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Severely impaired health-related quality of life in chronic hyperventilation patients: Exploratory data

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Summary
Patients with hyperventilation syndrome (HVS) report severe symptom-related suffering and often complain from insufficient medical attention. However, quality of life data in this context are scarce. We aimed at assessing the health-related quality of life (HRQoL) of HVS patients. Twenty-one HVS patients with extensive cardiorespiratory workup including cardiopulmonary exercise testing (CPET) filled in the generic SF-36 questionnaire and the results were compared to French normal values. Correlations between SF36 dimensions and clinical and functional data were established. All SF-36 scores were markedly decreased in HVS patients compared to healthy subjects: Physical Functioning: 44 ± 24, Social Functioning: 57 ± 27, Role Physical: 21 ± 32, Role Emotional: 48 ± 42, Mental Health: 51 ± 27, Vitality: 34 ± 20, Body Pain: 41 ± 21, General Health: 42 ± 21. These figures were all significantly lower in the HVS patients respective to the normal reference population. They were also lower than corresponding values published in patients with asthma or chronic obstructive pulmonary disease (COPD). "Vitality" and "Physical Functioning" scores were correlated with Nijmegen score ($r = -0.594$, $p = 0.047$) and peak respiratory frequency during CPET ($r = -0.644$, $p = 0.019$). The SF-36 Social Functioning score was correlated

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with the ventilatory threshold ($r = 0.629$, $p = 0.034$), peak $V'E/V'CO_2$ (ventilation/CO_2 production) ($r = 0.650$, $p = 0.016$) and peak $PaCO_2$ ($r = -0.664$, $p = 0.027$).

In conclusion, this study shows that HRQoL can be severely impaired in patients with HVS, which is one more reason to take this condition seriously.
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Background

The term "hyperventilation syndrome" (HVS) designates a condition comprising a variety of somatic and psychological symptoms associated with physiologically inappropriate alveolar hyperventilation [1,2] that may be chronic or triggered by mental stress or exercise. The symptoms (primarily dyspnea, but also chest pain, anxiety or even panic attacks [3] and many other manifestations) are episodic in nature. No clear pathophysiological mechanism has been identified. HVS is difficult to diagnose because of the labile nature of the symptoms, the absence of any readily identifiable somatic abnormality, and the absence of a gold standard diagnostic method. HVS may be isolated, in the presence of normal cardiorespiratory function ("idiopathic HVS"), but can also occur in patients with other respiratory diseases (for example, asthma), which further complicates the diagnostic. In these settings, the diagnosis of HVS can be considered when the documented abnormalities are insufficient to explain the symptoms or blood gas abnormalities. Several diagnostic tools have been proposed, including the Nijmegen questionnaire [4], reproduction of symptoms during voluntary hyperventilation challenge [5—8], measurement of gas exchanges during exercise [9] or during a shift from the sitting to the standing position [10]. However, none of these diagnostic tools are completely satisfactory. Of note, arterial hypocapnia at rest is a useful clue to HVS, but is probably the hallmark of more chronic and/or more severe forms of the condition.

For the above reasons (diversity and lability of symptoms, their intricate association with anxiety, lack of clear pathophysiology, diagnostic difficulties), HVS tends to be poorly perceived and often neglected by both general practitioners and specialists. However, clinical experience suggests that HVS patients may suffer severely from their condition. Exercise intolerance [11] and an exaggerated feeling of the unpleasantness of dyspnea for a given level of perceptual intensity are probably important causes of this suffering [12]. HVS patients report that the limited attention paid by doctors to their condition also contributes to their distress. The impact of HVS on health-related quality of life (HRQoL) has however not been extensively described. We hypothesized that HVS would have a major negative impact on HRQoL, and tested this hypothesis by applying the French version of the generic SF-36 questionnaire [13] in a population of patients diagnosed with HVS.

Methods

Setting

The study was conducted in a tertiary referral dyspnea clinic run by the 86-bed respiratory medicine unit of a teaching hospital. All patients referred to this clinic are systematically assessed by pulmonary function tests (PFTs), room air arterial blood gases and Doppler echocardiography when not already available in their charts. Cardiopulmonary exercise testing (CPET) is also performed for the purposes of differential diagnosis and to evaluate the disproportionateness of dyspnea in cases of HVS associated with respiratory abnormalities. When HVS is suspected on the basis of these examinations, the Nijmegen questionnaire (16 items related to common complaints due to chronic hyperventilation) is also applied and a hyperventilation provocation test (HVPT) is performed (see below, Methods). The French Sadoul dyspnea scale [14] and the Baseline Dyspnea Index [15] are systematically measured. The present study was approved by the French learned society institutional review board ("*Société de Pneumologie de Langue Française*" reference number CEPRO2012-009) and patients gave their consent to anonymous use of their data for research purposes.

