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Title

Evidence of ventilatory constraints during exercise in hypermobile Ehlers-Danlos syndrome

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Abstract

Purpose: Hypermobile Ehlers-Danlos syndrome (hEDS) is a connective tissue disorder with many different symptoms such as pain, fatigue, dysautonomia or respiratory symptoms. Among the respiratory manifestations described, the most frequent are exertional dyspnea and breathing difficulties. Mechanical ventilatory constraints during exercise could participate in these respiratory manifestations. The objective of this study was to explore the response of pulmonary flow-volume loops to exercise in patients with hEDS and to look for dynamic hyperinflation and expiratory flow limitation during exercise. **Methods:** For this purpose, breathing pattern and tidal exercise flow-volume loops were recorded at two workloads (30% and 80% of the peak power output) of a constant load exercise test. **Results:** Twelve patients were included (11 women, mean age 41±14 years). The results showed a decrease ($p = 0.028$) in the inspiratory capacity (from 3.12±0.49 L to 2.97±0.52 L), an increase ($p = 0.025$) in the end-expiratory lung volume (from 0.73±0.68L to 0.88±0.66L, i.e. from EELV comprising 17±12% to 21±12% of forced vital capacity) between the two workloads in favor of dynamic hyperinflation, and half of the patients had expiratory flow limitations. **Conclusion:** This exploratory study provides evidence for mechanical ventilatory constraints during exercise in patients with hEDS, which may induce discomfort during exercise and could contribute to the respiratory symptomatology.

Trial registration number: This study is part of a larger clinical trial (ID: NCT04680793, December 2020).

Keywords:

breathing, dynamic hyperinflation, expiratory flow limitation, flow-volume loops, hypermobility, lung

Abbreviation List:

CLET - constant load exercise test

EDS - Ehlers-Danlos syndrome

EELV - end-expiratory lung volume

EFL - expiratory flow limitation

EILV - end-inspiratory lung volume

f_b - breathing frequency

FEV_1 - forced expiratory volume in one second

FVC - forced vital capacity

hEDS - hypermobile Ehlers-Danlos syndrome

HR - heart rate

IC - inspiratory capacity

MVV - maximal voluntary ventilation

PPO - peak power output

RER – respiratory exchange ratio

SpO_2 - arterial oxygen saturation

T_i - inspiratory time

T_{tot} - total respiratory time

$\dot{V}CO_2$ - carbon dioxide output

$\dot{V}_E$ - minute ventilation

$\dot{V}O_2$ - oxygen uptake

V_T - tidal volume

Main text

Introduction

Ehlers-Danlos syndromes (EDSs) are a group of inherited connective tissue disorders mainly characterized by joint hypermobility, skin hyperextensibility, and tissue fragility (Malfait et al., 2017). These syndromes present great clinical and genetic heterogeneity and are classified in 13 subtypes (Malfait et al., 2017). The most common type is hypermobile Ehlers-Danlos syndrome (hEDS), whose diagnosis remains clinical (Sulli et al., 2018). In addition to the musculoskeletal manifestations, general symptoms, such as pain and fatigue, are usually presents in patients with hEDS, as well as dysautonomia, gastrointestinal disorders, anxiety, or respiratory symptoms (Castori et al., 2010; De Wandele et al., 2013; Tinkle et al., 2017). Breathing difficulties and exertional dyspnea are frequently reported (Bascom et al., 2021; Castori et al., 2010; Chohan et al., 2021; Hamonet et al., 2016; Morgan et al., 2007), but only a few experimental studies have been conducted on lung function in patients with hEDS (Reychler et al., 2019).

The respiratory symptoms of hEDS are still not clearly explained and raise many questions (Bascom et al., 2021). In patients with hEDS, some studies have reported preserved pulmonary function (Reychler et al., 2019), while other studies have found increased lung volumes (Morgan et al., 2007), restrictive or mixed respiratory insufficiencies (Castori et al., 2010), gas transfer anomalies (Ayres et al., 1985; Morgan et al., 2007) or deficits in inspiratory muscles strength (Reychler et al., 2019). Anomalies in lung or chest wall compliance and deformities of the thoracic cage have also been reported (Ayres et al., 1985; Morgan et al., 2007). These last impairments may be at the origin of mechanical ventilatory constraints during exercise, leading to dyspnea (Neder et al., 2019).

