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Early View

Research letter

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Chaotic breathing in post COVID-19 breathlessness: a key feature of dysfunctional breathing can be characterized objectively by approximate entropy

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Take home message: Post COVID-19 breathing pattern disorder can be characterised by application of non-linear statistical modelling of exercise ventilatory data.

Keywords: COVID-19, Breathlessness, Breathing pattern disorder, entropy

Introduction

Exertional breathlessness is highly prevalent in individuals with the post-COVID syndrome, reporting delayed recovery following SARS CoV-2 infection.[1] The pathophysiology underlying breathlessness in this setting remains unclear, however the use of cardiopulmonary exercise testing (CPET) has provided valuable insight, highlighting abnormalities in peripheral oxygen extraction, energy utilisation and autonomic dysfunction.[2-5] In addition, several studies have highlighted the presence of dysfunctional breathing and breathing pattern disorders (BPD) in this context.[6, 7] There remains however a lack of validated physiological metrics to characterise breathing pattern, in this context. We previously applied a non-linear statistical approach to mathematically describe deranged ventilatory response patterns to physical activity, in a group of individuals with confirmed BPD.[8] In the current study we aimed to utilise a similar approach, to mathematically describe the exercise ventilatory responses in patients with dyspnoea and BPD following COVID-19, reporting the approximate entropy (ApEN) of ventilatory response. We hypothesised that this approach could be used to identify and characterise this issue and thus potentially used in the future for illness surveillance and to assess response to treatment.

Method

Consecutive patients referred for persistent breathlessness after SARS CoV-2 infection, confirmed on PCR or antibody testing and diagnosed with BPD, within our specialist service between May 2020 to May 2021 were identified. The diagnosis of BPD was made following cardiopulmonary exercise testing (CPET) to rule out other pathological explanations for breathlessness and assessment with a highly experienced respiratory physiotherapist, using objective measures such as the Brompton breathing pattern assessment tool (BPAT).[9] Those with evidence of persistent parenchymal changes or thromboembolic disease on chest imaging, abnormal lung function tests or cardiac dysfunction on imaging were excluded. A historical cohort of patients with non-SARS-CoV-2 related BPD and healthy individuals published previously[8] were used to provide a reference comparator.

Maximal effort-limited tests were performed on an upright cycle ergometer. After a 2-minutes of rest period and a 3-minute period of unloaded exercise and gas exchange measurement to ensure ventilatory equilibration, participants underwent a continuous ramp protocol (10–25 W/min) to volitional

fatigue. Heart rate was continuously recorded during exercise using a 12-lead ECG system. Capillary blood gas analysis was performed during resting phase and at peak exercise in all patients. BORG scores were recorded at rest and at peak exercise. All CPETs were performed under both medical and physiologist supervision allowing the tests to be symptom limited, which reduced the possibility of submaximal effort confounding the results. Breath-by-breath data was extracted from SentrySuite™ Software without filters for analysis. Irregularity during exercise in tidal volume (VT), breathing frequency (BF) and minute ventilation (VE) quantified by ApEn to characterize unpredictability in the time-series data using methods previously described [8, 10] and compared to the control groups. The ApEn calculation was based on the entire exercise test data including resting phase. M value (length of the sequences to be compared) was set at 2 and r value (tolerance threshold for accepting similar patterns between two segments) was set as 0.2 times the standard deviation of the series for each patient. Higher values of ApEn signifies greater unpredictability and lower values suggesting less chaos in patterns within a series. Previous data shows ApEn >0.88 for VE has high sensitivity and specificity for BPD.[8]

Continuous variables were summarised as mean ± standard deviation or median ± inter quartile range (IQR). Statistical analyses were performed using SPSS Statistics V27 (IBM Corp., Armonk, NY, USA). Consent for the clinical CPET and assessments were obtained as per usual clinical practice. Institutional approval for this retrospective study was obtained (CIRIS approval #4364).