Inclusion criteria

Patients were included in the study when they met the following criteria:

- at least two compatible clinical symptoms among dyspnea, chest tightness, chest pain, palpitations, blurred vision, dizzy spells, bloated feelings in stomach, tingling fingers, stiff fingers or arms, feeling of tightness around the mouth, cold hands or feet, feeling tense or feelings of anxiety;
- resting hypocapnia with $PaCO_2$ <38 mmHg with a normal alveolar-arterial gradient for oxygen ($PA\text{-}aO_2$);
- absence of significant obstructive or restrictive ventilatory defects on PFTs;
- absence of pulmonary artery hypertension on Doppler echocardiography;
- absence of exercise-induced increase of $PA\text{-}aO_2$.
- at least two criteria among: Nijmegen score ≥ 23 [4]; reproduction of at least 2 usual symptoms during HVPT and delayed return of the end-tidal partial pressure of carbon dioxide in the expired gas ($PETCO_2$) to baseline during HVPT (see below).

Pulmonary function testing

Spirometry, plethysmography and single-breath lung diffusing capacity for carbon monoxide (D_LCO) were performed in all patients (Jaeger Masterscreens Body®) according to the joint guidelines of the American Thoracic Society and of the European Respiratory Society [16—18].

The results were expressed as percentages of predicted values [16—18].

Cardiopulmonary exercise testing

All patients underwent a maximal, symptom-limited, incremental and triangular exercise test on an Ergoline-Ergometrics 800® ergometric bicycle. The protocol consisted of a 3-min warm-up period (20 Watts) followed by progressively increasing work rate of 10 W/min until maximal tolerance, and then a 2-min recovery period. Heart rate, blood pressure, 12-lead electrocardiogram and oxyhemoglobin saturation were monitored continuously. The content of expired gases was determined on a breath-by-breath basis (Ergocard®, Medisoft, Sorinnes, Belgium) to monitor oxygen consumption ($V'O_2$), carbon dioxide production ($V'CO_2$), minute ventilation ($V'E$) and tidal volume (VT). Blood samples were taken from the radial artery at rest and at peak exercise to measure blood gases and lactic acid. Forced expiratory flow—volume curves were recorded at the end of exercise. The alveolar-arterial gradient in oxygen ($PA\text{-}aO_2$) was calculated from the alveolar gas equation [19]. The ventilatory "anaerobic" threshold (VThr) was determined by using both the "Equivalents" method and the "V′ slope" method [19]. Ventilatory reserve (VR) was calculated as recommended [19]. The dead space-to-tidal volume ratio (VD/VT) was calculated according to Bohr's equation corrected for the additional instrumental dead space [19]. The results were expressed as percentage of predicted values [19].

Hyperventilation provocation test

HVPTs were performed as previously described [6,7]. Briefly, patients were required to breathe through a large pneumotachograph (Hans Rudolph 2700 series, Hans Rudolph, Kansas City, MO, USA) and $PETCO_2$ was continuously monitored using a mainstream capnograph (Datex-Ohmeda, Limonest, France). A 3-min baseline recording period was followed by a 3-min voluntary hyperventilation period designed to decrease baseline $PETCO_2$ by 50%. Patients were then instructed to breathe normally for 10 min or until return of $PETCO_2$ to baseline, whichever occurred first. At the end of the test, the patients were asked to describe the symptoms experienced during the test. $PETCO_2$ recovery lasting more than 5 min was considered to be abnormal [6,7].

Health-related quality of life (HRQoL)

HRQoL was assessed by the validated French version of the Short Form 36 questionnaire (SF-36) [13]. This questionnaire comprises 36 questions organized into eight multi-item scales: physical functioning (PF), social functioning (SF), role limitations as a result of physical problems (RP), role limitations as a result of emotional problems (RE), mental health (MH), vitality (frequency of feeling full of energy vs. feeling tired, VT), body pain (BP) and general health perception (GH). A 0-100 score is allocated, where 100 indicates optimal conditions.

