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Description of three dysfunctional breathing patterns in post-COVID dyspnea

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ABSTRACT

Introduction: Dysfunctional breathing (DB) can be defined as a change in breathing pattern associated with respiratory and/or systemic symptoms, after ruling out underlying respiratory or cardiac disease. Recent evidence suggests that DB contributes to dyspnea in post-COVID-19 syndrome (PCS), as demonstrated by ventilation analysis during cardiopulmonary exercise testing (CPET). Nevertheless, the lack of a standardized classification for the different subtypes of DB poses challenges for accurate diagnosis and effective management. We hypothesized that analyzing the evolution of breathing parameters during CPET may help classify DB into three patterns.

Methods: We analyzed 79 CPETs performed between July 2020 and May 2022 on patients with persistent respiratory symptoms at least three months after COVID-19 infection. We classified patients into three different categories based on abnormal breathing patterns: hyperventilation (HYPV), erratic breathing (ERBR), and flattening (FLAT).

Results: Age, BMI, gender and peak O_2 uptake (VO_2) were similar between patterns. Compared to normal pattern (N), we found higher $V_E - VCO_2$ slope in HYPV and FLAT, and a lower VT/ V_E slope in FLAT and ERBR. The FLAT pattern was also characterized by a higher breathing frequency at peak exercise compared to the other patterns. ERBR and FLAT were associated with higher symptom scores (Nijmegen Questionnaire and Dyspnea-12) compared to N.

Conclusion: Analyzing the evolution of ventilatory parameters during incremental exercise enables the classification of dysfunctional breathing into three distinct breathing patterns: hyperventilation, erratic breathing, and flattening.

1. Introduction

More than 50 symptoms have been described in post-COVID-19 syndrome (PCS) (Nittas et al., 2022), with dyspnea being one of the most common (Nehme et al., 2021). Cardiopulmonary exercise testing (CPET) has been the investigation of choice to explore PCS in over 70 studies (Durstenfeld et al., 2022). The main findings include peripheral impairment, respiratory limitation and ventilatory inefficiency

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(Debeaumont et al., 2021; Skjørten et al., 2021; Piamonti et al., 2024). It has been suggested that dysfunctional breathing (DB) could be an explanation for post-COVID-19 dyspnea, particularly in outpatients (Frésard et al., 2022; Holley et al., 2024). Until now, studies have mainly focused on maximal parameters or cut-off points, such as peak oxygen uptake (VO_2 peak), peak work rate (PWR), ventilatory equivalents (V_E/VO_2 and V_E/VCO_2), breathing reserve (BR), but not on the temporal evolution of the ventilation. Evaluating the evolution of minute ventilation throughout exercise has been suggested to better unveil ventilatory inefficiency than comparing peak values alone(Guerreiro et al., 2023a).

DB refers to alterations in breathing patterns associated with both respiratory and non-respiratory symptoms (Boulding et al., 2016). Despite its clinical relevance, ambiguity persists regarding its definition and no clear consensus exists on its classification into different subtypes (Bokov et al., 2016; Boulding et al., 2016; Watson et al., 2021). Accurate characterization of the breathing pattern is essential for the effective management of DB, which relies mainly on physiotherapy interventions aimed at reducing symptoms and improving quality of life (Thomas et al., 2003; Reeves et al., 2024). Despite the absence of a gold standard diagnostic procedure, CPET is considered as one of the most comprehensive methods for identifying abnormal breathing patterns while excluding other causes of exercise limitation. It has some limitations, including the absence of specific diagnostic criteria and cut-off values for the diagnosis of DB. Among DB subtypes, hyperventilation syndrome (HVS) is the most frequently described. It can be defined as a " dysregulation of ventilation leading to hypocapnia, in the absence of somatic causes of hyperventilation, with symptoms that are not necessarily related to hypocapnia" (Molema and Folgering, 1997). DB may or may not be associated with hyperventilation and in the latter case, patients typically exhibit normal $PaCO_2$, an unaltered V_E/VCO_2 slope, and a preserved dead volume/tidal volume ratio (VD/VT). Given these uncertainties, there is a need for rigorous validation and precise characterization of DB to reduce the ambiguity surrounding its definition, diagnostic and management(Sanchez-Bracero et al., 2025).

The objective of this study is to improve assessment and standardization of dysfunctional breathing description during CPET by proposing subclasses of dysfunctional breathing patterns. We hypothesized that analyzing the evolution of ventilatory parameters throughout CPET could enable the classification of distinct breathing patterns.

2. Materials and methods

2.1. Design, study population and procedure

We retrospectively included 79 patients aged 18 years and older with microbiologically confirmed SARS-CoV-2 infection who underwent CPET at the Geneva University Hospitals between July 2020 and May 2022 for the evaluation of post-COVID-19 persistent respiratory symptoms. All patients provided written informed consent. Anthropometric data, clinical history, CPET results, and pulmonary function tests (PFTs) were collected. The study was part of the COVISQAR trial (NCT04881214) and approved by local ethical committee (BASEC 2020–01457). The CPET procedure has been previously described in detail (Guerreiro et al., 2023a) and followed the international recommendations (Weisman et al., 2003). Briefly, patients performed an incremental ramp test to volitional exhaustion on a cycle ergometer. Respiratory and gas exchange data were collected on a breath-by-breath basis throughout CPET.

