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Exercise Ventilatory Irregularity can be quantified by Approximate Entropy to detect Breathing Pattern Disorder

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ABSTRACT

Background: Breathing pattern disorder (BPD) is a prevalent cause of exertional dyspnea and yet there is currently no reliable objective measure for its diagnosis. We propose that statistical analysis of ventilatory irregularity, quantified by approximate entropy (ApEn), could be used to detect BPD when applied to cardiopulmonary exercise test (CPET) data. We hypothesized that ApEn of ventilatory variables (tidal volume (V_T), breathing frequency (B_f), minute ventilation (V_E)) would be greater, i.e. more irregular, in patients with BPD than healthy controls.

Methods: We evaluated ventilatory ApEn in 20 adults (14 female) with exertional dyspnoea, undergoing CPET and independently diagnosed with BPD by a specialist respiratory physiotherapist. Data were compared with 15 age- gender- and BMI-matched controls. ApEn for V_T, B_f and V_E were calculated for an incremental cycle exercise test.

Results: Patients with BPD more frequently rated breathlessness as the reason for exercise limitation and had a lower mean (SD) peak oxygen uptake compared with controls: 80 (18) vs. 124 (27) % predicted ($P<0.001$). ApEn was significantly greater for V_T ($p=0.006$) and V_E ($p=0.002$) in BPD than controls. ApEn V_E was inversely related ($r^2=0.24$, $p=0.03$) to peak oxygen uptake in BPD but not controls. ROC analysis revealed that ApEn V_E >0.88, conferred a sensitivity and specificity of 70% and 87% respectively, for detection of BPD.

Conclusions: Non-linear statistical interrogation of CPET-acquired ventilatory data has utility in the detection of BPD. A simple calculation of approximate entropy of ventilation, during an incremental cardiopulmonary exercise test, provides a quantitative method to detect BPD.

INTRODUCTION

Exertional dyspnea is a key feature in heart or lung disease and its presence mandates a systematic and thorough search for any underlying pathological cause.[1] Despite extensive investigation, however, in many cases the origin and aetiology of exertional dyspnea can remain unclear, or appear disproportionate to any underlying pathological condition identified. In such cases it is now recognized that this exertional dyspnea may arise from a maladaptive breathing pattern, termed a breathing pattern disorder (BPD).[2,3]

The best available data suggests that BPD is a common problem, particularly in primary care, where it is estimated to affect at least one in ten individuals.[4] It is also a prevalent co-morbid condition in airways disease[5] and evident in up to half of individuals with severe asthma.[6] The detection of BPD is important, given the beneficial impact of targeted physiotherapy intervention for both symptoms and quality of life.[7]

A reliable objective method for detecting BPD is currently lacking.[2] The diagnosis of BPD requires the exclusion +/- treatment optimization of a pathological problem combined with the positive identification of several distinct ventilatory abnormalities. This is most commonly achieved by expert respiratory physiotherapy assessment; central to which is the positive identification of periodic alterations in the depth and frequency of tidal volume, asynchrony of thoracic and abdominal motion and frequent sighing and yawning.[2,6] Objective techniques that have been utilized, in an attempt to quantify BPD, include assessment of rib cage inductance and structured light plethysmography.[8-10] These techniques however often require specialist technical expertise and equipment.

In contrast, the cardiopulmonary exercise test (CPET) now has an established place and is frequently used in the assessment of individuals with unexplained dyspnoea.[11] Data collected during CPET is typically utilised to identify and characterize either a ventilatory or cardiovascular impairment to exercise. However, CPET provides breath-by-breath ventilatory measurements and as such could be

used not only to rule out a cardiorespiratory aetiology for exercise intolerance but also to detect a chaotic ventilatory response and thus potentially to rule in a diagnosis of BPD; acting to stratify referral for further assessment and/or initiation of targeted treatment.[7]

Evaluating the variability and regularity in the exercise response pattern of physiological variables requires a non-linear approach to mathematical modelling.[12] In this context, approximate entropy (ApEn), a measure of statistical unpredictability, has been previously used to characterize regularity of breathing pattern in health[13], asthma[14] and in patients with hyperventilation and panic disorder.[15] We therefore utilised a similar approach to evaluate ApEn for exercise ventilatory parameters in a cohort of individuals with idiopathic dyspnoea and diagnosed with BPD and to compare them with a matched control group. We hypothesised that ApEn analysis of ventilatory variables from a standard incremental CPET could be used to detect BPD.