Statistical analysis

Statistical analyses were performed with SPSS® software (SPSS for Mac OS, version 11.0.2, 2006. Chicago: SPSS Inc, US). Results related to general characteristics and pulmonary function tests are expressed as median, first quartile (Q1) and third quartile (Q3). Results for SF-36 scores are expressed as mean and standard deviation, as all SF36 results were normally distributed (Kolmogorov—Smirnov test). Differences between means are expressed as mean and 95% confidence interval. Cronbach's α coefficients analysis was used to determine the internal consistency of each SF-36 item. Coefficients were considered robust when Cronbach's α values exceeded 0.7 [20]. Z-scores and 95% confidence intervals (95% CI) of the difference between means were used to describe differences in SF36 scores between HVS patients and a healthy French population [21]. Z-scores were compared to zero with a Wilcoxon signed-rank test, with $p = 0.05$ as the limit of statistical significance. Multiplicity was accounted for by using the Benjamini and Hochberg multiple testing correction [22]. A mean Z-score <-0.6 was considered to be not clinically significant. Clinical significance was considered minor for $-1.3 < Z < -0.6$, moderate for $-2 < Z < -1.3$, and major for $Z < -2$.

Results

Patient characteristics and pulmonary function tests

Twenty-one patients satisfied the inclusion criteria (Table 1). Ten of these patients were both non-smokers and completely free of any past or present respiratory disorders, while the other 11 patients did not meet these two criteria, but reported dyspnea with an intensity considered to be disproportionate to their respiratory status (3 smokers with normal spirometry; 3 asthmatics with stable and well controlled asthma according to the 5-item Asthma Control Questionnaire (ACQ-5 $<$ 1,5); 2 patients with a distant history of pulmonary embolism; 3 patients with a distant history of stage I sarcoidosis; 1 patient with pleural plaques). Fig. 1 summarizes the dyspnea scores.

Diagnosis of HVS

The diagnosis of HVS was adopted on the basis of a combination of a Nijmegen score $\geq$23 and reproduction of the usual symptoms by HVPT in 2 cases, a Nijmegen score $\geq$23 and delayed $PETCO_2$ recovery in 2 cases, reproduction of the usual symptoms during HVPT and delayed PETCO2 recovery in 4 cases; all three criteria were present in 13 cases. Of note, the estimated interval between the first HVS-related complaints and diagnosis exceeded 2 years in 50% of cases.

Cardiopulmonary exercise testing

All CPETs were maximal and symptom-limited and consistently demonstrated normal cardiac, pulmonary and

Table 1 Characteristics of HVS patients (n = 21) and pulmonary function test results.

	M (Q1—Q3)
General characteristics	
Age (years)	47 (36—54)
Sex ratio M/F	5/16
BMI (kg m^{-2})	24 (20—28)
Smoker/Ex-smoker/Never smoker	6/5/10
Pulmonary function testing	
FEV_1 (% pred)	103 (95—115)
FEV_1/FVC (%)	80 (78—85)
TLC (% pred)	106 (96—114)
DLCO/VA (% pred)	91 (81—106)
Resting arterial blood gases	
pH	7.45 (7,44—7.48)
PaO_2 (mmHg)	99.2 (92—104.7)
$PaCO_2$ (mmHg)	32.3 (29.3—34.9)

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; DLCO: diffusing capacity of the lungs for carbon monoxide, VA: alveolar volume.

muscle responses, therefore supporting the diagnosis of HVS. Aerobic capacity was reduced (namely below 84% pred) in 15/21 patients [19]. All but 2 of the HVS patients presented marked hyperventilation during exercise with elevated ventilatory equivalents ($V'E/V'CO_2$ = 38, median $V'E/V'O_2$ = 40, predicted values <34) [19]. The detailed CPET results are provided in Appendix 1.

Health-related quality of life

The SF-36 internal consistency was satisfactory for the whole questionnaire and for each subscale, as confirmed by high Cronbach's α coefficients [0.7—0.9]. SF-36 results are summarized in Table 2 and Fig. 2. HVS patients displayed significant impairment in all HRQoL domains, including physical (particularly role physical), mental and social dimensions, with a dramatic reduction of the physical components PF and RP.

Cross-correlations

Spearman's correlations coefficients were calculated between SF36 dimensions, dyspnea scores, Nijmegen score, resting ventilation and $PETCO_2$, and the various variables measured during CPET. Five of these tests resisted the Benjamini and Hochberg correction for multiple comparisons [22]. The SF-36 "vitality" score (VT) was significantly negatively correlated with the Nijmegen score, as a higher Nijmegen score was associated with a lower VT score (r = −0.594, p = 0.047). The SF-36 "physical functioning" (PF) score was significantly negatively correlated with peak respiratory frequency during exercise, as higher peak respiratory frequency was associated with lower PF score (r = −0.644, p = 0.019). The SF-36 "social functioning score" was significantly correlated with the ventilatory threshold $ATV'E$ (r = 0.629, p = 0.034) and peak $V'E/V'CO_2$ (r = 0.650, p = 0.016), and negatively correlated with $PaCO_2$ at peak exercise (r = −0.664, p = 0.027).