2.2. Data analysis

Breath-by-breath data were analyzed using MATLAB (version 2020b, The MathWorks, Inc., Natick, MA, USA) to obtain: (i) peak values, as the highest of 30 s sliding average; (ii) 1-minute average values at and after the ventilatory anaerobic threshold (VAT) (Sun et al., 2002); (iii) the nadir of $EqCO_2$, calculated as the mean of the 3 lowest consecutive 30-second data points (Sun et al., 2002); (iv) V_E/VCO_2 slope and y-intercept (Sun et al., 2002) using the MATLAB ROBUSTFIT function; (iv) the evolution of VT relative to V_E (VT/V_E slope), also computed by the MATLAB ROBUSTFIT function, with VT normalized to forced expiratory volume in one second (FEV1) rather than forced vital capacity (FVC) to avoid confusion in cases of obstructive patterns and to improve comparability across patients (Blackie et al., 1991). These last two were calculated over data up to VAT or over the entire ramp-test if VAT could not be determined.

2.3. Temporal evolution of ventilatory parameters

To account for differences in exercise duration between subjects, time was normalized to each individual's exercise duration and expressed as a percentage (Time %). V_E evolution was normalized to each subject's maximal ventilation and expressed as a percentage of total ventilation (%V_E max). Then, the average for each 10 % bin was calculated and presented as isotimes. For example, the 90–100 % interval is represented by the 95 % value.

2.4. Breathing patterns classification

The dominant breathing patterns (BP) during incremental exercise were determined based on graphic analysis using the clinical pathway suggested by Watson et al. (Watson et al., 2021) and the normal range values (Sun et al., 2002; Boulding et al., 2016; Brat et al., 2019; Ionescu et al., 2020; Frésard et al., 2022): (i) V_E/VCO_2 slope in the range of [19.6 – 30.4] and y-intercept [-1.5 – 6.3]; (ii) $PcCO_2$ at rest $>$ 35 mmHg and respiratory exchange ratio (RER) $<$ 0.9; (iii) VT $>$ 50–60 % percent predicted value (PPV) at the end of exercise (iv) resting $P_{ET}CO_2$ $<$ 30 mmHg or a decrease of less than 5 mmHg during exercise (Brat et al., 2019).

Four investigators (IG, AB, AT, FL), hereafter referred as the experts, independently analyzed every anonymized graphical and numerical representations of the ventilatory parameters (Sietsema et al., 2020) and sequentially assigned each patient to one of the four BP categories:

1. **Normal (N):** normal progression in terms of V_E, Bf, VT, V_E/VCO_2, RER, and $P_{ET}CO_2$ during exercise.
2. **Hyperventilation (HYPV):** hyperventilation at rest (RER $>$ 1, $P_{ET}CO_2$ $<$ 30 mmHg, PcCO2 $<$ 35 mmHg) and/or during exercise (increased V_E/VCO_2 slope, steady $P_{ET}CO_2$ and VCO_2 or inverse trend of $P_{ET}CO_2$ and VCO_2 kinetics).
3. **Erratic breathing (ERBR):** high unpredictability of VT and/or Bf evolution without evidence of hyperventilation.
4. **Flattening (FLAT):** slow and early linear increase of VT relative to V_E, with peak VT $<$ 60 % of PPV in the absence of hyperventilation and erratic pattern.

If at least three over four experts agreed, consensus was reached, and the BP was classified accordingly. In cases where consensus was not initially achieved, all four experts jointly re-evaluated the data to determine the predominant pattern across the entire CPET.

2.5. Questionnaires

Patients were asked to complete four questionnaires routinely administered at our center; 1) modified Medical Research Counsil (mMRC), 2) the Hospital anxiety and depression scale (HADS), 3) the Dyspnea-12 questionnaire (D-12), 5) the Nijmegen Questionnaire (NQ).

2.6. Statistical analysis

Continuous data are presented as median and interquartile range (median, [IQR]). For categorical data, comparison between groups were

performed using Pearson's χ^2 or, Fisher's exact test when appropriate. Continuous data were analyzed using Kruskal-Wallis test to assess group effects. Nonparametric tests were chosen due to the small sample size in each group and non-normal data. Data were analyzed as a function of time or as a function of $\%V_E$ max, using Kruskal-Wallis test for group effect at each $\%V_E$ point. The effects of time and V_E within each of the 4 groups were analyzed using the Friedman test. A two-tailed p value < 0.05 was considered statistically significant. Inter-rater agreement was assessed using Fleiss' kappa and overall percent agreement. All statistical analyses were performed with Prism (V9, GraphPad®, La Jolla, CA, USA).