METHODS AND MATERIALS

Study Design and Participants

We retrospectively analysed data from patients referred to a specialist unexplained dyspnoea service between January 2013 and April 2015. We identified those who received a diagnosis of BPD and who also undertook detailed physiological testing. All patients completed CPET and had normal pre-referral investigations, which included, but were not limited to, chest radiography (some with computer tomography), echocardiography, full pulmonary function testing and blood gas analysis.

An age-, gender- and BMI-matched healthy, asymptomatic, control group (n=15) was identified from data obtained in a concurrent study, for which participants provided written informed consent (REC: 12/LO/0088). The retrospective analysis of patient data was approved by the local research governance service evaluation team (RBH ♯1075).

Clinical Measurements

Patients attending the unexplained dyspnoea service undergo detailed clinical assessment, complete dyspnoea-related questionnaires (dyspnoea-12 [D12][16] and Nijmegen Questionnaire [NQ][17]), full pulmonary function tests, an incremental CPET with arterialised blood gas measurement. Incremental exercise was performed on a cycle-ergometer (Viasprint 150P/200P Bicycle Ergometer, Carefusion, USA) to volitional intolerance, with participants breathing through a mouthpiece to measure gas exchange variables (Oxycon pro, Carefusion, USA). Incremental exercise was imposed at 10-40 W/min; selected to ensure the exercise bout lasted between 8-12 minutes. Subjects rated 'shortness of breath' each minute using the modified Borg CR-10 scale (range 0–10).[18]

On the day of assessment, patients were also assessed by an expert respiratory physiotherapist (blinded to analysis of the ventilatory data) and a diagnosis of BPD was made if at least 3 of 5 following abnormalities were identified: (i) apical (i.e. upper chest) predominant thoracic excursion;

(ii) erratic and periodic changes in ventilatory pattern; (iii) oral predominant flow; (iv) respiratory rate greater than 25; and (v) noisy inspiratory and expiratory flow.[6]

Calculation of Ventilatory Irregularity by Approximate Entropy (ApEn)

Irregularity in tidal volume (V_T), breathing frequency (B_f) and minute ventilation (V_E) was assessed by approximate entropy (ApEn) to characterize unpredictability in the time-series data. ApEn is a non-negative regularity statistic, with higher values signifying greater unpredictability and lower values demonstrating a greater regularity in patterns within a series (Figure 1), as described previously.[13,19] The ApEn calculation was based on the entire exercise test data including resting phase (see online supplement).

Statistics

Continuous parametric and non-parametric data were analysed using independent student t-test and Mann-Whitney U test, respectively. Discrete data was analysed using either the Fishers Exact test or Chi-Squared test. Correlation was determined using the Spearman correlation coefficient. The ability of ApEN measures to detect BPD was assessed from a receiver operating characteristic (ROC) analysis and calculated sensitivity and specificity at relevant cut-off points. Data were analyzed with SPSS 24.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 6 (USA) and a P-value of <0.05 was considered significant.

RESULTS

Participant Characteristics and Pulmonary Function

Over the study period, fifty-one patients completed assessment. Twenty individuals with BPD were identified; others were excluded from further analysis because an alternative, non-optimized, cause for their symptoms was identified; e.g. cardiac (n=12), respiratory (n=15) or mixed cardiac/ventilatory (n=4) impairment. The BPD patients (n=20) and controls (n=15) were well matched (Table 1), although control subjects were taller (p=0.004). Lung function was similar between groups, with the exception of FEV_1, which was greater in patients (p=0.009). The majority of BPD patients were female (70%) and 6 (30%) were overweight (BMI>30 kg/m^2).