During exercise, in order to respond to the increase in metabolic demand, increased ventilation leads to an expansion of the tidal volume. In healthy young subjects, this tidal volume response results in the utilization of inspiratory and expiratory reserves (i.e., to a decrease in end-expiratory lung volume [EELV] and an increase in end-inspiratory lung volume [EILV]) (Milne et al., 2020). However, in the case of an increase in lung compliance (e.g., due to collagen or extracellular matrix abnormalities that can be found in EDS), the energy stored at the end of inspiration could be reduced and lead to an early involvement of the expiratory muscles and difficulties in ensuring sufficient exhalation. In this case, the increase in tidal volume is achieved with a temporary increase in EELV above its resting level and a decrease in inspiratory capacity (Langer et al., 2014). This breathing pattern is called dynamic hyperinflation and leads to early ventilatory limitation and functional weakness of the inspiratory muscles (Langer et al., 2014). It may be hypothesized that mechanical ventilatory constraints, such as dynamic hyperinflation and/or expiratory flow limitation, could exist in patients with hEDS during exercise.

To our knowledge, the pulmonary mechanical constraints during exercise have not been studied in patients with hEDS. These constraints are commonly explored using breathing reserve, which is a comparison of the ventilation achieved during exercise and the maximal voluntary ventilation (MVV) measured at rest (Guenette et al., 2013; Johnson et al., 1999; Neder et al., 2019; Nourry et al., 2006). But, breathing reserve does not provide precise information on the type or source of ventilatory constraints (Guenette et al., 2013; Johnson et al., 1999; Neder et al., 2019; Nourry et al., 2006). It was shown that the use of tidal exercise flow-volume loops plotted within the maximal flow-volume loop provide more specific information, in particular about the breathing strategy during exercise (Guenette et al., 2013; Johnson et al., 1999; Neder et al., 2019; Nourry et al., 2006). Furthermore, assessment of the response of flow-volume loops to exercise is a useful tool for the investigation of exercise intolerance and exertional dyspnea (Johnson et al., 1999; Neder et al., 2019). The degree of expiratory flow limitation (EFL) is an index of the balance between ventilatory demand and ventilatory capacity combined with how the subject chooses to regulate their EELV (Johnson et al., 1999).

The objective of this study was to explore the mechanical ventilatory constraints to exercise and to investigate the response of flow-volume loops at two exercise intensities in order to determine the achievement of dynamic hyperinflation and/or EFL in patients with hEDS. The hypothesis was that patients with hEDS could present ventilatory constraints to exercise as expiratory flow limitations or hyperinflation.

Materials and Methods

Patients

The participants were recruited among the patients who were undergoing a rehabilitation program in the Clinique de la Mitterie (Lomme, France). The rehabilitation program is based on physical activity (2/3) and on educational or mental well-being activities (1/3). It was designed for hEDS patients and is described elsewhere (Hakimi et al., 2020). Inclusion criteria were having performed recent cardiopulmonary exercise testing and having been diagnosed with hEDS according to the 2017 criteria (Malfait et al., 2017). All patients were volunteers and gave their informed consent. This study is part of a clinical trial that has been approved by a national ethics committee (CPP Ile de France IV, 2019/71).

Study design

First, patients performed an incremental cardiopulmonary exercise test before their inclusion in a rehabilitation program. Then, during the first week of the rehabilitation program, patients performed spirometry, followed by a constant load exercise test (CLET) with measurement of pulmonary flow-volume loops.

