



Original Research

Comparative analysis between available challenge tests in the hyperventilation syndrome

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ABSTRACT

Background: The hyperventilation syndrome (HVS) is characterized by somatic/ psychological symptoms due to sustained hypocapnia and respiratory alkalosis without any organic disease.**Objective:** The purpose of this study was to compare ventilatory parameters and symptoms reproducibility during the hyperventilation provocation test (HVPT) and cardiopulmonary exercise test (CPET) as diagnostic tools in patients with HVS, and to identify the most frequent etiologies of the HVS by a systematic assessment.**Methods:** After exclusion of organic causes, 59 patients with HVS according to Nijmegen's questionnaire (NQ) score ≥ 23 with associated hypocapnia ($\text{PaCO}_2/\text{PETCO}_2 < 35$ mm Hg) were studied.**Results:** The most frequent comorbidities of HVS were anxiety and asthma (respectively 95% and 73% of patients). All patients described ≥ 3 symptoms of NQ during the HVPT vs 14% of patients during the CPET ($p < 0.01$). For similar maximal ventilation (61 L/min during HVPT vs 60 L/min during CPET), the median level of PETCO_2 decreased from 30 mmHg at baseline to 15 mmHg during hyperventilation and increased from 31 mmHg at baseline to 34 mmHg at peak exercise (all $p < 0.01$). No significant difference for the ventilatory parameters was found between patients with HVS ($n = 16$) and patients with HVS + asthma ($n = 43$).**Conclusions:** In term of symptoms reproducibility, HVPT is a better diagnostic tool than CPET for HVS. An important proportion of patients with HVS has an atypical asthma previously misdiagnosed. The exercise-induced hyperventilation did not induce abnormal reduction in PETCO_2 , suggesting that the exercise could be a therapeutic tool in HVS.

1. Introduction

Dysfunctional breathing (DB) is an umbrella term used to describe a group of breathing disorders where chronic changes in breathing pattern result in dyspnoea and chest pain/tightness in the absence of an organic respiratory disease [1–3]. Disproportionate dyspnoea is frequently associated with hyperventilation (increased minute ventilation that exceed metabolic demands) resulting in a decrease in arterial partial pressure of carbon dioxide (PaCO_2) and respiratory alkalosis, associated with symptoms such as tingling, tetany and numbness [1]. Apart from clinical description, there are no standard diagnostic criteria for DB [3, 4]. As method of diagnosis, most of studies used the Nijmegen

questionnaire (NQ) [5]. DB may be objectively assessed during a cardiopulmonary exercise test (CPET) or a hyperventilation provocation test (HVPT) which have been used as diagnostic tools [6].

Different DB patterns have been described but the hyperventilation syndrome (HVS) is the most common form with a prevalence estimated of 6–10% in general population [1,7,8]. In the absence of validated diagnostic tools, in practice it is difficult to accurately determine the real prevalence of DB [1,9]. DB is associated with significant morbidity (e.g. anxiety, asthma) and health-related costs (e.g. high number of hospital presentations, overtreatment), low health-related quality of life (QoL) affecting school and work attendance [3,8,10–12]. Breathing retraining programs (e.g. the Buteyko method, lip breathing, yoga) could re-establish a regular breathing pattern, reduce the symptoms and

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Abbreviations/acronyms

DB	dysfunctional breathing
PaCO ₂	arterial partial pressure of carbon dioxide
NQ	Nijmegen questionnaire
CPET	cardiopulmonary exercise test
HVPT	hyperventilation provocation test
HVS	hyperventilation syndrome
QoL	quality of life
STAI	State-Trait Anxiety Inventory
ABGA	arterial blood gas analysis
PET _{CO2}	end-tidal carbon dioxide pressure
TL _{CO}	single-breath carbon monoxide transfer factor
FEV1	forced expiratory volume in one second

FVC	forced vital capacity
TLC	total lung capacity
sRaw	specific airway resistance
PD ₂₀	dose of methacholine causing a 20% fall in FEV1
RR	respiratory rate
HR	heart rate
SpO ₂	oxygen saturation
VE	minute-ventilation
ECG	electrocardiogram
VO ₂	oxygen consumption
RQ	respiratory quotient
SD	standard deviation
CT-scan	computer tomography scan

hospital visits, and improve the QoL [3,9,13].

The principal aim of this study was to compare ventilatory parameters and symptoms reproducibility during the HVPT and CPET as diagnostic tools in patients with HVS. Second, we aimed to identify the more frequent comorbidities of the HVS by a systematic assessment and to describe the characteristics of the different groups in order to improve the management of these patients and to define adapted therapeutic strategies.

2. Methods

2.1. Study design

An observational study was performed between January 2007 and December 2017 in the pulmonology departments at Nancy University Hospital (France) and Brugmann University Hospital (Belgium). The study was approved by the institutional review board at the French Society for Respiratory Medicine (*Société de Pneumologie de Langue Française*, reference CEPRO 2017-046). All patients provided prior written, informed consent to participation.