3. Results

A total of 79 patients (median age [interquartile range (IQR)], 54 [44−60] years; female 57 %) were recruited. Table 1 and Table S1 present the demographic data, PFT, and CPET results of the study population. Additional details have been described previously (Guerreiro et al., 2023a). Twenty-seven patients (34.2 %) were classified as FLAT, 17 (21.5 %) as ERBR, 11 (13.9 %) as HYPV, and 24 (30.4 %) as N pattern. There were no differences in age, BMI and gender between groups. Patients with N or FLAT patterns were more likely to have suffered from a severe COVID-19 infection requiring hospitalization (58 % in N and 59 % in FLAT, $p = 0.0262$) compared to ERBR (18 % of patients were hospitalized) **(**Table 1 and S1**)**. There were no differences in PFTs between groups compared to the N pattern.

All CPETs met maximal criteria (« ATS/ACCP Statement on cardiopulmonary exercise testing. », 2003). We found no differences in peak VO_2 or power. By definition, $PcCO_2$ was lower in HYPV compared to N and other patterns (29.6 [26.1 – 32.1] mmHg, $p < 0.0001$). VAT could be determined in all patients except three, all of whom belonged to the HYPV group (Table S1).

Fig. 1 illustrates the evolution of V_E, Bf and VT during the CPET for the 4 patterns (N, ERBR, FLAT and HYPN). V_E over time (expressed as % of individual exercise duration) and peak V_E did not differ significantly between groups (Fig. 1A and Table 1). Compared to the N group, VT was lower from 15 % to 95 % of $V_E$max in the FLAT group and from 35 % to 95 % of VEmax in the ERBR group ($p < 0.05$) (Fig. 1**b**). Peak VT expressed as a percentage of predicted value, was lower in the FLAT (62 % of predicted [57−66], $p < 0.001$) and ERBR (60 % of predicted [44−74], $p = 0.002$) compared with N (72.5 % of predicted [68–80.5]). Similar differences were observed compared to HYPV (72 % of predicted [60−85]) (Table 1). The slope of the VT-V_E relationship up to VAT was lower in FLAT and ERBR compared with N ($p = 0.0022$) (Table 1). Bf was higher in the FLAT group compared to the N group from 15 % to 95 % of $V_E$max ($p < 0.0001$) (Fig. 1**C**). Peak Bf in absolute value was also higher in FLAT compared with N ($p = 0.009$) and HYPV ($p = 0.009$) (Table 1).

Patients with FLAT and ERBR patterns reported more symptoms, with higher NQ, D-12 and HADS-Depression scores compared to N. Additionally, NQ scores were higher in ERBR compared to HYPV, while HADS-Depression scores were higher in FLAT compared to HYPV ($p = 0.01$) (Table 1). In contrast, no significant differences were observed among patterns for mMRC and mBorg scores when assessing peak dyspnea during CPET.

Fig. 2 illustrates the evolution of the $EqCO_2$, and $PetCO_2$ during the CPET for the four groups (N, ERBR, FLAT and HYPV). Compared to N pattern, the $EqCO_2$ was higher in ERBR and HYPV patterns throughout most of the exercise duration (entire duration for ERBR and up to 75 % of time for HYPV) (Fig. 2A). $P_{ET}CO_2$ was significantly lower in ERBR and HYPV compared to N during most of exercise (up to 75 % of $V_E$max for ERBR and 65 % for HYPV) (Fig. 2B). V_E - VCO_2 slope until VAT was higher in all patterns compared with the N pattern ($p = 0.0033$) (Table 2).

At the initial independent classification of breathing patterns, complete agreement among the four investigators was achieved in 48 Of 79

Table 1
Anthropometric data, symptom evaluation, and results from the pulmonary function tests and cardiopulmonary exercise testing, for each abnormal breathing pattern (FLAT: flattening; ERBR: erratic breathing; HYPV: hyperventilation) compared to normal (N).

