





Unilateral diaphragmatic paralysis: inspiratory muscles, breathlessness and exercise capacity

Mayra Caleffi Pereira ¹, Letícia Z. Cardenas^{1,2}, Jeferson G. Ferreira^{1,2}, Vinícius C. Iamonti¹, Pauliane Vieira Santana^{1,2}, André Apanavicius¹, Pedro Caruso^{1,2}, Angelo Fernandez³, Carlos R.R. de Carvalho¹, Daniel Langer ⁴ and André L.P. de Albuquerque^{1,5}

ABSTRACT

Background: Patients with unilateral diaphragmatic paralysis (UDP) may present with dyspnoea without specific cause and limited ability to exercise. We aimed to investigate the diaphragm contraction mechanisms and nondiaphragmatic inspiratory muscle activation during exercise in patients with UDP, compared with healthy individuals.

Methods: Pulmonary function, as well as volitional and nonvolitional inspiratory muscle strength were evaluated in 35 patients and in 20 healthy subjects. Respiratory pressures and electromyography of scalene and sternocleidomastoid muscles were continuously recorded during incremental maximal cardiopulmonary exercise testing until symptom limitation. Dyspnoea was assessed at rest, every 2 min during exercise and at the end of exercise with a modified Borg scale.

Main results: Inspiratory muscle strength measurements were significantly lower for patients in comparison to controls (all $p < 0.05$). Patients achieved lower peak of exercise (lower oxygen consumption) compared to controls, with both gastric (-9.8 ± 4.6 cmH₂O *versus* 8.9 ± 6.0 cmH₂O) and transdiaphragmatic (6.5 ± 5.5 cmH₂O *versus* 26.9 ± 10.9 cmH₂O) pressures significantly lower, along with larger activation of both scalene ($40 \pm 22\%$ EMGmax *versus* $18 \pm 14\%$ EMGmax) and sternocleidomastoid ($34 \pm 22\%$ EMGmax *versus* $14 \pm 8\%$ EMGmax). In addition, the paralysis group presented significant differences in breathing pattern during exercise (lower tidal volume and higher respiratory rate) with more dyspnoea symptoms compared to the control group.

Conclusion: The paralysis group presented with exercise limitation accompanied by impairment in transdiaphragmatic pressure generation and larger accessory inspiratory muscles activation compared to controls, thereby contributing to a neuromechanical dissociation and increased dyspnoea perception.



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The exercise capacity limitation in patients with unilateral diaphragmatic paralysis is characterised by an inefficient hemidiaphragm contraction. Consequently, there is a neuromechanical dissociation with an overload of inspiratory accessory muscles and higher breathlessness. <https://bit.ly/2XxAR4K>

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Introduction

The diaphragm dysfunction is an underdiagnosed cause of dyspnoea. It is characterised by partial loss of the ability to generate pressure, which is considered diaphragm weakness, or complete loss of function, which is considered diaphragm paralysis. The main mechanism related to this condition is the phrenic nerve disfunction caused by situations such as trauma, surgery, chest tumours, myopathies, neuropathies and metabolic or inflammatory disorders [1]. The commitment involves either one or both hemidiaphragms. Differently from the bilateral involvement in which dyspnoea is intense even at rest, patients with unilateral diaphragmatic paralysis (UDP) are usually asymptomatic at rest, but may experience exertional dyspnoea, depending upon the severity of the paralysis and comorbid condition including obesity and intrinsic lung disease. Additionally, patients with UDP may experience dyspnoea in supine position and difficulty sleeping [2]. The lung function may present normal or slightly reduced vital capacity (VC). However, measurements of lung volumes in seated position are nonspecific, the change in VC measured from the seated to supine position is more consistent to evaluate diaphragm disfunction. The dysfunction can be confirmed by measuring the inspiratory force or more specifically the transdiaphragmatic pressure (Pdi), in association with image evaluation (usually by ultrasound) [3, 4].

It is known that the inspiratory muscle function is correlated with exercise capacity, and patients with UDP have decreased exercise tolerance [5, 6]. However, the diaphragm contraction mechanism, the role of the nondiaphragmatic inspiratory muscles in exercise capacity and augmented dyspnoea in this population have not been thoroughly described. This is a highly relevant topic that included defining whether diaphragm dysfunction is the limiting factor of exercise impairment and higher dyspnoea, which is likely a good candidate for surgical correction and/or even ventilatory muscle training.

We hypothesised that the exercise limitation and the augmented exertional breathlessness in patients with UDP are justified by the noneffective force of involved hemidiaphragm in association to overloading the nondiaphragmatic inspiratory muscles. This study aimed to investigate the diaphragm and nondiaphragmatic inspiratory muscles activation with breathlessness during exercise in patients with UDP, compared with healthy individuals.

Methods

Subjects

This was a cross-sectional study involving 35 patients with UDP, who were consecutively recruited from a tertiary university hospital. All diagnoses were confirmed by the respiratory physician, using complementary imaging studies with chest computed tomography and chest radiography (elevated hemidiaphragm); the absence of diaphragm mobility was confirmed by ultrasound when the elevation of hemidiaphragm was not so marked (defined by the respiratory physician). Besides that, we included patients with FVC<80% of predicted, maximal inspiratory pressure ($P_{I_{max}}$)<80% of predicted, along with dyspnoea symptom, and body mass index between 20–30 kg/m². Patients with comorbidities that could develop exertional dyspnoea, including COPD, interstitial lung diseases, cardiac heart failure (EF<55%) and neuromuscular disorders were excluded. A control group composed of 20 healthy subjects, matched by sex and weight, with normal lung function (FEV₁>80% of predicted and forced vital capacity (FVC)>80% of predicted) who were physically inactive (exercise activity less than twice a week) was included.

Study approval

This study was approved by the local ethics committee (CapPesq) (protocol number: 0835/11) and all subjects provided written informed consent.