2.2. Study population and protocol

We included adult patients referred in our clinics by chest or emergency physicians, with severe dyspnoea and suspicion of HVS based on a screening NQ score >23 [14]. Subjects underwent systematic assessment including clinical history and examination; atopy status evaluation defined as at least one skin prick test positive [15]; anxiety evaluation by State-Trait Anxiety Inventory (STAI) (0–20: no anxiety; 21–40: mild anxiety; 41–60: moderate anxiety; 61–80: severe anxiety) [16]; lung function testing with methacholine bronchial challenge if normal values at baseline [17–21]; arterial blood gas analysis (ABGA) to evaluate the presence of respiratory alkalosis (pH > 7.45), hypocapnia (PaCO₂ < 35 mmHg) and bicarbonate level (22–26 mEq/L); the end-tidal carbon dioxide pressure (PET_{CO2}) measure by a capnograph (Zan, Germany) via a mouthpiece, after ≥2 min of resting. Arterial blood was sampled from the non-dominant radial artery under local anaesthetic ≥30 s and analysed immediately (AVL Medical Instruments AG, Switzerland). For the patients who refused ABGA, the PET_{CO2} value was accepted as accurately reflecting the PaCO₂ as previously demonstrated [22]. Additional exams were performed to eliminate secondary causes of HVS (Fig. 1). The patients with compatible clinical symptoms for HVS, NQ score >23,

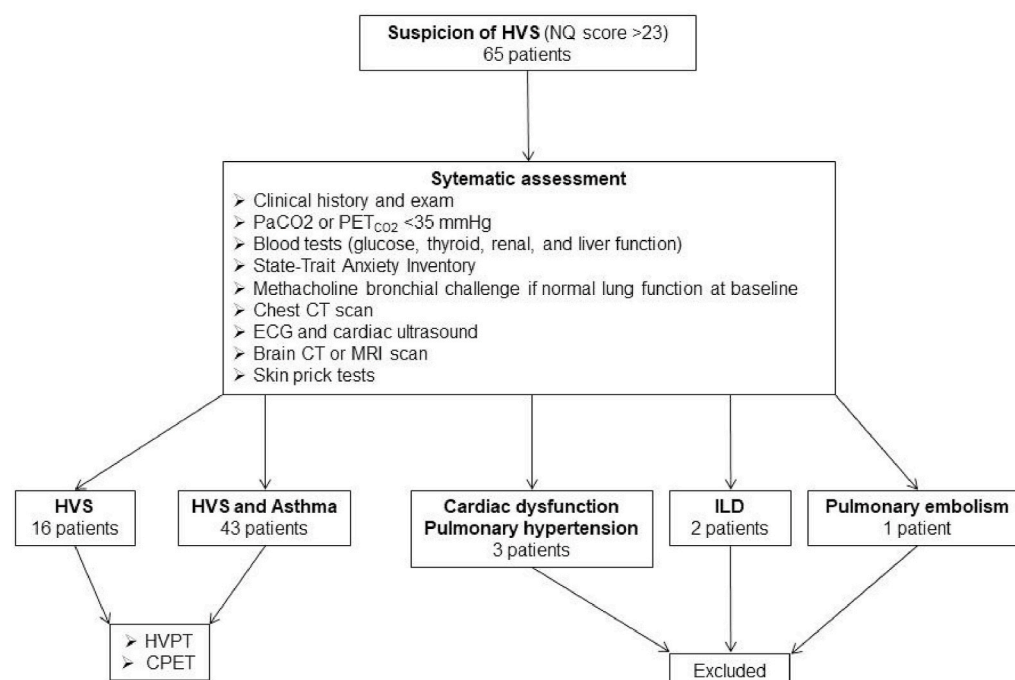


Fig. 1. Study design.

HVS: hyperventilation syndrome; NQ score: Nijmegen questionnaire score; PaCO₂: partial arterial pressure of carbon dioxide; PET_{CO2}: end-tidal carbon dioxide pressure; CT scan: computer tomography scan; ECG: electrocardiogram; MRI: magnetic resonance imaging; HVPT: hyperventilation provocation test; CPET: cardiopulmonary exercise testing; ILD: interstitial lung disease.

and a $\text{PaCO}_2/\text{PET}_{\text{CO}_2} < 35$ mmHg without another organic/metabolic aetiology underwent HVPT and CPET.

2.3. Pulmonary function testing and challenge tests

Patients performed forced spirometry, plethysmography and single-breath carbon monoxide transfer factor (TL_{CO}) testing according to current guidelines [17–19]. Lung function variables retained for analysis were forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, total lung capacity (TLC), specific airway resistance (sRaw) and TL_{CO} . Bronchial reactivity to methacholine was tested for all patients with a FEV1 > 60% of predicted or 1.5 L after lung function measurements [20,21]. The test was performed using an automatic dosimeter and the methacholine solution of 2.5% concentration was prepared so that the dosimeter delivered 100 µg/puff. The starting dose was 100 µg with subsequent doubling doses (administered with a 5-min interval between doses), with the respect of contraindications and safety cautions [20,21]. Methacholine inhalations were performed while patients inspired with sub-TLC breaths (in the range of tidal breaths to one half inspiratory capacity breaths) in order to avoid the bronchoprotective effect of TLC inhalations. Spirometry was performed at 90 s after each step and the symptoms and signs were recorded. The test was stopped if FEV1 decreased > 20% reported to baseline value (PD_{20}) or after the delivery of the maximum cumulative methacholine dose of 1600 µg. Cumulative calculation for PD_{20} was performed without factoring out evaporation so that a PD_{20} of 1600 µg approximates the 400 µg cut off of the 2017 European Respiratory Society Task Force [20]. A rapidly acting inhaled bronchodilator was then administered and the spirometry repeated to check the restitution to the baseline. A positive criteria for airway hyperresponsiveness was considered a 20% fall in FEV1 occurred at a cumulative dose of ≤ 1600 µg [20]. The asthma diagnosis was based on the history of asthma symptoms associated with the confirmation of airway hyperresponsiveness [23].