	N	FLAT	ERBR	HYPV
Number	24	27	17	11
Consensus [n (%)]	17 (71 %)	19 (70 %)	6 (35 %)	6 (55 %)
N. of females [n (%)]	11 (46 %)	16 (59 %)	9 (53 %)	9 (82 %)
Age (y)	55 [39−59]	56 [45−61]	54 [41−59]	44 [38−50]
Weight (kg)	77 [69−97]	78 [71−30]	73 [66−84]	74 [65−86]
Height (cm)	173 [166−191]	163 [159−173]	172 [166−177]	172 [166−177]
BMI (kg m^{-2})	28 [24−31]	29 [24−34]	24 [23−30]	30 [24−31]
Hospitalized [n (%)]	14 (58 %)	16 (59 %)	3 (18 %)*	4 (36 %)
Symptoms evaluation				
mMRC	1 [0−2]	1 [1−2]	2 [1−3]	2 [1−2]
Nijmegen Questionnaire	15 [11−20]	24 [18−33] *	30 [17−37] *,#	19 [9−28]
Dyspnea-12	7.5 [5−11]	16.5 [13−19] *	15 [10−24] *	12.5 [5–16.5]
HADS-Anxiety	6 [4−8]	10 [4−12]	6.5 [3–11.5]	6 [6−9]
HADS-Depression	4 [1−8]	10 [7−12] *,#	6 [4−13] *	6 [3−8]
Pulmonary function tests				
FVC (% of predicted)	96 [86−104]	86 [79−99]	92 [81−106]	105 [97−120]
FEV1 (% of predicted)	96 [92−110]	91 [79−101]	94 [86−103]	98 [94−119]
FEV1/FVC (% of predicted)	103 [98−107]	107 [101−110]	103 [98−110]	97 [92−100]
Z-score < −1.64 [n (%)]	0	0	1 (6 %)	1 (9 %)
DLCO (% predicted)	81 [69−100]	84 [69−98]	83 [69−89]	95 [79−119]
KCO (% predicted)	104 [81−104]	99 [94−109]	87 [75−105]	89.4 [82−110]
VA (% predicted)	92 [78−100]	82.5 [70.5–96.5]	84 [78−107]	94 [90−107]
CPET				
Days after COVID	163 [120−318]	178 [132−398]	271 [144−444]	181 [159−396]
Rampe (Watts/min)	11.25 [10–12.5]	10 [7.5–12.5]	10 [10–12.5]	10 [7.5–12.5]
mBorg dyspnea at peak	7 [5−9]	8 [6−9]	8 [6–9.5]	8 [7−9]
mBorg leg fatigue at peak	5 [4−9]	8 [7−9]	8 [7−9]	7 [6−10]
Peak power (W)	170 [127−199]	118 [98−168]	122 [94−166]	128 [100−156]
Peak HR (% predicted)	96.2 [87.7–101]	93.9 [88.0–97.7]	92.3 [75.5–98.2]	91.6 [82.9–97.3]
Peak [La]b (mmol l^{-1})	9.9 [7.4–14.3]	9.1 [7.6–11.7]	8.5 [6.4–12.1]	8.1 [5.6–10.8]
Peak VO_2 (ml min^{-1} kg^{-1})	21.0 [17.9–31.7]	18.3 [15.6–20.4]	20.1 [15.9–21.4]	18.9 [14.9–24.9]
Peak VO_2 (% predicted)	83.5 [77–101.5]	84 [74−102]	78 [62−86]	85 [70−104]
Peak ventilation (l min^{-1})	90 [68−120]	68 [55−105]	69 [57−98]	83 [67−94]
Peak ventilation (% predicted)	113 [98.5–152.5]	115 [100−133]	111.5 [92–125.5]	104 [88−129]
VT at peak (% predicted)	72.5 [68–80.5]	62 [57−66] *, #	60 [44−74] *, #	72 [60−85]
Bf at peak (min^{-1})	41 [37−46]	47 [42−54] *, #	43 [38−54]	39 [36−54]
$PcCO_2$ at rest (mmHg)	35.0 [33–37.5]	36.8 [34.7–39]	36.0 [33–38.3]	29.6 [26.1–32.1] *

Continuous data are reported as median [interquartile range] and the corresponding *p* value refers to Kruskal-Wallis results; categorical data are reported as

counts (n) and percentage proportion with respect to the corresponding total number (%), the related *p* value refers to the Pearson's χ^2 test. BMI: body mass index; mMRC: modified Medical Research Counsil; FVC: forced vital capacity; FEV1: forced expired volume in 1 s; KCO: carbon monoxide transfer coefficient, VA: alveolar volume, mBorg: modified Borg scale, [La]b: blood lactate concentration; VO_2: oxygen consumption; VT: tidal volume; Bf: breathing frequency, PcCO2: capillary partial pressure of carbon dioxide; * $p < 0.05$ vs. Normal, # $p < 0.05$ vs. Hyperventilation

patients (61 %). The highest agreement rate was obtained for the N pattern (17/24, 71 %). Agreement for FLAT was of 19/27 (70 %), HYPV of 6/11 (55 %) and ERBROf 6/17 (35 %). Overall agreement rate was 0.6835 with an inter-rater agreement (Fleiss' Kappa) of 0.5745 (95 % Ci: 0.54 – 0.60) between clinical evaluators (IG and FL).

4. Discussion

In this observational study, we classified ventilatory adaptation to exercise during incremental cardiopulmonary exercise test (CPET) into one normal pattern (N) and three abnormal breathing patterns: hyperventilation (HYPV), erratic (ERBR), and flattening (FLAT). We identified specific characteristics for each pattern regarding the V_E – VCO_2 slope and the evolution of VT and Bf throughout exercise, compared with the normal pattern. FLAT and ERBR exhibited the most pronounced abnormalities in breathing parameters and were associated with the most severe symptoms.

4.1. Breathing patterns analyses

Although there is no gold standard for the diagnosis of DB, CPET is commonly used to investigate unexplained dyspnea and is considered useful for its diagnosis (Ionescu et al., 2020). When analyzing breathing pattern, normalizing absolute VT by an index of the individual lung volume (FEV1) enables more accurate inter-subject comparisons by minimizing confounding effects related to height (Jones et al., 1985) or pathological alterations in lung volume or flow.