Discussion

The results of this study show that SF-36 domain scores can be extremely low in patients with hyperventilation syndrome.

Severity

To our knowledge, this is the first time that health-related quality of life has been specifically documented in a group of patients meeting strict criteria for HVS, namely a combination of symptoms and resting hypocapnia. However, Hagman et al. [23] reported low SF-36 subscores in 25 patients with "dysfunctional breathing", a term that describes patients presenting the HVS constellation of symptoms, but with or without breathing pattern abnormalities and with or without resting hyperventilation. In this study, "dysfunctional breathing" patients had significantly lower SF-36 scores than asthmatic controls. SF-36 subscores were as follows: physical functioning 78, social functioning 70, role limitations—physical 60, role limitations—emotional 64, mental health 71, vitality 47, bodily

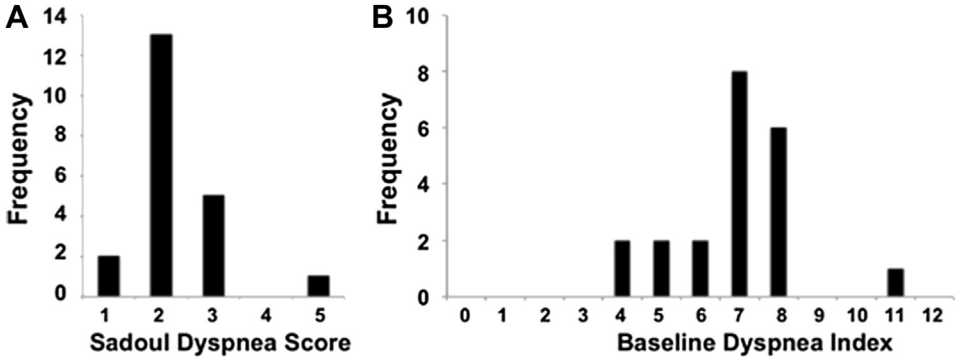

Figure 1 Dyspnea score histograms (Sadoul scale, A; baseline dyspnea index, B). The Sadoul scale ranges from 1 (dyspnea at intense exercise) to 5 (dyspnea for activities of daily living). The Baseline Dyspnea Index (BDI) ranges from 0 (resting dyspnea) to 12 (absence of dyspnea).

Table 2 Health-related quality of life in HVS patients: SF-36 raw scores and Z-scores, and difference of mean SF36 scores between HVS patients and a normal French cohort matched for age and sex.

	Raw data Mean ± SD	Z-scores Mean ± SD	*p*	Difference between means Mean (95% CI)
PF	44 ± 24	−2.5 ± 1.5	<0.001	−43 (−53 to −31)
RP	21 ± 32	−2.2 ± 1.0	0.007	−64 (−78 to −49)
BP	41 ± 21	−1.4 ± 1.0	<0.001	−33 (−42 to −23)
GH	42 ± 21	−1.6 ± 1.2	<0.001	−28 (−38 to −18)
VT	34 ± 20	−1.4 ± 1.1	<0.001	−26 (−35 to −17)
SF	57 ± 27	−1.2 ± 1.3	<0.001	−24 (−37 to −12)
RE	48 ± 42	−1.1 ± 1.3	0.001	−36 (−55 to −18)
MH	51 ± 27	−0.93 ± 1.5	<0.001	−16 (−29 to −4)

PF: physical functioning, SF: social functioning, RP: role limitations as a result of physical problems, RE: role limitations as a result of emotional problems, MH: mental health, VT: vitality, BP: body pain, GH: general health perception.

pain 62, and general health perception 53 [23]. These figures are much higher than those observed in our patients (Table 2), who all exhibited resting hypocapnia ($PaCO_2$ less than 38 mmHg constituted an inclusion criterion, see Methods). The presence of resting hypocapnia and the fact that these patients were referred to a tertiary care center strongly suggest that this population was biased toward more marked severity, as resting hypocapnia is not always present in HVS patients and many of them become hypocapnic only in response to emotional or physical stimulation. The differences between the values observed in our patients and normal French subjects are therefore particularly striking (Table 2). These values are also much lower than published SF-36 scores for patients with other respiratory diseases such as cystic fibrosis [24], chronic obstructive pulmonary disease [25] or severe asthma [26] (Table 3). They are also much lower than the scores observed in patients with social anxiety disorder and panic disorder not selected for the hyperventilation criterion [27].

