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## Feasibility of a Hypoxic Challenge Test Under Noninvasive Ventilation Versus Oxygen in Neuromuscular Patients with Chronic Respiratory Insufficiency

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1 Feasibility of a hypoxic challenge test under non-invasive ventilation versus oxygen in  
2 neuromuscular patients with chronic respiratory insufficiency

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28 Keywords:

- 29 - Hypoxic challenge test
- 30 - Non-invasive ventilation
- 31 - Chronic respiratory insufficiency
- 32 - Neuromuscular pathology
- 33 - Oxygen

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37 **Abstract**

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39 **Background:** The British Thoracic Society recommendations suggest that all patients with an  
40 oxygen saturation < 85% during a hypoxic challenge test (HCT) should receive supplemental  
41 oxygen during air travel. However, neuromuscular patients already using ventilatory support  
42 are a specific population and non-invasive ventilation (NIV) during a flight could be an  
43 alternative to oxygen for hypoxemia correction, through the augmentation of ventilation.

44 **Methods:** We conducted a comparative, observational study of neuromuscular patients with  
45 chronic respiratory failure, requiring nocturnal mechanical ventilation, who were planning to  
46 take a flight. HCT was performed with a ventilated canopy placed over the patient's head or the  
47 patient's home ventilator. The-positive threshold value chosen for the HCT was < 90% SpO<sub>2</sub>.

48 **Results:** HCTs were performed on 13 adults with neuromuscular diseases using their home  
49 ventilator. Among them, 11 had a positive HCT. For all patients with a positive test, hypoxemia  
50 was corrected (SpO<sub>2</sub> to > 90%) by oxygen therapy (+9 [6 to 12] %, p = 0.0029). Patient's home  
51 ventilator also significantly increased the SpO<sub>2</sub> by 8 [7 to 12] % (p = 0.016). Correction of SpO<sub>2</sub>  
52 during the HCT was not different between oxygen and NIV. NIV was associated with a  
53 significant decrease in PetCO<sub>2</sub> (-10 [-16 to -7.5] mmHg, p = 0.04).

54 **Conclusions:** The performance of an adapted HCT in home-ventilated patients with a  
55 neuromuscular pathology may be is useful in a personalized treatment plan for air travel. NIV  
56 can be a new alternative to oxygen therapy for neuromuscular patients planning to take a flight.

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66 **Introduction**

67 In 2018, four billion passengers were carried by air transport according to the International Civil  
68 Aviation Organization (ICAO's Annual Report of the Council, 2018). Among passengers  
69 planning air travel, patients with respiratory diseases are at high risk of in-flight complications  
70 (Noble et al., 1999; Ergan et al., 2018). Indeed, a commercial aircraft cabin is pressurized to a  
71 maximum altitude of 2,400 m and the oxygen pressure is equivalent to a  $FiO_2$  of 15.1%. In this  
72 condition, the partial pressure of arterial oxygen ( $PaO_2$ ) falls to 60-75 mmHg and the oxygen  
73 saturation ( $SpO_2$ ) measured by pulse oximetry is between 89 and 94% in healthy subjects. This  
74 results in moderate hyperventilation and moderate tachycardia. In 2011, the British Thoracic  
75 Society (BTS) recommended performing a hypoxic challenge test (HCT) for all patients  
76 planning air travel with severe restrictive lung disease (vital capacity < 1 litre), especially for  
77 those with hypoxemia and/or hypercapnia, as well as for those requiring ventilatory support  
78 (Ahmedzai et al., 2011). If the oxygen saturation at the end of the test remains > 85%, oxygen  
79 supplementation is not required. Below this value, it is recommended to add 2 to 4 l/min of  
80 oxygen via a nasal cannula. However, the correction of hypoxemia in patients with chronic  
81 respiratory failure due to advanced neuromuscular disease can be achieved by ventilatory  
82 support, which allows the patient to reach a level of ventilation equivalent to that of a normal  
83 subject (Mestry et al., 2009). Few studies have investigated the use of a ventilator instead of  
84 oxygen to correct hypoxia during air travel in these particular patients. This study was designed  
85 to evaluate the feasibility of a HCT under non-invasive ventilation (NIV) and to compare the  
86 correction of hypoxemia by increasing ventilation with NIV to that by oxygen therapy during  
87 a HCT in patients with chronic respiratory failure due to neuromuscular diseases already treated  
88 with home ventilatory support.