Study protocol

Dyspnoea assessment and respiratory function measurements, such as lung function tests and inspiratory muscle strength were performed at baseline. Metabolic, cardiovascular, and respiratory variables were

Affiliations: ¹Pulmonary Division, Heart Institute (InCor), Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil. ²Intensive Care Unit, AC Camargo Cancer Center, São Paulo, Brazil. ³Thoracic Surgery Division, InCor, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil. ⁴Faculty of Kinesiology and Rehabilitation Sciences, Dept of Rehabilitation Sciences, Research Group for Cardiovascular and Respiratory Rehabilitation, KU Leuven – University of Leuven, and Respiratory Rehabilitation and Respiratory Division, University Hospital Leuven, Leuven, Belgium. ⁵Sírio-Libanês Teaching and Research Institute, São Paulo, Brazil.

Correspondence: André L.P. de Albuquerque, Pulmonary Division, InCor, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Av. Dr Enéas Carvalho Aguiar, nº44, Cerqueira Cesar, São Paulo, 05403-900, Brazil. E-mail: alpalbuquerque@hotmail.com

assessed during an incremental maximal cardiopulmonary exercise test with continuous measurement of oesophageal (P_{oes}), gastric (P_{ga}), transdiaphragmatic (P_{di}) pressures and surface electromyography (EMG) of scalene and sternocleidomastoid muscles. All the measurements were completed during a single visit.

Measurements at rest

Dyspnoea assessment

All subjects were asked to identify their degree of dyspnoea, indicating the extent to which the breathlessness affects their mobility, according to the Medical Research Council Breathlessness Scale [7].

Pulmonary function

Forced expiratory volume in 1 s (FEV_1), FVC, inspiratory capacity (IC), maximal voluntary ventilation (MVV), total lung capacity (TLC), carbon monoxide diffusing capacity (D_{LCO}) and carbon monoxide diffusing capacity by alveolar ventilation (V_A) coefficient (D_{LCO}/V_A) were measured according to European Respiratory Society/American Thoracic Society guidelines [8–10]. The predicted values for lung function were derived from the Brazilian population [11–13]. Additional details on the methods for pulmonary function measurements are provided in the online data supplement.

Inspiratory muscle function

Maximal static inspiratory mouth ($P_{I_{max}}$) and sniff nasal inspiratory (SNIP) pressures were measured using a digital manovacuometer. Oesophageal, gastric and transdiaphragmatic pressures were measured during a sniff manoeuvre (sniff P_{oes} , sniff P_{ga} and sniff P_{di} respectively) and magnetic phrenic nerve stimulation (twitch P_{oes} , twitch P_{ga} and twitch P_{di} respectively), using two air-filled balloon catheters positioned and calibrated according to the technique described elsewhere [14]. The reference values for $P_{I_{max}}$ and SNIP were derived from the Brazilian population [15, 16]. Additional details on the methods for these inspiratory muscle function measurements are provided in the online data supplement.

Measurements during exercise

Exercise testing

All subjects underwent an incremental maximal cardiopulmonary exercise testing (CPET) on a cycle ergometer until exhaustion. During the test, respiratory and metabolic variables were recorded. The reference values for exercise testing were based on a sedentary adult Brazilian population [17]. The IC and the modified Borg Rating of Perceived Exertion Scale [18] were assessed at rest, every 2 min, and at the end of the exercise. Additional details on the methods for exercise testing are provided in the online data supplement.

Inspiratory muscle function

During the exercise, continuous recordings of oesophageal, gastric and transdiaphragmatic pressures, as described above, and surface electromyography (EMG) of scalene and sternocleidomastoid muscles were performed. Additional details on the methods for EMG signal acquisition are provided in the online data supplement.

All measurements were performed breath by breath, and mean values were drawn from the last 20 s of each stage (submaximal) and peak. AqDados 7.0 software (Lynx technology, Brazil) was used for data acquisition and the AqAnalysis 7.0 (Lynx technology, Brazil) for data analysis.

Statistical analysis

Statistical analysis was performed using SPSS 21.0 (IBM SPSS Statistics, USA) and SigmaPlot 12.3 (Systat Software Inc., USA). Normality of distributions was tested using the Shapiro–Wilk test. Data are expressed as mean \pm SD, mean \pm SEM for the graph presentations or median (25th–75th percentile) as appropriate. An independent *t*-test was performed to compare both paralysis and control groups at baseline and at exercise peak. A two-way repeated measures ANOVA was performed to observe the relationship between variables and both groups at iso-work rate or at similar ventilation. The significance level was set to 5% ($p < 0.05$).

Results

Subjects

Among the patients, 13 presented with right and 22 with left paralysis. Idiopathic and trauma were the most common causes of diaphragmatic dysfunction (29% and 37%, respectively). General characteristics of patients with unilateral diaphragm paralysis and healthy control subjects are presented in table 1.

TABLE 1 Demographic data of patients with unilateral diaphragmatic paralysis and control group

	Paralysis group	Control group	p-value
Male	17 (49)	10 (50)	0.92
Age years	55.8±9.9 (32–77)	49.8±6.4 (40–58)	0.03
Weight kg	75.5±11.8 (48–99)	78.7±9.8 (65–105)	0.32
Height m	1.63±0.1 (1.5–1.9)	1.68 ±0.1 (1.5–1.9)	0.07
BMI kg·m⁻²	28.4±3.4 (22.2–35.6)	27.9±2.1(22.5–29.8)	0.49
Left paralysis	22 (63)	–	–
Cause of paralysis			
Idiopathic	10 (29)	–	–
Trauma	13 (37)	–	–
After cardiac surgery	8 (23)	–	–
After thoracic surgery	4 (11)	–	–

Data are presented as mean±sd (range) or n (%), unless otherwise stated. BMI: body mass index.

Measurements at rest

Pulmonary function dyspnoea

The paralysis group presented with lower FEV₁ and FVC compared with controls. When performed with the patient in the supine position, a reduction by 12% was observed in the FVC. Paralysis patients had reduced TLC and D_{LCO}, with normal D_{LCO}/V_A. Scores for moderate dyspnoea were reported by 66% (40% for MRC 2 and 26% for MRC 3) of paralysis patients with one reporting severe dyspnoea (MRC 4) (table 2).

