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

Bruno RIBEIRO BAPTISTA (1,2), Morgane FAURE (1), Gimbada Benny MWENGE (3), Capucine MORELOT-PANZINI (1,4), Christian STRAUS (1,4), Thomas SIMILOWSKI (1,4), Jésus GONZALEZ-BERMEJO (1,4)

1- AP-HP, Groupe Hospitalier Universitaire Pitié-Salpêtrière-Charles Foix, Service de Pneumologie, Médecine Intensive et Réanimation (Département R3S), 75013, Paris, France

2- Département de pneumologie, CHRU de Nancy, rue du Morvan, 54500, Vandœuvre-lès-Nancy, France

3- Département de Pneumologie et centre de médecine du sommeil, cliniques universitaires Saint-Luc, université catholique de Louvain, 10 Av Hippocrate, 1200, Bruxelles, Belgique

4- Sorbonne Université, INSERM, UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique, 75005, Paris, France

Corresponding author:

Bruno RIBEIRO BAPTISTA

Department of Pneumology, CHRU Nancy, France

Email: bruno.baptista@hotmail.fr

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29 - Hypoxic challenge test

30 - Non-invasive ventilation

31 - Chronic respiratory insufficiency

32 - Neuromuscular pathology

33 - Oxygen

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Abstract

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

Methods: We conducted a comparative, observational study of neuromuscular patients with chronic respiratory failure, requiring nocturnal mechanical ventilation, who were planning to take a flight. HCT was performed with a ventilated canopy placed over the patient's head or the patient's home ventilator. The ~~positivity~~ positive threshold value chosen for the HCT was < 90% SpO₂.

Results: HCTs were performed on 13 adults with neuromuscular diseases using their home ventilator. Among them, 11 had a positive HCT. For all patients with a positive test, hypoxemia was corrected (SpO₂ to > 90%) by oxygen therapy (+9 [6 to 12] %, p = 0.0029). ~~Patient's home ventilator also significantly increased the SpO₂ by 8 [7 to 12] % (p = 0.016).~~ Correction of SpO₂ during the HCT was not different between oxygen and NIV. NIV was associated with a significant decrease in PetCO₂ (-10 [-16 to -7.5] mmHg, p = 0.04).

Conclusions: ~~The realization of a HCT adapted~~ The performance of an adapted HCT in home-ventilated patients with a neuromuscular pathology ~~may be is~~ useful ~~to choose in~~ a personalized treatment ~~plan~~ for air travel. ~~Oxygen therapy is the first choice but~~ NIV can be a new alternative to oxygen therapy for neuromuscular patients planning to take a flight.

69 Introduction

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

92 Methods

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

arterial hypertension, infectious tuberculosis, or ongoing pneumothorax with persistent air leak and major hemoptysis were excluded (Ahmedzai et al., 2011). Data collected were age, diagnosis, sitting and supine force vital capacity (FVC), oxygen saturation (SpO_2), expired CO_2 (PetCO_2), room air blood gases and daily adherence to home mechanical ventilation.

The HCT was performed with a ventilated canopy placed over the patient's head or the patient's home ventilator (Figure 1A) and connected to a hypoxia generator (HYPOXICO Inc., Jalhay, Belgium). The extraction of O_2 was adapted to obtain a stable FiO_2 of $15\% \pm 0.2\%$. FiO_2 was measured using a FiO_2 sensor (MAXTEC Inc., Utah, USA) placed inside the canopy. The measurement of oxygen saturation, PetCO_2 , heart rate, and respiratory rate was performed using an integrated monitor (Capnostream [®] Plus, Smiths Medical PM, Inc. Wisconsin 53186 USA), including pulse oximetry and nasal cannula for measuring CO_2 . Oxygen was administered using another nasal cannula previously placed in superposition of the Capnostream cannula. The HCT was performed with the patients seated at rest in four successive measurements (15 min each): 1) spontaneous ventilation, room air (baseline), 2) under the canopy, spontaneous ventilation, FiO_2 of 15% and, if the test was positive ($\text{SpO}_2 < 90\%$), 3) under the canopy, spontaneous ventilation, FiO_2 of 15%, with an oxygen flow of 2 l/min, and finally 4) under patient's home ventilator, FiO_2 of 15% (Figure 1B). Dyspnea and headaches were measured at the end of each period by visual analog scales (VAS) rated from 0-10.