1. *Incremental cardiopulmonary exercise test*

This incremental test was conducted on a calibrated, electromagnetically braked cycle ergometer (Ergoselect 200, Ergoline, Germany), with a computerized open-circuit gas collection system (Ergocard, Medisoft, Belgium). Before the start of each test, the airflow sensor was calibrated with a 3 L syringe, and gas analyzers were calibrated against known gases. It consisted of a 1-minute warm-up (the warm-up workload varied according to the fitness level), followed by a progressive increase of workload in a ramp of 10 W/min. The peak power output (PPO) was determined during this test. Heart rate (HR) and cycle by cycle data, including oxygen consumption ($\dot{V}O_2$), carbon dioxide output ($\dot{V}CO_2$), breathing frequency (f_b), tidal volume (V_T), and minute ventilation ($\dot{V}_E$), were measured. Predicted maximal HR ($HR_{max, pred}$) was estimated as follows: $HR_{max, pred}$ = (208-0.7) x age (Tanaka et al., 2001). The respiratory exchange ratio (RER) was calculated as follow: RER = $\dot{V}CO_2$/ $\dot{V}O_2$. Predicted maximal oxygen consumption was estimated as recommended by the American Thoracic Society with Wasserman equations (American Thoracic Society & American College of Chest Physicians, 2003; Wasserman, 2005).

2. *Spirometry*

A forced spirometry maneuver was conducted just before the CLET following the current recommendations (Graham et al., 2019). The material (the same as for the incremental test) was calibrated before each test. The spirometry allowed us to establish a maximal pulmonary flow-volume envelope. No bronchodilators were used. The equations used to calculate the predicted values are the global lung function initiative 2012 equations (Quanjer et al., 2012). The MVV was estimated as follows: MVV = FEV_1 x 40 (Campbell, 1982), where FEV_1 is the forced expiratory volume in 1 second measured with spirometry.

3. *Constant load exercise test (CLET)*

The CLET was conducted on the same ergometer with the same measurement system as the incremental cardiopulmonary exercise test. Patients started with 3 minutes of pedaling at a moderate workload of 30% of PPO. This was followed by 2 minutes of linear increase to 80% of PPO. Then, the patient was instructed to pedal for as long as possible at a target workload corresponding to 80% of PPO, with a maximum of 20 minutes. The target pedaling frequency was 60 rpm. If the patient could no longer maintain the pedaling frequency (55 rpm minimum) or reach the 20 minute limit, the test was stopped and the patient began a recovery period at 30% of PPO. The same data as for the incremental test were recorded, in addition to inspiratory time (T_i), total respiratory time (T_{tot}) and arterial oxygen saturation as indicated by pulse oximetry (SpO_2). Dyspnea was assessed at rest before and at the end of the exercise testing by the modified Borg scale (Borg, 1982).

In order to investigate ventilatory constraints, we performed tidal exercise flow-volume loops by using inspiratory capacity (IC) maneuvers at the third minute of the exercise at 30% of PPO and at the end of the exercise at 80% of PPO. These maneuvers correct the relative position of the tidal volume in the maximal flow-volume envelope during exercise and permit us to calculate the EELV and EILV in percentages of the forced vital capacity (FVC) as follows (Guenette et al., 2013):

$EELV = [(FVC-IC) \times 100] / FVC$

$EILV = [(EELV + V_T) \times 100] / FVC.$

Dynamic hyperinflation is considered in this study when EELV at 80% of PPO equals or exceeds the 30% of PPO value (Johnson et al., 1999). The EFL was graphically calculated as the volume that meets or exceeds the expiratory boundary of the maximal flow-volume loop and was expressed as a percent of V_T as previously described (Johnson et al., 1999).

Breathing reserve was estimated from MVV and $\dot{V}E$ reached during exercise, according to the following equation (Johnson et al., 1999):

$BR (\%) = [(MVV- \dot{V}_E) / MVV] \times 100.$

Ventilatory efficiency, which represents the quantity of ventilation needed to eliminate metabolically produced CO_2, was evaluated using the $\dot{V}_E/\dot{V}CO_2$ ratio (Neder et al., 2019; Sun et al., 2002). A mismatching between ventilation and CO_2 production can contribute to exercise dyspnea (Sun et al., 2002).

All cycle by cycle data measured during the CLET were averaged by minute. Every minute where an IC maneuver was conducted was removed from the analysis. The 3 minutes of exercise at 30% of PPO were averaged and used as the 30% of PPO values. The last minute of the exercise at 80% of PPO without IC maneuvers was used as the 80% of PPO value. If a subject failed to achieve at least 1 minute at 80% of PPO, the averaged minute was replaced by the last value measured at 80% of PPO.