Inspiratory muscle function

The paralysis group had global inspiratory weakness evidenced by P_{I_{max}}, SNIP and sniff P_{oes} significantly decreased compared with controls (table 3). A paradoxical response in P_{ga} (Fig. 1) was observed during the sniff manoeuvre in 86% of paralysis patients, resulting in lower sniff P_{di} values compared with that in controls. In addition, the transdiaphragmatic pressure in response to the magnetic phrenic nerve stimulation (twitch P_{di}) measurement evidenced diaphragm weakness at affected hemidiaphragm,

TABLE 2 Lung function and dyspnoea assessment of patients with unilateral diaphragmatic paralysis and control group at rest

	Paralysis group	Control group	p-value
Lung function			
FEV ₁ sitting L (% pred)	1.8±0.6 (59±13)	2.9±0.5 (92±9)	<0.001
FVC sitting L (% pred)	2.3±0.8 (62±13)	3.5±0.7 (92±8)	<0.001
FEV ₁ / FVC %	80±11	82±5	0.24
FVC supine L (% pred)	2.0±0.7 (56±13)	–	–
Δ FVC sitting versus supine %	–12±8	–	–
IC L (% pred)	1.7±0.5 (64±13)	2.7±0.5 (87±14)	<0.001
MVV L (% pred)	82.1±22.8 (65±13)	120.0±30.9 (85± 20)	<0.001
TLC L (% pred)	4.2±0.9 (73±21)	–	–
D _{LCO} (% pred)	20.1±8.3 (66±38)	–	–
D _L /V _A (% pred)	5.28±1.50 (107±35)	–	–
MRC			
1	11 (31)	20 (100)	<0.001
2	14 (40)	0 (0)	–
3	9 (26)	0 (0)	–
4	1 (3)	0 (0)	–
5	0 (0)	0 (0)	–

Data are presented as mean±sd or n (%), unless otherwise stated. FEV₁: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; IC: inspiratory capacity; MVV: maximal voluntary ventilation; TLC: total lung capacity, D_{LCO}: carbon monoxide diffusing capacity; D_L/V_A: carbon monoxide diffusing capacity by alveolar ventilation coefficient; MRC: Medical Research Council Breathlessness Scale.

TABLE 3 Respiratory muscle strength of patients with unilateral diaphragmatic paralysis and control group

	Paralysis group	Control group	p-value
Volitional inspiratory muscle strength			
P_{imax} cmH ₂ O (% pred)	-67±25 (55±23)	-103±30 (100±21)	<0.001
SNIP cmH ₂ O (% pred)	57±18 (58±15)	96±20 (89±28)	<0.001
Sniff P_{oes} cmH ₂ O	-44±13	-66±26	0.001
Sniff P_{ga} cmH ₂ O	-10±9	36±14	<0.001
Sniff P_{di} cmH ₂ O	34±17	102±26	<0.001
Nonvolitional inspiratory muscle strength			
Twitch P_{di} (bilateral) cmH ₂ O	5.3±2.7	15.3±5.7	<0.001
Twitch P_{di} Unaffected hemidiaphragm/right for control cmH ₂ O group	3.5±1.3	7.4±2.7	<0.001
Twitch P_{di} Affected hemidiaphragm/left for control cmH ₂ O group	2.5±1.1	8.9±3.4	<0.001

Data are presented as mean±SD, unless otherwise stated. P_{imax} : maximal static inspiratory pressure; SNIP: sniff nasal inspiratory pressure; Sniff P_{oes} : oesophageal pressure during sniff manoeuvre; Sniff P_{ga} : gastric pressure during sniff manoeuvre; Sniff P_{di} : transdiaphragmatic pressure during sniff manoeuvre; Twitch P_{di} : transdiaphragmatic pressure during phrenic nerve magnetic stimulation.

unaffected hemidiaphragm and bilateral stimulation in paralysis patients (table 3) compared with controls. There was no difference in the respiratory strength related to the paralysed side.

Measurements during exercise

Exercise testing

The paralysis group achieved lower peak work rate along with reduced oxygen consumption (V'_{O_2}) than did the control group, with 85% of maximal heart rate (table 4). The tidal volume (V_{T}), ventilation (V_{E})

