

Characteristics of episodic breathlessness as reported by patients with advanced chronic obstructive pulmonary disease and lung cancer: Results of a descriptive cohort study

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Abstract

Background: Episodic breathlessness is one form of refractory breathlessness. Better understanding of the symptom is necessary for effective management.

Aim: The aim was to describe the characteristics of episodic breathlessness in patients with advanced chronic obstructive pulmonary disease or lung cancer.

Design: This is a longitudinal cohort study. Outcomes were assessed monthly by up to 13 telephone interviews: peak severity (modified Borg scale: 0–10), duration, frequency, and timing of breathlessness episodes. Data from each episode were pooled and analyzed using descriptive statistics. Associations between outcomes were explored by correlation coefficients.

Setting/participants: Patients with chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease classification stage III or IV) or primary lung cancer (any stage) were recruited in two inpatient units (internal medicine) and two outpatient clinics in Oldenburg, Germany.

Results: A total of 82 patients (50 chronic obstructive pulmonary disease, 32 lung cancer), mean age (standard deviation) 67 years (8 years) and 36% female, were included reporting on 592 breathlessness episodes (chronic obstructive pulmonary disease: 403, lung cancer: 189). Peak severity was perceived significantly higher in chronic obstructive pulmonary disease patients than in lung cancer patients (mean (standard deviation) Borg scale: 6.2 (2.1) vs 4.2 (1.9); $p < 0.001$). Episodes described by chronic obstructive pulmonary disease patients were longer than those described by lung cancer patients (median (range): 7 min (0–600) vs 5 min (0.3–120), $p = 0.002$). Frequency was similar and most often daily in both groups. Severity and frequency of episodes were correlated in lung cancer patients ($r = 0.324$, $p = 0.009$).

Conclusion: Most breathlessness episodes are short (minutes) and severe with significant differences between chronic obstructive pulmonary disease and lung cancer patients. Effective management strategies are warranted to improve symptom relief and coping.

Keywords

Chronic obstructive pulmonary disease, cohort studies, dyspnea, episodic breathlessness, lung neoplasms, palliative care

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What is already known about the topic?

- Episodic breathlessness is one form of refractory breathlessness. It is a distressing and common symptom in advanced disease, but its characteristics have scarcely been described, yet. Clear information on the characteristics is necessary to enable effective management which is urgently needed for improving patients' quality of life.

What this paper adds?

- It adds information on the characteristics of 592 breathlessness episodes described by patients with advanced chronic obstructive pulmonary disease and lung cancer within a longitudinal cohort study. Breathlessness episodes are mainly described as severe, frequent (daily occurrence), and short (minutes only) with significant differences between the disease groups.

Implications for practice, theory, or policy

- Adequate management and coping strategies that correspond with the symptoms' characteristics, that is, the short duration, are urgently required to improve symptom relief and coping. In addition, the questions, what time span, what change in severity, or what other changes in the characteristics of episodic breathlessness mean a relevant difference for the patient should be addressed in future research.

Introduction

Refractory breathlessness (synonyms dyspnoea, shortness of breath, or difficult breathing) is a complex and distressing symptom in advanced disease that persists despite optimal treatment of the underlying condition.^{1,2} Prevalence is up to 94% or 70% in patients with advanced chronic obstructive pulmonary disease (COPD) or lung cancer (LC), respectively.^{3–6} Experience may be continuous/chronic breathlessness (breathless all the time and at rest or with minimal exertion) or episodic breathlessness.^{7,8} Episodic breathlessness is defined as one form of breathlessness characterized by a severe worsening of breathlessness intensity or unpleasantness beyond usual fluctuations in the patient's perception. Episodes are time-limited (seconds to hours) and occur intermittently, with or without underlying continuous breathlessness. Episodes may be predictable or unpredictable, depending on whether any trigger(s) can be identified [...].⁹

