Exertional oscillatory ventilation in subjects without heart failure reporting chronic dyspnoea

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To the Editor:

The persistence of limiting breathlessness in a patient who is thought to be under the maximal available therapy for their underlying cardiovascular and/or respiratory disease(s) has been termed residual exertional dyspnoea (RED) [1]. RED remains a challenge to the modern pulmonologist because the patient (and the referring physician) assumes that the "lung doctor" should invariably provide an effective plan to fight the symptom. A sizable fraction of these subjects is eventually referred for cardiopulmonary exercise testing (CPET) in the hope that the test will shed light on the underlying mechanisms [2]. We herein report a series of carefully selected subjects with RED in whom CPET uncovered cycles of waxing and waning of ventilation (V'_E) meeting the extant criteria for exertional oscillatory ventilation (EOV) [3]. Rather surprisingly, no subject had heart failure (HF) with reduced (r), mid-range or preserved ejection fraction (EF), *i.e.* the diseases traditionally related to EOV [4]. Although it is already known that EOV may occur in subjects without HF [5], the presence of EOV in non-HF subjects with RED has never been described.

In a multicentre study, we analysed clinical, resting functional and CPET data from 21 non-HF, EOV-positive subjects who, in the opinion of the attending cardiologist and/or pulmonologist, were under the best available therapy for the underlying cardiopulmonary disease(s) but still reported activity-related dyspnoea (modified Medical Research Council questionnaire score ⩾2), *i.e.* RED. Results were compared with those from 20 age- and sex-matched EOV-positive subjects with stable HFrEF, the closest correlate of EOV [3]. 15 subjects with RED were referred by the specialist for repeat CPET after a mean of 10 months (ranging from 6 to 16 months).

Pulmonary function tests, including arterial blood gases for dead space (V_D)/tidal volume (V_T) calculation, were performed according to current guidelines. CPET on a cycle ergometer with serial dyspnoea (0–10 Borg scale) and inspiratory capacity (IC) measurements [6] followed a 1-min, stepwise incremental protocol (10–15 W·min^{-1}). EOV was established if the V'_E (10-s arithmetic mean of all breaths) *versus* time plot showed three or more regular oscillations with amplitude (change between apex and nadir) ⩾15% of the average resting V'_E that lasted for ⩾60% of the incremental phase [3]. EOV amplitude, dynamic lung volumes and dyspnoea scores were calculated over each quartile of exercise duration. Capillary blood gases were measured from arterialised ear lobe blood at rest and at exercise cessation (N=10 in RED and N=11 in HF). Unpaired t-tests (or Mann–Whitney when appropriate) was used to compare differences between groups. χ^2 tests were use to compare frequencies. A $p<0.05$ level of significance was used for all analyses.

The typical subject with RED was an overweight or obese man in his late 60s presenting with chronotropic incompetence (if not on a β-blocker), atrial and/or ventricular arrythmias, diastolic dysfunction, type 2 diabetes mellitus, and metabolic syndrome (table 1). Most subjects (18 out of 21, 85.7%) were followed by a cardiologist either alone or in association with a respirologist (12 out of 21, 57.1%). A previous diagnosis of "medically unexplained dyspnoea" was common (11 out of 21, 52.3%) and approximately a quarter (six out of 21, 28.5%) had undergone invasive procedures, which were nondiagnostic. A minority of subjects presented with a chronic respiratory disease (seven out of 21, 33.3%), usually mild COPD (n=5) and/or incipient or mild interstitial lung disease (n=3). Lung function was largely within normal range in subjects with RED; conversely, HF patients tended to present with mild restriction ($p<0.05$). Arterial blood gases revealed normoxaemia associated with mild hypocapnia or arterial carbon dioxide

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TABLE 1 Resting and exercise characteristics of non-heart failure (HF) subjects with residual exertional dyspnoea (RED) and HF patients

