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

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- Hypoxic challenge test
- Non-invasive ventilation
- Chronic respiratory insufficiency
- Neuromuscular pathology
- Oxygen

Abstract

Background: The British Thoracic Society recommendations suggest that all patients with an oxygen saturation < 85% during a hypoxic challenge test (HCT) 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, through 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 positive threshold value chosen for the HCT was < 90% SpO_2.

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 (SpO_2 to > 90%) by oxygen therapy (+9 [6 to 12] %, p = 0.0029). Patient's home ventilator also significantly increased the SpO_2 by 8 [7 to 12] % (p = 0.016). Correction of SpO_2 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 performance of an adapted HCT in home-ventilated patients with a neuromuscular pathology may be ~~is~~ useful in a personalized treatment plan for air travel. NIV can be a new alternative to oxygen therapy for neuromuscular patients planning to take a flight.

Introduction

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

Methods

We conducted a comparative, observational study in the respiratory medicine department of the Pitié Salpêtrière Hospital (Paris) over a six months period. We extracted retrospectively the data from the medical files from patients tested before air travelling. The study was approved by the ethics committee from the Institutional Review Board of the French Learned Society for Respiratory Medicine (CEPRO 2012-039). Written informed consent was obtained from all subjects. Patients were included if they suffered from chronic respiratory failure due to neuromuscular disorders and requiring nocturnal mechanical ventilation and if they were planning a flight. Patients with non-treated cardiovascular diseases, recent myocardial infarction, cardiac arrhythmia, pregnancy, FEV1 < 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% ± 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 (Capnocheck ® 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 Capnocheck 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 (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 positive value for the HCT of < 90% 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 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

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

Results

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

At baseline, median blood gas measures were a PaO_2 of 82 mmHg and a $PaCO_2$ of 41 mmHg. All patients performed the HCT. The median SpO_2 was 95% at baseline. By the end of the test, the SpO_2 of 11 patients had fallen to < 90% (Figure 2). Among these patients, the SpO_2 of two had fallen to < 85%. The median fall of oxygen saturation was 7 [5.5 to 8.5] % relative to the baseline SpO_2 ($p < 0.001$). There was no significant change in the $PetCO_2$ during spontaneous ventilation at the end of the HCT.

An oxygen flow of 2 l/min allowed a correction of SpO_2 to > 90% for all positive HCT patients (+9 [6 to 12] %, $p = 0.0029$). In comparison, patient's home ventilator significantly increased the SpO_2 by 8 [7 to 12] % ($p = 0.016$). Oxygen was not more effective than NIV for SpO_2 correction during the HCT (Figure 3). There was a significant decrease in $PetCO_2$ only with NIV (-10 [-16 to -7.5] mmHg, $p = 0.04$). The HCT was not associated with a significant increase in the respiratory rate and the VAS score for dyspnea. Three tests were prematurely stopped: one because of dyspnea (at the end of HCT), one because of dyspnea and headache (at the end of HCT + O_2 period), one at the request of the patient (at the end of HCT). No other patients reported a change in the VAS for dyspnea or headache.

Discussion

Our study shows that a pre-flight HCT is feasible under NIV in neuromuscular patients. The study also shows that SpO2 drops below 90% under a 15% FiO_2 in the majority of such patients (11 out of 13 in this study) and that NIV correct hypoxemia in all cases.

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

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

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

Conclusion

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

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Competing statement:

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

Authors' contributions:

Concepting and design: JG, TS, CMP, CS

Analysis and interpretation: BRB, GM, TS, JG

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

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

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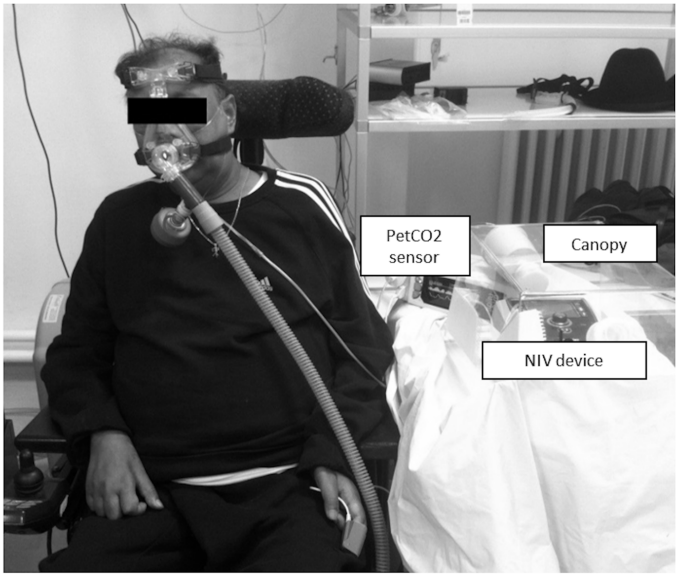
Table 1. Baseline characteristics (n = 13). The values shown are median and interquartile range, except for gender and disease. [a] Other: Central core disease, Steinert's disease, two diaphragmatic dysfunction and two Charcot Marie Tooth neuropathy.

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 $PetCO_2$ 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 + O2) and the hypoxic challenge test with NIV (HCT+NIV).