We chose a ~~positivity~~ positive value for the HCT of $< 90\% \text{ SpO}_2$, which is different from that of the BTS recommendation (positive $< 85\%$ of SaO_2). Indeed, patients with neuromuscular disease or extrapulmonary restrictive chest wall deformity are more at risk of hypoxemia during a HCT, even with a resting saturation of $> 95\%$ (Masa et al., 1997). Our choice of 90% was ~~motivated~~ selected for two reasons. First, the related effect of hypoxemia, such as an increase in respiratory rate, was observed at $< 90\%$ of the SpO_2 , suggesting a lower respiratory tolerance. Second, the BTS threshold is common to all respiratory disease, broadly based on studies that include obstructive lung disease. Our patients had normal lung parenchyma associated with reduced ventilatory adaptation in a hypoxemia condition. Thus, a threshold of 90% appeared to be more clinically relevant for this neuromuscular population. It was a choice of caution; it is difficult to formally prove that a patient with severe diaphragmatic dysfunction can remain with a SpO_2 between 85 and 90% for a long time.

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

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

140 141 **Results**

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

144 At baseline, median blood gas measures were a PaO₂ of 82 mmHg and a PaCO₂ of 41 mmHg.
145 All patients performed the HCT. The median SpO₂ was 95% at baseline. By the end of the test,
146 the SpO₂ of 11 patients had fallen to < 90% (Figure 2). Among these patients, the SpO₂ of two
147 had fallen to < 85%. The median fall of oxygen saturation was 7 [5.5 to 8.5] % relative to the
148 baseline SpO₂ (p < 0.001). There was no significant change in the PetCO₂ during spontaneous
149 ventilation at the end of the HCT.

150 An oxygen flow of 2 l/min allowed a correction of SpO₂ to > 90% for all positive HCT patients
151 (+9 [6 to 12] %, p = 0.0029). In comparison, patient's home ventilator significantly increased
152 the SpO₂ by 8 [7 to 12] % (p = 0.016). Oxygen was not more ~~efficient~~ effective than NIV for
153 SpO₂ correction during the HCT (Figure 3). There was a significant decrease in PetCO₂ only
154 with NIV (-10 [-16 to -7.5] mmHg, p = 0.04). The HCT was not associated with a significant
155 increase in the respiratory rate and the VAS score for dyspnea. Three tests were prematurely
156 stopped: one because of dyspnea (at the end of HCT), one because of dyspnea and headache (at
157 the end of HCT + O₂ period), one at the request of the patient (at the end of HCT). ~~No other~~
158 ~~patients reported a modification change in the VAS for dyspnea or headache.~~

159 **Discussion**

160 Our study shows that a pre-flight HCT is feasible under NIV in neuromuscular patients. The
161 study also shows that SpO₂ drops below 90% under a 15% FiO₂ in the majority of such patients
162 (11 out of 13 in this study) and that NIV correct hypoxemia in all cases.

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

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

172 NIV was always as effective as oxygen therapy in our group of patients. NIV appeared to be an
173 acceptable alternative therapy, with physiological advantages like decreasing ~~capnia~~ CO_2 level.
174 Furthermore, Winck et al. showed that a patient with a neuromuscular disease who is correctly
175 ventilated, without supplemental oxygen, can maintain oxygen saturation throughout a flight
176 (Winck et al., 2010). In our study, the PetCO_2 did not significantly decrease during the HCT
177 because of a possible lack of ventilatory adaptation in this particular population. Indeed,
178 hypoxemia normally induces a stimulation of the central respiratory drive leading to an
179 augmentation of ventilation to maintain the oxygen level. In the case of normal respiratory
180 mechanics, it should have led to a significant decrease in ~~capnia~~ CO_2 level. The interpretation
181 of the PetCO_2 is limited by the measurement method and should be considered with caution
182 given the potential for washout of this signal by NIV flows. However, the evolution of this
183 parameter is in favor of the absence of hypercapnia during an HCT with oxygen or NIV. We
184 can assume that this favorable effect of NIV would be even more obvious for patient with more
185 advanced respiratory failure. Even if it's not significant, probably because of the small number
186 of subjects, the increase in respiratory rate at the initiation of hypoxia was well corrected by
187 NIV. Importantly, this respiratory frequency was always higher than the minimum frequency
188 set on the ventilator and therefore corresponded to the patients' "voluntary" frequency. These
189 results suggest that the respiratory effort under NIV is reduced, and therefore the risk of
190 respiratory exhaustion during longer exposure to hypoxemia, such as during air travel lasting
191 prolonged several hours, may decrease with NIV.