In 2009, Reddy et al.⁸ found that “breakthrough dyspnea” was the most frequent presentation of breathlessness (81%) in a cohort of patients with advanced cancer which described breathlessness episodes as rather short but as interfering with patients' function and activity. Preliminary information on the characteristics of episodic breathlessness has also been explored in a cross-sectional analysis of patients with different chronic diseases.¹⁰ Here, the majority of episodes were described as severe and lasting 10 min or less. Although empirical research on episodic breathlessness has increased over the most recent years, it had previously been rather neglected causing both a lack of understanding and insufficient management options.^{7–12} Therefore, the SYMPATIE cohort study was initiated to describe the courses of refractory breathlessness in patients with advanced COPD and LC. Data on the patterns of overall

breathlessness severity, functional status, distress, and palliative care needs over time have been reported elsewhere.¹³ This article reports on the characteristics of episodic breathlessness and its patterns over the last year of life. Since the consensus definition of episodic breathlessness was established after the start of this study, we relied on the working definition of Reddy et al.:⁸ “a clinically significant aggravation of dyspnea in patients with continuous dyspnea or occurring intermittently.”

Methods**Study design**

This is a prospective, longitudinal cohort study. Ethical approval has been obtained from the State Medical Chamber of Lower Saxony, Hannover, Germany (Bo/20/2009). This article follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline for cohort studies.¹⁴

Participants and setting

Patients aged ≥ 18 years with COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification stage III or IV) or primary LC (small cell LC (SCLC) or non-small cell LC (NSCLC) at any stage) were eligible. Patients received optimal treatment for their underlying condition as judged by the treating physician. Exclusion criteria were non-willingness or non-ability to provide written informed consent, poor physical condition not allowing assessment (judged by the treating physician), cognitive impairment (judged by the treating physician), or non-ability to speak German.

Participants were recruited in two inpatient units (internal medicine) and two outpatient clinics in Oldenburg, Germany, by the treating physicians from February 2010 to April 2011.

Data collection

General information on the data collection procedures has been described in detail elsewhere.¹³ In short, data were collected at study entry (structured face-to-face interview at baseline) and then monthly (4 ± 2 weeks) by up to 13 structured follow-up telephone interviews. Baseline data included socio-demographics, diagnosis, spirometry, medication, functional status (Karnofsky Performance Status (KPS) scale¹⁵), and comorbidities (Charlson Comorbidity Index (CCI)¹⁶).

In each interview, patients were asked whether episodic breathlessness had occurred. To explore the characteristics of episodic breathlessness, the following patient reported outcomes were assessed by two trained researchers. Peak severity was assessed by the modified Borg scale.^{17,18} Patients were asked to quantify the duration of episodes (in seconds, minutes, or hours). Frequency was evaluated by the categories: per day, per week, or less than per week, or alternatively: (1) 1–3/day, (2) 4–6/day, (3) 7–10/day, (4) 11–20/day, and (5) >20/day. Finally, patients were asked for the timing of their breathlessness episodes (during the day, at night, or both).

Analysis

Data were subsequently entered in a person-period dataset using EpiData 3.1 which provides programmed data entry and automatic error detection features. If patients used ranges (e.g. 5–10 min for the duration of episodes), means of the ranges were calculated and entered in the dataset. Electronic data were checked for correctness by a second researcher, and the final data were cleaned by a third researcher (screening for incomplete, implausible, or missing data and their correction, where appropriate). Analysis was conducted using SPSS Statistical Software for Windows, version 21 (SPSS, Inc.). We did not use imputation to replace missing data as we considered this inappropriate for our data.

For this analysis, the main outcomes were peak severity (modified Borg scale^{17,18}), duration, frequency, and timing of breathlessness episodes. Therefore, only patients suffering from breathlessness episodes at least once during the study period were included in the analysis.

Descriptive analysis was conducted for baseline and longitudinal data (percentage, mean, standard deviation (SD), 95% confidence interval (CI), median, and range), comparing all outcomes between the disease groups. According to the Borg scale descriptions, breathlessness was defined as severe for scores ≥ 5 .^{17,18} Categories for

the duration and frequency were created post hoc based on the data.

