirometry [1, 2]. This is because auscultatory findings are assumed to have low levels of specificity and sensitivity in early COPD [1–3]. However, international guidelines emphasize that abnormal respiratory sounds such as wheezing and coughing are characteristic clinical signs of COPD, especially – but not exclusively – during an acute exacerbation [1, 4–7]. Since it has also been shown that wheezing patients have more symptoms detected by the COPD Assessment Test (CAT) and have reduced forced expiratory volume in 1 s (FEV_1) with more frequent exacerbations, the identification of wheezing could be important for ascertaining a prognosis in COPD patients [8]. Nonetheless, manual auscultation can only assess the patient’s current state and might, therefore, miss intermittent wheezing episodes. Electronic pulmonary auscultation technology has advanced dramatically in the last few years [9], with different methods now available to detect respiratory sounds. Furthermore, healthcare professionals have access to special computer-based software tools that can analyze respiratory sounds over long-term periods or even several nights [9, 10]. Thus, long-term pulmonary auscultation could provide additional information about the respiratory system by monitoring acute COPD (AE-COPD) exacerbations or by identifying wheezing phenotypes amongst stable COPD patients, who could otherwise not be identified by manual spot-check auscultation.

A recently published trial examined computerized respiratory sounds that were recorded for 20 s in stable versus exacerbated COPD patients and found significant differences between these 2 groups in terms of crackle and wheezing frequencies [11]. However, this analysis did not extend to day/night variability in these patients [11]. Therefore, information about wheezing frequencies in stable and exacerbated COPD patients during the course of the day is still lacking. Moreover, there are inconsistencies in the literature regarding wheezing rates in stable COPD [11, 12]. In addition, the work of Oliveira showed that computer-assisted auscultation can be used to monitor exacerbated patients. It is important to emphasize the short application over 20 s because here also no data about the diurnal course can be made. In this study, it could be shown that inspiratory crackles persist for more than 15 days after exacerbation [13]. The aim of this trial was, therefore, to compare long-term respiratory sounds in stable versus exacerbated COPD patients by means of a software-based analysis of data obtained by an portable acoustic computerized respiratory sound monitor. This trial especially focused on ascertaining any variability in respiratory sounds, such as wheezing and coughing, and used validated questionnaires to correlate this with respiratory symptoms.

Methods

This study protocol was approved by the Institutional Review Board for Human Studies at University of Witten/Herdecke, Germany, and performed in accordance with the ethical standards laid down in the Declaration of Helsinki (last revised in October 2013) [14]. Written informed consent was obtained from all subjects. In addition, a written agreement for the usage of the photographs has been obtained. This study was prospectively registered at the German Clinical Trials Register (DRKS00010715).

Subjects

Adults with stable or severely exacerbated COPD with an FEV_1 of <50% were enrolled between August 2016 and February 2017 at the Department of Pneumology, Cologne-Merheim Hospital, Kliniken der Stadt Köln gGmbH, Witten/Herdecke University Hospital. The diagnosis of COPD was based on criteria established by the GOLD report [1].

COPD patients were classified as stable if they had no clinical signs of exacerbation [1, 15] 4 weeks prior to enrollment. Severely exacerbated patients were defined as having an acute worsening of respiratory symptoms that resulted in hospital admission [1]. Patients with cognitive impairment who are unable to understand the main aspects of the study and, therefore, cannot be informed or those receiving any form of mechanical ventilation were excluded from the study.

Study Design and Measurements

Spirometry (Micro I spirometer CareFusion, Heidelberg, Germany) was performed in each patient prior to long-term auscultation. Subjective evaluation of dyspnea was assessed by 3 different questionnaires (COPD Assessment Test – CAT [16, 17], Borg-dyspnea Questionnaire [18], and Clinical COPD Questionnaire-CCQ [19–21]). Demographic data and routine laboratory measurements (leucocyte, eosinophil granulocyte, pro-brain natriuretic peptide, and C-reactive protein) were documented.

