Overnight registration of crackles, cough and wheezing in patients with interstitial lung disease

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Abstract

Introduction

Clinical symptoms of Diffuse Parenchymal Lung Disease (DPLD) are dyspnoea and dry cough. On auscultation, crackles can be detected at an early stage. The aim of this study was to analyse whether the extent of abnormal breath sounds (crackles, wheezes and coughs) provides an indication of the disease severity and aetiology.

Methodology

In 25 patients with DPLD, an in- hospital overnight recording of physiological and abnormal breath sounds was performed with the LEOSound® monitor. The severity of pulmonary fibrosis was assessed by body plethysmography and GAP score. The perceived breathlessness was assessed by King's Brief Interstitial Lung Disease (K-Bild) questionnaire.

Results

In 16 out of 25 patients, all data were completed in good quality for analysis. Five patients were women (31.3%). The patients' mean age was 65.8 ± 7.3 years, the mean BMI 28.0 ± 2.4 kg/m2. One patient met GAP I criteria, eight patients GAP II and seven patients met GAP III criteria. The findings of eight patients with idiopathic pulmonary fibrosis (IPF) were compared with those of eight patients with secondary interstitial lung disease (ILD). Both, the number of inspiratory crackles and coughs showed significant correlations with the severity of dyspnoea and ILD-pattern. Wheezing occurred in 15 patients, with a median of 25.7 wheezes/h.

Discussion

Overnight long-term auscultation in patients with pulmonary fibrosis proved feasible in our study. Regardless of the aetiology and disease severity, crackles were detected in the recordings of all fibrosis patients, but not cough. Wheezing occurred in 15 out of 16 patients, the significance of which for clinical practice must still remain unclear.

Introduction

More than 200 different interstitial lung diseases (ILD) can be split aetiologically into secondary and idiopathic types (1, 2). Secondary types range from infections, inhaled noxious agents and systemic diseases to drug-induced ILD. If no cause for the fibrotic remodelling processes can be found, the diagnosis of idiopathic interstitial pneumonia (IIP) is made. The idiopathic pulmonary fibrosis (IPF) is the most common form of IIP, accounting for the majority of diagnoses (3, 4). Great progress has been made in the diagnosis and treatment of IPF when diagnosed in an early stage (2, 5). In clinical practice, ILP disease is often considered too late for successful treatment outcome. On average, it takes one to two years from the first symptoms to diagnosis (6, 7).

A gold standard for early diagnosis and follow-up assessment has not been established yet (8, 5). Auscultation is an essential part of the diagnosis of pulmonary fibrosis (9). Typical auscultation findings of interstitial lung processes consist of basal fine crackles (Velcro crackles), which are evident long before radiological abnormalities (10, 11). Fine crackles commonly occur during the inspiration. The sound is probably caused by the sudden reopening of peripheral airways that were compressed during expiration.

Cough is another common symptom of pulmonary fibrosis. Ryerson and colleagues described cough as independent predictor of fibrosis progression (12). Velcro crackles in combination with clinical symptoms such as cough and breathlessness were found in more than 80% of IPF patients (13). Berger and colleagues showed that cough occurred primarily during wake, while during sleep this symptom was reduced significantly (14).

However, auditory auscultation requires considerable experience by the examiner. It's, thus, mildly surprising that interrater reliability studies of breath sound recognition showed at best moderate consensus, regardless of whether the studies were carried out nationally (15), or internationally where the terminology varied also (16, 9). Leuppi et al studied 233 patients with chest problems (17). The comparison of auscultation to detect airway obstruction compared to the results of spirometry provided a sensitivity by lung auscultation of 72.6% and a specificity of 46.3%, which resulted in a negative predictive value of 68% and the positive predictive value of just 51%. These results highlight the importance for the need of validated automatic evaluation.

Computer-assisted auscultation and sound analysis can compensate for individual differences in sound perception and evaluation, as well as limitations of the human auditory system. A detailed recording, processing and assessment of respiratory sounds became possible (18). Recent studies have highlighted the diagnostic potential of sound analysis both in early detection and the severity assessment of pulmonary fibrosis (11, 19, 20).