Patients underwent a HVPT according to a protocol previously described with 3 min of resting breathing, 1 min of voluntary hyperventilation, and 5 min of recovery [24]. This protocol was chosen because the 3 min of voluntary hyperventilation recommended by others protocols [25] are difficult to maintain in practice for most patients due to the onset of symptoms. HVPT was performed using a capnograph with a mouthpiece and a pulse-oxymeter (Zan, Germany) recorded to a computer with measurements of PET_{CO_2} , respiratory rate (RR) and heart rate (HR), oxygen saturation (SpO_2), minute-ventilation (VE). HVPT was considered positive when ≥ 3 items of NQ were reproduced by the test and PET_{CO_2} remained < 35 mmHg during the recovery [24–26].

Symptom-limited incremental CPET was performed on cycle ergometer (Ergoline, Ergometrics 800, Germany) with a stepwise increase in workload of 25 W/min, starting with unloaded cycling. Prior to the test, patients were encouraged to reach maximal exhaustion and motivational interventions were used during exercise. All tests were performed in room air, with continuous monitoring by a physician of electrocardiogram (ECG), SpO_2 and oxygen consumption (VO_2), VE, HR, PET_{CO_2} , VE/VCO_2 ratio at rest and at peak, as recommended by current guidelines [27]. A respiratory quotient (RQ) ≥ 1.1 was considered as indicator of maximal exercise. Dyspnoea was quantified according to Modified Borg scale. Expired gases were collected and analysed by the PowerCube-Ergo system (Ganshorn Medizin Electronic GmbH, Germany). HVS was confirmed if an abnormal breathing pattern was assessed by the physician during the exercise (e.g. irregularity and unsteadiness of breathing) without exercise-induced bronchoconstriction at clinical exam and good exercise tolerance [3] with an abnormally large increase in VE comparable to the value obtained during the voluntary hyperventilation from HVPT. The presence of symptoms from NQ was evaluated at the end of the exercise testing.

2.4. Statistical analysis

Statistical analysis was performed using the SAS University Edition (SAS Institute, Cary, NC, USA). Qualitative variables were expressed as number (percentage). Quantitative variables were expressed as the mean ± standard deviation (SD) if normally distributed or median [25th; 75th percentile] if not normally distributed. Patients were divided in 2 groups according to clinical history and methacholine test response: *HVS group* (patients with a negative test defined as $\text{PD}_{20} > 1600$ µg), and *HVS + Asthma group* (patients with a positive test defined as $\text{PD}_{20} \leq 1600$ µg, presence of asthma symptoms and bronchoconstriction at clinical exam). Comparisons between groups were performed using paired or unpaired t-tests, as appropriate, or Fisher's exact test. The threshold for statistical significance was set to $p < 0.05$.

3. Results

Sixty-five patients with HVS were addressed to our clinics and had a systematic assessment for HVS. All patients had normal blood tests (glucose, thyroid, renal, and liver function). Six patients were excluded because additional exams found secondary etiologies of HVS (Fig. 1). The final analysis was conducted on the remaining 59 patients, mean age of 44 ± 15 years and mean NQ score of 36 ± 7 (Table 1).

Table 1
Demographic and clinical characteristics of the study population.

Parameter	Total population N = 59	HVS N = 16	HVS + asthma N = 43	P
Age (years) (mean ± SD)	44 ± 15	46 ± 13	42 ± 16	0.46
Sex ratio F/M	48/11	13/3	35/8	0.99
BMI (mean ± SD)	27.69 ± 6.71	26.70 ± 6.24	28 ± 7.43	0.57
Smoking – n (%)				0.30
Non-smokers	40 (68)	11 (69)	29 (67)	
Former smokers	16 (27)	5 (31)	11 (26)	
Active smokers	3 (5)	0 (0)	3 (7)	
Pack-year (mean ± SD)	2.19 ± 3.49	2.13 ± 3.42	2.21 ± 3.56	0.94
Atopy – n (%)	20 (34)	4 (25)	16 (37)	0.38
NQ score (mean ± SD)	36.14 ± 7.28	36 ± 6.71	35.47 ± 7.45	0.83
STAI score (mean ± SD)	55.27 ± 10.60	53.75 ± 13.46	56.81 ± 9.57	0.40
Anxiety state and level – n (%)				
No anxiety	3 (5)	2 (12)	1 (2)	
Mild	6 (10)	2 (13)	4 (9)	
Moderate	19 (32)	5 (31)	14 (33)	0.11
Severe	31 (53)	7 (44)	24 (56)	0.42
Lung function (mean ± SD)	94.41 ± 9.74	96.50 ± 11.04	92.53 ± 9.18	0.23
FEV1 (%)	102.39 ± 9.82	100.00 ± 10.86	101.69 ± 9.30	0.61
FVC (%)	82.66 ± 7.72	79.00 ± 3.84	84.22 ± 8.86	0.06
FEV1/FVC (%) sRaw	1.67 ± 0.88	1.28 ± 0.69	1.68 ± 0.89	0.17
TLC (%)	106.22 ± 12.34	104.33 ± 14.28	106.06 ± 10.02	0.65
TL_{CO} (%)	85.22 ± 11.28	82.17 ± 8.70	84.34 ± 7.97	0.44
Arterial blood gas (mean ± SD)				
(n = 28) pH	7.48 ± 0.01	7.49 ± 0.01	7.47 ± 0.01	<0.01
PaO_2 (mm Hg)	92.16 ± 9.99	93.22 ± 8.48	91.88 ± 10.53	0.78
PaCO_2 (mm Hg)	31.08 ± 2.57	30.90 ± 1.87	31.13 ± 2.77	0.85
Bicarbonate (mEq/L)	23.41 ± 1.52	22.98 ± 0.92	23.53 ± 1.65	0.45