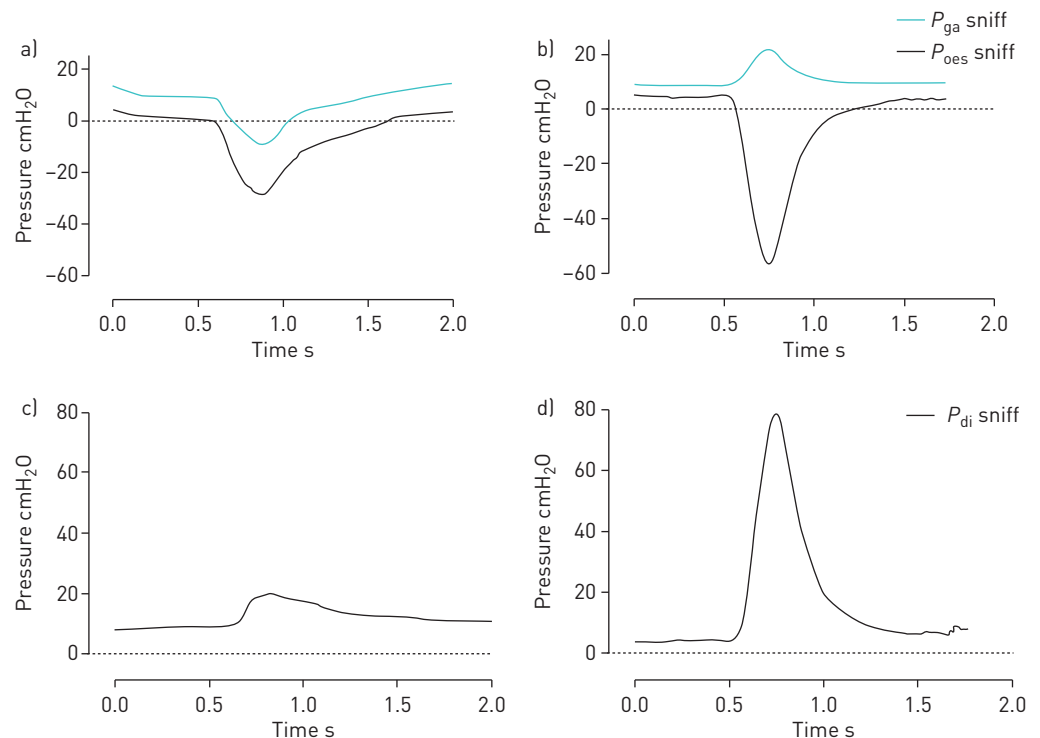


FIGURE 1 Illustration of oesophageal (P_{oes}), gastric (P_{ga}), transdiaphragmatic (P_{di}) pressure curves during sniff manoeuvre in a patient with unilateral diaphragm paralysis (a,b) and in a healthy control subject (c,d).

TABLE 4 Metabolic, respiratory, and cardiovascular parameters recorded at peak of incremental cardiopulmonary exercise testing (CPET) in patients with unilateral diaphragmatic paralysis and control group

	Paralysis group	Control group	p-value
CPET performance			
Work rate W (% pred)	83.9±38.5 (54±26)	152.3±55.2 (90±41)	<0.001
V_{O_2} mL·kg ⁻¹ ·min ⁻¹ (% pred)	18.7±5.5 (90.2±20.1)	25.3±9.5 (106.7±21.8)	0.01
RER	0.99±0.13	1.09±0.09	0.01
Ventilation and gas exchange			
V_T L	1.3±0.5	1.9±0.4	<0.001
V_T /IC %	72±11	72±8	0.93
V_E L·min ⁻¹	51.5±16.9	74.7±23.7	0.001
RR bpm	42±9	39±9	0.24
V_E /MVV	0.6±0.3	0.6±0.2	0.44
IC L	1.6±0.4	2.8±0.5	<0.001
Δ IC (peak-rest) L	0.0±0.2	0.6±1	0.03
V_E/V_{CO_2}	36±5	35±3	0.86
S_{pO_2} %	93±3	95±1	0.06
Cardiovascular			
HR bpm (% pred)	138±22 (85±12)	157±19 (93±10)	0.003
O_2 pulse mL·bpm ⁻¹ (% pred)	14±3 (82±21)	15±5 (89±28)	0.15
Symptoms			
Borg modified (dyspnoea)	9 (7–10)	5 (3.25–9)	0.001
Borg modified (legs effort)	9 (7–10)	7 (5–8.75)	0.02

Data are presented as mean±SD and median (25th–75th percentile), unless otherwise stated. V_{O_2} : maximal oxygen consumption; RER: respiratory exchange ratio; V_T : tidal volume; V_E : pulmonary ventilation; RR: respiratory rate; MVV: maximum voluntary ventilation; IC: inspiratory capacity; V_{CO_2} : CO₂ production; S_{pO_2} : peripheral oxygen saturation; HR: heart rate.

and the increment of IC (Δ IC) were decreased. In addition, the symptoms of dyspnoea and leg effort were higher in the paralysis group compared with the controls at peak exercise (table 4).

Both groups had similar V_{O_2} , V_E and V_T at most iso-work rate comparisons with a significant difference between them at the peak of exercise (figure 2a–c). However, the paralysis group had a higher respiratory rate (RR) at submaximal exercise intensities (figure 2d) and reported higher leg effort perception scores with higher dyspnoea even at very light exercise compared with the control group (figure 2e,f).

Inspiratory muscle function

Throughout incremental exercise, at iso-work rate, the paralysis group generated higher P_{oes} along with higher scalene (EMG_{sca/sca}, max) and sternocleidomastoid (EMG_{scm/scm}, max) activation compared with the control group (figure 3a,d,e). In contrast with healthy individuals who increased the P_{ga} and P_{di} during exercise, in the paralysis group P_{ga} was progressively negative, and, as a consequence, the P_{di} did not increase through exercise (figure 3b,c). At peak of exercise, lower respiratory pressures were found in the paralysis group, compared to controls, with -9.8 ± 4.6 cmH₂O versus 8.9 ± 6.0 cmH₂O for gastric pressure and 6.5 ± 5.5 cmH₂O versus 26.9 ± 10.9 cmH₂O for transdiaphragmatic pressure. In addition, paralysis group presented larger activation of both scalene (40±22% EMG_{max} versus 18±14% EMG_{max}) and sternocleidomastoid (34±22% EMG_{max} versus 14±8% EMG_{max}) compared to control group.

Furthermore, correcting for similar ventilation, a lower P_{di} was observed in the paralysis group with higher $P_{oes}/P_{oes,max}$ generation, EMG_{sca/sca}, max activation, and dyspnoea perception compared with controls (figure 4).

Discussion

Our main finding was the impaired mechanism of diaphragm contraction in UDP patients, characterised by the paradoxical response of the gastric pressure (negative values), which worsens during effort and is associated with relevant clinical implications, such as higher recruitment of inspiratory accessory muscles and higher dyspnoea, contributing to the reduced exercise capacity, compared to healthy subjects.