The main outcomes were analyzed as follows:

1. The main analysis was based on the unit “breathlessness episode.” For this, data on the outcomes of each episode described during any interview over the study time were pooled and analyzed using descriptive statistics. To consider repeated measurement in individuals, the patient was also considered as unit of analysis. By calculating means or medians for the available data on the characteristics of episodes per patient, an average profile of the breathlessness episodes per patient was achieved. The aggregated data were also analyzed using descriptive statistics.
2. The relationship between the characteristics of episodes was explored using correlation analysis. First, bivariate correlation coefficients (r) were calculated for each patient over each point of measurement; second, means of these values were computed separately for COPD and LC patients. One-sample t-tests were used to test the difference of these values versus 0; two-sample t-test was used to compare outcomes between the disease groups.
3. For patients who died, the patterns of outcomes were explored over the last 365 days before death.

To test for differences in continuous data, independent t-test or Mann–Whitney U-test was applied as appropriate (approximately normally or not normally distributed data, respectively). Categorical data were compared using chi-square test or Fisher’s exact test, as appropriate.

Because this study was of descriptive rather than confirmatory character, the level of significance was set to $p < 0.05$, two-sided for all analyses.

Results

Study population

A total of 82 (50 COPD, 32 LC) patients were included in the analysis (Table 1). Median study duration tended to be longer in COPD than in LC patients (178 days (range=1–393 days) vs 151 days (0–386 days), $p=0.071$). A total of 34 patients (42%; 26 COPD, 8 LC) completed maximum data collection of 13 interviews (for numbers per follow-up interview, see Table 2 (online supplement)). A total of 13 patients (3 COPD, 10 LC) died during the data collection phase (total deaths: 8 COPD and 23 LC patients before final subsequent collection (5 September 2012), see also Weingärtner et al.¹³). A total of 35 patients (21 COPD, 14 LC) did not finish the 12-month period of data collection due to other reasons than death (15 worsening of medical

Table 1. Patient characteristics.

Number of patients	Total	COPD		LC ^a		Difference (<i>p</i> -value)
	n (%)	n (%)		n (%)		
	82 (100)	50 (100)		32 (100)		
Socio-demographic details						
Age (years), mean (SD)	67.2 (7.8)	67.7 (7.6)		66.4 (8.2)		0.472
Female, n (%)	30 (37)	21 (42)		9 (28)		0.203
Smoking (MD=2)						
Never	7 (9)	3 (6)		4 (13)		0.317
Former	63 (77)	39 (78)		24 (75)		
Still	10 (12)	8 (16)		2 (6)		
Clinical characteristics						
CCI, median (range)	1.0 (0–11)	1.0 (0–10)		2.0 (0–11)		0.150
KPS, mean (SD)	73.5 (14.9)	69.4 (14.3)		80.0 (13.7)		0.001
Suppl. Oxygen, n (%)	31 (38)	27 (54)		4 (13)		<0.001
Disease-specific details						
		GOLD	n (%)	TNM	n (%)	
		III	20 (40)	IIIa	4 (12.5)	
		IV	30 (60)	IIIb	3 (9.4)	
				IV	22 (68.7)	
				MD	3 (9.4)	
		FEV ₁ %	Mean (SD)	Metastases ^b	n	
			32.1 (11.6)	Lymph node	11	
				Pulmonary	15	
				Cerebral	4	
				Liver	4	
				Bone	13	
				Pleura	5	

CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; KPS: Karnofsky Performance Status; LC: lung cancer; MD: missing data; SD: standard deviation; TNM: tumor–nodes–metastases classification; SCLC: small cell lung cancer; NSCLC: non–small cell lung cancer.

Bold *p*-values indicate statistical significance.

^aSCLC: n=4, NSCLC: n=28; two lung cancer patients also had a diagnosis of COPD.