89  
90 **Methods**

91  
92 We conducted a comparative, observational study in the respiratory medicine department of the  
93 Pitié Salpêtrière Hospital (Paris) over a six months period. We extracted retrospectively the  
94 data from the medical files from patients tested before air travelling. The study was approved  
95 by the ethics committee from the Institutional Review Board of the French Learned Society for  
96 Respiratory Medicine (CEPRO 2012-039). Written informed consent was obtained from all  
97 subjects. Patients were included if they suffered from chronic respiratory failure due to  
98 neuromuscular disorders and requiring nocturnal mechanical ventilation and if they were  
99 planning a flight. Patients with non-treated cardiovascular diseases, recent myocardial  
100 infarction, cardiac arrhythmia, pregnancy,  $FEV_1 < 30\%$  due to obstructive disease, pulmonary

101 arterial hypertension, infectious tuberculosis, or ongoing pneumothorax with persistent air leak  
102 and major hemoptysis were excluded (Ahmedzai et al., 2011). Data collected were age,  
103 diagnosis, sitting and supine force vital capacity (FVC), oxygen saturation (SpO<sub>2</sub>), expired CO<sub>2</sub>  
104 (PetCO<sub>2</sub>), room air blood gases and daily adherence to home mechanical ventilation.

105 The HCT was performed with a ventilated canopy placed over the patient's head or the patient's  
106 home ventilator (Figure 1A) and connected to a hypoxia generator (HYPOXICO Inc., Jalhay,  
107 Belgium). The extraction of O<sub>2</sub> was adapted to obtain a stable FiO<sub>2</sub> of 15% ± 0.2%. FiO<sub>2</sub> was  
108 measured using a FiO<sub>2</sub> sensor (MAXTEC Inc., Utah, USA) placed inside the canopy. The  
109 measurement of oxygen saturation, PetCO<sub>2</sub>, heart rate, and respiratory rate was performed using  
110 an integrated monitor (Capnocheck ® Plus, Smiths Medical PM, Inc. Wisconsin 53186 USA),  
111 including pulse oximetry and nasal cannula for measuring CO<sub>2</sub>. Oxygen was administered using  
112 another nasal cannula previously placed in superposition of the Capnocheck cannula. The HCT  
113 was performed with the patients seated at rest in four successive measurements (15 min each):  
114 1) spontaneous ventilation, room air (baseline), 2) under the canopy, spontaneous ventilation,  
115 FiO<sub>2</sub> of 15% and, if the test was positive (SpO<sub>2</sub> < 90%), 3) under the canopy, spontaneous  
116 ventilation, FiO<sub>2</sub> of 15%, with an oxygen flow of 2 l/min, and finally 4) under patient's home  
117 ventilator, FiO<sub>2</sub> of 15% (Figure 1B). Dyspnea and headaches were measured at the end of each  
118 period by visual analog scales (VAS) rated from 0-10.

119 We chose a positive value for the HCT of < 90% SpO<sub>2</sub>, which is different from that of the BTS  
120 recommendation (positive < 85% of SaO<sub>2</sub>). Indeed, patients with neuromuscular disease or  
121 extrapulmonary restrictive chest wall deformity are more at risk of hypoxemia during a HCT,  
122 even with a resting saturation of > 95% (Masa et al., 1997). Our choice of 90% was selected for  
123 two reasons. First, the related effect of hypoxemia, such as an increase in respiratory rate, was  
124 observed at < 90% of the SpO<sub>2</sub>, suggesting a lower respiratory tolerance. Second, the BTS  
125 threshold is common to all respiratory disease, broadly based on studies that include obstructive  
126 lung disease. Our patients had normal lung parenchyma associated with reduced ventilatory  
127 adaptation in a hypoxemia condition. Thus, a threshold of 90% appeared to be more clinically  
128 relevant for this neuromuscular population. It was a choice of caution; it is difficult to formally  
129 prove that a patient with severe diaphragmatic dysfunction can remain with a SpO<sub>2</sub> between 85  
130 and 90% for a long time.

131

132 A p-value of < 0.05 was considered statistically significant. Quantitative variables were  
133 compared using a Friedman's test and a post hoc Dunn test and the results expressed as their  
134 standard value (median and interquartile range). Qualitative variables were compared using

135 Fisher's exact test and are expressed in terms of numbers and percentage. All statistical analyses  
136 were performed using GraphPad Prism software.

137

## 138 **Results**

139 Thirteen patients were included, of whom 7 had amyotrophic lateral sclerosis. Their  
140 characteristics are presented in Table 1.