The aim of the overnight study was to objectify the frequency of inspiratory and expiratory crackles, coughs and wheezes as typical phenomena of pulmonary fibrosis in the context of interstitial lung disease. A standardised recording tool for sound analysis could be useful in both early detection and assessment of disease progression.

Methods

Study design and patients

The protocol was approved by the Marburg Ethics Committees, the institutional review board for human studies, before study initiation (file number study 41/19). The study was performed in accordance with ethical standards the Declaration of Helsinki (October 2013) and written informed consent was obtained from all subjects.

Twenty- five patients with interstitial lung disease (ILD) were included in the study between July end the end of August 2019. The data collection took place at the Schön Klinik in Berchtesgadener Land (Germany), at the Centre for Pneumological Rehabilitation. All patients underwent inpatient treatment for pneumological rehabilitation at the time of acoustic registration. Exclusion criteria were an acute infection, which was confirmed clinically and/or haematologically.

Long-term registration of crackles and coughs

The LEOSound® device (Löwenstein Medical GmbH, Bad Ems, Germany) was used to record and evaluate respiratory as well as ambient sounds. The portable recorder obtained data from four microphones, three body microphones for respiratory sounds and the fourth microphone detecting ambient sounds integrated within the device. Two bioacoustic sensors were fixed over the basal lung segments, an additional sensor placed paratracheally (see Fig. 1).

The recordings were performed overnight to reduce artefacts and to ensure high quality. The registrations took place in the patients' hospital room over a period of about 8 hours (22.00h to 06.00h) considering the individual sleeping time.

LEOSound analyser

The overnight recorded sounds were transferred to the associated software of the LEOSound analyser. A validated automatic evaluation of wheezing, coughing and respiratory rate was performed. The description of the recorder, sensitivity and specificity of the data analysis were described in detail in previous publications (21–23). An audio-visual verification of crackles, coughs and wheezes in 30s epochs complemented the software-based analysis (24).

LSARate software

The LSARate software was used for further evaluation of normal and adventitious respiratory sounds. The programme was developed as a supplement to the LEOSound analyser in order to carry out in-depth sound evaluations that were not automatically analysed. The in-depth scoring used qualifying recording ranges defined by the LEOSound analyser. The evaluation was done audio-visually for each respiratory cycle of the evaluable epochs. The data were evaluated by one trained person to avoid inter-individual differences. Cough and wheezing events were scored, and crackles were divided into inspiratory and expiratory crackles.

Diagnostic procedures

Lung function and diffusing capacity of the lungs for carbon monoxide (DLCO)

A body plethysmography was performed during the hospital stay according to international recommendations of the ATS (American Thoracic Society) and the ERS (European Respiratory Society) (25, 26). Furthermore, the DLCO was determined in patients with sufficiently high inspiratory vital capacity.

GAP Score

The GAP (Gender, Age, Physiology) score was used to describe the severity of interstitial lung disease. The cumulative score was composed of four parameters: gender, age, and the percentages of forced vital capacity (FVC) and DLCO (27).

Questionnaires

King's Brief Interstitial Lung Disease (K-BILD) questionnaire

K-BILD was used to assess the subjective severity of breathlessness (27). K-BILD is a questionnaire specifically designed and validated for patients with ILD to assess health-related quality of life. The higher the score, the better the perceived health-related quality of life (28).

Statistical analysis

The statistical analysis was carried out with the programme IBM SPSS Statistics Version 24 (IBM, Ehningen, Germany). The Kolmogorov-Smirnov test was used for normal distribution of small sample sizes. The test showed deviations from normal distribution for the majority of the variables. The Mann-Whitney U test was used for group comparisons (IPF vs. ILD; GAP 2 vs. GAP 3). The Spearman-Rho correlation coefficient was calculated for correlation analyses. Statistical significance was assumed at $p < 0.05$ (two-sided).