^bMultiple answers possible.

condition and/or hospital stay, 13 unavailable for more than 6 weeks, 4 loss of interest, 2 illness or death of relative, and 1 “feeling too healthy”).¹³

Characteristics of all breathlessness episodes described

Episodic breathlessness was reported at all interviews in 58 (71%) patients. Occurrence at all interviews was more often reported in COPD compared to LC patients (40 (80%) vs 18 (56%); *p*=0.021). In each interview over time, 81%–97% of patients with COPD and 75%–88% of patients with LC reported breathlessness episodes (data per interview provided in Table 2 (online supplement)).

In total, the cohort reported 592 breathlessness episodes (COPD: 403, LC: 189) during the study (Table 3). One COPD patient reported the occurrence of breathlessness episodes only once during data collection but was not able to describe its characteristics. Similarly, two LC patients could not determine the frequency of their episodes. Peak severity of episodes described by COPD patients was higher than in LC patients (*p*<0.001), and correspondingly, severe scores (≥5) were more often reported in COPD patients (*p*<0.001).

Median duration of episodes described by COPD patients was 2 min longer than of episodes reported by LC patients (*p*=0.002; Table 3). Although most episodes were described as lasting 20 min or less, some episodes were

Table 3. Characteristics of breathlessness episodes as described by the cohort.

	Total	COPD	LC	Difference (p-value)
	n (%)	n (%)	n (%)	
Total number of episodes, n (%)	592 (100)	403 (100)	189 (100)	<0.001
Peak severity ^a , valid n	589	400	189	
Mean (SD) Borg score	5.6 (2.3)	6.2 (2.1)	4.2 (1.9)	<0.001
Severe scores (≥ 5), n (%)	374 (63.5)	311 (77.8)	63 (33.3)	<0.001
Average duration ^b , valid n	576	392	184	
Median (range), min	5.0 (0.02–600)	7.0 (0.02–600)	5.0 (0.3–120)	0.002
≤ 5 min, n (%) cumulative	303 (52.6)	188 (50.0)	115 (62.5)	0.001
≤ 10 min, n (%) cumulative	414 (71.9)	267 (68.1)	147 (79.9)	0.003
≤ 20 min, n (%) cumulative	515 (89.4)	339 (86.5)	176 (95.7)	0.001
≤ 30 min, n (%) cumulative	546 (94.8)	366 (93.4)	180 (97.8)	0.025
≤ 60 min, n (%) cumulative	563 (97.7)	381 (97.2)	182 (98.9)	0.196
≤ 120 min, n (%) cumulative	569 (98.8)	385 (98.2)	184 (100.0)	0.103
≤ 600 min, n (%) cumulative	576 (100.0)	392 (100.0)	184 (100.0)	–
Frequency ^{c,d} , valid n	546	373	173	
>3 per day	123 (22.5)	90 (24.1)	33 (19.1)	0.342
1–3 per day	274 (50.2)	178 (47.7)	96 (55.5)	
Weekly	144 (26.4)	102 (27.3)	42 (24.3)	
Less than weekly	5 (0.9)	3 (0.8)	2 (1.2)	
Timing, valid n (%)	589	400	189	
Solely during the day	479 (81.3)	296 (74.0)	183 (96.8)	<0.001
At night only or both	110 (18.7)	104 (26.0)	6 (3.2)	

COPD: chronic obstructive pulmonary disease; LC: lung cancer; MD: missing data; SD: standard deviation.

Numbers and percentages are presented if not stated otherwise. Bold p-values indicate statistical significance.

^aMD=3.

^bDetermination of duration was not possible for patients in 12 episodes (COPD 7, LC 5); MD=4.

^cOriginal categories were summed as presented.

^dDetermination of frequency was not possible for patients in 14 episodes (COPD 8, LC 6); MD=32.

reported as lasting only a few seconds, and some episodes were said to last for hours (Figure 1).

Summed categories for the frequency of episodes were created based on the data (Table 3). Frequency of episodes was similar in both groups and most often described as being a daily occurrence and even several times a day (397 (73%); COPD: 268 (72%), LC: 129 (75%); $p=0.507$).

Most episodes occurred during the day. Nighttime episodes occurred more often in the COPD group than in the LC group (Table 3).