141 At baseline, median blood gas measures were a PaO<sub>2</sub> of 82 mmHg and a PaCO<sub>2</sub> of 41 mmHg.  
142 All patients performed the HCT. The median SpO<sub>2</sub> was 95% at baseline. By the end of the test,  
143 the SpO<sub>2</sub> of 11 patients had fallen to < 90% (Figure 2). Among these patients, the SpO<sub>2</sub> of two  
144 had fallen to < 85%. The median fall of oxygen saturation was 7 [5.5 to 8.5] % relative to the  
145 baseline SpO<sub>2</sub> (p < 0.001). There was no significant change in the PetCO<sub>2</sub> during spontaneous  
146 ventilation at the end of the HCT.

147 An oxygen flow of 2 l/min allowed a correction of SpO<sub>2</sub> to > 90% for all positive HCT patients  
148 (+9 [6 to 12] %, p = 0.0029). In comparison, patient's home ventilator significantly increased  
149 the SpO<sub>2</sub> by 8 [7 to 12] % (p = 0.016). Oxygen was not more effective than NIV for SpO<sub>2</sub>  
150 correction during the HCT (Figure 3). There was a significant decrease in PetCO<sub>2</sub> only with  
151 NIV (-10 [-16 to -7.5] mmHg, p = 0.04). The HCT was not associated with a significant increase  
152 in the respiratory rate and the VAS score for dyspnea. Three tests were prematurely stopped:  
153 one because of dyspnea (at the end of HCT), one because of dyspnea and headache (at the end  
154 of HCT + O<sub>2</sub> period), one at the request of the patient (at the end of HCT). No other patients  
155 reported a change in the VAS for dyspnea or headache.

## 156 **Discussion**

157 Our study shows that a pre-flight HCT is feasible under NIV in neuromuscular patients. The  
158 study also shows that SpO<sub>2</sub> drops below 90% under a 15% FiO<sub>2</sub> in the majority of such patients  
159 (11 out of 13 in this study) and that NIV correct hypoxemia in all cases.

160 HCT is achievable for patients using NIV under a canopy coupled to a hypoxia generator. In  
161 contrast to other already available methods using a Douglas bag or a Venturi mask, it is easily  
162 achievable directly at the patient's bedside, making it accessible to patients with motor  
163 disabilities or respiratory failure. Its speed of acquisition (45 minutes for a complete test) allows  
164 its routine use. Moreover, unlike conventional methods, it allows the evaluation of alternative  
165 therapies, such as mechanical ventilation. The order of the different periods of the test was  
166 planned to avoid the necessity of re-establishing a stable hypoxia multiple times which would



167 have lengthened the experiment. However, a potential effect of the sequence cannot be  
168 excluded and the results could be different with another sequence.

169 NIV was always as effective as oxygen therapy in our group of patients. NIV appeared to be an  
170 acceptable alternative therapy, with physiological advantages like decreasing CO<sub>2</sub> level.  
171 Furthermore, Winck et al. showed that a patient with a neuromuscular disease who is correctly  
172 ventilated, without supplemental oxygen, can maintain oxygen saturation throughout a flight  
173 (Winck et al., 2010). In our study, the PetCO<sub>2</sub> did not significantly decrease during the HCT  
174 because of a possible lack of ventilatory adaptation in this particular population. Indeed,  
175 hypoxemia normally induces a stimulation of the central respiratory drive leading to an  
176 augmentation of ventilation to maintain the oxygen level. In the case of normal respiratory  
177 mechanics, it should have led to a significant decrease in CO<sub>2</sub> level. The interpretation of the  
178 PetCO<sub>2</sub> is limited by the measurement method and should be considered with caution given the  
179 potential for washout of this signal by NIV flows. However, the evolution of this parameter is  
180 in favor of the absence of hypercapnia during an HCT with oxygen or NIV. We can assume  
181 that this favorable effect of NIV would be even more obvious for patient with more advanced  
182 respiratory failure. Even if not significant, probably because of the small number of subjects,  
183 the increase in respiratory rate at the initiation of hypoxia was well corrected by NIV.  
184 Importantly, this respiratory frequency was always higher than the minimum frequency set on  
185 the ventilator and therefore corresponded to the patients' "voluntary" frequency. These results  
186 suggest that the respiratory effort under NIV is reduced, and therefore the risk of respiratory  
187 exhaustion during longer exposure to hypoxemia, such as during air travel prolonged several  
188 hours, may decrease with NIV.

189

## 190 **Conclusion**

191 We conclude that performing an adapted HCT for home-ventilated patients with a  
192 neuromuscular pathology is useful to choose a personalized treatment for air travel. NIV allows  
193 sufficient hypoxemia correction for certain patients and can be used instead of oxygen therapy  
194 during air travel for this population. NIV can therefore be a new alternative for patients planning  
195 to take a flight.