Variables	RED	HF
Subjects	21	20
Demographic/anthropometric		
Age, years	69.1±8.4	68.3±7.2
Men	12 (57.1)	11 (55)
Body mass index, $kg \cdot m^{-2}$	30.8±6.2*	26.5±7.3
Obesity, absence/mild/moderate/morbid	5/10/4/2	11/7/1/1
Clinical		
General		
Dyspnoea duration, months, median (range)	18 (6–32)	16 (4–20)
mMRC dyspnoea score, 0/1/2/3/4	0/0/12/8/1	0/3/9/6/2
Current/previous smokers	12 (57.1)*	16 (80)
Anxiety	9 (42.8)	7 (35)
Depression	11 (52.3)*	6 (30)
Renal impairment	2 (9.5)*	13 (65)
Anaemia	1 (4.7)*	8 (40)
NT-pro-BNP, $pg \cdot mL^{-1}$	168±62	1412±231
Sleep disordered breathing	6/10 (60)	4/8 (50)
Cardiovascular		
LVEF, %	63.6±8.0*	30.2±6.9
Previous/current cardiovascular conditions	18 (85.7)	20 (100)
NYHA functional class 2–3	15 (71.4)	16 (80)
Ischaemic dilated cardiomyopathy	0*	14 (70)
Hypertension	12 (57)*	6 (30)
Atrial fibrillation/flutter	11 (52.3)	9 (45)
Supraventricular tachycardia	7 (33.3)	6 (30)
Ventricular arrythmias	6 (28.5)*	14 (70)
Other arrhythmias	6 (28.5)*	10 (50)
LA enlargement, none/mild/moderate/severe	13/6/2/0*	2/5/5/8
Diastolic dysfunction, none/mild/moderate/severe	9/9/2/1	4/13/2/1
Implantable cardioverter–defibrillator or pacemaker	0*	17 (85%)
Previous pulmonary embolism	3 (14.2)*	6 (30)
Pulmonary hypertension	4 (19)*	10 (50)
Previous myocardial infarction	4 (19)*	14 (70)
Previous cardioversion	2 (9.5)*	6 (30)
Metabolic		
Metabolic syndrome	12 (57)	10 (50)
Type 2 diabetes mellitus	13 (61.9)	9 (60)
Hyperthyroidism	3 (14.2)	2 (10)
Main medications		
Diuretics	6 (28.5)*	20 (100)
β-blockers	6 (28.5)*	18 (83)
ACE inhibitors or ARBs	3 (14.5)*	13 (65)
Sacubitril–valsartan	0*	6 (30)
Antiarrhythmic	10 (47.6)	12 (60)
Lung function		
FVC, % predicted	89.9±14.3*	71.6±10.9
FEV_1, % predicted	88.1±13.6*	70.4±11.7
FEV_1/FVC	0.70±0.06*	0.78±0.10
TLC, % predicted	95.7±15.8*	79.3±13.0
D_{LCO}, % predicted	73.6±14.4*	58.3±11.4
P_{aO_2}, mmHg	74±6	75±5
P_{aCO_2}, mmHg	34±4*	39±3
V_D/V_T	0.35±0.06 *	0.42±0.05
MIP, % predicted	89.3±14.5*	71.9±10.4
CPET		
Metabolic/cardiovascular		
Peak WR, % predicted	65.1±13.0	62.3±10.8
Peak V'_{O_2}, % predicted	64.1±10.6*	49.6±9.7

Continued

TABLE 1 Continued

Variables	RED	HF
V'_{O_2}–WR slope, mL·min^{-1}·W^{-1}	9.8±2.0*	6.7±1.4
Chronotropic incompetence[#]	7/13 (53.8)	NA
Peak MAP, mmHg	119±24*	101±20
Ventilatory		
V'_E–V'_{CO_2} slope	38.6±9.1	39.2±8.3
EOV duration, % test	79.3±10.1	80.1±9.4
Amplitude of V'_E cycles, L·min^{-1}		
1st test quartile	16.3±10.2*	13.4±8.0
2nd test quartile	14.7±6.4*	12.6±7.0
3rd test quartile	11.4±7.8	10.8±6.4
Duration of V'_E cycles, s		
1st test quartile	55.4±12.3	52.1±11.5
2nd test quartile	53.41±9.0	56.31±10.1
3rd test quartile	44.6±10.4	47.4±9.7
Lung-mechanical/breathing pattern		
V_T/IC		
1st test quartile	0.64±0.06*	0.60±0.05
2nd test quartile	0.68±0.07*	0.64±0.05
3rd test quartile	0.74±0.09	0.69±0.07
IRV, % TLC		
1st test quartile	35.4±9.2*	41.7±10.1
2nd test quartile	29.1±7.5*	35.4±8.3
3rd test quartile	18.2±8.3*	22.1±8.7.0
Pulmonary gas exchange		
Peak S_{pO_2}, %	94±3	93±4
Peak P_{ETCO_2}, mmHg	33±4*	28±4
Peak P_{cCO_2}, mmHg[¶]	32±3*	35±3
Peak P_{c-ETCO_2}, mmHg[¶]	−1±3*	7±4
Peak V_D/V_T[¶]	0.30±0.07*	0.41±0.04
Sensory		
Dyspnoea scores		
1st test quartile	3 (0.5–4)*	1 (0–3)
2nd test quartile	4 (2–6)*	2 (0–4)
3rd test quartile	4.5 (3–8)	3.5 (1–5)
Peak	7 (4–10)*	4 (2–8)
Peak leg effort scores	4 (2–7)*	6.5 (4–9)
Peak dyspnoea−leg effort score differences	2.5 (−2–6)*	−3 (−4–3)
Peak dyspnoea ⩾leg effort scores	15 (71.4)*	7 (35)