Results

In total, data from 25 patients were collected. The data from 16 patients were included in the study, the remaining 9 patients were excluded due to poor recording quality or background noise. Aetiologically, eight patients showed an idiopathic pulmonary fibrosis (IPF) while the other eight patients presented a secondary interstitial lung disease (ILD). Table 1 provides an overview of the demographic data, the pulmonary function parameters and the results of the questionnaires.

Table 2 gives an overview of the individual results of the acoustic registration, the aetiology of the interstitial lung disease and the GAP stages. All subjects presented inspiratory as well as expiratory crackles. Inspiratory crackles were found in a median of 95.5% of the evaluated epochs. Expiratory

crackles were found in a median of 16.4% of the evaluated epochs. The median number of inspiratory crackles per hour was 1,130 (1,036 - 1,331), for expiratory crackles it was 61.5 (22.3 - 178.4) per hour.

Not all subjects showed cough events during the night. Overall, the number of cough events was low, with a median of 0.43 cough events per hour. In percentage terms, nocturnal cough events were found in only 0.35% of the epochs assessed. Epochs with wheezing could be objectified in 15 of the 16 patients, with a median of 25.7 (3.86 - 35.62) wheezes per hour.

Table 1 Average anthropometric data and clinical test results of the patients (n = 16). Indication of number (percent); All values except the Tiffeneau index (FEV1/FVC) were normally distributed and represented by mean and standard deviation (SD). The Tiffeneau index (FEV1/FVC) (*) was represented by median and the first and third quartiles (Q1, Q3).

Clinical Data	**N = 16**	
Clinical Data		SD (±)
Women (n)	5	31.25%
Men (n)	11	68.75%
Age (years)	65.75	7.25
BMI (kg/m^2)	27.97	2.43
Etiology	n	%
IPF-patients	8	50
ILD-patients	8	50
lung function parameters	mean (* median)	SD (±) (* Q1.Q3)
AF (breath/min)	20.76	2.31
VC In (% of target)	51.86	20.08
FVC (% of target)	56.15	22.36
FEV1 (% of target)	62.84	25.06
FEV1/FVC (actual)	* 90.51	* 84.11 -93 .08
TLC (% of target)	56.22	13.47
Questionnaire	Score	SD (±)
KBILD		
Breathlessness and activity	11.81	5.66
Total score	53.63	13.49
GAP stages	n	%
I (0 -3 points)	1	6.25%
II (4-5 points)	8	50%
III (6-8 points)	7	43.75%
Aetiological distribution	n	%
ILD	8	100
GAP stage I	1	12.5
GAP stage II	3	37.5
GAP stage III	4	50.0

IPF	8	100
GAP stage I	0	0
GAP stage II	5	62.5
GAP stage III	3	37.5

Table 2 Descriptive individual data of the overnight recordings (n = 16). Aetiology (aetio) IPF: Idiopathic pulmonary fibrosis. ILD: secondary interstitial lung disease. GAP: GAP points. IC: Number of inspiratory crackles per hour. EC: expiratory crackles per hour. Coughs: coughs per hour. Wheezes: wheezes per hour. Time: recording duration in hr:min. Epochs: number of 30s epochs scored. Variables presented as mean and standard deviation (SD) or median and the first and third quartile (Q1, Q3).

N = 16		Aetio	GAP	IC	EC	coughs	wheezes	time	Epochs
1	IPF		5	1268	48	0.0	38.0	4:04	487
2	ILD		6	1023	106	0.3	121.9	7:58	955
3	ILD		4	1223	202	0.0	0.0	3:20	401
4	IPF		3	1007	75	0.6	2.9	7:19	878
5	IPF		6	1449	94	1.4	3.2	5:43	686
6	ILD		6	1098	182	0.3	2.1	3:17	394
7	ILD		5	1073	10	7.5	34.4	6:40	800
8	IPF		7	1351	41	6.9	23.7	6:40	799
9	ILD		5	1015	268	0.0	15.7	5:44	688
10	ILD		4	1114	12	0.0	34.8	4:08	496
11	ILD		7	1420	380	0.0	5.4	3:41	441
12	IPF		6	1095	31	4.3	99.9	3:32	424
13	IPF		5	1449	166	2.3	32.0	4:17	514
14	IPF		5	1146	19	1.3	41.8	5:37	674
15	IPF		7	1231	16	0.0	4.1	2:56	352
16	ILD		5	853	38	1.6	27.8	6:49	817
mean,	.		5.4					5:06	612.9
median				1130	61	0.4	25.7		
SD (**±**)	50		1.15					1:38	96.4
Q 1; Q 3				1036; 1331	221; 78	0.0; 2.2	3.9; 35.6		

Sounds in relation to GAP disease severity.