Data shown as mean $\pm$ SD. F: female; M: male; n: number; NQ: Nijmegen questionnaire score; STAI score: State-Trait Anxiety Inventory score; FEV1: forced expiratory volume in one seconde; FVC: forced vital capacity; sRaw: resistance; TLC: total lung capacity; TLCO: transfer lung capacity of carbon monoxide; PaO₂: partial pressure of arterial oxygen; PaCO₂: partial pressure of arterial carbon dioxide; mm Hg: millimeter of mercury; mEq/L: milliequivalents per liter.

According to clinical history and methacholine test results, 43 patients (73%) were diagnosed with *HVS + Asthma* and 16 (27%) with *HVS* only. The population was characterized by a predominance of females (81%), non-smokers (68%), with overweight (27.69 ± 6.71 kg/m²), low prevalence of atopy (34%), and high prevalence of anxiety (95%). The mean STAI score was at 55.27 ± 10.60 suggesting the presence of a moderate/severe anxiety [16]. Lung function testing showed mean FEV1 of $94 \pm 10\%$ of predicted, mean TLC of $106 \pm 12\%$ of predicted and mean TLCO of $85 \pm 11\%$. Only 28 patients (47%) accepted the ABGA which confirmed the presence of respiratory alkalosis with mean pH of 7.48 ± 0.01 and mean PaCO₂ of 31 ± 3 mm Hg.

Both groups were comparable in term of sex ratio, BMI, smoking and atopy status, NQ and STAI scores and baseline lung function (Table 1). No significant difference was seen between the groups concerning the anxiety state. ABGA showed significantly higher pH value in the *HVS* vs *HVS + Asthma* group (7.49 ± 0.01 vs 7.47 ± 0.01 , $p < 0.01$).

Physiological parameters measured during HVPT and CPET are presented for all patients and both groups in Tables 2 and 3.

During HVPT, RR, HR, VE and SaO₂ were significantly increased compared to baseline in total population and in each group ($p \leq 0.02$) while PETCO₂ was significantly lower during hyperventilation ($p < 0.01$) with PETCO₂ baseline/hyperventilation ratio of 2.07 ± 0.10 that did not return to the baseline value at 5 min of recovery, PETCO₂ baseline/recovery ratio of 1.26 ± 0.21 (Table 2, Fig. 2).

Data shown as median [IQR]. HR: heart rate; L: litter; mm Hg: millimeter of mercury; min: minute; PETCO₂: partial pressure of end-tidal carbon dioxide; RR: respiratory rate; SaO₂: blood oxygen saturation; VE: minute ventilation.

During CPET, in total population, RR, VE, PETCO₂ and dyspnoea were significantly higher at peak exercise compared with baseline ($p < 0.01$), with consequently lower VE/VCO₂ ratio and a PETCO₂ baseline/peak exercise ratio at 0.94 ± 0.19 (Table 3, Figs. 2 and 3).

In *HVS* and *HVS + Asthma* group, RR, VE and dyspnoea were statistically increased at peak exercise vs baseline ($p < 0.01$) while PETCO₂ was significantly higher and VE/VCO₂ lower in *HVS + Asthma* group ($p \leq 0.01$) but not different in *HVS* group (Table 3).

Data shown as median [IQR]. Dyspnoea estimated according to

Table 3

Evolution of respiratory and clinical parameters during CPET.

Parameter	Baseline (1)	Peak exercise (2)	P 1 vs 2
PETCO₂ (mm Hg)			
Total population	31 [28–33]	34 [30–37]	<0.01
HVS	31 [29–36]	35 [31–39]	0.26
HVS + asthma	31 [28–33]	34 [30–37]	<0.01
RR (breaths/min)			
Total population	18 [15–22]	39 [33–45]	<0.01
HVS	19 [16–26]	37 [30–45]	<0.01
HVS + asthma	18 [15–22]	39 [33–45]	<0.01
VE (L/min)			
Total population	11 [4–33]	60 [45–82]	<0.01
HVS	10 [6–33]	54 [37–64]	<0.01
HVS + asthma	11 [4–25]	61 [50–84]	<0.01
VE/VO₂ ratio			
Total population	32 [27–44]	33 [30–41]	0.53
HVS	38 [27–47]	34 [31–47]	0.93
HVS + asthma	30 [27–42]	33 [30–39]	0.38
VE/VCO₂ ratio			
Total population	39 [32–48]	32 [28–37]	<0.01
HVS	43 [30–51]	32 [28–38]	0.11
HVS + asthma	38 [32–48]	33 [28–37]	0.01
Dyspnoea			
Total population	1 [0–3]	9 [7–10]	<0.01
HVS	2 [0–4]	9 [6–10]	<0.01
HVS + asthma	1 [0–2]	9 [7–10]	<0.01

Modified Borg's scale; L: litter; mm Hg: millimeter of mercury; min: minute; PETCO₂: partial pressure of end-tidal carbon dioxide; RR: respiratory rate; VE: minute ventilation; VE/VCO₂ ratio: minute ventilation/carbon dioxide output ratio (ventilatory efficiency); VE/VO₂ ratio: minute ventilation/oxygen consumption ratio.