Statistical analysis

Data are described with mean and standard deviation (SD). Statistical analysis was performed on SigmaStat Version 3.5 (Systat Software Inc). Before each test, normality of the data distribution and equality of variances were tested. Differences between the 30% of PPO values and the 80% of PPO values from the CLET were tested with a paired t-test or a Wilcoxon signed rank test. Results were considered as significant for a p-value < 0.05.

Results

1. *Patients*

Twelve patients, including 11 women and 1 man, were included in this study. All patients were diagnosed with hEDS according to the 2017 criteria. Anthropometric data are presented in Table 1.

2. *Incremental cardiopulmonary exercise test*

Data from the incremental test are presented in Table 2. Overall, the patients showed limited aerobic fitness, with a mean of 79% of the predicted $\dot{V}O_{2peak}$. Only two patients conserved a $\dot{V}O_{2peak}$ of more than 100% of the predicted value. All other patients were between 57% and 83% of the predicted $\dot{V}O_{2peak}$ values.

3. *Spirometry*

The spirometry data were within the normal range (Table 1), except for one patient with FEV_1 at 74% of the predicted value and FVC at 73% of the predicted value but a FEV_1/FVC ratio of 83% (102% of the predicted value). Three subjects present FEV_1 values ≥ 100% of the predicted value, four subjects between 90% and 99% and four subjects between 80% and 89%. In the same way, two subjects had FVC values ≥ 100% of the predicted value, six subjects between 90% and 99% and three subject between 80% and 89%. The FEV_1/FVC ratios were between 75% and 93%.

4. *Constant load exercise test*

No patient reached the maximum 20 minutes on the cycle exercise at 80% of PPO. The average time to exhaustion at 80% of PPO was 200 ± 165 seconds. Most of the patients (n=8) stopped for exhaustion with inability to further maintain the pedaling frequency of 55 rpm, 2 patients stopped for dyspnea, and 2 patients because of articular pain in the legs. The mean cardiorespiratory data and the breathing pattern corresponding to 30% of PPO and 80% of PPO are presented respectively in Tables 3 and 4. There was a significant ($p < 0.05$) increase in the $\dot{V}O_2$, HR, $\dot{V}_E$, f_R, V_T and T_i/T_{tot} ratio. There was a significant increase in dyspnea assessed by the modified Borg scale from 0.9 ± 1.4 at rest to 5.5 ± 1.7 at the end of the test. No significant change for neither the SpO_2 nor for the $\dot{V}_E/\dot{V}CO_2$ ratio was observed.

Regarding the mechanical ventilatory constraints to exercise, breathing reserve significantly ($p < 0.001$) decreased from 83% ± 4% to 60% ± 12% between 30% and 80% of PPO. A significant decrease in the IC ($p = 0.028$) and a significant increase in EELV ($p = 0.025$) associated with a significant increase in EILV ($p < 0.001$) were observed (Table 5 and Figure 1). All patients showed an increase in EILV (from 4.0% to 25.3% of FVC). Three patients showed a decrease in EELV (4.6%, 3.8% and 0.2% of FVC, respectively) and nine patients showed dynamic hyperinflation (i.e., an increase from 1.3% to 13.4% of FVC). In addition, EFLs were found in six patients (50%), with a mean limitation equal to 46% of V_T (from 16% to 75%) at 30% of PPO and equal to 43% of V_T (from 33% to 58%) at 80% of PPO. There was no significant change for the EFL between the exercise at 30% of PPO and the exercise at 80% of PPO.

Discussion

The main objective of this study was to explore the pulmonary mechanical constraints to exercise in patients with hEDS and to investigate the response of flow-volume loops to exercise. The results showed a significant increase in EELV during exercise in favor of dynamic hyperinflation, and half of the patients had EFL.