The number of crackles were similar between patients in GAP stages 2 and 3. This was true for both inspiratory and of expiratory crackles. The median number of coughs was 1.6 events/h in patients of GAP stage 2 which was comparable to 1.9 events/h in patients of GAP stage 3.

Table 3 shows the correlations between respiratory sound assessment and the disease severity parameters. The respiratory rate showed a positive correlation to the number of inspiratory crackles (rs = 0.601; p = 0.014). A negative association was found between the breathlessness score of the quality-of-life questionnaire (K-BILD) and the number of inspiratory crackles per hour (rs = -0.545; p = 0.029). The breathlessness score showed also a negative association with the number of cough events per hour (rs= -0.524; p = 0.037).

A significant positive correlation was found between the number of expiratory crackles and the Tiffenau index. (rs = 0.521; p = 0.039). The other lung function parameters did not show any significant correlations with the number of inspiratory or expiratory crackles.

Crackles in relation of disease aetiology

Patients with ILD and IPF showed a similar extent of crackles during the overnight recording (see table 2). Expiratory crackles were seen in 19.4 % of the epochs in IPF patients and in 12.5% (p=0.574) of ILD patients. Cough events were recorded in 0.1% of evaluated epochs in IPF patients, and in 0.52% of evaluated epochs in ILD patients (p = 0.195) only. Inspiratory crackles and cough events were not correlated significantly (rs= -0.057; p = 0.833).

Table 3 Correlation analyses between respiratory sounds and assessment of disease severity parameters. IC: Inspiratory crackles. EC: Expiratory crackles. K-BILD LA K-BILD breathlessness score. IVC Inspiratory vital capacity, FCV: Forced vital capacity. TLC: Total lung capacity. FEV: Forced expiratory volume. Spearman correlation coefficient Rho, (rs), significance level (p). Values in bold indicate significant correlations (p<0.05).

N = 16	K-Bild BS	IVC	FVC	TLC	FEV	Tiffeneau	RF
IC /h							
r_s	-0.545	-0.346	-0.335	-0.229	-0.359	0.374	0.601
p	**0.029**	0.189	0.204	0.393	0.172	0.154	**0.014**
EC / h							
r_s	0.059	-0.124	-0.121	-0.215	-0.121	0.521	0.236
p	0.828	0.648	0.656	0.425	0.656	**0.039**	0.380
cough / h							
r_s	-0.524	-0.178	-0.160	-0.205	-0.103	-0.079	-0.368
p	**0.037**	0.511	0.554	0.445	0.705	0.773	0.161

Discussion

In the present study, respiratory sounds (crackles, coughs and wheezing) were recorded overnight in patients with interstitial lung disease and related to objective and subjective disease severity. To the best of our knowledge, this is the first study to investigate inspiratory and expiratory crackles as well as cough events in patients with pulmonary fibrosis as part of an overnight long-term measurement. In addition, our study is the first to record crackles concurrent with the main symptoms of fibrosis, dyspnoea and cough intensity, and correlate them with the severity parameter GAP score.

Night-time was chosen to reduce extraneous noise and artefacts during the recording. A good recording quality is necessary especially for the quantitative analysis of crackles. Inspiratory crackles, and cough were negatively correlated with the breathlessness score of the K-BILD questionnaire. A relevant difference of cough, wheezes and crackle events related to GAP severity level 2 and 3 could not be detected. The extent of symptoms did not indicate towards the aetiology of the lung disease. Wheezing episodes were detectable in 15 out of the 16 patients. Wheezing in patients with ILD has not been widely described yet and would benefit from more investigation and attention.