Minute-ventilation was comparable at baseline and during challenge tests, while PETCO₂ was similar at baseline but significantly decreased during voluntary hyperventilation vs peak exercise ($p < 0.01$) (Table 4).

The evolution of VE and PETCO₂ during both challenge tests are represented in Fig. 2.

All 59 (100%) patients had ≥ 3 daily life complaints from NQ reproduced/recognized at the end of HVPT in contrast with a lower proportion (14%) during CPET ($p < 0.01$) (Table 4, Fig. 3).

No significant difference was found between the groups for respiratory parameters, PETCO₂, RR, VE, SaO₂, and HR at baseline, during voluntary hyperventilation and recovery period for HVPT or at baseline and at peak exercise for CPET (Table 5).

VE/VO₂, VE/VCO₂ and dyspnoea were similar between groups at baseline and at peak exercise. The exercise was stopped due to near

Table 2

Evolution of respiratory parameters and heart rate during HVPT.

Parameter	Baseline (1)	Hyperventilation (2)	Recovery (3)	P 1 vs 2	P 1 vs 3	P 2 vs 3
PETCO₂ (mm Hg)						
Total population	30 [27–32]	15 [13–15]	24 [20–27]	<0.01	<0.01	<0.01
HVS	30 [26–32]	15 [12–15]	23 [19–27]	<0.01	<0.01	<0.01
HVS + asthma	29 [27–32]	14 [13–16]	24 [20–28]	<0.01	<0.01	<0.01
RR (breaths/min)						
Total population	20 [16–23]	50 [42–59]	24 [20–27]	<0.01	0.12	<0.01
HVS	21 [18–22]	51 [46–58]	21 [18–29]	<0.01	0.64	<0.01
HVS + asthma	19 [15–24]	49 [42–59]	21 [18–28]	<0.01	0.12	<0.01
VE (L/min)						
Total population	12 [10–15]	61 [43–86]	13 [10–16]	<0.01	0.32	<0.01
HVS	10 [9–16]	53 [40–85]	13 [9–19]	<0.01	0.42	<0.01
HVS + asthma	12 [10–14]	63 [47–87]	13 [11–15]	<0.01	0.53	<0.01
SaO₂ (%)						
Total population	98 [97–99]	99 [98–100]	98 [98–99]	<0.01	0.20	0.19
HVS	98 [98–99]	99 [98–100]	99 [98–100]	<0.01	0.52	0.65
HVS + asthma	98 [97–99]	99 [98–100]	98 [98–99]	0.02	0.28	0.21
HR (beat/min)						
Total population	79 [71–94]	102 [89–120]	79 [70–93]	<0.01	0.98	<0.01
HVS	80 [72–98]	100 [85–117]	79 [75–90]	0.01	0.96	0.02
HVS + asthma	79 [71–93]	105 [90–120]	77 [68–94]	<0.01	0.95	<0.01

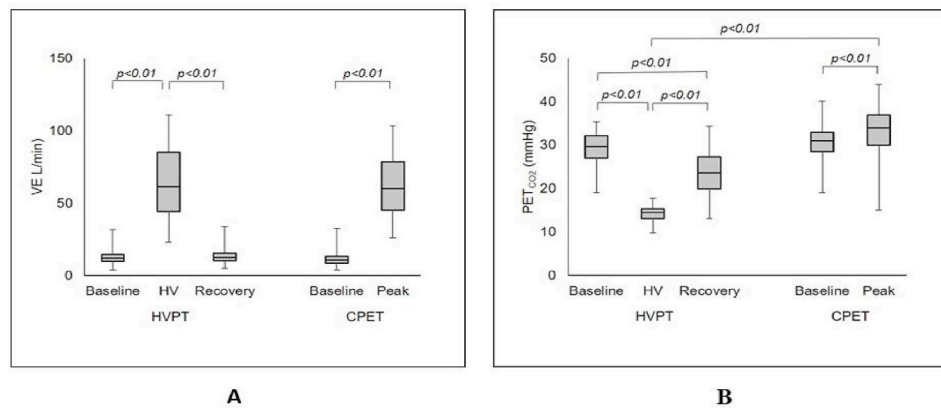


Fig. 2. Comparative analyses of minute-ventilation (A) and PET_{CO2} (B) evolution during both challenge tests in the studied population.

HVPT: hyperventilation provocation test; CPET: cardio-pulmonary exercise testing; VE: minute-ventilation; L/min: liter per minute; HV: hyperventilation; PET_{CO2}: end-tidal carbon dioxide pressure. Data were represented as median and confidence interval.

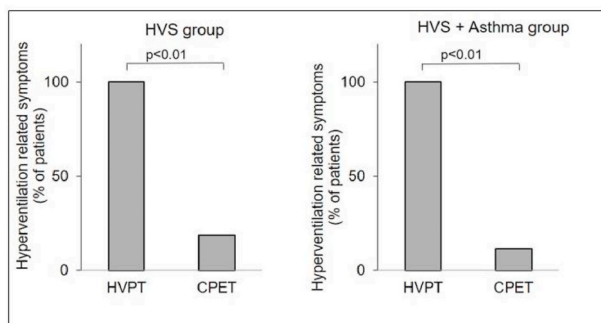


Fig. 3. Hyperventilation-related symptoms during challenge tests.