Based on patients as unit of analysis, the results on the characteristics of breathlessness episodes did not differ from these findings. There was great variation in the characteristics both between and within the individuals at different assessment points, respectively.

Backward analysis: patterns of episodes described in the last year of life

A total of 30 (8 COPD, 22 LC) of the 31 patients who died before subsequent assessment provided data within their last 365 days of life. Episodes were predominantly described as lasting less than 30 min in the COPD group

and less than 20 min in the LC group (Figure 2(a)). Of note, breathlessness episodes lasting longer than 30 min were described only four times by LC patients who died and predominantly occurred when they were in their last days of life. Moreover, these episodes were all described as severe (≥ 5) (Figure 2(b)). Although the descriptions of episodes in COPD patients were on average more severe than those of LC patients, severity differed strongly between the single episodes described within both disease groups (Figure 2(b)).

Correlation analysis

The peak severity was positively correlated with the frequency of episodes described by LC patients (mean $r=0.324$, $p=0.009$; p difference=0.028) but not COPD patients (Table 4). No further associations between the characteristics were statistically significant.

Discussion

This is the first study comparing longitudinal data on the self-assessed characteristics of episodic breathlessness in

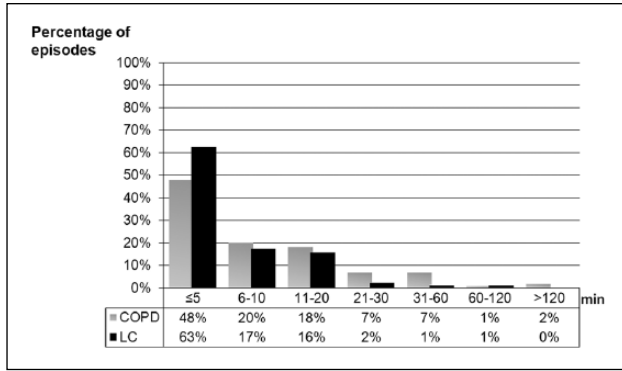


Figure 1. Distribution of the average duration of breathlessness episodes. The graph shows the percentage of breathlessness episodes per duration (minutes) described by patients in each disease group. COPD: chronic obstructive pulmonary disease; LC: lung cancer.

Table 4. Mean Pearson correlations of the characteristics of breathlessness episodes described.

	COPD	<i>p</i> ^a	LC	<i>p</i> ^a	<i>p</i> difference ^b
Peak severity— duration	-0.032	0.679	0.057	0.653	0.527
Peak severity— frequency	0.011	0.892	0.324	0.009	0.028
Duration— frequency	-0.037	0.630	-0.055	0.636	0.900

COPD: chronic obstructive pulmonary disease; LC: lung cancer.

Bold *p*-values indicate statistical significance.

^aDifference to 0 (one-sample *t*-test, $\alpha=0.05$).

^bDifference between COPD and LC patients (two-sample *t*-test, $\alpha=0.05$).

patients with different underlying diseases. Patients with COPD perceived breathlessness episodes as severe, and peak severity was significantly higher than that described by LC patients. Breathlessness episodes were predominantly described as short in both groups, that is, lasting only minutes. However, the duration of episodes described by COPD patients was slightly longer compared to episodes described by LC patients. Episodes occurred mainly daily in both groups although there was fluctuation between groups and within individual patients.

These findings underline the burden of episodic breathlessness (high severity and frequency) and the challenge regarding its management (short duration). Disease-specific, needs-based care for patients with COPD and LC suffering from episodic breathlessness is needed, and effective management and coping options are still warranted.