In recent years, (semi-) automated detection systems of respiratory sounds and respiratory rate have improved considerably (29–31). While, in contrast, the computer-assisted analysis of respiratory sounds is still in its infancy (32, 33). In patients with chronic interstitial lung disease, auscultation is considered an essential part of diagnostics. Even at an early stage of the disease, fine-bubble crackles are perceptible, which must suggest an interstitial remodelling process of the lung.

The diagnosis of an interstitial lung process is usually made with a considerable time lag. The literature describes that it usually takes more than a year from the onset of the first symptoms until the diagnosis is made (34). The reasons for this are multifactorial (35). From the point of view of therapy efficiency, however, it is sensible and important that the diagnosis phase is significantly shortened. The search for reliable predictors remains unchanged, especially since patients with idiopathic pulmonary fibrosis show a dismal prognosis. Patients with repeated basal fine-bubble crackles that cannot be eliminated by coughing or a few deep breaths should therefore be subjected to further pneumological diagnostics.

There is evidence that the number of crackles assessed during the day is associated with the severity of the disease (19, 36, 20). In our overnight study, however, no increase in crackles was found between patients in GAP severity 2 and 3. Inspiratory crackles, and coughs were correlated with the subjective breathlessness score of the K-BILD quality of life questionnaire. The correlations between respiratory rate and inspiratory crackles and between the Tiffeneau index and expiratory crackles should be further explored in a larger study.

The number of cough events proved to be low, which can be explained by our overnight recording schedule. Berger and colleagues have also been able to show in a 24 hrs study during which they recorded breathing and respiratory sounds in patients with interstitial lung disease that cough frequency decreases significantly during sleep (14). Similar to Berger et al., we found a small number of cough

events in our overnight study, and their severity correlated negatively with the breathlessness score of the K-BILD questionnaire. The breathlessness score was also negatively correlated with the number of inspiratory crackles. The severity of coughs and inspiratory crackles, however, did not show a significant correlation. This could indicate that crackles and coughing contributed to the breathlessness in different ways.

Shortly after the data collection of this study, Berger et al 2021 described wheezing in ILD patients for the first time. They described bronchial obstruction (wheezing) in their patients both during the day and at night. Wheezing tended to be more pronounced at night than during the day. This finding is interesting and could also be confirmed by our recordings. All but one of our 16 patients showed multiple episodes of wheezing. In addition to the circadian influence, increased nocturnal wheezing is most likely due to the lying position. The nocturnal increased wheezing was documented, however, the significance of which for clinical practice must still remain unclear. One explanation for this could be that the interstitial lung remodelling process leads to obstruction of the smaller airways and thus to valve mechanisms.

In our study wheezing did not show any relevant correlations to the marker of subjective quality of life, the lung function parameter or other respiratory sounds recorded. This was for us a slightly surprising result. Larger studies are needed to explore the relevance of wheezing to the entity of ILDs. This kind of larger and also longitudinal studies are facilitated by the help of standardised long-term recordings.

Conclusions

Long-term digital recording of respiratory and respiratory sound is an innovative examination method for assessing the frequency of crackles, cough and wheezing in relation to the disease progression. It allows symptom objectification through a standardised recording procedure, which can then be followed up regularly. Digital recording and analysis of crackles also has potential as a diagnostic tool. An additional audio-visual supervision of the data analyses will be indispensable to ensure the quality of the analysis.

In patients with interstitial lung disease, fine-bubble inspiratory crackles (velcro crackles) were found at an early stage of the disease. About 90% of all recorded crackles were inspiratory sounds. Early diagnosis ensures accelerated therapy, which would be particularly useful in patients with idiopathic pulmonary fibrosis.