Compared to N, the HYPV pattern was characterized by a higher V_E - VCO_2 slope and EqCO2 at VAT and lower PcCO2. The FLAT pattern exhibited lower VT throughout and at peak exercise, a low VT/ V_E slope, high peak Bf, and a high V_E - VCO_2 slope. ERBR characteristics based on ventilatory parameters were the less evident, which was expected since ERBR relies on a subjective evaluation of the dispersion of breathing parameters using unfiltered graphs rather than averaged measurements. Nevertheless, ERBR showed high EqCO2 and an impaired increase in VT relative to V_E (low VT/ V_E slope) throughout exercise and at peak exercise. Most patients with a mild COVID-19 infection and normal PFTs presented ERBR and HYPV patterns. Despite a higher proportion of patients with severe COVID-19 infection in the N and FLAT patterns, associated with reduced TLC and DLCO, this did not result in significant differences in pulmonary function across groups.

The evolution of VT relative to V_E (Fig. 1**B**) demonstrates that the ERBR and FLAT patterns are characterized by an impaired VT response throughout incremental exercise, regardless of the selected ramp rate. Among the different groups, the FLAT also exhibited the highest Bf for a given V_E (Fig. 1**C**).

Several PCS studies have reported higher V_E/VCO_2 slope values in patients with PCS compared to control subjects (Agostoni et al., 2024; Piamonti et al., 2024) while others have found similar V_E/VCO_2 values at VAT (Szekely et al., 2021) or V_E/VCO_2 nadir (Alba et al., 2021). Our study confirms, in line with recent studies, that patients with PCS exhibit ventilatory inefficiency (von Gruenewaldt et al., 2022; Frésard et al., 2022; Durstenfeld et al., 2022; Holley et al., 2024).

Patients with FLAT and ERBR patterns reported a greater symptom burden, with higher scores on the NQ and D-12. In contrast to previous studies, we did not observe an association between anxiety and DB (Reilly et al., 2020; Genecand et al., 2023). Interestingly, the HYPV

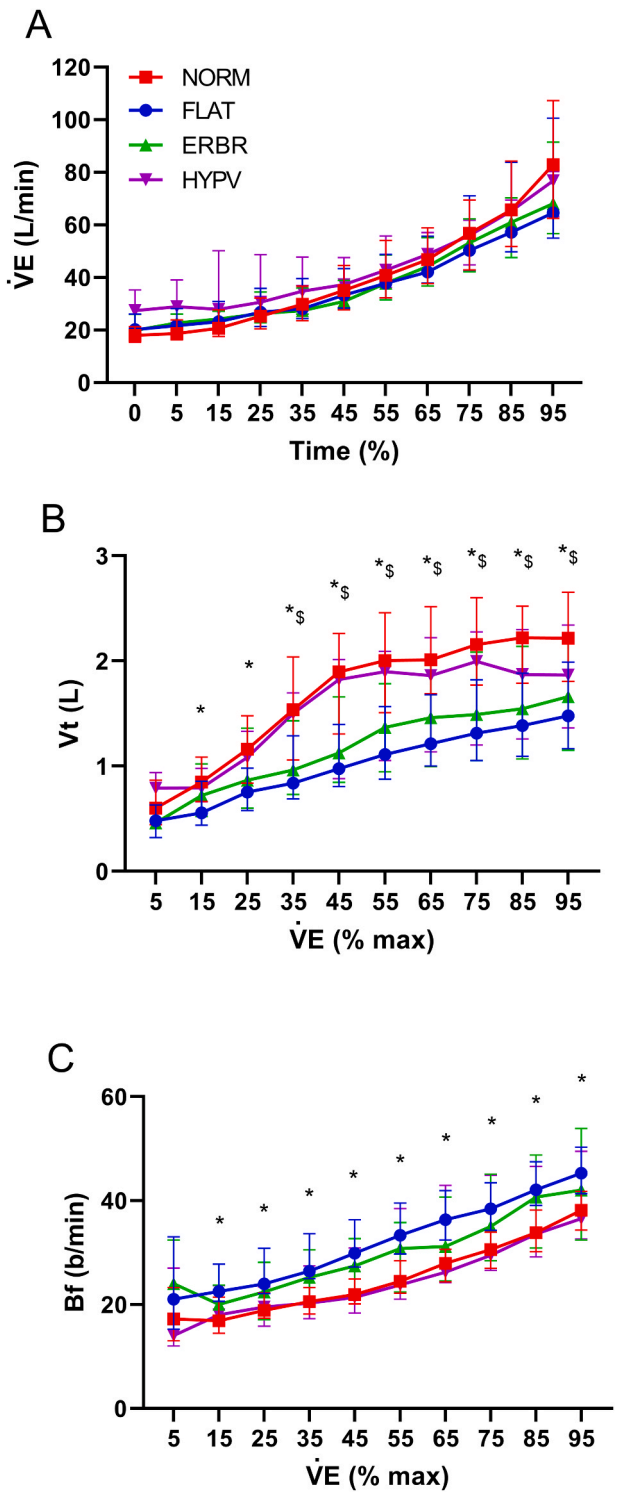

Fig. 1. Evolution of minute ventilation (V_E) breathing frequency (Bf) and tidal volume (VT) during the CPET for the 4 patterns. (A) Minute ventilation (V_E, in L/min), as a function of time (expressed in % of individual exercise duration), for the 4 groups; Time 0 refers to warm-up; (B) Tidal volume (VT, expressed as a percentage of individual FEV1 value), as a function V_E (expressed in % of individual peak value for V_E, i.e V_E max), for the 4 groups; (C) Breathing frequency (Bf, in b/min), as a function V_E (expressed in % of individual peak value for V_E, i.e V_E max), for the 4 groups. *: $p < 0.05$ between Flattening and Normal; $: $p < 0.05$ between Erratic and Normal; #: p 0.05 between Hyperventilation and Normal.