193 Conclusion

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

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209 Competing statement:

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

211

212 Authors' contributions:

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

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

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

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

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References:

- Ahmedzai S, Balfour-Lynn IM, Bewick T, Buchdahl R, Coker RK, Cummin AR, Gradwell DP, Howard L, Innes JA, Johnson AOC, Lim E., Lim W.S., McKinlay KP, Partridge MR, Popplestone M, Pozniak A, Robson A, Shovlin CL, Shrikrishna D, Simonds A, Tait P, Thomas M, British Thoracic Society Standards of Care Committee (2011). Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. *Thorax* 66 Suppl 1, i1-30.
- Ergan B, Akgun M, Pacilli AMG, Nava S (2018). Should I stay or should I go? COPD and air travel. *Eur. Respir. Rev.* 27(148) 180030.
- ICAO's Annual Report of the Council (2018). www.icao.int/annual-report-2018
- Masa JF, Celli BR, Riesco JA, Sánchez de Cos J, Disdier C, Sojo A (1997). Noninvasive positive pressure ventilation and not oxygen may prevent overt ventilatory failure in patients with chest wall diseases. *Chest* 112, 207–213.
- Mestry N, Thirumaran M, Tuggey JM, Macdonald W, Elliott MW (2009). Hypoxic challenge flight assessments in patients with severe chest wall deformity or neuromuscular disease at risk for nocturnal hypoventilation. *Thorax* 64, 532–534.
- Noble JS, Davidson JA (1999). Cor pulmonale presenting in a patient with congenital kyphoscoliosis following intercontinental air travel. *Anaesthesia* 54, 361–363.
- Winck JC, Gonçalves MR, Silva N (2010). Oxygen or ventilation during flight for patients with

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255 neuromuscular disease? Thorax 65, 370–371.

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Figure legends

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

Figure 1. (A) Hypoxic challenge test with non-invasive ventilation (NIV). The NIV device is placed under a canopy connected to a hypoxic generator. The gas used by the NIV to ventilate the patient is at a FiO₂ of 15% during the test. A PetCO₂ sensor is connected to the system. (B) Diagram of the four stages of the test: at baseline, during the hypoxic challenge test (HCT), the hypoxic challenge test with 2L/min oxygen flow (HCT + O₂) and the hypoxic challenge test with NIV (HCT+NIV).

Figure 2. Oxygen saturation (SpO₂) at baseline and at the end of the hypoxic challenge test. Each line represents one patient (n = 13). Two patients shared lines from 96 to 89% and 93 to 88%. The dashed line indicates the positivity threshold of the test.

Figure 3. Comparison of SpO₂ (A), PetCO₂ (B), respiratory rate (C) of patients with a positive HCT who have completed all periods of the protocol: at baseline, during the hypoxic challenge test (HCT), the hypoxic challenge test with 2L/min oxygen flow (HCT + O₂) and the hypoxic challenge test with NIV (HCT+NIV). Median and interquartile range, *p < 0.05, **p < 0.01

Table 1

Baseline characteristics	Median [interquartile range]
Age	60 [43-62]
Males (%)	9 (69 %)
Disease (Amyotrophic lateral sclerosis/Other ^a)	7/6 ^a
Body mass index (kg/m ²)	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 ₂ on room air (mm Hg)	82 [76.25-89.5]
PaCO ₂ 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 ₂ O)	14.7 [11-22]
NIV backup respiratory rate (/min)	14 [13.7-16]

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B

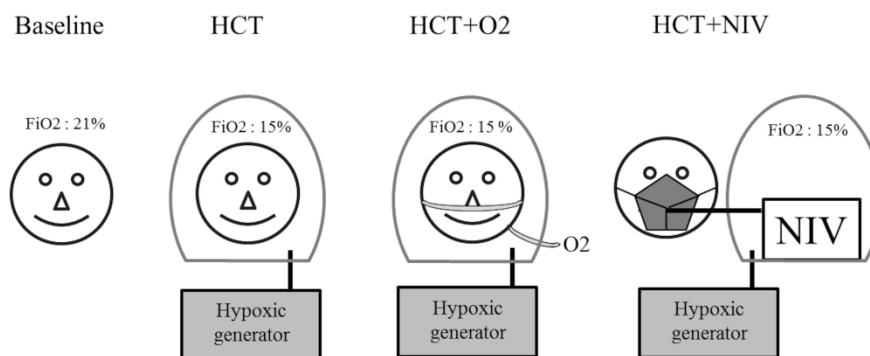


Figure 1. (A) Hypoxic challenge test with non-invasive ventilation (NIV). The NIV device is placed under a canopy connected to a hypoxic generator. The gas used by the NIV to ventilate the patient is at a FiO_2 of 15% during the test. A PetCO_2 sensor is connected to the system. (B) Diagram of the four stages of the test: at baseline, during the hypoxic challenge test (HCT), the hypoxic challenge test with 2L/min oxygen flow (HCT + O_2) and the hypoxic challenge test with NIV (HCT+NIV).