Patients were dyspneic at rest, as indicated by high D12 (50% ≥12/36) and NQ scores (60% ≥23/64) (Table 1). This was also reflected in a greater resting CR-10 dyspnoea score compared with controls (1.4 (1.3) vs. 0.2 (0.6); p=0.009) (Table 2).

Arterialized (earlobe) pH and bicarbonate in the BPD cohort was within the normal range (7.45 (0.05) and 22.0 (2.67) mmol/L respectively). Resting P_aCO_2 was slightly below normal in patients with BPD and 40% had a P_aCO_2 <4kPa, however did not differ statistically from controls (4.3 (0.7) vs. 4.7 (0.5) kPa; p=0.13).

Incremental Exercise Responses

BPD patients had a lower peak power output and peak oxygen uptake (VO_{2peak}) compared with controls (Table 2). Patients also reached exercise intolerance with a greater heart rate reserve than controls (30 (20) vs. 2 (13) beats/min; p<0.0001; Table 2).

In BPD patients, V_T and B_f were within the normal range at rest, increased appropriately with exertion, and were similar at peak exercise to controls (Table 2). However, BPD patients had a lower $P_{ET}CO_2$ at peak exercise compared with controls (4.3 (0.5) vs. 4.8 (0.8) kPa; p=0.04; Table 2). There

was a trend towards a greater nadir in the ventilatory equivalent for CO_2 (V_E/VCO_2) in BPD patients (28.5 (5.2) vs. 25.6 (3.6); p=0.07).

Approximate Entropy of Ventilatory Variables

BPD patients had greater ApEn for both V_T and V_E compared with controls (Table 3), suggesting greater unpredictability in the time-series data. The greatest difference in breathing irregularity was observed in ApEn V_E between groups (P<0.01).

Relationships Among Approximate Entropy of Ventilatory Variables, Aerobic Capacity and Breathing Pattern Disorder

ApEn V_E was inversely related to VO_{2peak} in both BPD patients (r^2=0.24, p=0.03) and for the whole study cohort (r^2=0.23, p=0.004) (Figure 2A), i.e. aerobic capacity was lower in subjects with a more irregular ventilatory pattern. A similar relationship was evident for peak power (r^2=0.18, p=0.01 for all subjects) (Figure 2B). There was an inverse relationship between peak exercise V_T and ApEn V_E for all subjects (r^2=0.13, p=0.049) (Figure 2C). A weak direct relationship was found between ApEn V_E and D12 score (r^2=0.3, p=0.02), but not for NQ score (Figure 3). No relationships were seen with ApEn for V_E, V_T or B_f and resting dyspnoea scores (CR-10).

The diagnostic potential of ApEn to detect BPD was evaluated using ROC curve analysis and a cut-off value to differentiate BPD was determined where both sensitivity and specificity of the test were greatest. The area under the curve for ApEn V_E was 0.81 with an ideal cut off score of ApEn V_E >0.88, where sensitivity and specificity were 70% and 87%, respectively (p=0.002; Figure 4).

DISCUSSION

This is the first study to objectively quantify exercise ventilatory irregularities in patients with unexplained dyspnoea and BPD using non-linear mathematical modelling. The findings reveal that ApEn analysis of ventilatory variables, acquired from a standard incremental CPET, can differentiate controls from patients with BPD as compared with the 'gold standard' of specialist multi-disciplinary team assessment. This approach would be simple to automate, such that BPD detection could be rapidly algorithmically determined from ventilatory data obtained during this widely available and commonly employed clinical investigation.