Results

Over the study period, 20 patients (mean age 41 years (SD 10), 14 (70%) female) fulfilled inclusion criteria. The patients remained symptomatic and thus underwent CPET and dysfunctional breathing assessments at a median of 4 months (range 3-10) following COVID-19 infection. Chest and cardiac imaging was normal in all included patients. Spirometric indices were within normal range and the mean (SD) DLCO and KCO were 83% (11.7) and 94% (9.5) predicted, respectively (Table 1). On exercise testing, most COVID-19 patients stopped secondary to dyspnoea, with a BORG median at 5 (i.e. ‘severe’) but had a normal VO_2 peak (107% predicted) and gas exchange response, with low indices of

VQ inequality (Table 1). Significant variability was observed in the ventilatory parameters in post COVID-19 BPD patients (Table 1).

Table 1: Baseline characteristics and exercise measurements

	Post COVID-19 BPD (N = 20)	Non-COVID BPD (N = 20) [a]	Healthy controls (N = 15) [a]
BASELINE CHARACTERISTICS			
Age / years	41 (10)	49 (14)	50 (18)
Gender M:F	6:14	6:14	9:6
BMI (kg/m^2)	25 (4)	26 (5)	25 (4)
Nijmegen score (/64)	23 (12-44) [b]	23 (14–41)	-
FEV1 (% pred)	111 (13)	107 (16) *	96 (6)
FVC (% pred)	118 (14)	114 (16)	107 (12)
FEV1/FVC Ratio	80 (6)	78 (6)	75 (12)
Resting SpO2 (%)	98 (95-100)	99 (94–100)	97 (96–99)
Resting PaCO2 (kPa)	4.4 (0.8)	4.3 (0.7)	4.7 (0.5)
Resting BORG CR-10 dyspnoea (/10)	0.8 (0.7)	1.4 (1.3) *	0.2 (0.6)
PEAK exercise CPET Variables			
Duration of test (minutes)	12 (4)	9 (2)	15 (3)
Main reason for exercise cessation	Legs = 6	Legs = 8	Legs = 6
	Breathing = 14	Breathing = 12	Breathing = 4
BORG CR-10 dyspnoea (/10)	End=5.3 (2.3)	End=4.2 (1.5)	End=4.1 (1.7)
Peak VO2 (L/min)	2.18 (0.87)	1.52 (0.62) *	2.77 (1.22)
Peak VO2 (% predicted)	106.5 (33.1)	79.8 (17.5) *	124.8 (27.3)
Peak VO2 (mL/min/kg)	29.6 (7.6)	20.7 (7.1) *	37.8 (14.8)
Peak Heart Rate (beats/ min)	160 (12.6)	141 (26) *	167 (15)
Heart Rate Reserve (beats/ min)	14 (12)	30 (20) *	2 (13)
Peak VE (L/min)	89 (26)	60 (27) *	96 (35)
Peak Tidal Volume (L)	2.6 (1.3)	1.86 (0.88)	2.37 (0.71)
Peak Breathing Frequency (/min)	38 (23)	31 (9)	33 (8)
Peak SpO2 (%)	97 (93-100)	99 (94–100) *	95 (73–98)
PEAK exercise gas exchange values			
PaO2 (kPa)	13.3 (3.2)	13.8 (1.2)	13.7 (1.2)
PaCO2 (kPa)	4.4 (1.1)	4.2 (0.7)	4.1 (0.7)
PETCO2 (kPa)	4.2 (0.6)	4.3 (0.5) *	4.8 (0.8)
P(A-a)O2 difference (kPa)	2.8 (1.2)	2.1 (0.9)	2.6 (0.9)
P(a-ET)CO2 difference (kPa)	- 0.10 (0.25)	− 0.09 (0.37)	−0.35 (0.53)
Approximate entropy (ApEn) of ventilatory variables during incremental exercise			
ApEn Tidal Volume	1.61 (0.21)	1.28 (0.23) *	1.02 (0.29)
ApEn Breathing Frequency	1.40 (0.14)	1.41 (0.20)	1.32 (0.21)
ApEn Minute Ventilation	1.22 (0.19)	0.97 (0.30) *	0.65 (0.23)

Data shown as mean (SD) or median (IQR); M:F: Male:Female; IQR, Interquartile range; BMI, body mass index; SpO2, oxygen saturation; HR, heart rate; V̇O2, oxygen consumption; VE, minute ventilation; PETCO2, end-tidal carbon dioxide; PaO2, partial pressure of oxygen; PaCO2, partial pressure of carbon dioxide; A-a gradient, alveolar-arterial gradient; MVV, maximum voluntary ventilation; ApEN: approximate entropy.
a: Data obtained from a historical cohort of patients with non-SARS-CoV-2 related BPD and healthy individuals published previously[8]
b: Nijmegen score available in n=15 in the Post COVID-19 BPD group.
* represents $p < 0.05$ vs healthy controls.