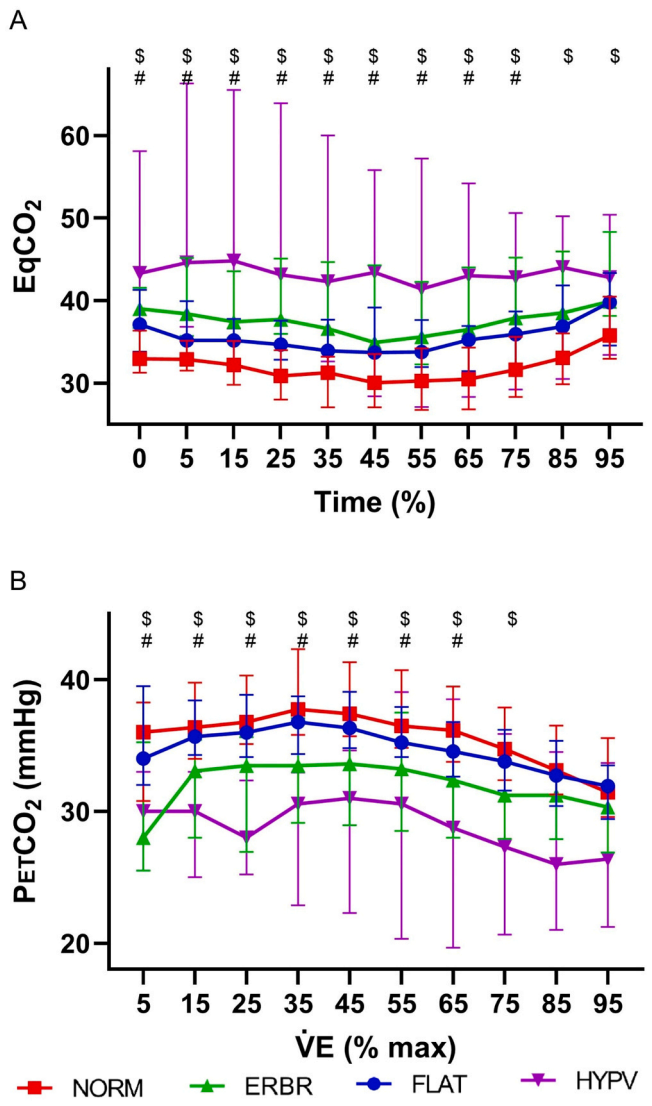

Fig. 2. Evolution of Ventilatory equivalent for CO_2 ($EqCO_2$) and end-tidal pressure of CO_2 ($P_{ET}CO_2$), during the CPET for the 4 patterns. **(A)**; Ventilatory equivalent for CO_2 ($EqCO_2$), as a function of time (expressed in % of individual exercise duration) for the 4 groups; Time 0 refers to warm-up; **(B)** End-tidal pressure of CO_2 ($P_{ET}CO_2$, in mmHg), as a function of V_E (expressed in % of individual peak value for V_E i.e V_E max), for the 4 groups. *: $p < 0.05$ between Flattening and Normal; $: $p < 0.05$ between Erratic and Normal; #: p 0.05 between Hyperventilation and Normal.

pattern was not linked to more severe symptoms. These findings underscore the importance of accurately analyzing and classifying DB patterns. Moreover, the lack of differences in commonly used score such as mBorg at peak exercise and mMRC, reinforces the complex and multidimensional nature of dyspnea (Banzett et al., 2015) and highlights the need of more specific scales to evaluate DB.

To the best of our knowledge, this is the first study to propose the FLAT pattern as an impairment in the ability to increase VT - a characteristic previously described in patients with neuromuscular diseases (Christle et al., 2023; Regmi et al., 2023) and those with obstructive disorders, including chronic obstruction pulmonary disease (O'Donnell et al., 2012). One possible explanation for this impaired ability to increase VT could lie in a respiratory muscle weakness during exercise, as PFTs were similar between groups without restrictive or obstructive ventilatory impairment (Hennigs et al., 2022; Severin et al., 2022). Studies have reporter a correlation between persistent post-COVID-19 dyspnea and respiratory muscle weakness, independently of the severity of the initial disease or the need of mechanical ventilation (Leo et al., 2023; Regmi et al., 2023).