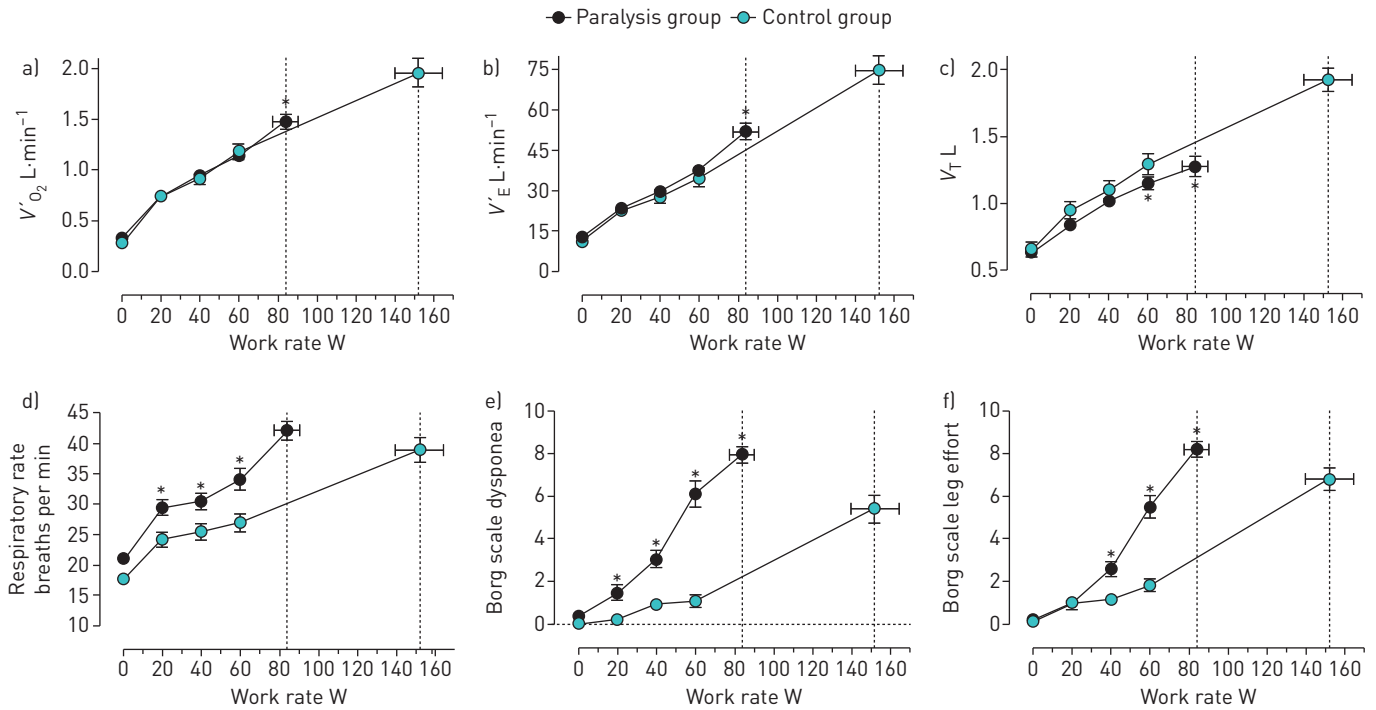


FIGURE 2 Metabolic and respiratory variables during incremental cycling exercise in patients with unilateral diaphragmatic paralysis (paralysis group) and healthy control group (CG). a) Peak oxygen uptake ($V'O_2$), b) Ventilation (V_E), c) Tidal volume (V_T), d) respiratory rate (RR), e) Borg score for dyspnoea and f) Borg score for leg effort. Dotted lines represent the peak of exercise for each group. Values represent mean \pm SEM. * $p < 0.05$ for paralysis group versus CG at iso-work rate or peak of exercise.