CPET: cardio-pulmonary exercise testing; HVPT: hyperventilation provocation test; HVS: hyperventilation syndrome. Data were represented as median and confidence interval.

Table 4

Comparison for clinical and respiratory parameters during HVPT and CPET.

Parameter	HVPT	CPET	P
Baseline			
PET_{CO2} (mm Hg)			
Total population	30 [27–32]	31 [28–33]	0.07
HVS group	30 [26–32]	31 [29–36]	0.18
HVS + asthma group	29 [27–32]	31 [28–33]	0.28
VE (L/min)			
Total population	12 [10–15]	11 [4–33]	0.45
HVS group	10 [9–16]	10 [6–33]	0.85
HVS + asthma group	12 [10–14]	11 [4–25]	0.24
During Hyperventilation or Exercise			
PET_{CO2} (mm Hg)			
Total population	15 [13–15]	34 [30–37]	<0.01
HVS group	15 [12–15]	35 [31–39]	<0.01
HVS + asthma group	14 [13–16]	34 [30–37]	<0.01
VE (L/min)			
Total population	61 [43–86]	60 [45–82]	0.55
HVS group	53 [40–85]	54 [37–64]	0.59
HVS + asthma group	63 [47–87]	61 [50–84]	0.83
Symptoms of Hyperventilation n (%)			
Total population	59 (100)	8 (14)	<0.01
HVS group	16 (100)	3 (19)	<0.01
HVS + asthma group	43 (100)	5 (12)	<0.01

Data shown as median [IQR]. L: liter; mm Hg: millimeter of mercury; min: minute; PET_{CO2}: partial pressure of end-tidal carbon dioxide; VE: minute-ventilation.

maximal dyspnoea for most of patients for a maximal effort ($RQ \geq 1.1$) but the median VO_2 was inferior to the normal predicted (median value 73% [25–121]) (Table 5).

Data shown as median [IQR]. PET_{CO2}: partial pressure of end-tidal carbon dioxide; RR: respiratory rate; VE: minute-ventilation; SaO₂: blood oxygen saturation; HR: heart rate; mm Hg: millimeter of mercury; L: liter; min: minute; VE/ VO_2 ratio: minute-ventilation/oxygen consumption ratio; VE/ VCO_2 ratio: minute-ventilation/carbon dioxide output ratio (ventilatory efficiency); VO_2 : oxygen consumption; RQ: respiratory quotient.

4. Discussion

This study has demonstrated that for similar minute-ventilation, HVPT is a better objective diagnostic tool for patients with HVS in term of symptoms reproducibility (≥ 3 items of the NQ) than CPET. The most frequent comorbidities of HVS identified in our population by a systematic assessment (including bronchial challenge tests, STAI, chest CT-scan, brain imaging, ECG and echocardiography) were anxiety and asthma.

HVS diagnosis was established in the studied population based on compatible clinical symptoms, NQ score >23 and hypocapnia [2,5,28,29]. In line with previous data, there are more middle-aged women [3,30,31], with overweight and non/former smokers [11]. By systematic screening for psychiatric morbidity using STAI and for airway responsiveness by methacholine test, we found that almost all patients with HVS had anxiety and three quarter of them asthma. Two other studies showed similar prevalence, with up to 80% of patients with HVS having asthma when specific investigations were made [32,33]. Conversely, HVS prevalence in asthmatic patients is difficult to accurately assess in the absence of gold standard diagnostic criteria [1]. When NQ was used, 34% of asthmatics had HVS [34] but this prevalence could be over-estimated due to symptoms like dyspnoea, chest pain/tightness and polypnoea common to both conditions [1,7,35].

In our study, the clinical characteristics of HVS + Asthma group were similar to the general population (Table 1) and comparable with other studies, being predominantly women, in middle-age, non-smokers, with low prevalence of atopy, overweight and comorbid anxiety [3,4,6,8,11,12]. The lung function was normal for all asthmatics suggesting a mild and atypical asthma which could explain the previous misdiagnosis [22,28]. Even if the relationship between chronic hyperventilation and asthma is complicated and the underlying mechanisms not fully understood [6,7,35,36], it is well-known that the presence of HVS in asthmatic patients is associated with poor asthma control, frequent exacerbations, low QoL, overtreatment, limitation of activity, and altered mental health [3,6,11,12,36]. It is thus mandatory to identify the

Table 5
Group comparison for the HVPT and CPET.