The characteristics of the FLAT pattern, with swallow breathing (low VT and high Bf), share some similarities with the breathing pattern observed in interstitial lung disease (Gille and Laveneziana, 2021). However, the FLAT pattern exhibits distinctive features, including the absence of exercise-induced hypoxemia during exercise, a normal alveolar-arterial oxygen gradient and normal peak V_E. Although DLCO and VA values were close to the lower limit of normal, they did not differ significantly from those of other patterns. The retrospective design of the study did not allow for the analysis of respiratory muscle strength or inspiratory capacity.

4.2. *Inter-rater agreement*

Gruenewaldt et al. published the only study analyzing the inter-rater agreement for the evaluation of DB patterns (von Gruenewaldt et al., 2022). The authors categorized patients in either "normal", "abnormal" or "borderline" with pre-specified cut-off values and evolution during exercise. They found an inter-rater agreement of 0.67 (0.66 – 0.77) between three investigators. We found a smaller inter-rater agreement (Fleiss Kappa score) of 0.5745 (95 %CI 0.54 – 0.60) between the two clinicians (IG and FL). This difference between studies may be explained by the larger number of categories in the present study and by some overlap among the different breathing patterns.

4.3. *Objective evaluation of the erratic breathing pattern*

We chose to evaluate breathing pattern through usual ventilatory parameters. Several methods have been proposed to assess the dispersion of the breathing parameters during CPET, including breath-by-breath dispersion analysis (Brutsche et al., 2023; Genecand et al., 2025a). Entropy-based approaches have been developed to analyze predictability and complexity in linear time-series data (Pincus, 1991). This method has been applied to demonstrate reduced unpredictability in VT and V_E in patients with dysfunctional breathing (Caldirola et al., 2004; Bansal et al., 2018; Guerreiro et al., 2023b). More recently, Chinthaka et al. reported lower predictability in VT and V_E in post-COVID-19 patients with dysfunctional breathing compared to healthy controls (Chinthaka B. Samaranayake et al., 2023). However, because this method has not been developed for data with trends, there is considerable uncertainty regarding its accuracy in evaluating the true predictability of ventilatory parameters during exercise without trend correction (Delgado-Bonal and Marshak, 2019; Genecand et al., 2025b). Other methods have assessed variability of breathing parameters based on hypotheses of respiratory control and loop gain (Bokov et al., 2016), time intervals between tidal excursions (Frey et al., 1998), and objective analysis of sighs (Genecand et al., 2025c). Applying these statistical techniques would ideally require a larger sample size for group comparisons.

5. Limitation, perspectives and significance

Our study has some limitations. The classification of the three breathing patterns is based on a relatively limited literature, particularly regarding ERBR and FLAT. Mixed patterns were not permitted in our analysis, and the distinction between the proposed patterns and normal breathing remains subtle and involves some subjectivity. Additionally, the sample size within each subgroup may have resulted in insufficient statistical power to detect significant differences.

A key strength of our study is to introduce of a novel pattern, termed FLAT, based on the analysis of the evolution of ventilatory parameters during CPET. Our findings also confirm that DB is not always associated with hyperventilation (Brat et al., 2019). The FLAT pattern highlights the importance of assessing respiratory muscle function and suggests potential benefits of targeted respiratory muscle training (McNarry

Table 2
Ventilatory efficiency parameters during cardiopulmonary exercise testing for each breathing pattern.

	Normal	Flattening	Erratic	Hyperventilation	Kruskal-Wallis between groups
Number	24	27	17	11	
VE - VCO_2 relationship up to VAT					
Slope	27.3 [24.5–29.4]	31.2 [27.9–34.0] *	32.9 [27.6–37.4] *	34.8 [27.2–44.4] *	p = 0.0033
N. of normal [n (%)]	19 (79 %)	11 (41 %)	6 (35 %)	2 (18 %)	
Y-intercept (l min^{-1})	4.2 [2.6–5.7]	4.3 [1.4–6.2]	4.1 [2.8–7.1]	4.9 [2.9–12.5]	p = 0.5300
N. of normal [n (%)]	19 (79 %)	20 (74 %)	12 (71 %)	7 (64 %)	
N. of slope and Y-intercept normal [n (%)]	14 (58 %)	8 (30 %)	4 (24 %)	2 (18 %)	
VT - VE relationship up to VAT					
Slope (min^{-1})	0.037 [0.027–0.048]	0.018 [0.014–0.028] *	0.023 [0.012–0.030]*	0.019 [0.006–0.050]	p = 0.0022
Physiological variable or parameter value at VAT					
Work rate (W)	99 [65−125]	74 [56−94]	76 [56−109]	85 [58−100]	p = 0.3284
Heart rate (min^{-1})	120 [104−129]	129 [112−135]	115 [102−144]	124 [122−152]	p = 0.3115
VO_2 (L min^{-1})	1.15 [0.88–1.48]	1.02 [0.81–1.40]	1.04 [0.82–1.30]	1.03 [0.81–1.39]	p = 0.6509
VO_2 (ml min^{-1} kg^{-1})	13.9 [11.3–20.5]	12.5 [11.0–16.2]	12.6 [10.6–16.4]	13.9 [10.1–16.5]	p = 0.2325
VCO_2 (L min^{-1})	1.12 [0.91–1.44]	1.11 [0.86–1.38	1.02 [0.76–1.34]	0.95 [0.72–1.48]	p = 0.6489
RER	0.99 [0.96–1.01]	0.99 [0.95–1.07]	1.03 [0.97–1.07]	0.95 [0.81–1.07]	p = 0.3313
VT (L)	1.57 [1.39–2.19]	1.10 [0.94–1.57] *	1.34 [1.14–2.02]	1.56 [1.09–1.70]	p = 0.0020
Bf (min^{-1})	22 [19−25]	31 [28−40] *	29 [22−38] *	33 [18−45]	p < 0.0001
V_E (L min^{-1})	35 [29−50]	39 [30−48]	41 [33−49]	43 [29−56]	p = 0.7869
$P_{ET}O_2$ (mmHg)	103 [99−106]	106 [103−108]	109 [105−112] *	115 [99−118]	p = 0.0092
$P_{ET}CO_2$ (mmHg)	38 [36−42]	37 [35−39]	33 [29−39] *	29 [24−40] *	p = 0.0034
$EqCO_2$	30.5 [27.2–33.5]	33.6 [30.3–36.1]	35.6 [30.9–43.0] *	42.9 [26.9–48.4] *	p = 0.0078