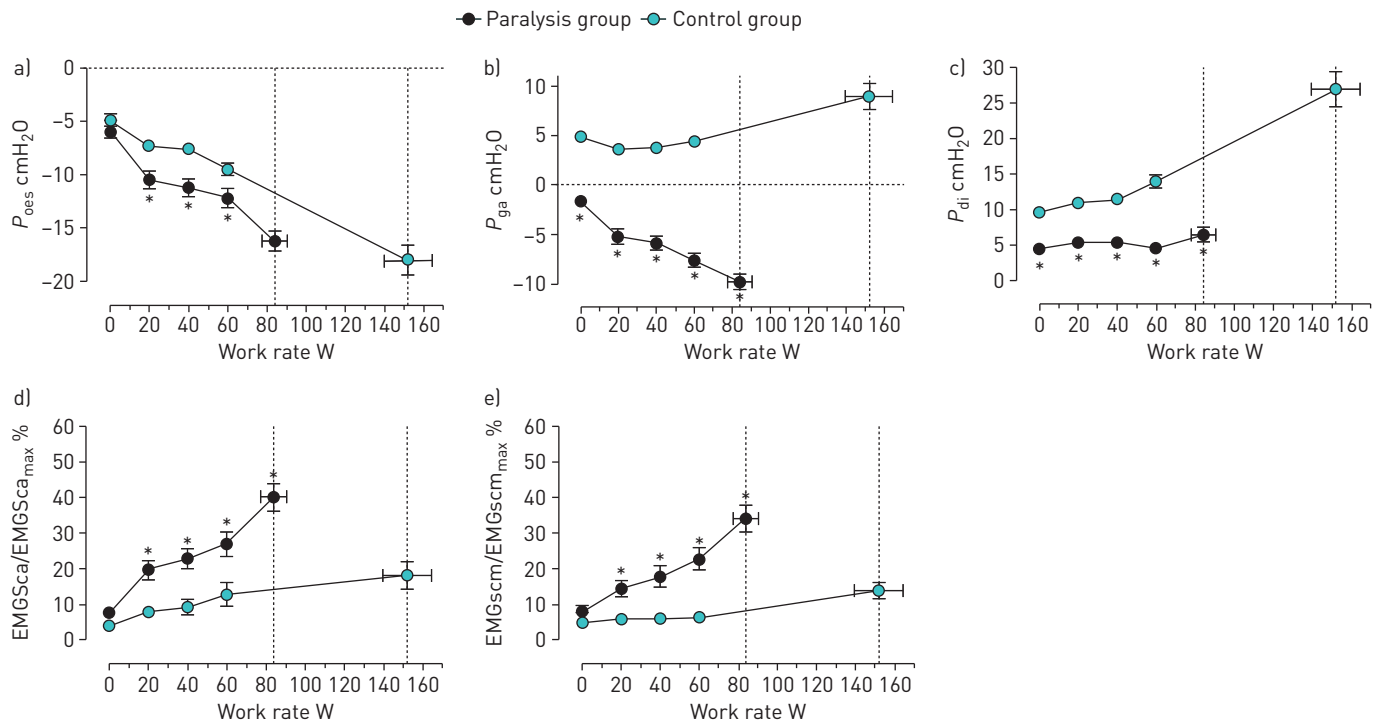


FIGURE 3 Inspiratory oesophageal (P_{oes}), gastric (P_{ga}), transdiaphragmatic (P_{di}) pressures [a–c] and percentage of maximal scalene [EMGsc_a/EMGsc_a, max] and sternocleidomastoid [EMGsc_m/EMGsc_m, max] muscle activation [d, e] during incremental cycling exercise in patients with unilateral diaphragmatic paralysis (paralysis group) and healthy control group (CG). Dotted lines represent the peak of exercise for each group. Values represent mean \pm SEM. * $p < 0.05$ for paralysis group versus control group at iso-work rate or peak of exercise.

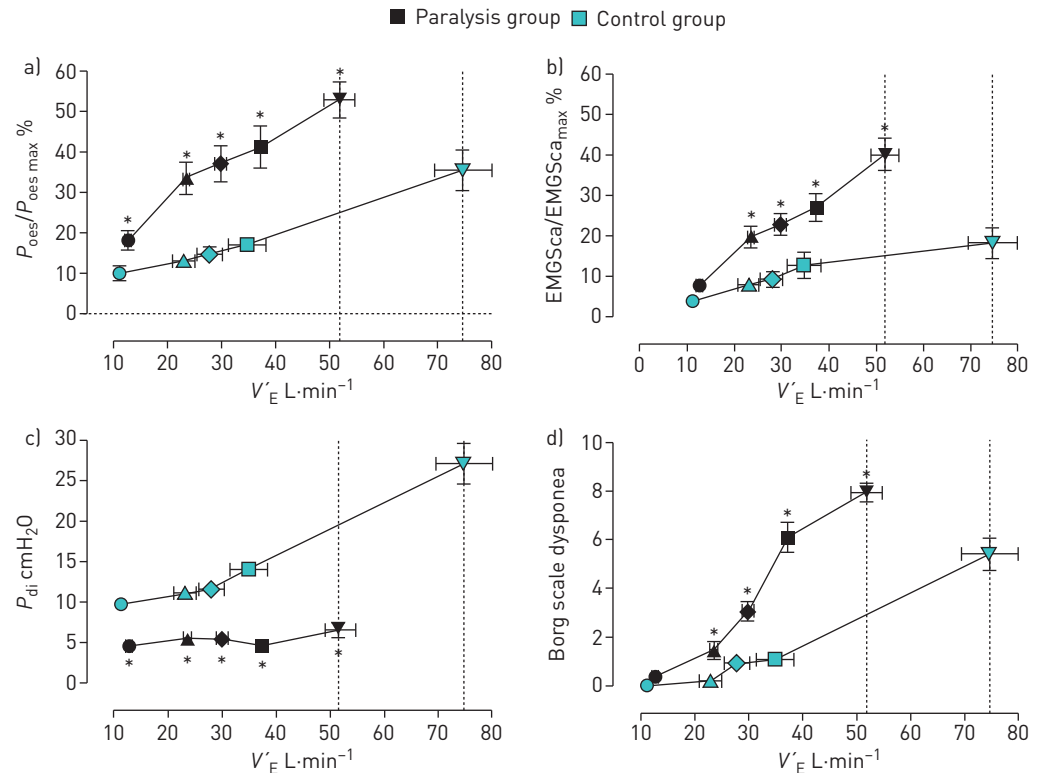


FIGURE 4 Percentage of maximal oesophageal pressure generation ($P_{oes}/P_{oes,max}$) [a]; percentage of maximal scalene activation [EMG_{sca}/EMG_{sca,max}] [b]; transdiaphragmatic pressure [P_{di}] [c]; and Borg score for dyspnoea [d] during incremental cycling exercise in patients with unilateral diaphragmatic paralysis (paralysis group) and healthy control group (CG) at similar ventilation. V_E : ventilation. Dotted lines represent the peak of exercise for each group. Values represent mean \pm SEM. *: $p < 0.05$ for paralysis group versus control group at similar V_E or peak of exercise (matching symbols).

Measurements at rest

Pulmonary function

After clinical and image evaluation, diaphragmatic dysfunction in the paralysis group was confirmed by a reduction of 35% in the FVC, with a further decrease of 12% when the FVC manoeuvre was performed with the patient in the supine position (Table 2). It is well established that unilateral diaphragmatic involvement is related to a mild decrease (10 to 30%) in VC and a further decrease of 10–20% with the patient in the supine position [1, 19, 20]. Koo *et al.* [21] described a change in VC performed in the supine position of 5.3% for normal diaphragm function, 13.8% for unilateral paralysis and 37% for bilateral paralysis.

Inspiratory muscle function

Our patients had significant inspiratory muscle weakness compared to control group, with 55% and 58% of predicted for $P_{I,max}$ and SNIP, respectively (table 3). The sniff manoeuvre with pressure measurement also evidenced significant global inspiratory muscle weakness compared with the controls (table 3). Although there are no normal values described for the sniff manoeuvre, the range can vary between 52 to 150 cmH₂O for sniff P_{oes} and 82 to 204 cmH₂O for sniff P_{di} in healthy subjects [4, 22] and a variation has been described between subjects in the oesophageal and gastric pressures contribution to the sniff P_{di} [22]. Of note, the low sniff P_{di} in the paralysis group is probably related to the paradoxical response (negative values) in the P_{ga} during the manoeuvre, which reflects the impaired diaphragm contraction mechanism (figure 1; table 3). Recently, a paradoxical response of the P_{ga} during the sniff manoeuvre was described in a man with unilateral diaphragmatic dysfunction [23], but it is not described in the healthy control subjects. MILLS *et al.* [24] suggest that the fall in P_{ga} during the sniff manoeuvre is due to the diaphragm being pushed up into the chest, reducing abdominal pressure.