Many individuals with 'idiopathic' or unexplained breathlessness are now recognized to have irregularities in the pattern and control of their breathing, both at rest and during exercise.[20,21] Historically, individuals with this clinical presentation were described as chronically 'hyperventilating'. Defining and characterising this abnormality, based on the presence of systemic hypocapnia, has however proven difficult.[22] Specifically, many patients appear to have only intermittent evidence of hypocapnia[23] and hyperventilation provocation testing has proven to be diagnostically imprecise.[24]

Accordingly, more recent work has focussed on detecting irregularities in breathing pattern.[2,6,20] Such breathing pattern irregularities appear to be ubiquitous in those with idiopathic breathlessness or hyperventilation[20,25] yet new, readily-accessible, objective techniques are needed to quantify these breathing pattern abnormalities. Caldirola and colleagues[15] utilised the mathematical approach of ApEn analysis to evaluate ventilatory indices acquired from resting breath-by-breath data, to successfully quantify increased ventilatory irregularity in a cohort of individuals with anxiety disorders.

Our finding of greater ApEn V_E in patients with BPD, suggests a similar approach characterizes maladaptive ventilatory behaviour in this patient population. Moreover, this greater ventilatory

irregularity was detectable during an exercise bout; a finding that is clinically pertinent given exercise intolerance is a key clinical symptom in this condition. We found that patients with BPD had lower aerobic capacity than our control group, and presented with VO_{2peak} values bordering the lower limit of normal (80%). Moreover, a weak association between ApEn V_E and both VO_{2peak} and peak power output was evident.

Historically, clinical conditions associated with dysfunctional or maladaptive breathing patterns have been diagnosed predominantly using a questionnaire-based approach; most commonly by application of the NQ.[26] We found a poor relationship between resting dyspnea and the NQscore and markers of ventilatory irregularity. This is in keeping with our recent study utilizing a breathing pattern assessment tool to diagnose BPD.[6] The latter, a physiotherapy directed assessment tool, was used to quantify BPD in individuals at rest referred with refractory asthma; in these a poor relationship was found between total BPAT and NQ scores. These findings most likely indicate the inadequacy of a questionnaire-based approach or resting snap shot assessments of dyspnoea to diagnose BPD, likely also confounded by the non-specific nature of questionnaire scores. This may also relate to a relative 'adaptation' by an individual to accept a higher baseline dyspnea and thus alter reporting of baseline resting measures.

The mechanism underlying heightened exercise ventilatory irregularity in BPD is currently unclear. Jack and colleagues[21] previously reported a heightened ventilatory response to incremental exercise in patients with chronic idiopathic hyperventilation. The latter was defined by the presence of a reduced $PaCO_2$ (typically below < 4kPa) in the presence of a compensated respiratory alkalosis with depletion of the rapidly exchanging CO_2 stores. The individuals described by Jack et al.[21] were similar to our cohort in terms of both their clinical characteristics and exercise performance. They differ however, in that only 40% of our patient group had a resting $PaCO_2$ <4 kPa. We identified a slightly greater nadir in V_E/VCO_2 in BPD patients than our controls, potentially indicating a maintained relative hypocapnia during exercise, but this was not elevated to the magnitude reported by Jack et al.[21]

Our study extends that of Jack et al.[21] by adding additional information regarding breathing pattern irregularity during exercise. Evaluating irregularity, 'chaos' or temporal fluctuation within physiological time-series data provides heretofore unexplored insight into the clinical disease state. Specifically, in both respiratory and cardiac disorders, evaluating non-linear statistical models of temporal fluctuation in ventilatory and/or airflow parameters appears to be associated with disease control and prognosis.[20,27-29] Perhaps the most comprehensively studied variable, in this context, is heart rate variability (HRV)[30] several studies indicate that reduced HRV is associated with a poor cardiac prognosis. Thus generally speaking it is believed that irregularity in a time series of physiological data is desirable and associated with 'favourable' pliability within a physiological system. This is presumably associated with a heightened ability to respond to feedback control inputs. Temporal or periodic fluctuations in ventilatory response to exercise are observed in patients with heart failure, pulmonary hypertension and in central sleep apnoea (i.e. exercise oscillatory ventilation (EOV) and Cheyne-Stokes respiratory patterns), however these fluctuations appear to be highly ordered states and as such are likely to have low scores of temporal variability, i.e. a low ApEN score. This requires further study and it is currently unclear whether the mechanisms underlying periodic fluctuations of ventilation and the heightened complexity of ventilatory organisation in BPD overlap, in terms of chemo-responsiveness.