Data are presented as mean±SD, n (%) or n/N (%), unless otherwise stated. All subjects presented with exertional oscillatory ventilation (EOV) during an incremental cardiopulmonary exercise test (CPET). Data relative to the last quartile of CPET are not shown due to the low frequency of EOV close to exercise termination. mMRC: modified Medical Research Council scale; NT-pro-BNP: N-terminal pro-hormone of B-type natriuretic peptide; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; LA: left atrium; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; D_{LCO}: capacity of the lung for carbon monoxide; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; V_D: dead space volume; V_T: tidal volume ratio; MIP: maximal inspiratory pressure; WR: work rate; V'_{O_2}: oxygen uptake; MAP: mean arterial pressure; V'_E: ventilation; V'_{CO_2}: carbon dioxide output; IC: inspiratory capacity; IRV: inspiratory reserve volume; S_{pO_2}: oxygen saturation by pulse oximetry; P_{ETCO_2}: end-tidal carbon dioxide tension; P_{cCO_2}: capillary carbon dioxide tension; P_{c-ETCO_2}: capillary–end-tidal carbon dioxide gradient; NA: not available. [#]: Wilkoff index [7]; [¶]: n=10 and n=11 for RED and HF, respectively. *: $p<0.05$.

tension (P_{aCO_2}) close to the lower limit of normal in the RED group. A mildly elevated V_D/V_T was found in two out of 21 (~10%) subjects with RED, contrasting with nine out of 20 (45%) HF patients. Similar to resting values, subjects in the former group showed lower exercise capillary carbon dioxide tension and V_D/V_T ($p<0.05$) (table 1); moreover, only three of them showed mild exertional hypoxaemia, *i.e.* oxygen saturation by pulse oximetry ⩾90% and <94%.

The V'_E oscillations were of greater amplitude (but with similar duration) in subjects with RED compared to those with HF from the earlier stages of exercise. Higher amplitude was associated with larger V_T;

therefore, subjects from the former group used a greater fraction of the volume available for tidal expansion (IC), breathing closer to total lung capacity, *i.e.* they showed lower inspiratory reserve volumes. Accordingly, higher dyspnoea scores were reported in the RED group throughout exercise ($p<0.05$) (table 1). In keeping with a higher dyspnoea burden, all subjects with RED, but only eight out of 20 (40%) HF patients, reported scores above the 75th centile of the predicted value [8] at the highest work rate (WR) common to all participants (40 W). The severity of lung mechanical abnormalities and exertional dyspnoea did not differ between subjects with or without a previous diagnosis of chronic respiratory disease(s) ($p>0.05$). Notably, EOV was no longer identified in seven out of 15 subjects (46.6%) with RED who repeated CPET. Of note, while these subjects presented with significantly lower dyspnoea at 40 W (second −first test difference (median (range)) −2 (−5–2) Borg units) and higher peak WR (15 (–10–30) W), no significant between-test differences were found in those with persisting EOV ($p>0.05$). There were no significant differences in clinical, resting functional or CPET variables between subjects with resolved or persisting EOV ($p>0.05$).