The twitch P_{di} measurement evidenced substantial diaphragm weakness in the paralysis group compared with the control group (table 3). Although normal values for twitch P_{di} in adults are lacking, the literature shows that a twitch P_{di} of <15 cmH₂O [4] or <20 cmH₂O [2], and a unilateral twitch P_{di} of <10 cmH₂O [2]

are indicative of diaphragmatic weakness. However, some variability must be considered even in healthy individuals, in which involves also technical aspects like pressure sensors and properties of tube [25]. Our results showed a unilateral twitch P_{di} of 2.5 ± 1.1 cmH₂O (affected hemidiaphragm) in the paralysis group, in comparison to the control group, which agree with those described by HART *et al.* [6], who consider a right and/or left twitch $P_{di} < 3.5$ cmH₂O as indicative of UDP. In addition, a previous study [14] described this important reduction twitch P_{di} in patients with UDP, with impairment of the force generation even of the preserved contralateral hemidiaphragm.

Like the $P_{I_{max}}$ and SNIP measurements, the sniff manoeuvre is a global measurement of the strength of the inspiratory muscle, that is, combined measures of diaphragmatic and nondiaphragmatic inspiratory muscle strength. On the other hand, the twitch P_{di} is useful to assess the diaphragm function specifically. However, it is an invasive technique and cause some patient discomfort. The ultrasound is a useful tool to evaluate the diaphragm function, since it is less invasive, simple and allows direct evaluation [2, 4]. In patients with UDP, the ultrasound is an important technique to assess the diaphragm mobility and thickness, as described previously [14].

Measurements during exercise

Exercise testing

The paralysis group had similar V'_{O_2} and V_E compared with the controls at iso-work rate. However, they had reduced exercise capacity (lower peak work rate and V'_{O_2}) with a significant decrease in V_E and V_T at peak exercise. Interestingly, patients had increased RR and dyspnoea in very early exercise progression (figure 2). According to BONNEVIE *et al.* [5], these patients have exercise limited by a pathological ventilatory pattern (low V_t and excessive RR). HART *et al.* [6] affirm that the exercise limitation is primarily associated with the reduced peak minute ventilation. However, in both studies the sample size is small and there was not any measurement of diaphragm or inspiratory accessory muscles, besides dyspnoea during exercise.

Inspiratory muscle function

Looking at diaphragm function and its mechanism of contraction during exercise, a higher P_{oes} generation along with a paradoxical response in the P_{ga} generation was observed, resulting in a very low P_{di} compared with that in the control group (figure 3a–c). Of note, the pathological contraction pattern characterised by the negative values of P_{ga} is present not only at rest but worsens with increasing work rate. It is probably the result of the diaphragm being suctioned into the chest (paradoxical movement during inspiration), as described during the sniff manoeuvre [24]. HART *et al.* [6] had already described this pattern at rest and its correlation with a worse exercise performance and reduced ventilation. We observed this paradoxical movement of the P_{ga} at rest in 75% of the patients, with increase to 94% at 20 w and to 100% at other loads and peak of the exercise.

At iso-work rate, the paralysis group had a greater percentage of activation of scalene (EMG_{sca}/EMG_{sca}, max) and sternocleidomastoid (EMG_{scl}/EMG_{scl}, max) than the controls had. At peak exercise, they reached twice the percentage of the controls (figure 3d,e). This result indicates that, at submaximal exercise, paralysis group probably maintained similar ventilatory conditions to that in the control group at the expense of the scalene and sternocleidomastoid activation. This result is in line with the statement that in face of the impaired diaphragm contraction, the inspiratory function is supposed to be partially compensated by other inspiratory muscles than the diaphragm [26]. In addition, the high activation of these muscles explains the higher P_{oes} generation compared with controls (figure 3a) because the P_{oes} measured during hyperpnoea condition is the result not only of diaphragm contraction but also of the nondiaphragmatic inspiratory muscles. This recruitment certainly results in higher dyspnoea sensation during exercise, even at mild intensities.

Briefly, the paralysis group present an increased inspiratory muscle effort combined with reduced tidal volume and increased RR at a given work rate or ventilation compared to the controls. It may reflect a mismatch between the respiratory drive and the mechanical responses (neuromechanical dissociation), probably resulting in increased dyspnoea [27]. Despite it is a mechanism of better adaptation to achieve a higher ventilation, the ultimate consequence is an overload of inspiratory accessory muscles and higher breathlessness.

Although the static respiratory muscle function is well described in patients with diaphragmatic dysfunction [2, 3, 14, 19, 20, 24, 28], only two studies [5, 6] have described the influence of inspiratory muscle function on the exercise capacity in these patients. However, none of them applied the respiratory muscle function measurements during the exercise. This is the first study that shows a more comprehensive and dynamic evaluation of all inspiratory muscles and symptom-implication over the exercise. Our study measured the respiratory muscle function continuously throughout the exercise, with

important results of over recruitment of the respiratory muscles and altered respiratory pressures responses in these patients compared to healthy subjects. Despite the statistical difference in the age between the groups, the average values (55.8 ± 9.9 years for paralysis group and 49.8 ± 6.4 years for control group) are clinically very similar.

Limitations

Some limitations are present in this study. First, we based the impaired diaphragm contraction on the respiratory pressure responses. The diaphragm EMG measurements could provide us with additional information about diaphragm activation during exercise. Second, we studied the mechanisms of pressure generation and muscle activation only during inspiration. Results during expiration, such as abdominal activation or gastric pressure generation, could improve the findings. Third, we used unpotentiated twitch pressures instead of potentiated, which might be more sensitive. Fourth, we did not assess the reason for stopping the exercise, which could bring more detailed information about symptom limitation. Finally, the ultrasound could be a useful adjacent tool to identify the paradoxical diaphragm movement, but this measurement would be difficult to perform during the exercise.