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206 **Competing statement:**

207 There is no financial and non-financial competing interests for any authors of this manuscript.

208

209 **Authors' contributions:**

210 Concepting and design: JG, TS, CMP, CS

211 Analysis and interpretation: BRB, GM, TS, JG

212 Drafting the manuscript for important intellectual content: BRB, MF, GM, CS, CMP, TS, JG

213 All authors have reviewed and approved the manuscript prior to submission.

214

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218

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225

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249 kyphoscoliosis following intercontinental air travel. *Anaesthesia* 54, 361–363.

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251 Winck JC, Gonçalves MR, Silva N (2010). Oxygen or ventilation during flight for patients with

252 neuromuscular disease? *Thorax* 65, 370–371.

253

254

255 Table 1. Baseline characteristics (n = 13). The values shown are median and interquartile range,  
256 except for gender and disease. <sup>a</sup> Other: Central core disease, Steinert's disease, two  
257 diaphragmatic dysfunction and two Charcot Marie Tooth neuropathy.

258

259 Figure 1. (A) Hypoxic challenge test with non-invasive ventilation (NIV). The NIV device is  
260 placed under a canopy connected to a hypoxic generator. The gas used by the NIV to ventilate  
261 the patient is at a FiO<sub>2</sub> of 15% during the test. A PetCO<sub>2</sub> sensor is connected to the system. (B)  
262 Diagram of the four stages of the test: at baseline, during the hypoxic challenge test (HCT), the  
263 hypoxic challenge test with 2L/min oxygen flow (HCT + O<sub>2</sub>) and the hypoxic challenge test  
264 with NIV (HCT+NIV).

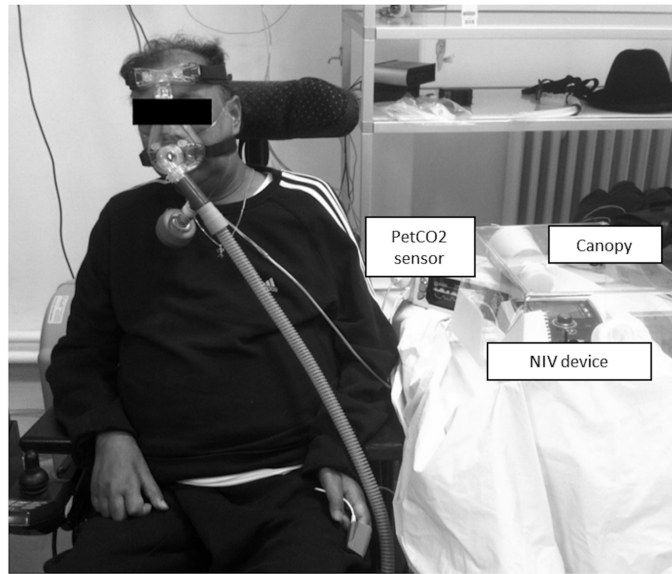
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266 Figure 2. Oxygen saturation (SpO<sub>2</sub>) at baseline and at the end of the hypoxic challenge test.  
267 Each line represents one patient (n = 13). Two patients shared lines from 96 to 89% and 93 to  
268 88%. The dashed line indicates the positivity threshold of the test.

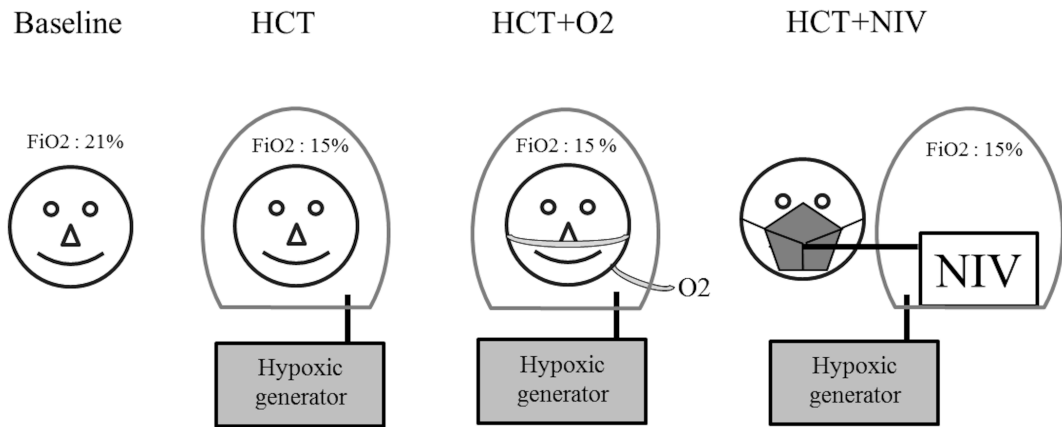
269 Figure 3. Comparison of SpO<sub>2</sub> (A), PetCO<sub>2</sub> (B), respiratory rate (C) of patients with a positive  
270 HCT who have completed all periods of the protocol: at baseline, during the hypoxic challenge  
271 test (HCT), the hypoxic challenge test with 2L/min oxygen flow (HCT + O<sub>2</sub>) and the hypoxic  
272 challenge test with NIV (HCT+NIV). Median and interquartile range, \*p < 0.05, \*\*p < 0.01