Long-term auscultation was performed by a portable computerized respiratory sound monitor that allows continuous recording of respiratory sounds over a period of 24 h, without restricting free movement (LEOSound®, Heinen + Löwenstein Medizin-Elektronik GmbH, Bad Ems, Germany) as described in previous studies [22]. All measurements were performed as an inpatient. It was possible for the patients to stay outside the room at the ward floor level in order to ensure that the situation was as transferable as possible to everyday life. Two bioacoustic sensors monitored respiratory sounds at the back of the chest, while another sensor was placed next to the trachea with an appropriate adhesive patch (Fig. 1). An additional microphone that is integrated into the monitor was carried around the neck of the patient with a carrying strap in front of the chest at xiphoid level to discriminate respiratory sounds from surrounding sounds. Following the 24-h period, data

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Fig. 1. Long-term computerized acoustic monitor "LEOSound."

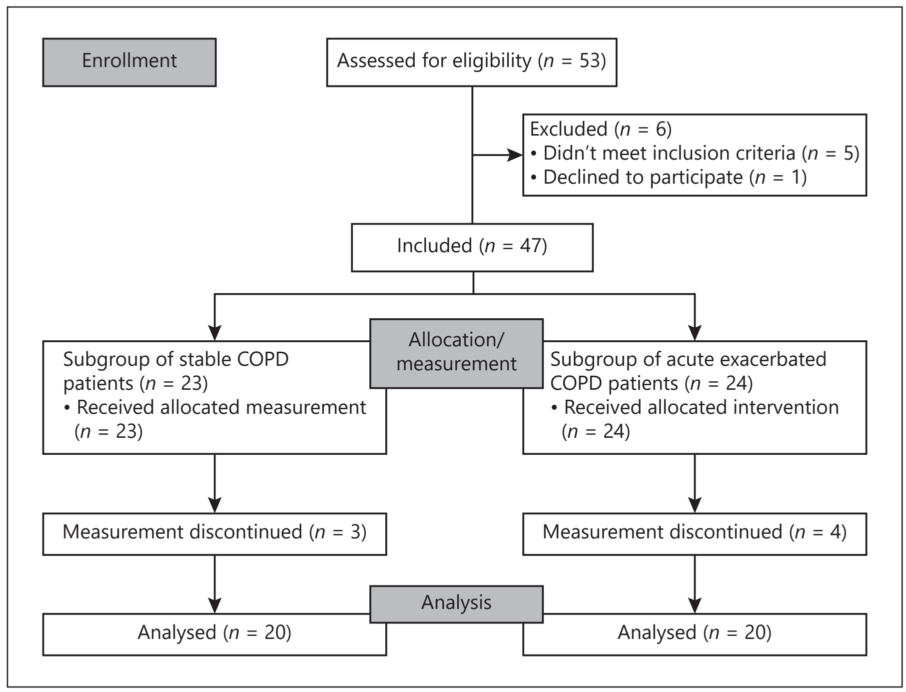

Fig. 2. Flowchart of the study according to consort guideline [27]. COPD, chronic obstructive pulmonary disease.

were evaluated by the corresponding software "LEOSound analyzer" (Löwenstein Medical, Medizin-Elektronik GmbH, Bad Ems, Germany), which automatically calculated both the amount of coughing and wheezing during 30-s sequences (referred to as wheezing and coughing epochs) and respiratory rate [23]. The software-based evaluation of the auscultation data is based on the results of the CORSA and MARS database [24, 25]. A preliminary validation study demonstrated high sensitivity and specificity for the detection of cough and sensitivity of 98% and specificity of 96% for wheezing detection, respectively [26].

Statistics

The trial was conducted as a pilot study because no preliminary data were available. Therefore, a sample size calculation was not performed. Data analysis was descriptive. All statistical calculations were performed using SigmaPlot 12.3 (Systat Software GmbH, Erkrath, Germany) for Windows. Unpaired *t* tests were used for quantitative measurements. Comparison of long-term auscultation between groups was performed using a *t* test for normally distributed data and the Mann-Whitney-Rank-Sum test for data with non-normal distribution. Pearson's correlation test was used for the correlation analysis. Statistical significance was assumed for a *p* value of ≤0.05.

Results

A total of 53 patients were assessed for eligibility. Five patients did not meet the inclusion criteria and were hence excluded from the study. One patient declined to participate and 7 measurements were excluded due to incomplete data. Ultimately, 20 patients were each allocated to the stable COPD and severely exacerbated COPD subgroups, respectively (Fig. 2).