The majority of patients showed reduced peak oxygen consumption in comparison with predicted values during the incremental test. This is an indicator of reduced exercise capacity (American Thoracic Society & American College of Chest Physicians, 2003). As mentioned by some authors, fear of trauma and pain can lead to deconditioning and exercise intolerance, which could contribute to the exertional dyspnea observed during the CLET (Baeza-Velasco et al., 2019; Syx et al., 2017). The cycling time to exhaustion recorded by the patients at 80% of PPO (200 ± 165 seconds) was relatively low. Indeed, it is comparable to the times observed in patients with chronic obstructive pulmonary disease (about 4 minutes) at 75% of their PPO (van 't Hul et al., 2003). This supports impaired exercise capacity in patients with hEDS. However, we have to take into account that the participants in this study were recruited among future participants in a rehabilitation program and that respiratory comorbidities were not recorded although this could have been interesting.

At the end of the incremental exercise or during CLET, breathing reserves were relatively substantial (around 60% during CLET at 80% PPO), as it is generally reported in healthy subjects (American Thoracic Society & American College of Chest Physicians, 2003). This result did not support existence of mechanical ventilatory constraints during exercise. Nevertheless, it was not surprising because, during CLET, the exercise intensities were submaximal and the spirometric data were mostly within the normal ranges. However, analysis of breathing reserve alone is insufficient to estimate mechanical limitations of breathing, as largely described in the literature (Guenette et al., 2013; Johnson et al., 1999; Neder et al., 2019; Nourry et al., 2006). The use of tidal exercise flow-volume loops during exercise has provided additional information on the respiratory pattern of these patients. The significant increase in EELV found during exercise is an argument for dynamic hyperinflation in patients with hEDS. For these patients, the tidal volume expansion during exercise is achieved by a major reduction in the inspiratory reserve volume (represented by the increase in EILV), which is normally compensated in healthy subjects by a decrease in EELV (Milne et al., 2020). This theoretical reduction in EELV allows the optimal positioning of the V_T on the pressure-volume curve of the respiratory system (Langer et al., 2014; Milne et al., 2020). As there is no decrease here, the reduction in length of the inspiratory muscles translates to a diminished force generating capacity and to an increased elastic load (Langer et al., 2014).

In addition, EFL was observed in half of the patients. It may be due to abnormalities such as the tendency toward airway collapse, as highlighted by Morgan et al. (2007). This tendency toward EFL may be one of the causes of dynamic hyperinflation, with the need to increase operational lung volumes to reduce these flow limitations. However, as half of the patients do not have EFL, this hypothesis does not fully explain the general trend towards hyperinflation.

Based on the hypothesis that lung compliance may be increased in hEDS (Morgan et al., 2007), the energy stored at the end of inspiration could be reduced. In this case, active and premature involvement of the expiratory muscles may be necessary. This early work of the expiratory muscles associated with a potential limited strength of these muscles (Reychler et al., 2019) could explain the absence of a decrease in EELV. However, this mechanism should be compensated by the drop in compliance as EILV approaches the maximal lung volume (Johnson et al., 1999). Therefore, compliance impairment does not completely explain hyperinflation either. Further investigations are needed in order to clarify the involved mechanisms. A study with electromyographical activation of respiratory muscles during exercise and of lung compliance in hEDS could provide further information.

In addition, the inspiratory muscle weakness that has been shown in patients with hEDS (Reychler et al., 2019) could be also at the origin of a decrease in the velocity of inspiratory muscle contraction, thus an increase in inspiratory time leading to dynamic hyperinflation. In our case, the inspiratory time increase between 30% and 80% of PPO from 39% of the respiratory total time to 45%. Although these values increase, they remain below or within the described values from healthy sedentary individuals of between 45% and 47% (Neder et al., 2003). The changes in inspiratory times alone, therefore, do not explain the dynamic hyperinflation.

Proprioceptive impairment has been shown in hEDS (Rombaut et al., 2010; Scheper et al., 2017). It is possible that these sensory disorders also affect the proprioceptive receptors of the rib cage and respiratory muscles. Thus, poor perception of lung volumes could also be a partial explanation for the dynamic hyperinflation. Abnormalities in sensory perception could also influence the thresholds of dyspnea perception, particularly in a predominantly female population in which greater dyspnea perception is found compared to men (Archiza et al., 2021). However, these hypothesis need to be explored in further studies.