EOV in HF is the result of: 1) low reserves of oxygen and carbon dioxide in the lungs and tissues; 2) delay of lung–central/peripheral chemoreceptor signal transmission; 3) increased afferent stimulation induced by interstitial oedema and ergoreceptor overstimulation; 4) increased pulmonary pressures with right ventricle–pulmonary circulation uncoupling; 5) impaired baroreflex activity; and 6) a high gain of chemoreceptors and/or central response to afferent signals [9]. It is noteworthy that, in contrast to HF, a high V_D/V_T (wasted ventilation) was rarely seen in subjects with RED [10]. Thus, an increased V'_E/carbon dioxide output (V'_{CO_2}) relative to the predicted value led to a low P_{aCO_2}: the resulting lower carbon dioxide "set-point" may have fuelled further hyperventilation. In fact, the physiological consequences of the cardiocirculatory/metabolic abnormalities found in the RED group have been associated with increased ventilatory stimulation, *e.g.* sympathetic overexcitation and autonomic imbalance, high left ventricular filling/capillary wedge pressures, exertional pulmonary hypertension, and increased muscle ergoreceptor stimulation [1, 11]. Exercise-induced pulmonary hypertension and haemodynamic abnormalities akin to HF with preserved ejection fraction, in particular, might hold an important role in eliciting EOV in the RED group. Thus, it is conceivable that EOV in non-HF subjects with chronic dyspnoea conflates multiple sources of heightened neurochemical afferent stimulation, which jointly conspire against the stability of the ventilatory control system in a predisposed subject.

Reduced peak oxygen uptake (V'_{O_2}) relative to predicted values in the RED group was associated with higher amplitude of V'_E oscillations which prompted: 1) larger V_T and, consequently, greater mechanical constraints; and 2) exertional dyspnoea compared to HF. Higher (*i.e.* normal) V'_{O_2}–WR slope plus the extra V'_{O_2} from the overloaded respiratory muscles may explain why subjects in the former group showed similar peak WR but higher peak V'_{O_2} (table 1). Although the ventilatory output relative to metabolic demand (V'_E–V'_{CO_2}) did not differ between the groups, subjects with RED may have detected more pronounced increased in the respiratory neural drive secondary to both: 1) "excessive"; and 2) "impeded" breathing [12]. It also called our attention that exercise onset was associated with larger V'_E fluctuations, which started earlier in in the RED group. Thus, feed-forward (collateral) increase in V'_E simultaneous to motor activation may have a greater role in triggering EOV in non-HF than HF subjects, particularly on a background of a lower carbon dioxide "set-point" [13]. Due to the repetitive, short-duration pattern of daily-life physical activities, EOV-related breathlessness may have an even greater impact on long-term dyspnoea in the former population.

In keeping with the observational, "real-life" nature of this study, we did not suggest any specific intervention to the specialist in charge of the patient, nor did we interfere with their decision to request a follow-up CPET or not. The significant association between longitudinal EOV disappearance and improvement in exertional dyspnoea may reflect a cause–effect relationship and/or the positive effects of the intervention(s) on the underlying determinants of both EOV and breathlessness. Due to the small number of subjects and multitude of interventions between CPETs (*e.g.* rhythm control instead of rate control in atrial arrhythmias, pacemaker insertion in those with severe chronotropic incompetence, and stricter control of hypertension and diabetes), we were unable to identify which of them more consistently led to EOV reversal. A clear signal towards the underlying mechanism(s) of improvement may emerge from "acute", proof-of-concept interventional studies using pharmacological interventions known to lessen or eliminate EOV, such as oral sildenafil [14]. What is the actual prevalence of EOV in unselected, chronically dyspnoeic subjects who were never referred for CPET? Are we describing the "tip of the iceberg" or is ours a biased sample of particularly susceptible subjects (to dyspnoea)? Does EOV predict negative outcomes (including poorer survival) and sleep disordered breathing in this population? What happens with EOV if the subject eventually develops HF? These questions and others remain to be prospectively investigated.

In conclusion, EOV during incremental CPET might prove helpful to indicate that the underlying cardiovascular and metabolic abnormalities (table 1) are mechanistically related to persisting dyspnoea despite apparent treatment optimisation. In this context, CPET should be requested early in the investigation of indetermined dyspnoea [15] to: 1) lessen the psychological burden associated with lack of a clear explanation for a disabling symptom; 2) avoid potentially iatrogenic procedures; and 3) trigger efforts to further improve the management of common comorbidities that jointly predispose to EOV in individual subjects.

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