Unilateral diaphragmatic paralysis: inspiratory muscles, breathlessness and exercise capacity

Mayra Caleffi Pereira, Leticia Z. Cardenas, Jeferson G. Ferreira, Vinicius C. Iamonti, Pauliane Vieira Santana, André Apanavicius, Pedro Caruso, Angelo Fernandez, Carlos R.R. de Carvalho, Daniel Langer and André L.P. de Albuquerque

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±22% EMGmax versus 18±14% EMGmax) and sternocleidomastoid (34±22% EMGmax versus 14±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 dysfunction 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 dysfunction. 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_{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 Clinicas 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 Clinicas 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, n°44, Cerqueira Cesar, São Paulo, 05403-900, Brazil. E-mail: alpalbuquerque@hotmail.com

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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 ($P_{imax}$) 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 $P_{imax}$ 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.

**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±SD, mean±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.
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 DLCO, with normal DLCO/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 PImax, SNIP and sniff Poes significantly decreased compared with controls (table 3). A paradoxical response in Pga (Fig. 1) was observed during the sniff manoeuvre in 86% of paralysis patients, resulting in lower sniff Pdi values compared with that in controls. In addition, the transdiaphragmatic pressure in response to the magnetic phrenic nerve stimulation (twitch Pdi) measurement evidenced diaphragm weakness at affected hemidiaphragm.

| 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

|                          | Paralysis group | Control group | p-value |
|-------------------------|-----------------|---------------|---------|
| 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.

| 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                                               |                                      |         |
| FEV₁, 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 |
| FEV₁/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]                                             | 92.1±22.9 (65±13)                     | 120.4±30.9 (85±20) | <0.001 |
| TLC L [% pred]                                              | 4.2±0.9 (73±21)                        | –           | –       |
| Dl,CO (%)                                                  | 20.1±8.3 (66±38)                      | –           | –       |
| Dl /V'A (%)                                                | 5.28±1.50 (107±35)                     | –           | –       |

MRC

| Paralysis group | 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; Dl,CO: carbon monoxide diffusing capacity; Dl /V'A: carbon monoxide diffusing capacity by alveolar ventilation coefficient; MRC: Medical Research Council Breathlessness Scale.
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 ($V'_{\text{O}_2}$) than did the control group, with 85% of maximal heart rate (table 4). The tidal volume ($V_T$), ventilation ($V_E$),

\[
\begin{array}{l}
\text{TABLE 3 Respiratory muscle strength of patients with unilateral diaphragmatic paralysis and control group} \\
\begin{array}{|c|c|c|}
\hline
\text{Volitional inspiratory muscle strength} & \text{Paralysis group} & \text{Control group} & \text{p-value} \\
\hline
P_{\text{Imax}} \text{ cmH}_2\text{O} (% \text{ pred}) & -67\pm25 (55\pm23) & -103\pm30 (100\pm21) & <0.001 \\
\text{SNIP cmH}_2\text{O} (\% \text{ pred}) & 57\pm18 (58\pm15) & 64\pm10 (99\pm28) & <0.001 \\
\text{Sniff } P_{\text{oes}} \text{ cmH}_2\text{O} & -44\pm13 & -66\pm26 & 0.001 \\
\text{Sniff } P_{\text{ga}} \text{ cmH}_2\text{O} & 34\pm17 & 102\pm26 & 0.001 \\
\hline
\text{Nonvolitional inspiratory muscle strength} & & & \\
\text{Twitch } P_{\text{e}} \text{ (bilateral) cmH}_2\text{O} & 5.3\pm2.7 & 15.3\pm5.7 & <0.001 \\
\text{Twitch } P_{\text{e}} \text{ Unaffected hemidiaphragm/right for control cmH}_2\text{O} & 3.5\pm1.3 & 7.4\pm2.7 & <0.001 \\
\text{Twitch } P_{\text{e}} \text{ Unaffected hemidiaphragm/left for control cmH}_2\text{O} & 2.5\pm1.1 & 8.9\pm3.4 & <0.001 \\
\hline
\text{Data are presented as mean±sd, unless otherwise stated. } P_{\text{Imax}} \text{: maximal static inspiratory pressure; SNIP: sniff nasal inspiratory pressure; Sniff } P_{\text{oes}} \text{: oesophageal pressure during sniff manoeuvre; Sniff } P_{\text{ga}} \text{: gastric pressure during sniff manoeuvre; Sniff } P_{\text{di}} \text{: transdiaphragmatic pressure during sniff manoeuvre; } P_{\text{e}} \text{: transdiaphragmatic pressure during phrenic nerve magnetic stimulation.}
\end{array}
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\]

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

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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 $V'_{O2}$, $V_E$ 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 (EMGscal) and sternocleidomastoid (EMGscm) 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 $-9.8±4.6$ cmH$_2$O versus $8.9±6.0$ cmH$_2$O for gastric pressure and $6.5±5.5$ cmH$_2$O versus $26.9±10.9$ cmH$_2$O for transdiaphragmatic pressure. In addition, paralysis group presented larger activation of both scalene ($40±22$% EMGmax versus $18±14$% EMGmax) and sternocleidomastoid ($34±22$% EMGmax 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, EMGscal, 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.

### 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  |
| $V'_{O2}$ 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    |
| $V_T$ L·min$^{-1}$                    | 51.5±16.9      | 74.7±23.7     | 0.001   |
| RR bpm                                | 42±9           | 39±9          | 0.24    |
| $V_T$/MVW                             | 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    |
| $V_T$/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. $V'_{O2}$: 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; $V_{CO_2}$: CO$_2$ production; $S_pO_2$: peripheral oxygen saturation; HR: heart rate.

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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 ($V_T$), 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±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 [EMGsca/ EMGsca, max] and sternocleidomastoid [EMGscm/ EMGscm, 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 means±SEM. *p<0.05 for paralysis group versus control group at iso-work rate or peak of exercise.
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 PImax 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 Pea and 82 to 204 cmH2O for sniff Pdi in healthy subjects [4, 22] and a variation has been described between subjects in the oesophageal and gastric pressures contribution to the sniff Pdi [22]. Of note, the low sniff Pdi in the paralysis group is probably related to the paradoxical response (negative values) in the Ppa during the manoeuvre, which reflects the impaired diaphragm contraction mechanism (figure 1; table 3). Recently, a paradoxical response of the Ppa 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 Ppa during the sniff manoeuvre is due to the diaphragm being pushed up into the chest, reducing abdominal pressure.

The twitch Pdi measurement evidenced substantial diaphragm weakness in the paralysis group compared with the control group (table 3). Although normal values for twitch Pdi in adults are lacking, the literature shows that a twitch Pdi of <15 cmH2O [4] or <20 cmH2O [2], and a unilateral twitch Pdi 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 cmH$_2$O (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}<$3.5 cmH$_2$O 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 $P_{max}$ 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 $V'_{CO_2}$ and $V_E$ compared with the controls at iso-work rate. However, they had reduced exercise capacity (lower peak work rate and $V'_{CO_2}$) 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 $P_{iho}$ 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 $P_{di}$ 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 $P_{iho}$ 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 (EMGscsa/EMGscsa, max) and sternocleidomastoid (EMGscm/EMGscm, 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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