210x190mm (600 x 600 DPI)

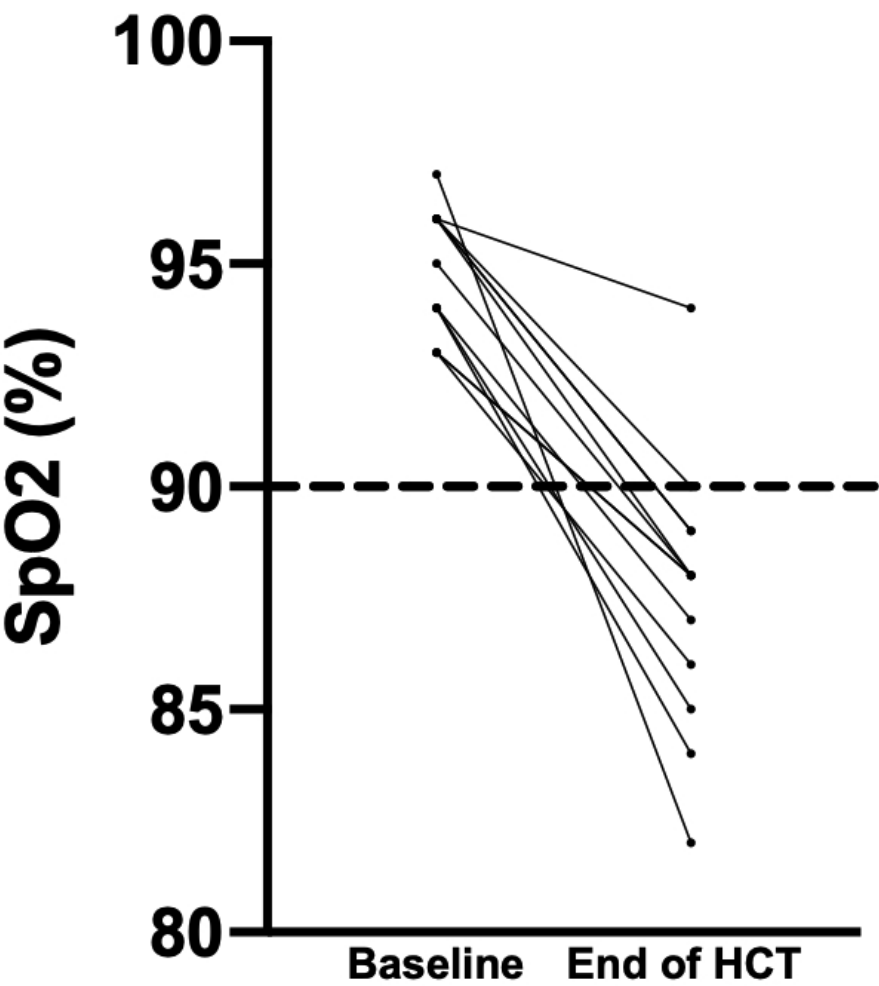


Figure 2. Oxygen saturation (SpO2) at baseline and at the end of the hypoxic challenge test. Each line represents one patient (n = 13). Two patients shared lines from 96 to 89% and 93 to 88%. The dashed line indicates the positivity threshold of the test.

57x58mm (300 x 300 DPI)

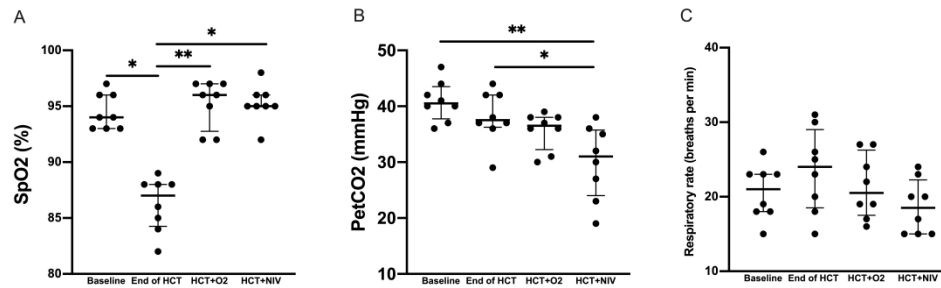


Figure 3. Comparison of SpO₂ (A), PetCO₂ (B), respiratory rate (C) of patients with a positive HCT who have completed all periods of the protocol: at baseline, during the hypoxic challenge test (HCT), the hypoxic challenge test with 2L/min oxygen flow (HCT + O₂) and the hypoxic challenge test with NIV (HCT+NIV). Median and interquartile range, *p < 0.05, **p < 0.01

239x73mm (1200 x 1200 DPI)