Conclusion

In conclusion, patients with UDP had the pathological mechanism of diaphragm contraction (paradoxical Pga) that worsens during effort. This happens along with a neuromechanical dissociation, illustrated by the over recruitment of the nondiaphragmatic inspiratory muscles and lower tidal volume with higher RR, reducing the exercise performance and contributing to the higher dyspnoea.

This study carries an important clinical relevance since it reinforces the important role of the nondiaphragmatic inspiratory muscles in the exercise performance. Inspiratory muscle training has been described as an alternative to improve inspiratory muscle function in patients with unilateral diaphragm paralysis [23, 29–31], which likely has a positive impact on inspiratory accessory muscles. Nevertheless, studies are needed to further establish its benefits on exercise capacity in this population.

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References

- 1 McCool FD, Tzelepis GE. Dysfunction of the diaphragm. *N Engl J Med* 2012; 366: 932–942.
- 2 McCool FD, Manzoor K, Minami T. Disorders of the diaphragm. *Clin Chest Med* 2018; 39: 345–360.
- 3 Laveneziana P, Nierat MC, LoMauro A, et al. A case of unexplained dyspnoea: when lung function testing matters! *Breathe* 2018; 14: 325–332.
- 4 Laveneziana P, Albuquerque A, Aliverti A, et al. ERS statement on respiratory muscle testing at rest and during exercise. *Eur Respir J* 2019; 53: 1801214.
- 5 Bonnevie T, Gravier FE, Ducrocq A, et al. Exercise testing in patients with diaphragm paresis. *Respir Physiol Neurobiol* 2018; 248: 31–35.
- 6 Hart N, Nickol AH, Cramer D, et al. Effect of severe isolated unilateral and bilateral diaphragm weakness on exercise performance. *Am J Respir Crit Care Med* 2002; 165: 1265–1270.
- 7 Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988; 93: 580–586.
- 8 Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005; 26: 720–735.
- 9 Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
- 10 Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; 26: 511–522.
- 11 Neder JA, Andreoni S, Castelo-Filho A, et al. Reference values for lung function tests. I. Static volumes. *Braz J Med Biol Res* 1999; 32: 703–717.
- 12 Neder JA, Andreoni S, Peres C, et al. Reference values for lung function tests. III. Carbon monoxide diffusing capacity (transfer factor). *Braz J Med Biol Res* 1999; 32: 729–737.
- 13 Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. *J Bras Pneumol* 2007; 33: 397–406.

- 14 Caleffi-Pereira M, Pletsch-Assuncao R, Cardenas LZ, *et al.* Unilateral diaphragm paralysis: a dysfunction restricted not just to one hemidiaphragm. *BMC Pulm Med* 2018; 18: 126.
- 15 Araujo PR, Resqueti VR, Nascimento Junior J, *et al.* Reference values for sniff nasal inspiratory pressure in healthy subjects in Brazil: a multicenter study. *J Bras Pneumol* 2012; 38: 700–707.
- 16 Neder JA, Andreoni S, Lerario MC, *et al.* Reference values for lung function tests. II. Maximal respiratory pressures and voluntary ventilation. *Braz J Med Biol Res* 1999; 32: 719–727.
- 17 Neder JA NL. Teste de exercício cardiopulmonar. *J Pneumol* 2002; 28: S166–S206.
- 18 Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982; 14: 377–381.
- 19 Laroche CM, Mier AK, Moxham J, *et al.* Diaphragm strength in patients with recent hemidiaphragm paralysis. *Thorax* 1988; 43: 170–174.
- 20 Lisboa C, Pare PD, Pertuze J, *et al.* Inspiratory muscle function in unilateral diaphragmatic paralysis. *Am Rev Respir Dis* 1986; 134: 488–492.
- 21 Koo P, Oyieng'o DO, Gartman EJ, *et al.* The maximal expiratory-to-inspiratory pressure ratio and supine vital capacity as screening tests for diaphragm dysfunction. *Lung* 2017; 195: 29–35.
- 22 Miller JM, Moxham J, Green M. The maximal sniff in the assessment of diaphragm function in man. *Clin Sci* 1985; 69: 91–96.
- 23 Caleffi Pereira M, Dacha S, Testelmans D, *et al.* Assessing the effects of inspiratory muscle training in a patient with unilateral diaphragm dysfunction. *Breathe* 2019; 15: e90–e96.
- 24 Mills GH, Kyroussis D, Hamnegard CH, *et al.* Cervical magnetic stimulation of the phrenic nerves in bilateral diaphragm paralysis. *Am J Respir Crit Care Med* 1997; 155: 1565–1569.
- 25 Luo YM, Hart N, Mustafa N, *et al.* Reproducibility of twitch and sniff transdiaphragmatic pressures. *Respir Physiol Neurobiol* 2002; 132: 301–306.
- 26 Xu Y, Rui J, Zhao X, *et al.* Effect of isolated unilateral diaphragmatic paralysis on ventilation and exercise performance in rats. *Respir Physiol Neurobiol* 2014; 196: 25–32.
- 27 Manning HL, Schwartzstein RM. Pathophysiology of dyspnea. *N Engl J Med* 1995; 333: 1547–1553.
- 28 Dube BP, Dres M. Diaphragm dysfunction: diagnostic approaches and management strategies. *J Clin Med* 2016; 5: 113.
- 29 Chatham K, Gelder CM, Lines TA, *et al.* Suspected statin-induced respiratory muscle myopathy during long-term inspiratory muscle training in a patient with diaphragmatic paralysis. *Phys Ther* 2009; 89: 257–266.
- 30 Kodric M, Trevisan R, Torregiani C, *et al.* Inspiratory muscle training for diaphragm dysfunction after cardiac surgery. *J Thorac Cardiovasc Surg* 2013; 145: 819–823.
- 31 Petrovic M, Lahrmann H, Pohl W, *et al.* Idiopathic diaphragmatic paralysis--satisfactory improvement of inspiratory muscle function by inspiratory muscle training. *Respir Physiol Neurobiol* 2009; 165: 266–267.