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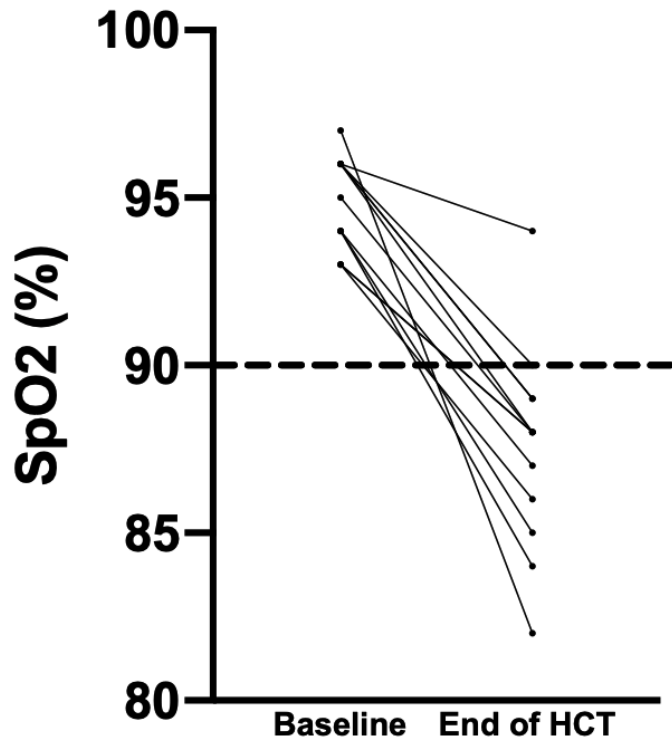


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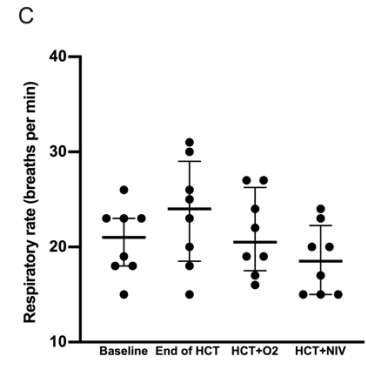
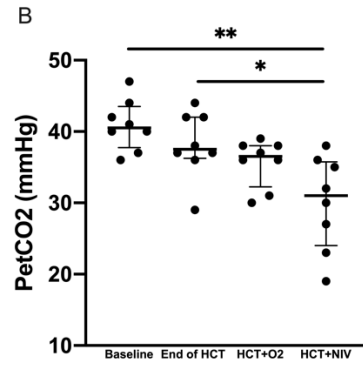
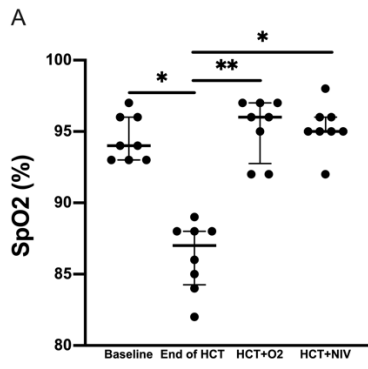
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<b>Baseline characteristics</b>	<b>Median [interquartile range]</b>
Age	60 [43-62]
Males (%)	9 (69 %)
Disease (Amyotrophic lateral sclerosis/Other <sup>a</sup> )	7/6 <sup>a</sup>
Body mass index (kg/m <sup>2</sup> )	21.7 [19.89-26.24]
Sitting FVC (ml and % predicted)	1980 [1405-2573], 49% [32-60]
Supine FVC (ml and % predicted)	1570 [1390-2290], 38% [34-66]
PaO <sub>2</sub> on room air (mm Hg)	82 [76.25-89.5]
PaCO <sub>2</sub> on room air (mm Hg)	41 [38.25-47]
Average hours of NIV use per night	6.4 [3.7-8.2]
NIV inspiratory pressure (cm H <sub>2</sub> O)	14.7 [11-22]
NIV backup respiratory rate (/min)	14 [13.7-16]