Interpretation of main findings

Although the assessment of duration, severity, and frequency must be considered as explorative and the patients’ retrospective assessment of their breathlessness episodes may be subject to recall bias, our results are in line with previous cross-sectional research and provide important information on the characteristic manifestation of this distressing symptom.^{8,10,11,19,20} In another study by our group evaluating a mixed population of 129 patients with COPD, LC, chronic heart failure (CHF), or motor neuron disease (MND), the duration of episodes described was 10 or 20 min maximal in 75% or 91%, respectively.¹⁰ In the observational study of Reddy et al.,⁸ 50 of 57 (87%) cancer patients reported episodes of 10 min maximum. In two qualitative studies, LC patients predominantly reported the duration of 5–15 min.^{20,21} Finally, Maddocks et al.¹⁹ found a median recovery time of only 4 min particularly for exercise-induced breathlessness in LC patients based on real-time measurement. These data support our findings on both the short duration of episodes in general and the significantly shorter duration in the cancer compared to the non-cancer group.

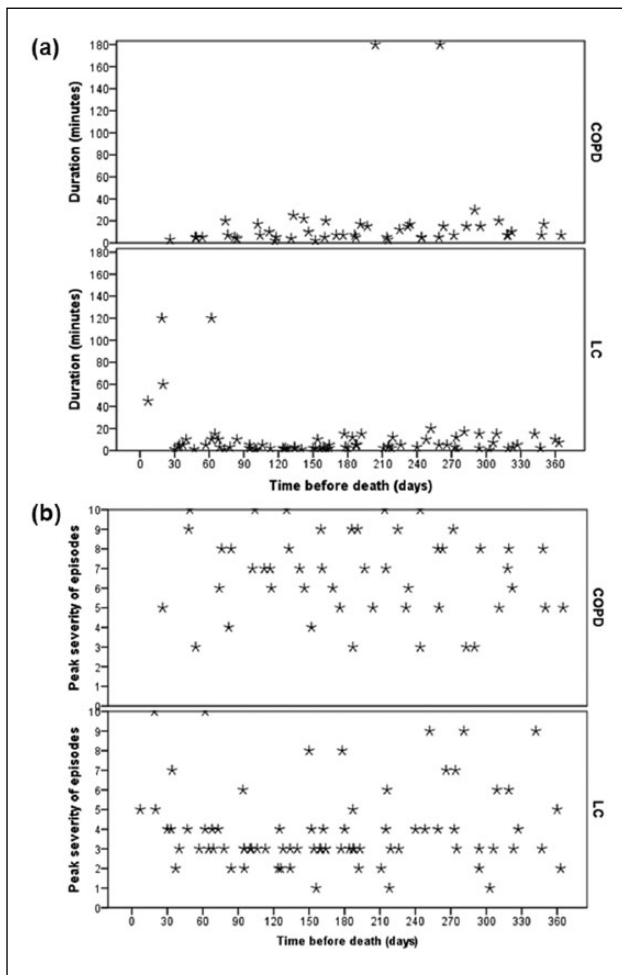


Figure 2. (a) The duration (minutes) of breathlessness episodes as described by decedents in each disease group within their last 365 days of life. (b) The severity of breathlessness episodes (modified Borg scale: 0–10) as described by decedents in each disease group within their last 365 days of life. COPD: chronic obstructive pulmonary disease; LC: lung cancer.

The high severity of breathlessness episodes in COPD patients is supported by the findings of Heinzer et al.,²² reporting a mean severity of 7/10 (Borg) in 41 COPD inpatients. Reddy et al.⁸ found a median severity of 5/10 (Numerical Rating Scale (NRS)) for cancer patients, which is slightly higher than in our cohort particularly with LC patients. However, the differences are small and may be due to the different measurement instruments.

The revealed significant differences between COPD and LC patients' episodes are in contrast to a previous study by our group comparing the characteristics of breathlessness episodes between diverse disease groups.¹⁰ Considering the higher number of episodes analyzed in this study and the results of the studies on single entities mentioned above, it may be possible that the breathlessness episodes experienced by COPD patients differ from those experienced in LC patients. However, there is yet no evidence about the relevance of these differences in the characteristics of episodic breathlessness for the patients.