Table 1. Characteristics of the study cohort

	Total, $n = 40$	AECOPD, $n = 20$	Stable, $n = 20$	p value
Male, n (%)	26 (65)	12 (60)	14 (70)	0.523
Age, years	65.4±8.8	65.4±10.0	65.35±7.69	1.000
BMI	24.4±5.3	24.2±6.1	24.6±4.6	0.806
Smoking status (active:previous)	12:28	6:14	6:14	0.930
Smoking index (pack years)	54.5±34.1	49.1±26.5	60.9±41.3	0.297
Pulmonary function testing				
FEV_1, L	0.9±0.4	0.8±0.3	1.0±0.4	0.024
FEV_1, % pred	33.0±15.2	30.2±15.2	35.9±15.1	0.151
FVC, L	2.0±0.7	1.7±0.5	2.4±0.7	<0.001
FVC, %	58.7±20.8	51.3±19.5	66.4±19.8	0.021
FEV_1/FVC, %	46.1±13.9	47.5±15.8	44.6±11.8	0.534
Supplemental oxygen flow rates, L/min ($n = 16$)	2.3±0.8	2.4±0.7	2.1±0.8	0.505
Eosinophil granulocytes, /nL	0.2±0.2	0.1±0.1	0.2±0.2	0.360
Leukocytes, /nL	11.6±6.9	12.5±4.8	10.8±8.5	0.035

Values are given as mean ± standard deviation. n, number; AECOPD, acute exacerbation of COPD; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 2. Symptom scores in stable and exacerbated COPD patients

	Stable COPD Median (IQR)	AECOPD Median (IQR)	p value
CAT	22.5 (19.25–26.5)	33.0 (30.0–35.75)	<0.001
Total CCQ score	3.45 (2.83–4.35)	4.7 (4.5–5.48)	<0.001
Symptom score	3.13 (2.56–3.94)	4.86 (4.06–5.5)	<0.001
Mental state score	3.25 (2.13–4.88)	5.5 (3.5–6)	0.014
Functional state score	3.75 (2.63–4.5)	5.25 (4.25–5.75)	0.004
Borg dyspnea score at rest	4.0 (3.0–5.75)	7.0 (5.25–9.0)	<0.001

Values are given as median with 25 and 75% quartiles (= IQR, interquartile range). COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of COPD.

Demographic data as well as lung function parameters are provided in Table 1. According to the questionnaires used for this study, exacerbated patients were significantly more symptomatic than stable patients (Table 2). Wheezing events were recorded in all the participants of the study with a large interindividual variance. In AECOPD patients, long-term auscultation showed significantly more wheezing epochs than stable COPD patients (591 [IQR: 145–1,645] vs. 152 [IQR: 90–400]; $p = 0.021$) (Fig. 3).

Analysis of cough epochs showed no difference in AECOPD and stable patients (213 [IQR: 140–327] vs. 162 [IQR: 123–243]; $p = 0.256$) (Fig. 4). Analysis of 24-h fluctuations in coughing showed a significant difference in the occurrence of cough epochs between day and night periods (each 12 h), both in AECOPD (146 [IQR: 57–198] vs. 87 [IQR: 35–104]; $p = 0.024$) and stable patients (124 [IQR: 74–171] vs. 42 [IQR: 32–73]; $p < 0.001$). This indicated that coughing occurs predominantly during the day. Coughing epochs showed no significant correlation with lung function parameters, nor with any of the laboratory findings, for example, eosinophil granulocytes ($r = 0.35$, $p = 0.092$) and leukocytes ($r = 0.04$, $p = 0.810$).

However, pairs of variables for cough epochs and CAT score showed a significant, albeit weak, positive correlation ($r = 0.32$, $p = 0.046$). In addition, total score ($r = 0.41$,