Abbreviations

ATS: American Thoracic Society

DLCO: Diffusing capacity of the lungs for carbon monoxide

DPLD: Diffuse Parenchymal Lung Disease

EC: Expiratory crackles

ERS: European Respiratory Society

FEV: Forced expiratory volume

FEV1: Forced expiratory volume in 1 second

FVC: Forced vital capacity

GAP: Gender, Age, Physiology

IC: Inspiratory crackles

IIP: Idiopathic interstitial pneumonia

ILD: Interstitial lung disease

IPF: Idiopathic pulmonary fibrosis

IVC: Inspiratory vital capacity

K-Bild: King's Brief Interstitial Lung Disease questionnaire

Q1: First quartiles

Q3: Third quartiles

SD: Standard deviation

TLC: Total lung capacity

VC: Vital capacity

Declarations

Ethics approval and consent to participate

The protocol was approved by the Marburg Ethics Committees, the institutional review board for human studies, before study initiation (file number study 41/19). The study was performed in accordance with ethical standards the Declaration of Helsinki (October 2013) and written informed consent was obtained from all subjects.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

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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Authors' Contributions

NK, UK, WC, OH, VG, RK, PF and CV made significant contribution conception, study design, execution and acquisition of the data. NK, WC, RC, MD and CV contributed to the analysis and interpretation of the data. RC, UK, VG, WC and CV took part in drafting and revising the article. All authors have critically reviewed the article. All authors agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Figures

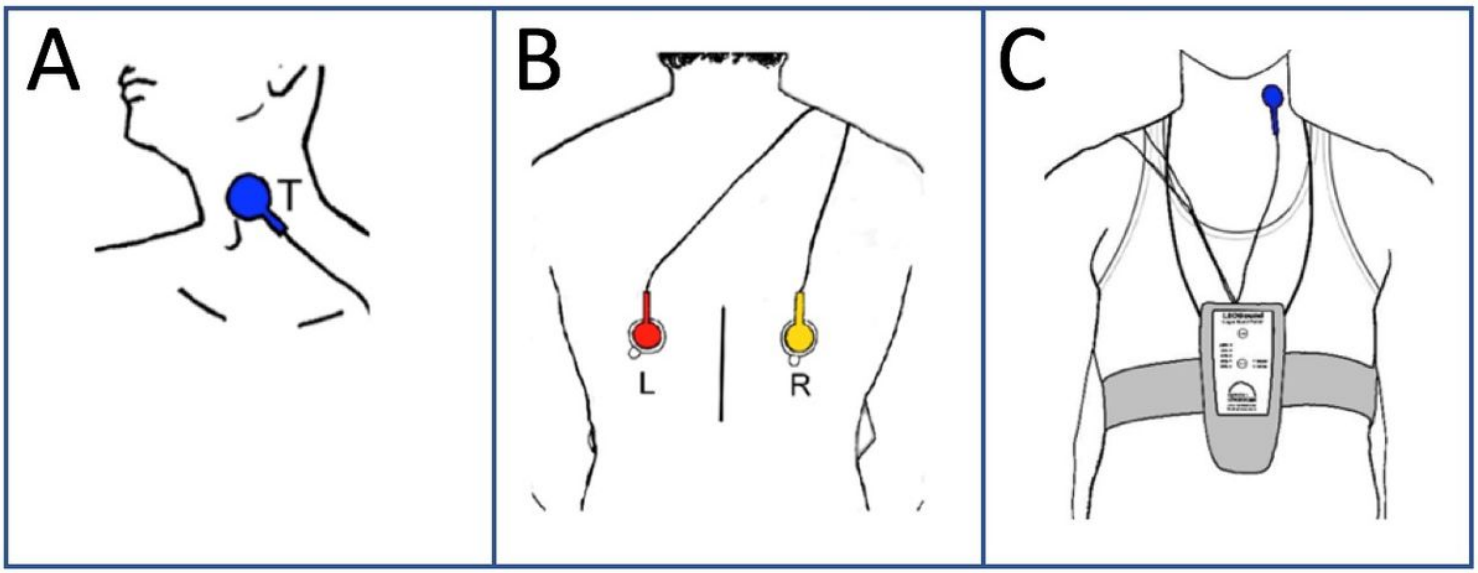

Figure 1

Position of the microphones (LEOSound®, Instructions for Use, 2017). (A) position of the tracheal sensor. (B) position of the left (L) and right (R) bronchial sensors over the basal lung sections. (C) Fixation of the LEOSound system with a chest strap.