Chronobiology in breathlessness across 24 h in people with persistent breathlessness

Received: 23 April 2024
Accepted: 4 Aug 2024

To the Editor:

Breathlessness is associated with impaired quality of life, comorbidities, more frequent hospitalisation and premature mortality. Breathlessness leads to people avoiding things that trigger their breathlessness, such as physical activity [1–3].

The intensity of breathlessness varies over time both as exacerbations of the underlying aetiologies and among individuals with "stable" disease [4]. A definition of clinically important *variability* of breathlessness is lacking, and reports of daily symptom variability differ substantially between studies [4–6]. Approximately 44% experience symptom variability during the day [4–6]. Breathlessness intensity is highest on waking, continuing through people's morning routines and tapering later in the day [4]. Daytime symptoms are associated with poorer quality of life and higher anxiety [4, 7–10].

In this secondary analysis derived from the Relating Experienced To Recalled breathlessness Observational study (RETRO) [11, 12] we evaluate variability of experienced breathlessness intensity over each 24-h period, linking this to self-reported physical activity and exertional breathlessness.

Participants were recruited between March 2018 and April 2020 through clinical visits with patients from primary care facilities and pulmonary clinics in Lund, Karlskrona and Örebro in Sweden. Eligibility criteria, baseline questionnaires and main assessments were collected using an application installed on the participant's smartphones using mobile ecological momentary assessment methodology. The study design is detailed elsewhere [12].

We included physically (no expected need for hospital admission within 1 week) and mentally stable individuals aged ⩾18 years with self-reported average breathlessness intensity during the last two weeks of ⩾3 on a 0–10 numerical rating scale (NRS), which was not caused by an acute infection [12]. Participants provided written informed consent, and the regional ethical review board at Lund University approved the study (DNr 2017/149).

Physical activity was assessed using the Grimby–Frändin scale, which is validated and frequently used in Swedish speaking contexts [13]. The scale consists of categories one (hardly any activity), two (light physical activity), three (moderate physical activity around 3 h per week), four (moderate physical activity for more than 4 h per week), five (moderate exercise or heavy physical activity) or six (strenuous activity several times per week). The level of activity was dichotomised as "inactive" (ratings 1 and 2) or "active" (ratings 3–6), as previously used [13]. Exertional breathlessness was assessed using the modified Medical Research Council (mMRC) breathlessness scale [14] and dichotomised as 0–2 *versus* 3–4.

The momentary breathlessness (0–10 NRS) was assessed each waking hour for 7 days [15]. Nightly breathlessness was recalled each morning for the preceding night. Mean breathlessness intensity compared using ANOVA between activity and mMRC groups. Marginal means and corresponding 95% confidence intervals for each waking hour of the day were calculated using a multi-level, mixed-effects linear regression analysis. The results were visualised using plots of margins. Hours with very few responses (hours 3, 4, 22 and 23) were excluded.

Shareable abstract (@ERSpublications)
Breathlessness has relatively low variability in daily life, with a gradual decline throughout the day after a morning peak. People who were inactive, and those with more intense breathlessness limiting their exertion had higher levels of breathlessness. https://bit.ly/3WVbCrF

Cite this article as: Sandberg J, Sundh J, Anderberg P, *et al*. Chronobiology in breathlessness across 24 h in people with persistent breathlessness. *ERJ Open Res* 2025; 11: 00417-2024 [DOI: 10.1183/23120541.00417-2024].

A total of 114 people downloaded the mobile phone application, of whom 30 were excluded due to errors in data collection (n=1), insufficient number of breathlessness ratings (n=10), missing baseline (n=5) or other exclusion criteria (n=14). 84 participants were included in the study, generating 6132 measurements of *breathlessness now* (mean 72.1 per participant) during the 7-day study period. 1936 prompt-responses were missing giving a compliance rate of 76.0%. In the final cohort, 60% (n=51) were female, mean±SD age was 64.6±12.7 years, and body mass index was 28.2±5.3 $kg \cdot m^{-2}$). Baseline mMRC was rated 0 by 2% (n=2), 1 by 38% (n=32), 2 by 26% (n=22) and 3–4 by 34% (n=29). Underlying conditions were assessed by self-report from a pre-defined list, allowing as many responses as applied. The most frequent responses were: COPD (40%); asthma (39%); cancer (13%); atrial fibrillation (12%); and heart failure (8%). 64% reported previous smoking and 6% were current regular/occasional smokers. 24 (28%) individuals were labelled "inactive", while the rest were "active".

As shown in figure 1, daytime *breathlessness now* was relatively stable with higher levels during the morning hours until midday, with a gradual decline throughout the afternoon and evening (coefficient for total change throughout the day: −0.03, 95% CI −0.04 to −0.02) (figure 1a).

Mean±SD daytime *breathlessness now* was 3.6±1.9 in the inactive group and 2.6±1.6 in the active (p=0.02). The nightly mean±SD was 2.7±2.3 for the inactive and 1.6±1.8 (p=0.02) for the active group. The differences between groups were not statistically significant in the regression analysis (figure 1b).