Implications for clinical practice

Today, the differentiation of chronic and breakthrough pain is well established in clinical practice and substantially considered for effective management.^{23–26} Similarly, the differentiation of continuous and episodic breathlessness is increasingly recognized as being relevant for effective symptom relief.^{7,27} Based on our findings, breathlessness episodes might be even shorter than pain episodes which last a median duration of 30–60 min.^{26,28,29}

Currently, immediate-released morphine (IRM) is the standard pharmacological treatment for episodic breathlessness. In studies of pain, IRM showed an onset of action after 20–30 min.³⁰ Our findings indicate that the duration of the vast majority of breathlessness episodes is much shorter, and therefore, IRM might be inadequate. However, the data of onset of action for IRM come from pain studies, and the onset of action for breathlessness is yet unknown. An ongoing study by our group is currently evaluating the onset of action of opioids (including IRM) for breathlessness and will hopefully provide this relevant information (EudraCT Number: 2011-005797-32). Moreover, even fast-acting drugs, for example, fentanyl, might not effectively relieve these short breathlessness episodes. However, these drugs may still be a preventive option for predictable episodes, for example, exertion-induced breathlessness.

Implications for future research

One major finding of this study is the predominantly short duration of episodes of breathlessness which poses a challenge for its management and particularly for pharmacological options as the onset of action of most drugs in use takes longer than the majority of episodes last.

The recently established categorization into predictable or unpredictable episodes, depending on whether any trigger(s) can be identified (e.g. exertion, emotions, or external factors), might be an explanation for the significant variance within and between patients' perceptions of breathlessness episodes in this study.^{7,9} The distinction between episodic breathlessness categories needs to be assessed in future research.

Existing studies suggest substantial effects of episodic breathlessness on the quality of life of both patients and their relatives.^{8,12,31} However, the most relevant characteristics (severity, frequency, duration, predictability, and concurring emotions) which affect patients most and should be top priority for management strategies remain unknown and need to be determined—including the minimal clinical important differences.

Clinical research evaluating the effectiveness of fast-acting drugs and non-pharmacological options, such as psychological and cognitive strategies for the palliation of episodic breathlessness, is still rare. Moreover, data on coping strategies are scarce and should be assessed by affected patients and relatives based on the established international definition and categorization.⁹

Clarifying the consequences of the symptom and related needs will further facilitate improvement in health-care provision and patients' quality of life. Finally, it seems relevant to examine whether different manifestations of breathlessness are related to death and whether specific treatments or care are required with nearing death or, contrarily, should then be omitted.

Limitations

The number of patients included was smaller than originally planned, and several participants dropped out due to a deterioration of their overall health condition. This confirms the advanced stage of diseases but limited the use of more in-depth statistical analysis. The results and statistical tests have to be interpreted solely descriptively. The overall condition and cognitive status of patients were evaluated as criteria for inclusion by the treating physician without the use of objective measures, which might be judged as a limitation for replication.

There is a possibility of recall bias since patients reported their episodes retrospectively. However, recent data support our findings on the characteristics of breathlessness episodes.^{8,10,11,19}

Due to the small number of patients providing data for each point in time before death, we decided to conduct backward analysis only exploratively and without statistical testing. In particular, the patterns of the characteristics shortly before death should be addressed further in future research.

Patients had received optimal treatment of their underlying condition at baseline. However, this was not assessed at follow-ups. Similarly, concomitant medication were

allowed but only assessed at baseline and not considered for the analysis. The impact of both treatment and additional medications on episodic breathlessness should be addressed in future research.

Finally, after conducting this study, the amended definition and categorization of episodic breathlessness have been established.⁹ However, the new definition does not conflict but only further specifies the previous definition of Reddy et al.⁸

Conclusion

Episodes of breathlessness perceived by patients with COPD differ from episodes perceived by patients with LC by a higher severity and longer duration; however, duration was short (minutes) in both disease groups. More research is required to describe and compare the specific causes, care needs, and therapeutic targets of patients with predictable or unpredictable episodes of breathlessness and differences between disease groups, respectively.

Since the onset of action of most drugs in use is longer than breathlessness episodes usually last, effective non-pharmacological management alternatives that adapt to the short duration of episodes and coping strategies are urgently warranted in order to relieve symptom suffering and to improve quality of life in affected patients.

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Declaration of conflicting interests

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