One interpretation of our findings therefore, of a heightened disorganisation in the exercise ventilatory response in BPD, is that high ApEn V_E is favourable and in keeping with a 'fluid' or responsive physiological system. Another interpretation is that normal physiological control is somehow impaired or lost, such that the disordered appearance of exercise ventilation reflects an ineffective ventilatory control system. The reduced aerobic capacity and heightened symptoms in BPD suggest that the latter is more likely, and there appears to be a balance between a favourable degree of variability that responds appropriately to physiological inputs and one that simply reflects increased chaos and impaired control.

Critique of Methodology

Our findings provide a proof of concept that BPD may be diagnosed using ApEn V_E from CPET assessment. More detailed work is now needed before ApEn analysis could be considered a routine part of the portfolio of techniques used to support a BPD diagnosis. Nevertheless the concept is appealing since the process is quantitative and may be automated and applied during a well-standardized diagnostic test.

There is no accepted 'gold standard' comparator for the diagnosis of BPD. We therefore employed the widely-accepted clinical diagnostic standard of an expert physiotherapy-based assessment. It would now be desirable to study a larger sample size, use multiple sites and evaluators together with the use of a second independent expert adjudicator to make a diagnosis. Indeed the current study only includes relatively few subjects and thus this work should be viewed as preliminary and in need of further prospective validation. Moreover, any development of this technology will also require a cohort to undergo testing on multiple occasions to determine test-retest variability.

Implications

While a relatively small sample, our study confirms that despite the absence of 'organic pathology' BPD patients experience symptoms as demonstrated by a low peak power output and VO_{2peak}, heightened resting dyspnoea. Identification and treatment of these patients both reduces cost due to unnecessary investigations and, at least on the basis of some, albeit small, randomised controlled trials, can improve outcome.

In conclusion, these data confirm that patients with BPD experience heightened dyspnoea and exercise limitation compared with controls. Compared with expert physiotherapist diagnosis, quantifying disordered breathing using ApEn V_E >0.88 during an incremental exercise test provides a

sensitivity and specificity of 70% and 87%, respectively to determine BPD. ApEn V_E during CPET therefore provides a promising tool to better guide referrals for assessment and treatment of BPD.

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FIGURE LEGENDS

Figure 1. Examples of the tidal volume response to incremental exercise in participants with increasingly chaotic breathing pattern. 1A: Low entropy (– 0.447), **1B**: Medium Entropy (–1.13), **1C**: High Entropy (–1.59)

Figure 2. Relationships among the approximate entropy (ApEn) of minute ventilation during exercise and peak exercise variables. 2A: VO_2peak vs ApEn minute ventilation, **2B**: Power vs ApEn minute ventilation, **2C**: Peak tidal volume vs ApEn minute ventilation.

Figure 3. **Relationship between approximate entropy (ApEn) of minute ventilation and subjective dyspnoea indices. 3A**: Nijmegen Score vs ApEn. **3B**: Dyspnoea–12 score vs ApEn. NB, some BPD patients did not complete a D-12 (n=4) or a NQ (n=3) questionnaire.

Figure 4. Receiver operating characteristic (ROC) analysis for approximate entropy (ApEn) minute ventilation during exercise in the diagnosis of breathing pattern disorder (BPD). Area under curve = 0.8 with optimum sensitivity and specificity of 70% and 87%, respectively.