Individuals with mMRC grades 3–4 had mean±SD daytime breathlessness intensity of 3.9±1.8 compared to 2.3±1.4 in those with mMRC 0–2 (p<0.01). Corresponding numbers for nighttime were 2.8±2.2 *versus* 1.4±1.7 (p=0.02). The difference remained in regression analysis (figure 1c). Sensitivity analysis of only individuals with either COPD or asthma showed no large differences, but groups were small.

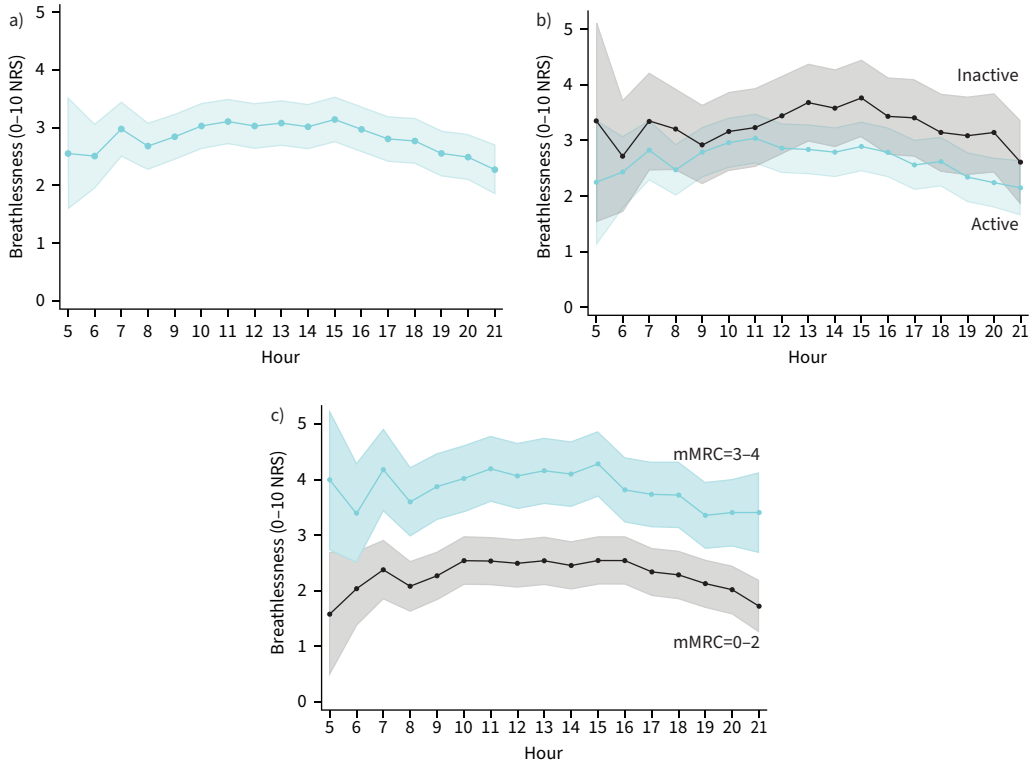

FIGURE 1 Plot of marginal means for the level of momentarily assessed daytime breathlessness (a) for each hour of the day for 7 days, with corresponding 95% confidence intervals calculated by multilevel mixed-effects linear regression. Subgroup analysis on individuals reporting being active and inactive (b) and individuals reporting high and low exertional breathlessness on the modified Medical Research Council (mMRC) scale (c). The total number of recordings in the models is 6132. NRS: numerical rating scale; Inactive: individuals rating 1 or 2 on the Grimby–Frändin scale of physical activity; Active: individuals rating 3–6 on the Grimby–Frändin scale of physical activity. Inactive: n=24; Active: n=61; mMRC 0–2: n=56; mMRC 3–4: n=29.

The main findings of this study include low variability of breathlessness throughout the day with minor differences between self-reported activity groups. We also found that different ratings on mMRC corresponded to different levels of momentarily assessed *breathlessness now* across the day.

The findings presented here may relate to the Grimby–Frändin activity scale asking about the amount of physical activities performed. In contrast, the mMRC asks if breathlessness would arise if the individuals were to perform actions. The breathlessness levels among the "inactive" individuals in this population might therefore be underestimated. The inactive group would likely have higher breathlessness ratings at a standardised level of exertion. This might suggest a mechanism for the so-called invisibility of breathlessness: it is not seen because patients reduce their activities to avoid it [3]. The level of statistical power might also be too low to detect a significant difference between the groups.

Our findings also suggest that the mMRC reflects *breathlessness now* in daily life better than previously thought. This could be important for clinical care and more studies using real life data are needed.

There was a tendency for lower *breathlessness now* levels in the later afternoon and evening, which is in accord with previous reports. This is probably explained by higher activity in the morning and lower levels of activity as the day progress. Nighttime symptoms were generally lower than the daytime symptoms but still present. However, the nighttime symptoms are assessed using a recall (for obvious reasons), limiting any comparisons with the daytime ratings.