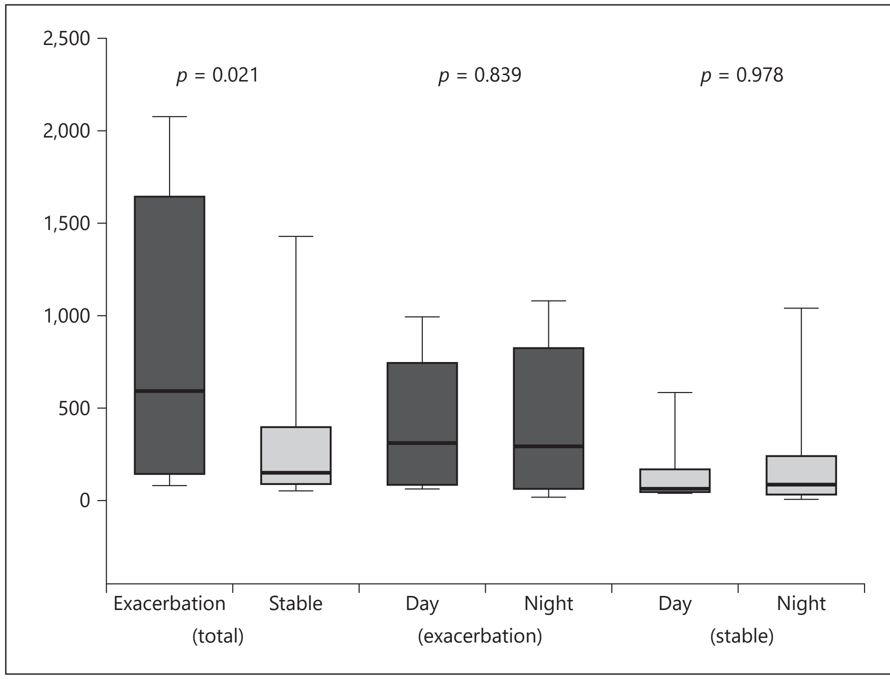

Fig. 3. Differences between mean wheezing epochs in exacerbated versus stable chronic obstructive pulmonary disease patients and differences between day (12 h) and night (12 h) wheezing epochs in both groups. Error bars represent standard errors.

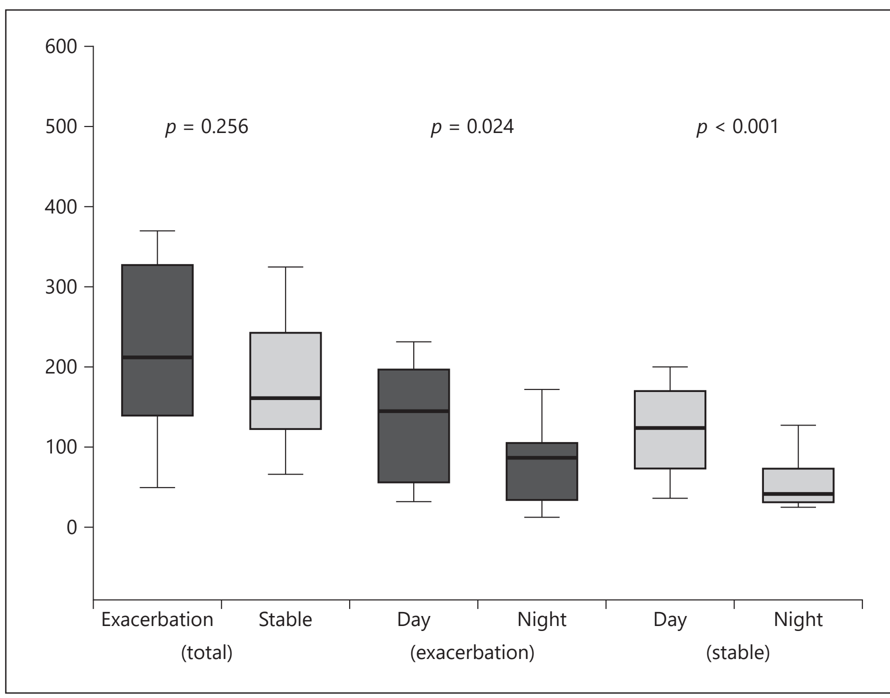

Fig. 4. Differences between mean coughing epochs in exacerbated versus stable chronic obstructive pulmonary disease patients and differences between day (12 h) and night (12 h) coughing epochs in both groups. Error bars represent standard errors.