Functional correlations

In addition to indicating the possible severity of HVS-related impairment of HRQoL, this study also demonstrated statistically significant correlations between SF-36 subscores and physiological characteristics. The physical functioning subscore was negatively correlated with peak respiratory frequency during exercise, whereas the social functioning subscore was negatively correlated with $PaCO_2$ at maximal exercise, an indicator of the intensity of hyperventilation. These results reinforce our findings and give further support to the "reality" of the patients' suffering, as the intensity of hyperventilation appears to be directly correlated with the severity of HRQoL impairment. The correlation between the Nijmegen score and the SF-36 vitality subscore can be considered to support the value of the Nijmegen questionnaire.

Methodological considerations and limitations

In this study, we chose to use the SF-36 as a generic measure of HRQoL rather than a more specific respiratory questionnaire. One reason to choose the SF-36 over a

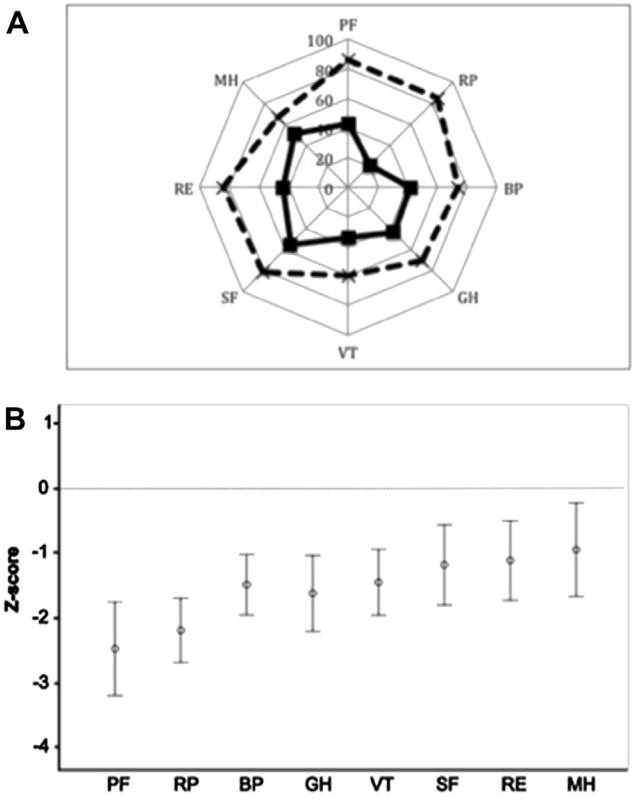

Figure 2 A. Radar plot showing mean SF-36 scores in HVS patients included in this study (solid line) and in the general healthy French population (dotted line). Each spoke on the plot represents a SF-36 dimension. PF, physical functioning; SF, social functioning; RP, role limitations as a result of physical problems; RE, role limitations as a result of emotional problems; MH, mental health; VT, vitality (the frequency of feeling full of energy vs. feeling tired); BP, body pain; GH, general health perception. Plots are read from the center outward along each spoke. Scores are shown on concentric circles beginning with 0 (at the center) and increasing to 100 (outer line). "Healthy" values are derived from [21]. B. SF-36 Z-scores of patients with HVS (mean with standard deviation) compared with age- and sex-matched controls in a French cohort (zero line). A negative Z-score indicates a lower health status in the HVS group. PF: physical functioning, RP: role physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role emotional, MH: mental health.

Table 3 Published SF-36 scores in patients with cystic fibrosis [24] chronic obstructive pulmonary disease [25], asthma [26] and HVS (our study) (mean ± SD).