Implications of these findings include that potential medications targeting breathlessness would need to be long-acting in order to reduce symptoms in the morning hours. The role of fast-acting agents to help facilitate activity in people with persisting breathlessness is still being explored. The findings also add to the understanding of the connection between ratings of breathlessness and lived experience, which is critical for improving healthcare communication and patient-centredness.

Strengths of this study include the large number of measurements recorded using a new and reliable method which allows for immediate assessment of *breathlessness now* throughout everyday life. Limitations include the fact that activity was not objectively measured but self-reported although intra-rater reliability was good.

In conclusion, our study shows levels of *breathlessness now* have relatively low chrono-variability in daily life, with a gradual decline throughout the day after a morning peak. People who were inactive, and those with more intense breathlessness limiting their exertion had higher levels of *breathlessness now*.

Jacob Sandberg[1,2], **Josefin Sundh**[3], **Peter Anderberg**[1,4], **Miriam J. Johnson**[4], **David C. Currow**[5,6] **and Magnus Ekström**[2]

[1]Department of Health, Blekinge Institute of Technology, Karlskrona, Sweden. [2]Department of Clinical Sciences, Division of Respiratory Medicine and Allergology, Lund University, Lund, Sweden. [3]Department of Respiratory Medicine, School of Medical Sciences, Örebro University, Örebro, Sweden. [4]School of Health Sciences, University of Skövde, Skövde, Sweden. [5]Wolfson Palliative Care Research Centre, Hull York Medical School, University of Hull, Hull, UK. [6]Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, Australia.

Corresponding author: Jacob Sandberg (jacob.sandberg@bth.se)

Provenance: Submitted article, peer reviewed.

Ethics statement: Participants provided written informed consent and the Regional Ethical Review Board at Lund University approved the study (DNr 2017/149).

Conflict of interest: No conflicts of interest exist for the authors.

Support statement: The study was supported by unrestricted grants from the Swedish Heart–Lung Foundation. J. Sandberg was supported by unrestricted grants from the Scientific Committee of Blekinge Region Council. M. Ekström was supported by unrestricted grants from the Swedish Society for Medical Research and the Swedish Research Council (Dnr: 2019-02081). Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Spathis A, Booth S, Moffat C, *et al.* The Breathing, Thinking, Functioning clinical model: a proposal to facilitate evidence-based breathlessness management in chronic respiratory disease. *NPJ Prim Care Respir Med* 2017; 27: 27.

2 Parshall MB, Schwartzstein RM, Adams L, *et al.* An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012; 185: 435–452.

3 Ramon MA, Ter Riet G, Carsin AE, *et al.* The dyspnoea-inactivity vicious circle in COPD: development and external validation of a conceptual model. *Eur Respir J* 2018; 52: 1800079.

4 Tsiligianni I, Kocks JWH. Daytime symptoms of chronic obstructive pulmonary disease: a systematic review. *NPJ Prim Care Respir Med* 2020; 30: 6.

5 Kessler R, Partridge MR, Miravitlles M, *et al.* Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *Eur Respir J* 2011; 37: 264–272.

6 Wu M, Wang Z, Li M, *et al.* Daily symptom variability in patients with stable COPD: a narrative review. *West J Nurs Res* 2018; 40: 1543–1561.

7 Miravitlles M, Izquierdo JL, Esquinas C, *et al.* The variability of respiratory symptoms and associated factors in COPD. *Respir Med* 2017; 129: 165–172.

8 Miravitlles M, Worth H, Soler Cataluña JJ, *et al.* Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. *Respir Res* 2014; 15: 122.

9 Tsiligianni I, Metting E, Van Der Molen T, *et al.* Morning and night symptoms in primary care COPD patients: a cross-sectional and longitudinal study. An UNLOCK study from the IPCRG. *NPJ Prim Care Respir Med* 2016; 26: 16040.

10 Kim M-A, Suh M-K, Park J, *et al.* Impact of symptom variability on clinical outcomes in COPD: analysis of a longitudinal cohort. *Int J Chron Obstruct Pulmon Dis* 2019; 14: 2135–2144.

11 Sandberg J, Sundh J, Anderberg P, *et al.* Comparing recalled versus experienced symptoms of breathlessness ratings: an ecological assessment study using mobile phone technology. *Respirology* 2022; 27: 874–881.

12 Sandberg J, Lansing R, Anderberg P, *et al.* Relating Experienced To Recalled breathlessness Observational (RETRO) study: a prospective study using a mobile phone application. *BMJ Open Respir Res* 2019; 6: e000370.

13 Grimby G, Frändin K. On the use of a six-level scale for physical activity. *Scand J Med Sci Sports* 2018; 28: 819–825.

14 Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988; 93: 580–586.

15 Schuler T, King C, Matsveru T, *et al.* Wearable-triggered ecological momentary assessments are feasible in people with advanced cancer and their family caregivers: feasibility study from an outpatient palliative care clinic at a cancer center. *J Palliat Med* 2023; 26: 980–985.