Finally, as frequently described in the literature (Chohan et al., 2021), the results showed significant dyspnea in patients with hEDS during the CLET. The observed $\dot{V}_E/\dot{V}CO_2$ ratios of 38.4% at 30% of PPO and of 37.5% at 80% of PPO are above the recommended value of 34% for establishing ventilatory inefficiency (Neder et al., 2019). This ventilatory inefficiency associated with the dynamic hyperinflation may reflect neuromotor uncoupling and could partly explain the exertional dyspnea (Neder et al., 2019).

The exploratory nature of this study is associated with certain methodological limitations such as the absence of measurement of inspiratory capacity at rest, which would have provided information on the presence of possible hyperinflation at rest, and the absence of measurement of the Borg scale at 30% PPO. Future studies should investigate mechanical ventilatory constraints in hEDS more systematically with repeated measurements of inspiratory capacity, including at rest, as well as dyspnea.

Conclusion

In conclusion, this exploratory study provides, for the first time, evidence for ventilatory constraints during exercise in patients with hEDS, such as dynamic hyperinflation and EFL. These constraints may induce discomfort during exercise. Further investigations of lung function in hEDS, during exercise and at rest, are needed to better understand the underlying mechanisms and to generalize to a wider patient population with hEDS.

Statements and declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Compliance with Ethical Standards:

This study is part of a clinical trial that has been approved by a national ethics committee (CPP Ile de France IV, 2019/71). All patients were volunteers and gave their informed consent.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contribution

AH, CB, and PM contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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Figures

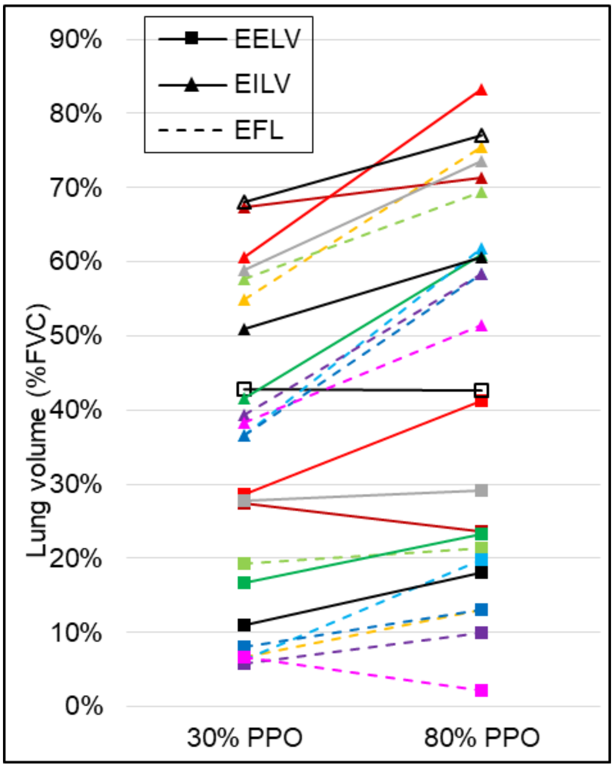

Fig. 1 Individual changes in EELV and EILV for all patients (n = 12) between 30% of PPO and 80% of PPO. The male participant is represented by empty markers.

Table 1: Anthropometric and spirometry data.

Data (n = 12)	**Mean ± SD** **[Min : Max]**
Age (years)	41 ± 14 [23 : 65]
Height (cm)	172 ± 9 [159 : 192]
Weight (kg)	79 ± 13 [58 : 99]
BMI (kg/m^2)	26.6 ± 3.6 [21.4 : 32.0]
Beighton score	5.2 ± 1.5 [3 : 7]
FVC (L) (% predicted value)	3.85 ± 0.84 (92 ± 9%)
FEV$_1$ (L) (% predicted value)	3.18 ± 0.75 (93 ± 11%)
FEV$_1$/FVC (%) (% predicted value)	82 ± 5 (100 ± 6%)
MVV (L/min)	127 ± 30

Abbreviations: BMI, body mass index; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 second; MVV, maximal voluntary ventilation.

Table 2: Ventilatory threshold and peak data during incremental cardiopulmonary exercise.