	Parameter	Total population N = 59	HVS N = 16	HVS + asthma N = 43	P
HVPT	Baseline				
	PET _{CO2} (mm Hg)	30 [27–32]	30 [26–32]	29 [27–32]	0.54
	RR (breaths/min)	20 [16–23]	21 [18–22]	19 [15–24]	0.58
	VE (L/min)	12 [10–15]	10 [9–16]	12 [10–14]	0.91
	SaO ₂ (%)	98 [97–99]	98 [98–99]	98 [97–99]	0.59
	HR (beats/min)	79 [71–94]	80 [72–98]	79 [71–93]	0.57
	During hyperventilation				
	PET _{CO2} (mm Hg)	15 [13–15]	15 [12–15]	14 [13–16]	0.67
	RR (breaths/min)	50 [42–59]	51 [46–58]	49 [42–59]	0.73
	VE (L/min)	61 [43–86]	53 [40–85]	63 [47–87]	0.37
	SaO ₂ (%)	99 [98–100]	99 [98–100]	99 [98–100]	0.94
	HR (beats/min)	102 [89–120]	100 [85–117]	105 [90–120]	0.72
	Recovery				
	PET _{CO2} (mm Hg)	24 [20–27]	23 [19–27]	24 [20–28]	0.55
	RR (breaths/min)	21 [18–28]	21 [18–29]	21 [18–28]	0.97
	VE (L/min)	13 [10–16]	13 [9–19]	13 [11–15]	0.63
	SaO ₂ (%)	98 [98–99]	99 [98–100]	98 [98–99]	0.20
	HR (beats/min)	79 [70–93]	79 [75–90]	77 [68–94]	0.55
CPET	Baseline				
	PET _{CO2} (mm Hg)	31 [28–33]	31 [29–36]	31 [28–33]	0.87
	RR (breaths/min)	18 [15–22]	19 [16–26]	18 [15–22]	0.47
	VE (L/min)	11 [4–33]	10 [6–33]	11 [4–25]	0.16
	VE/VO ₂ ratio	32 [27–44]	38 [27–47]	30 [27–42]	0.47
	VE/VCO ₂ ratio	39 [32–48]	43 [30–51]	38 [32–48]	0.66
	Dyspnoea	1 [0–3]	2 [0–4]	1 [0–2]	0.48
	Peak exercise				
	PET _{CO2} (mm Hg)	34 [30–37]	35 [31–39]	34 [30–37]	0.77
	RR (breaths/min)	39 [33–45]	37 [30–45]	39 [33–45]	0.65
	VE (L/min)	60 [45–82]	54 [37–64]	61 [50–84]	0.10
	VE/VO ₂ ratio	33 [30–41]	34 [31–47]	33 [30–39]	0.44
	VE/VCO ₂ ratio	32 [28–37]	32 [28–38]	33 [28–37]	0.87
	Dyspnoea	9 [7–10]	9 [6–10]	9 [7–10]	0.63
	VO ₂ (%)	73 [25–121]	71 [38–121]	74 [25–112]	0.79
	RQ	1.1 [0.9–1.9]	1.2 [1–1.9]	1.1 [0.9–1.9]	0.15

patients with both conditions in order to better adapt the therapeutic strategy.

A high prevalence of anxiety was found in our population, as previously reported [8,29]. Conversely, HVS is commonly seen in patients with anxiety-related disorders [37] but currently it is difficult to assess whether HVS is causative or secondary to anxiety-related disorders [1]. A recent psychosomatic theory proposes stress and anxiety as triggers of primary DB but needs validation [9]. In the studied population, no significant differences were found between asthmatics and non-asthmatics for different anxiety states (Table 1). Previous studies identified anxiety as a significant independent risk factor for DB in asthmatics, especially in patients with difficult-to-treat asthma [3,8]. However, both anxiety and DB represent comorbid treatable traits in asthma and their specific management by psycho-educational interventions, breathing retraining and anxiolytic treatment, improve

asthma control and QoL, reduce exacerbation rate and health care utilisation [6,13,36,38,39].

In concordance with most previous studies, we used a positive NQ as method of diagnosis for DB as no validated tool exists to date. Although NQ was validated only in subjects with exercise-induced HVS, its use has been extrapolated to aid the diagnosis of all forms of DB in many settings [1]. NQ score is a sum of responses related to stress, respiration and anxiety with a high overlap with symptoms of panic disorder or asthma. NQ mainly reflects the subjective, psychic dimension of breathing and should be part of the assessment process in HVS diagnosis along with another more objective test [5,26].

HVPT was considered to be the cornerstone in the diagnosis of HVS [1,25,26]. Different protocols exist, but generally this test is performed by asking the patient to voluntary hyperventilate for 1–3 min and considered positive if symptoms of HVS are reproducible [1,37,39]. Additional physiological criteria have been emphasised, as resting PET_{CO2} <30 mmHg, a decrease of resting PET_{CO2} value by 50% during voluntary hyperventilation and/or a delayed recovery of PET_{CO2} after the test (e.g. a ratio baseline PET_{CO2}/PET_{CO2} after 5 min recovery >1.1) [24–26,40]. All our patients had ≥3 major daily life complaints of NQ and most of additional criteria, e.g. lower resting PET_{CO2}/PaCO₂, a PET_{CO2} baseline/hyperventilation ratio at 2.07 and a slow recovery with a PET_{CO2} baseline/recovery ratio 1.26 at 5 min (Tables 1 and 2). The majority of symptoms and signs from NQ (Appendix) described during HVPT are related to hypocapnic alkalosis induced by acute hyperventilation. Respiratory alkalosis produces the Bohr Effect that increased the binding of oxygen to haemoglobin and reduced oxygen delivery to the tissues, but also causes a reduction in serum calcium and phosphorus levels (the last one due to altered glucose metabolism) (2). Hypocapnia was associated with evidence of myocardial hypoxia and could induce chest pain and atrial arrhythmias, so HVPT should be avoided in people with pre-existing coronary disease. Voluntary hyperventilation can produce cerebral vasoconstriction leading to symptoms such as visual disturbance, dizziness, confusion and skin vasoconstriction associated with cold extremity sensation. Paraesthesia developed in the hands, face, and trunk may be due to increase in neuronal excitability by hypocapnia but also by hypocalcemia, and decrease of cerebral perfusion. Muscle spasms and tetany seems to be related to respiratory alkalosis, hypophosphatemia and hypocalcemia (2). Taken together these data reflect the complexity of physiological process involved in hyperventilation and explain the difficulties to fully understand its pathogenesis. The high reproducibility of symptoms and signs from NQ by the HVPT found in this study supports the association of both methods for an accurate diagnosis of HVS in our practice.