TABLES

Table 1. Participant characteristics and pulmonary function

		Controls	Breathing Pattern Disorder
		N=15	N=20
Age		50 (18)	49 (14)
Sex (M:F) [a]		9:6	6:14
Height (cm)		174 (7)	166 (9)**
Mass (kg)		75 (14)	72 (16)
BMI (kg/m^2)		25 (4)	26 (5)
Smoking status [b]	Current	2	1
	Former	2	7
	Never	11	12
Nijmegen score (/64)		-	23 (14-41)
Dyspnoea-12 score (/36)		-	20 (4-32)
FEV_1 (L)		3.2 (0.7)	3.1 (0.8)
FEV_1 (% pred)		96 (6)	107 (16)**
FVC (L)		4.4 (0.8)	3.9 (1.1)
FVC (% pred)		107 (12)	114 (16)
FEV_1/FVC		75 (12)	78 (6)
Resting S_pO_2 (%)[c]		97 (96-99)	99 (94-100)
Resting HCO_3^- (earlobe) (mmol/L)		24 (2)	22 (3)
Resting P_aCO_2 (kPa)		4.7 (0.5)	4.3 (0.7)

Data shown as mean (SD) or median (range). *P <0.05 **P<0.01 vs. healthy controls. [a] Chi Squared test. [b] Fishers exact test . [C] Mann Whitney U test. Definition of abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

Table 2. Ventilatory, cardiac and blood gas responses to incremental exercise

	Controls	Breathing Pattern Disorder
	N=15	N=20
Resting BORG CR-10 dyspnoea (/10)	Rest = 0.2 (0.6)	Rest =1.4 (1.3)**
Peak exercise CPET variables		
Duration of test (minutes)	15 (3)	9 (2)**
Main reason cited for exercise cessation [# a]	Legs=6; Breathing=4	Legs=8; Breathing=12*
BORG CR-10 dyspnoea (/10)	End = 4.1 (1.7)	End = 4.2 (1.5)
Peak Power (W)	195 (97)	124 (77)*
Peak VO_2 (L/min)	2.77 (1.22)	1.52 (0.62)***
Peak VO_2 (% predicted)	124.8 (27.3)	79.8 (17.5)***
Peak VO_2 (mL/min/kg)	37.8 (14.8)	20.7 (7.1)****
Peak Heart Rate (beats/min)	167 (15)	141 (26)**
Heart Rate Reserve (beats/min)	2 (13)	30 (20)***
Peak V_E (L/min)	96 (35)	60 (27)**
Peak Tidal Volume (L)	2.37 (0.71)	1.86 (0.88)
Peak Breathing Frequency (/min)	33 (8)	31 (9)
Peak S_pO_2 (%) [b]	95 (73-98)	99 (94-100)**
Peak exercise blood gas values		
P_aO_2 (kPa)	13.7 (1.2)	13.8 (1.2)
P_aCO_2 (kPa)	4.1 (0.7)	4.2 (0.7)
$P_{ET}CO_2$ (kPa)	4.8 (0.8)	4.3 (0.5)*
HCO_3^- (mmol/L)	17.4 (1.7)	18.5 (2.7)
Base excess (mmol/L)	-6.2 (1.18)	-5.3 (2.9)
P(A-a)O_2 difference (kPa)	2.6 (0.9)	2.1 (0.9)
P(a-$_{ET}$)CO_2 difference (kPa)	-0.35 (0.53)	-0.09 (0.37)

Data shown as mean (SD) or median (range). [#] data from 10 controls. *P <0.05 **P<0.01 ***p<0.0001 **** p<0.00001 vs. healthy controls. [a] Chi squared test [b] Mann Whitney U test

Table 3. Approximate entropy (ApEn) of ventilatory variables during incremental exercise in patients with breathing pattern disorder and controls

	Controls	Breathing Pattern Disorder
	N=15	N=20
ApEn Tidal Volume	1.02 (0.29)	1.28 (0.23)**
ApEn Breathing Frequency	1.32 (0.21)	1.41 (0.20)
ApEn Minute Ventilation	0.65 (0.23)	0.97 (0.30)**

Data shown as mean (SD) ** P<0.01 vs controls.