Data (n = 12)	**Mean ± SD**	
	Ventilatory threshold	Peak
Power Output (W)	64 ± 20	108 ± 34
$\dot{V}O_2$ (L/min) *(% predicted value)* (mL/kg/min)	0.96 ± 0.26 *(53 ± 13)* 12.3 ± 3.3	1.42 ± 0.38 *(79 ± 23)* 18.4 ± 4.9
HR (bpm) *(% predicted value)*	120 ± 18 *(66 ± 7)*	151 ± 21 *(84 ± 9)*
$\dot{V}_E$ (L/min)	32 ± 8	58 ± 19
Breathing reserve (%)	69 ± 6	47 ± 15
Respiratory exchange ratio	0.99 ± 0.08	1.15 ± 0.12
f_b (breaths/min)	23.7 ± 4.2	31.0 ± 6.2
V_T (L)	1.3 ± 0.38	1.8 ± 0.4

Abbreviations: $\dot{V}O_{2peak}$*, oxygen uptake at peak exercise; HR, heart rate;* $\dot{V}_E$*, minute ventilation; MVV, maximal voluntary ventilation;* f_b*, breathing frequency;* V_T*, tidal volume.*

Table 3: Mean cardiorespiratory data during constant load exercise test.

Data (n = 12)	**30% PPO**	**80% PPO**
Workload (W)	32 ± 10	86 ± 27*
$\dot{V}O_2$ (L/min) *(% predicted value)*	0.67 ± 0.12 *(38 ± 10)*	1.33 ± 0.33* *(76 ± 25)*
HR (bpm) *(% predicted value)*	102 ± 14 *(57 ± 8)*	142 ± 23* *(79 ± 14)*
SpO_2 (%)	96.4 ± 1.8	97.1 ± 1.5

Values are mean ± SD. Abbreviations: $\dot{V}O_2$*, oxygen uptake; HR, heart rate;* SpO_2*, arterial oxygen saturation.*
**Significant difference with 30% PPO.*

Table 4: Breathing pattern during constant load exercise test.

Data (n = 12)	**30% PPO**	**80% PPO**
$\dot{V}_E$ (L/min)	20.5 ± 4.4	49.8 ± 16.4*
Breathing reserve (%)	83 ± 4	60 ± 12*
f_b (breaths/min)	20 ± 4	26 ± 6*
V_T (L)	1.08 ± 0.22	1.91 ± 0.30*
$\dot{V}_E/\dot{V}CO_2$	38.4 ± 3.9	37.5 ± 7.9
T_i/T_{tot}	0.39 ± 0.04	0.45 ± 0.04*

Values are mean ± SD. Abbreviations: $\dot{V}_E$, minute ventilation; MVV, maximal voluntary ventilation; f_b, breathing frequency; V_T, tidal volume; $\dot{V}CO_2$, carbon dioxide output; T_i, inspiratory time; T_{tot}, total respiratory time.

**Significant difference with 30% PPO.*

Table 5: Pulmonary flow volume data during constant load exercise.

	30% PPO	**80% PPO**
IC (L)	3.12 ± 0.49	2.97 ± 0.52*
EELV (%FVC)	17 ± 12	21 ± 12*
EELV (L)	0.73 ± 0.68	0.88 ± 0.66*
EILV (%FVC)	51 ± 12	67 ± 10*
EILV (L)	2.00 ± 0.81	2.60 ± 0.81*
Number of subjects with EFL (% of total number)	6 (50%)	6 (50%)
EFL (L)	0.55 ± 0.27	0.75 ± 0.28
EFL (%V_T)	46 ± 22	43 ± 10

Values are mean ± SD, except for number of subjects with EFL which is the number of subjects and the percentage of the total number of subjects.

Abbreviations: IC, inspiratory capacity; EELV, end-expiratory lung volume; FVC, forced vital capacity; EILV, end-inspiratory lung volume; V_T*, tidal volume; EFL, expiratory flow limitation.*

IC, EELV, and EILV are expressed for all the subjects (n = 12). EFL in L and %V_T *are expressed only for the six expiratory flow limited subjects.*

**Significant difference with 30% PPO.*