The corresponding *p* value refers respectively to results of Kruskal-Wallis test for group effect; number of patients having normal data refers to values with z-score > -1.64, calculated on data from Sun et al. (Sun et al., 2002); Continuous data are reported as median [interquartile range] . Categorical data are reported as counts (n) and percentage proportion with respect to the corresponding total number (%). VO_2: oxygen consumption; VCO_2: carbon dioxide production; RER: respiratory exchange ratio; VT: tidal volume; Bf: breathing frequency; V_E: minute ventilation; $P_{ET}O_2$: end-tidal pressure of O_2; $P_{ET}CO_2$: end-tidal pressure of CO_2; $EqCO_2$: ventilatory equivalent for CO_2; *: $p < 0.05$ vs. Normal.

et al., 2022). Our study provides perspectives for improving the treatment and management of dyspnea associated with PCS and, more broadly, dysfunctional breathing. Patterns, such as FLAT and ERBR appear to be associated with greater symptom burden and may benefit from tailored physiotherapeutic approaches.

Future prospective studies should include robust statistical analyzes to better characterize the dispersion of breathing parameters (Genecand et al., 2025a). Identifying the most precise and clinically useful methods for assessing irregularity should be a priority (Sanchez-Bracero et al., 2025). Although our results require confirmation in larger cohorts (Debeaumont et al., 2025) and in populations with non-COVID-19-related DB, we believe they contribute to a deeper understanding of DB, encourage a more systematic analysis of ventilatory patterns, and offer opportunities to improve diagnosis and treatment.

Disclosures

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Author contributions

FL was the PI of the study. FL and IG conceived and designed research. IG coordinated the study. AB and IG oversaw patient screening, enrolment, and follow-up. AB, IG performed experiments. AB, AT, FL, IG, LG interpreted results of experiments. AB, IG prepared figures. AB, AT, FL, IG, LG drafted and edited manuscript. All authors read and approved the final version of the manuscript.

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Leverington Viva: Writing – original draft. **Weber Pascal:** Writing – original draft. **Bringard Aurélien:** Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Investigation, Formal analysis. **Guerreiro Ivan:** Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Taboni Anna:** Writing – original draft, Software, Investigation, Formal analysis. **Genecand Léon:** Writing – original draft, Validation. **Kharat Aileen:** Writing – original draft. **Lador Frédéric:** Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the author(s) used COPILOT in order to improve the fluidity of the English. After using this tool/service, the authors reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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Data availability

Data will be made available on request.

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Glossary

Bf: Breathing frequency
BMI: Body mass index
BR: Breathing reserve
CPET: Cardiopulmonary exercise testing
D-12: Dyspnea-12
DB: Dysfunctional breathing
$EqCO_2$: Ventilatory equivalent for CO_2
ERBR: Erratic breathing pattern
FEV1: Forced expiratory volume in one second
FLAT: Flat pattern
FVC: Forced vital capacity
HADS: Hospital Anxiety and Depression Scale
HYPV: Hyperventilation pattern
HVS: Hyperventilation syndrome
IQR: Interquartile Range
mBorg: modified Borg scale
mMRC: modified Medical Research Council
N: Normal pattern
NQ: Nijmegen Questionnaire
$PaCO_2$: Arterial blood CO_2 pressure

PCS: Post-COVID-19 syndrome
$PcCO_2$: Capillary blood pressure of CO_2
$P_{ET}CO_2$: End tidal partial pressure of CO_2
PFT: Pulmonary function test
PPV: Percent predicted value
PWR: Peak work rate
SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2
RER: Respiratory exchange ratio
VAT: Ventilatory anaerobic threshold
VE: Ventilation
VD/VT: Dead space volume – tidal volume ratio
VO_2: O_2 uptake
VT: Tidal volume
VCO_2: CO_2 production
VO_2 peak: Peak oxygen uptake