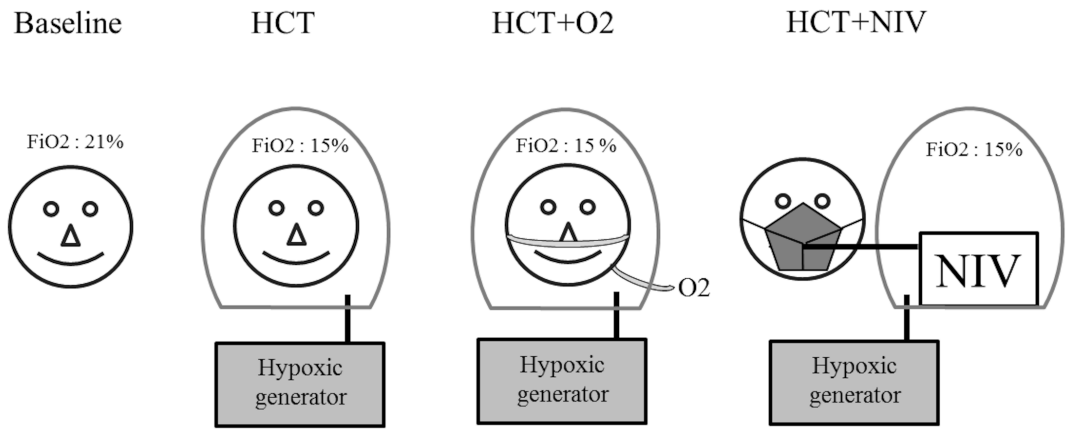
Figure 2. Oxygen saturation (SpO_2) at baseline and at the end of the hypoxic challenge test. Each line represents one patient (n = 13). Two patients shared lines from 96 to 89% and 93 to 88%. The dashed line indicates the positivity threshold of the test.

Figure 3. Comparison of SpO_2 (A), $PetCO_2$ (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, *$p < 0.05$, **$p < 0.01$

A


PetCO2 sensor
Canopy
NIV device

B


Baseline
HCT
HCT+O2
HCT+NIV
FiO2 : 21%
FiO2 : 15%
FiO2 : 15 %
O2
FiO2 : 15%
NIV
Hypoxic generator
Hypoxic generator
Hypoxic generator

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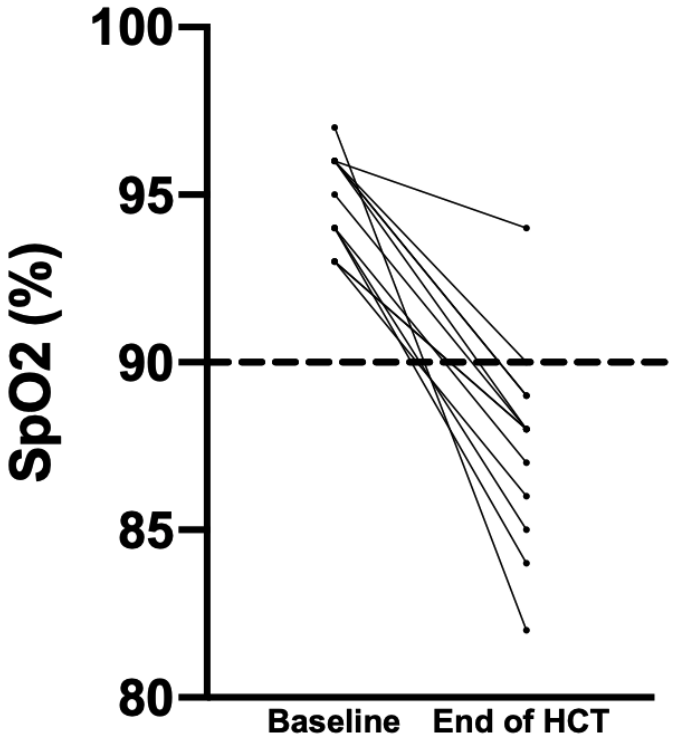

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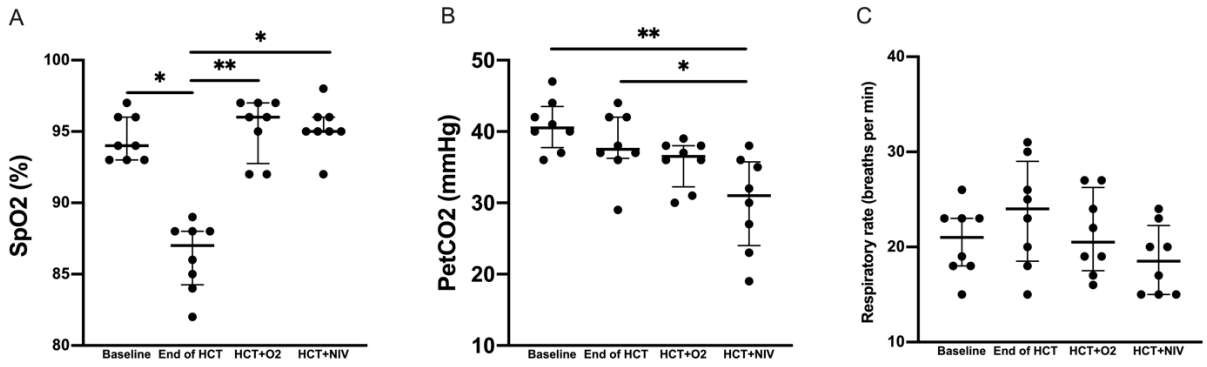

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Baseline characteristics	**Median [interquartile range]**
Age	60 [43-62]
Males (%)	9 (69 %)
Disease (Amyotrophic lateral sclerosis/Other[a])	7/6[a]
Body mass index (kg/m^2)	21.7 [19.89-26.24]
Sitting FVC (ml and % predicted)	1980 [1405-2573], 49% [32-60]
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_2O)	14.7 [11-22]
NIV backup respiratory rate (/min)	14 [13.7-16]