Discussion

In a cohort of patients with persistent exertion breathlessness and BPD following COVID-19, we objectively quantified exercise ventilatory irregulates using non-linear mathematical modelling.. Despite the presence of heightened resting dyspnoea, patients with post-COVID BPD, in this enriched cohort, appeared to have similar cardiopulmonary exercise performance compared to healthy controls. In patients with post-COVID BPD there was significant variability and unpredictability in the VT and VE during exercise with an elevated ApEn for both measurements.. Peak exercise BF appeared to be similar between the three study groups. Our results highlight the presence of a derangement in the control of ventilation and thus a chaotic breathing pattern during exercise in breathless patients following COVID-19, who otherwise have normal cardio-pulmonary findings.

Unlike the non-COVID BPD group, the post-COVID BPD group in our study had a normal peak exercise oxygen uptake, heart rate and minute ventilation. Although deconditioning is a common pattern seen in CPET studies in unselected patients following severe COVID-19 illness,[4] peripheral factors did not contribute to breathlessness in our selected cohort of post-COVID BPD patients. A number of studies have now identified disordered ventilatory responses to exercise with hyperventilation in patients with exertional breathlessness following COVID-19.[5, 6, 11] Dysfunctional breathing without hyperventilation has also been demonstrated to be an important pathophysiological mechanism of dyspnoea following COVID-19 infection in younger patients.[7] These studies however utilised pattern recognition or arbitrary assessment of the appearance of ventilatory response during exercise without quantification of variability in breathing during exercise.

A strength of our study was that the cohort was well phenotyped and patients with other potential confounding causes of breathlessness and exercise impairment were excluded. All patients underwent blood-gas analysis at rest and peak-exercise, which allowed us to assess pulmonary dead-space and

thus to be able to identify subtle pulmonary vascular phenotypes, which are reported in patients with persistent breathlessness following COVID-19 infection.[12]

There are several limitations to this observational study. Firstly, the cohort size is small and highly selected. Thus application of ApEN of ventilatory measures should now be applied across a broader population set. The data for control groups were obtained from historical published dataset [5] and we have not made direct and detailed statistical comparison with the COVID-19 BPD group due to the lack of contemporaneous measurements, and therefore only used as a reference comparator. Regardless, it is apparent that the values reported in the post COVID-19 BPD group have values that are similar or in excess of those reported previously in the non-COVID BPD group and controls. Patients with regular sighs, which can be an important component of BPD, results in infrequent large outliers in the measurements and likely to be under-estimated by ApEN calculation. The influence of variable duration of tests included in an ApEN calculation is unknown, which is relevant in this study given the variable duration of the tests in the three groups. The use of a single measure to detect and characterise ventilatory irregularity may also overlook other forms of dysfunctional breathing that are reported following COVID-19 and thus should be considered in addition to other markers of BPD.

A further limitation relates to the fact that there is no accepted ‘gold standard’ for the diagnosis of BPD and we therefore employed the widely accepted clinical diagnostic standard of an expert physiotherapy-based assessments. In the future, it would be helpful to compare ApEN measures to other means of identifying BPD, such as opto-electronic plethosmography, if and when they are further validated in this context.[13] Additionally, we do not have sufficient follow-up data from this cohort of post COVID-19 BPD group and therefore unable to determine the significance of BPD in long-term clinical outcomes. Longitudinal data on the natural history of BPD following COVID-19 infection would be clinically relevant, but was beyond the scope of the current study.

Despite the limitations, this study provides proof-of-concept that post-COVID BPD can be characterised by application of non-linear statistical modelling of exercise ventilatory data. This approach now needs further validation to facilitate application in automated CPET equipment, to identify and highlight this important differential diagnosis.

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