In the present study, ventilatory responses and symptoms reproducibility during HVPT were compared with the same parameters during CPET, another method used in clinical practice to identify patients with HVS. An inappropriate ventilation pattern with an abnormally large increased in VE (comparable to the value obtained during the voluntary hyperventilation from HVPT) were observed for all our patients during CPET as positive criteria for the diagnosis of HVS without exercise-induced bronchoconstriction at clinical exam. The test was stopped for most patients for a near maximal dyspnoea, but VO₂ was inferior to the normal predicted value suggesting a deconditioning due to HVS, but also to their overweight (Table 3) [10,26]. Contrarily to other previous data concerning patients with HVS [41], in our population, at peak exercise, PET_{CO2} was significantly increased and VE/VCO₂ ratio decreased compared to baseline, a physiological phenomenon when exercise is intense enough (maximal in our population) and the automatic mechanisms of control override the presumed corticogenic drive [42]. Previous data showed that sustained hyperventilation is associated with hypocapnic attenuation of peripheral chemoreceptor sensitivity to hypoxic drive and abnormal ventilatory response [43]. During a moderate-intensity exercise, the ventilatory response is appropriate for the reduced PaCO₂ set point and breath holding time is short suggesting an additional sustained component of ventilatory drive

that operate throughout exercise [44], but the brain mechanisms underlying the respiratory controller's intelligent subliminal decision-making governing the maintenance of normocapnia in some circumstances and leading to submissive hypocapnia in others, remain to be determined [45].

All patients described dyspnoea at rest and near maximal dyspnoea at exercise (Tables 3 and 5). Resting dyspnoea in these patients is considered as "allodyspnoea" (dyspnoea for a non-dyspnoeic trigger) and may reflect an inappropriate cortical processing of respiratory-related sensory inputs with a central nervous system sensitisation [44, 46] whereas exercise-induced dyspnoea is usually defined as "hyper-dyspnoea" (dyspnoea that is disproportionate to the level of ventilation) [43,45].

The most interesting finding of our study was that, for similar minute-ventilation, HVPT was a better method in term of symptoms reproducibility in patients with HVS (≥ 3 NQ items) than CPET. This significant difference could be the consequence of different PET_{CO2} levels during HVPT and CPET, several symptoms from NQ such as tingling, numbness, dizziness, and neuromuscular symptoms being clearly related to hypocapnia [2,40,47]. There was no significant difference between asthmatics and non-asthmatics with HVS during HVPT and CPET. To the best of our knowledges, no previous study compared these two methods to identify HVS, a condition frequently under- or misdiagnosed due to the absence of validated diagnostic tests and/or the use of inappropriate assessment tools (e.g. the NQ only) both in research and clinical practice [5,9]. According to our findings, HVPT must be added as objective criteria to NQ to assess HVS. On the other hand, CPET is interesting to be performed in patients with HVS to confirm DB pattern, the absence of symptoms during exercise and also to obtain the baseline parameters before starting an exercise training program in these patients who have chronic dyspnoea and deconditioning. Pulmonary rehabilitation was shown to improve dyspnoea and could be a complementary therapeutic method to the breathing retraining for the management of patients with HVS, asthmatics or not [1,13,48].

HVS represents an important yet poorly understood topic and a

standard set of diagnostic criteria is lacking. By a systematic assessment, we found that HVPT could be an interesting objective method in the diagnosis of HVS and an important proportion of patients with HVS have an atypical asthma previously misdiagnosed due to the presence of similar respiratory symptoms. Further research for diagnostic tools in HVS is required to confirm our results on large scale. The specific management of the most important etiologies of HVS is mandatory to improve patients' outcomes and reduce health-related costs.

Authors' contribution

AT- Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing - original draft, review & editing; II- Formal analysis, Validation, Visualization, Writing - original draft, review & editing; MP- Validation, Visualization, Writing - original draft, review & editing; CS- Validation, Visualization, Writing - original draft, review & editing; SAK- Conceptualization, Investigation, Methodology, Validation, Visualization, Writing - original draft, review & editing.

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Declaration of competing interest

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Appendix

Table A.1
Nijmegen Questionnaire

	Never 0	Rare 1	Sometimes 2	Often 3	Very often 4
Chest pain					
Feeling tense					
Blurred vision					
Dizzy spells					
Feeling confused					
Faster or deeper breathing					
Short of breath					
Tight feelings in chest					
Tingling fingers					
Unable to breathe deeply					
Stiff fingers or arms					
Tight feelings round mouth					
Cold hands or feet					
Palpitations					
Feeling of anxiety					

*A score of over 23 out of 64 suggest a positive diagnosis of hyperventilation syndrome [25].

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2021.106329>.

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