$p = 0.008$), symptom score ($r = 0.44$, $p = 0.004$), and mental score ($r = 0.34$, $p = 0.033$) of the CCQ were significantly correlated with coughing, as assessed by respiratory sound monitoring. On the other hand, neither the Borg-dyspnea scale ($r = 0.24$, $p = 0.142$) nor the functional score of the CCQ ($r = 0.28$, $p = 0.078$) showed significant correlations with cough epochs. Borg-dyspnea scale scores ($r = 0.19$, $p = 0.250$), CAT scores ($r = 0.22$, $p = 0.172$), and total CCQ score ($r = 0.12$, $p = 0.470$) were not correlated with wheezing frequency. In addition, there was no significant correlation between wheezing frequency and laboratory findings such as eosinophil granu-

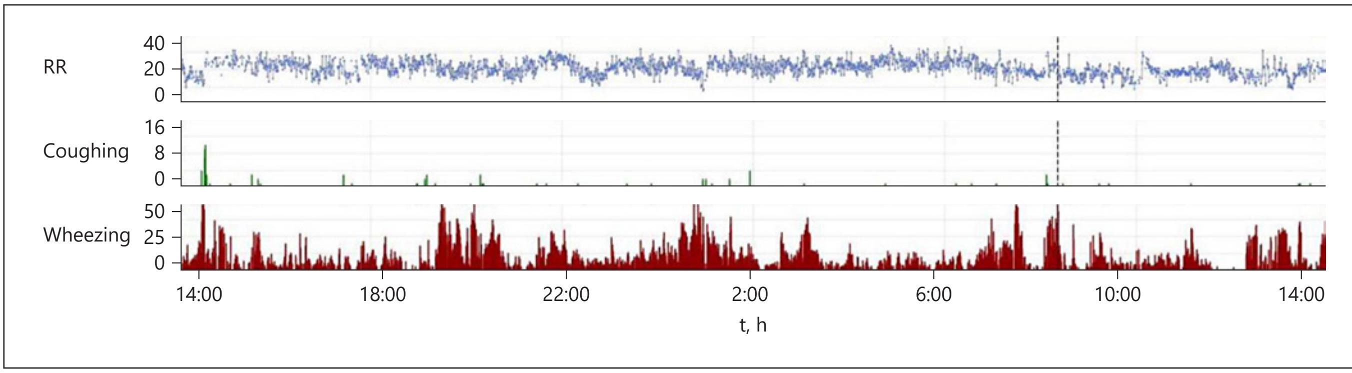

Fig. 5. Case study showing an acute-exacerbated chronic obstructive pulmonary disease patient with severe wheezing.

locytes ($r = -0.19$, $p = 0.323$), or lung function parameters such as FEV_1 (0.23, $p = 0.891$).

Case Report

A 60-year-old acute-exacerbated COPD patient (FEV_1 1.5 L – 45% predicted) was admitted to hospital with severe dyspnea symptoms as a consequence of severe acute exacerbation of COPD. Initially, the patient presented with tachypnea with a breathing rate above 30 breaths per minute. Long-term auscultation data are shown in Figure 5, showing that severe wheezing prevailed during the day and overnight. These findings were also evident during the physical examination.

Discussion

To the best of our knowledge, this is the first study to investigate the pattern of respiratory sounds in acute exacerbated versus stable COPD patients over a 24-h period. The main finding is that severe symptoms such as dyspnea, along with 24-h wheezing, are significantly more frequent in patients with AECOPD than those with stable COPD, as expected. This underscores dyspnea and severe wheezing as important clinical signs of exacerbation that can be reliably detected by long-term auscultation. On the other hand, coughing frequency did not differ between stable and exacerbated COPD patients: this result was unexpected in view of the statements of the GOLD guidelines [1] since coughing was reported to occur more frequently in exacerbated than stable COPD patients.

In addition, a more sophisticated approach to determining the occurrence of wheezing needs to be taken for the following reasons: first, there was a wide range of wheezing epochs in both stable and exacerbated COPD patients. Thus, the assessment of wheezing frequency by long-term auscultation is suggested to be incapable of reliably discriminating between exacerbated and stable COPD patients. Severe wheezing in stable patients may instead indicate a different COPD phenotype or even the existence of comorbidities such as asthma, although such morbidities were not evident in the current cohort. Conversely, interindividual differences in wheezing frequency in exacerbated COPD patients may indicate different underlying causes of exacerbation. However, this notion remains purely speculative for the current study and requires further investigation.