	HVS	Cystic fibrosis	Asthma	COPD
PF	41 ± 23	76 ± 24	78 ± 20	60 ± 20
SF	54 ± 28	80 ± 24	85 ± 19	83 ± 21
RP	17 ± 29	73 ± 38	75 ± 40	68 ± 33
RE	39 ± 42	77 ± 37	70 ± 35	88 ± 27
MH	49 ± 24	74 ± 18	63 ± 19	79 ± 13
VT	34 ± 18	58 ± 23	57 ± 21	61 ± 14
BP	41 ± 23	83 ± 21	73 ± 27	89 ± 18
GH	42 ± 20	43 ± 24	61 ± 22	49 ± 16

PF: physical functioning, SF: social functioning, RP: role limitations as a result of physical problems, RE: role limitations as a result of emotional problems, MH: mental health, VT: vitality, BP: body pain, GH: general health perception, COPD: chronic obstructive pulmonary disease.

respiratory disease specific questionnaire lies in the fact that patients with the HVS describe an array of symptoms that go way beyond dyspnea and respiratory abnormalities. This is well attested to by the very content of the Nijmegen questionnaire that includes digestive symptoms, neuropsychological manifestations, etc. In addition, generic HRQoL measures have the advantage of allowing comparison between clinical groups and healthy populations or between clinical groups [28]. Our data can therefore be compared to published data for the general French healthy population [21,28]. Of note, as SF-36 has not been previously used in HVS patients, its internal consistency had to be evaluated in our population [20,29]. Cronbach's α coefficient values obtained in this study (>0.7) were reassuring. The small size of our study population and the likely bias toward severity (see above) preclude any attempt at generalization. The fact that about one half of the patients in this study were symptomatic smokers or had a past history of respiratory diseases could also constitute confounding factors, but these patients did meet the defined HVS criteria including normal resting cardiopulmonary function and their breathlessness clearly appeared to be disproportionate. Finally, our study is subject to the same limitations as other HVS studies, namely the lack of a formal positive diagnostic test. The Nijmegen score has high sensitivity but lacks specificity [4] and the hyperventilation provocation test can give false-positive results [4,8]. However, as stated above, our diagnostic criteria for HVS were more stringent than those used in most studies.

Conclusions

Despite its limitations, this study highlights the putatively very strong impact of HVS on health-related quality of life. These results cannot be considered definitive, and it would be important to extend their scope to a primary care population. However, they provide sufficient incentive for larger and more detailed studies and support the use of HRQoL as an outcome measure of therapeutic intervention studies of HVS. For example, breathing retraining techniques are recommended in HVS patients with or without coexisting asthma [30], but their impact on HRQoL has yet to be determined. In any case, the findings of this study are a reminder that HVS patients suffer from a debilitating condition and warrant medical attention.

Conflict of interest

This study did not involve external funding and did not involve any financial conflict of interest, for any of the authors, or any other type of conflict of interest that would need disclosure.

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Appendix 1. Detailed CPET results.

All CPET were maximal and symptom-limited. Aerobic capacity was reduced (<84% pred [19]) in 15/21 patients. A premature ventilatory threshold (<40% of predicted peak VO_2 [19]) was observed in 3 patients. All but 2 of the HVS patients presented marked hyperventilation during exercise as demonstrated by increased ventilatory threshold (VThr) $V'E/V'CO_2$ and $V'E/V'O_2$ (predicted values < 34 [19]). Breathing pattern and ventilatory rate increased normally during exercise (peak RR < 60/min; peak VT/FVC > 40% [19]) except in two patients who presented with both a peak RR higher than 60/min and a VT/FVC less than 40%. Ventilatory reserve was reduced in 10 patients (normal V'E/MVV > 30% [19]). Expiratory flow—volume curves did not show any airflow limitation at the end of exercise. Peak alveolar-arterial PO_2 pressure difference ($P(A\text{-}a)O_2$) was normal (normal < 35 mmHg [19]) in all patients and no hypoxemia was observed during exercise. Peak dead space-to-tidal volume ratio (VD/VT) was normal (<0.30 [10]) except in 6 patients. In these cases, the increased peak VD/VT was attributed to changes in breathing pattern with major hyperventilation, small tidal volume and tachypnea after exclusion of vascular and hemodynamic diseases. Cardiovascular adaptation was within normal limits in all patients.

	M (Q1—Q3)
Peak $V'O_2$ (% pred)	79 (68—86)
$V'E/V'CO_2$, at VThr	38 (34—48)
$V'E/V'O_2$, at VThr	40 (34—48)
Peak $P(A-a)O_2$ (mmHg)	19 (15—23)
Peak PaO_2 (mmHg)	103 (94—109)
Peak VD/VT	0.25 (0.22—0.31)

$V'O_2$: oxygen consumption, V'E: minute ventilation, $V'CO_2$: carbon dioxide production, VThr: ventilatory threshold, ($PA\text{-}aO_2$): alveolar-arterial PO_2 pressure difference, PaO_2: oxygen alveolar pressure, VD/VT: dead space-to-tidal volume ratio.

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