Second, an assessment of symptom severity over 24 h revealed no relationship with the amount of wheezing epochs, which is in contrast to the findings from a short-term auscultation trial in Taiwan [8]. However, the present study cannot be compared to the Taiwanese trial because the latter only investigated the occurrence of wheezing. In particular, dyspnea was not aggravated in patients with frequent wheezing episodes. The etiology of dyspnea is complex, and this particularly holds true for COPD patients [28]. In this regard, the current study has shown that dyspnea is not exclusively related to airway obstruction, which is clinically evidenced by wheezing. Furthermore, wheezing was not related to lung function testing, particularly FEV_1 and FEV_1/FVC. Thus, wheezing is suggested to be a complex clinical finding and may not even reflect real airway obstruction. Finally, wheezing frequency did not correlate with laboratory findings in exacerbated and stable COPD patients, again indicating the complexity of this clinical finding. However, wheezing was clearly more frequent in exacerbated COPD patients. From this data, it can be concluded that wheezing is an interesting phenomenon in COPD patients that is still not fully understood. Therefore, further studies are needed to verify the results of the present study and to more conclusively understand their importance in the clinical assessment of patients, which, in turn, needs to be more sophisticated than what is currently described by the current GOLD guidelines [1].

Moreover, there was no significant day/night variability in terms of the amount of wheezing that took place, even though in individual cases wheezing may predominantly occur overnight. This is supported by recent data demonstrating the occurrence of nocturnal wheezing episodes in stable COPD patients [12]. Conversely, coughing occurs more frequently during the day compared to nighttime. Thus, wheezing and coughing are suggested to represent 2 symptoms in COPD patients which are equally important but differ in regard to their etiology and clinical manifestation, as well as their clinical impact. Moreover, further studies are needed to evaluate these aspects in the long-term follow-up before and after acute exacerbation.

There are some limitations of the current study that need to be addressed. First, although 24-h measurements were performed, treatment was started in exacerbated COPD patients as soon as they were admitted to hospital. This is because it was deemed unethical to postpone exacerbation management in order to perform long-term auscultation on a treatment-naïve basis. Thus, medication and other treatments may have interfered with the results observed in exacerbated patients. Second, moderately exacerbated COPD patients were not included in the study because only patients who were hospitalized for exacerbation management were studied. Thus, the present results are not valid for exacerbated COPD patients who are managed as outpatients. Third, from a methodological point of view, wheezing, and coughing are technically differentiated by sound frequencies. This, however, allows the detection of respiratory sound frequencies, but not their intensity and peculiarity. The importance of these grades needs to be investigated in the future.

In conclusion, auscultation of respiratory sounds needs to undergo a renaissance in clinical routine. Indeed, long-term auscultation is capable of providing meaningful data on both wheezing and coughing frequency. Thereby, the current study has shown that wheezing occurs more frequently in exacerbated COPD patients than stable patients, while coughing does not. On the other hand, coughing is related to symptoms, but wheezing is not. This study, therefore, shows that wheezing and coughing serve as important but different clinical signs in COPD patients. However, if assessed by long-term auscultation over a period of 24 h, the clinical manifestation of wheezing and coughing is more complex than international guidelines suggest.

Acknowledgements

We acknowledge all participants for the effort they devoted to this study. We acknowledge Dr. Sandra Dieni, Ph.D. for helpful comments on the manuscript before submission.

Statement of Ethics

This study protocol was approved by the Institutional Review Board for Human Studies at University of Witten/Herdecke, Germany, and performed in accordance with the ethical standards laid down in the Declaration of Helsinki (last revised in October 2013) [14]. Written informed consent was obtained from all subjects. In addition, a written agreement for the usage of the photographs has been obtained. This study was prospectively registered at the German Clinical Trials Register (DRKS00010715).

Conflict of Interest Statement

The authors S.B.S., W.W., D.M., J.C., and F.S.M. have accepted speaking honoraria and/or travel funding from companies involved in mechanical ventilation. M.P. has no conflicts of interest.

Funding Sources

A research grant including study devices and consumables were provided by Löwenstein Medical (Löwenstein Medical GmbH, Bad Ems, Germany). The authors state that neither the study design, results, interpretation of the findings, nor any other subject discussed in the submitted manuscript was dependent on financial support.

Author Contributions

S.B.S. is the guarantor of the content of the manuscript, including the data and analysis. S.B.S., M.P., and W.W. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, especially including any adverse effects. S.B.S., M.P., W.W., F.S.M., J.C., and D.M. contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work.

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