Nasal High Flow at 25 L/min or Expiratory Resistive Load do Not Improve Regional Lung Function in Patients with COPD: A Functional CT Imaging Study

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Research

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Abstract

Background: Nasal high flow (NHF) is a non-invasive breathing therapy that is based on the delivery via a large-caliber nasal cannula of heated and humidified air at flow rates that exceed peak inspiratory flow. It is thought that positive airway pressure generated by NHF can help reduce gas trapping and improve regional lung ventilation. There are no data to confirm this hypothesis at flow rates applicable in stable COPD patients.

Methods: In this study, we used non-rigid registration of CT images acquired at maximal expiration and inspiration to compute regional lung attenuation changes (Δ HU), and lung displacement (LD), indices of regional lung ventilation. Eight COPD patients were assessed at baseline (BL) and after 5 min of NHF and expiratory resistive loading (ERL).

Results: Δ HU was: BL: 81.7 ± 28.8 ; NHF: 77.3 ± 28.1 ; ERL: 70 ± 26.7 HU ($p=0.164$) and LD: 30.2 ± 12.7 ; 21.9 ± 10.1 and 20.6 ± 5.8 mm ($p=0.044$) in the 3 conditions, respectively. Respiratory rate significantly decreased with both treatments (BL: 17.6 ± 2.9 ; NHF: 13 ± 3.6 ; ERL: 11.6 ± 2.8 bpm; $p < 0.001$) while end-expiratory volume tended to increase.

Conclusions: Neither NHF at 25 L/min nor ERL significantly improve the regional lung ventilation of stable COPD patients with gas trapping, based on the registration of expiratory and inspiratory CT images. Further studies are needed to assess the potential effect of higher flow rates of NHF.

Trial registration: This study was registered with <https://clinicaltrials.gov/> under: NCT03821311.

Summary At A Glance

We assessed the effect of nasal high flow (NHF) on regional lung function using non-rigid registration of CT images acquired at maximal expiration and inspiration, in 8 stable COPD patients with gas trapping. Our data show that NHF at 25 L/min did not significantly improve regional lung ventilation.

Background

Nasal high flow (NHF) is a non-invasive breathing therapy that is based on the delivery via a large-caliber nasal cannula, of heated and humidified air at flow rates that exceed peak inspiratory flow[1]. The therapy is used for a variety of conditions including chronic obstructive pulmonary disease (COPD) [2]. The device consists of an air/oxygen blender connected to a nasal cannula, through a heated and humidified inspiratory circuit. It delivers a fraction of inspired oxygen (FiO_2) from 21–100%, with a flow rate up to $60 \text{ L} \cdot \text{min}^{-1}$. With this device, FiO_2 can be adjusted independently of the flow rate. NHF is increasingly considered as a supportive therapy in critically ill patients with acute respiratory failure, as an alternative to standard oxygen therapy and non-invasive ventilation, including post-operative respiratory failure, or during intubation of patients with mild-to-moderate hypoxemia [3]. However, there is limited clinical data

on the effectiveness of NHF in patients with stable COPD. Moreover, the physiological mechanisms of action of NHF are not fully understood.

Our working hypothesis was that the positive airway pressure generated by NHF particularly during expiration, can help maintain transbronchial pressure and small peripheral airway patency, thereby reducing gas trapping. This mechanism somewhat resembles pursed-lips breathing (PLB), a behavior which is thought to have a similar benefit in severe COPD patients [4]. Although small airways cannot be directly imaged, gas trapping and indices of regional lung function can be quantified based on attenuation analysis of registered computed tomography (CT) images obtained at high and low lung volumes. Moreover, indices of regional lung ventilation and motion measured using this novel non-invasive approach which does not rely on exogenous contrast media, have been proposed as biomarkers of functional small airway obstruction [5, 6].

The goal of this study was to assess gas trapping and indices of regional lung function using CT image registration analysis in patients with COPD at baseline and under NHF at 25 L/min. Because the beneficial effect of PLB in severe COPD patients has a similar hypothetical mechanism to NHF, we also assessed expiratory resistive loading (ERL) to produce a controlled amount of positive pressure only during expiration, with a positive expiratory pressure (PEP) mask, thus mimicking PLB.

Methods

Ethics and consent

Patients included in this study were part of a COPD cohort of 77 patients attending Grenoble University Hospital (Grenoble, France). This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Comité de Protection des Personnes, Grenoble - approval: 2018-A00363-52. Trial registration: [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/record/NCT03821311), NCT03821311. Registered 29 January 2019, clinicaltrials.gov/ct2/show/record/NCT03821311. Participant registration took place from Jan-2019 to Dec-2019. All adult participants provided written informed consent to participate in this study.

Patients

Eight patients with COPD, aged > 18 years, followed up at the Grenoble University Hospital outpatient pulmonology clinic were included in the cohort. Patients with evolving cancer, pregnancy or subject to an exclusion period in another investigation were not included in the study. Of the 77 patients initially included, 8 subsequent patients having accepted to participate in this ancillary study were enrolled.

Study protocol

Following baseline inspiratory and expiratory CT acquisition, image acquisition was repeated at both lung volumes after 5 minutes and during NHF (AIRVO-2, Fisher & Paykel, Auckland, New Zealand) using a medium-sized nasal cannula (Optiflow, Fisher & Paykel, Auckland, New Zealand), and after 5 minutes and during ERL, using a TheraPEP system (Smiths Medical, Portex, U.K.) set to level 6, connected to a face

mask (Vitera, Fisher & Paykel, Auckland, New Zealand). The order of NHF and ERL treatments was randomized using a random choice generator in Microsoft Excel. Patients were instructed to keep their mouths closed during NHF. Five to 10 minutes of washout were allowed between each treatment.

CT Imaging and image processing

Chest CT was performed at the Grenoble University Hospital Department of Radiology, with a 256-slice scanner (GE Revolution CT, GE Medical Systems, Milwaukee, USA) with the following settings: 120 kV, tube current modulation and collimation width of 0.625 mm. Images were acquired upon breath-hold at both full inspiration and full expiration. The patients were instructed by the technician prior to, and coached during image acquisition. Images were reconstructed with a standard convolution kernel. Average dose-length product was 262 ± 47 mGy·cm.

Details of the image processing methodology are explained in the online supplement. The image processing workflow is shown in Fig. 1. Briefly, images were processed with the python programming language (Python Software Foundation; Python Language Reference, version 2.7), running on a desktop computer (CPU: Intel Xenon @2.4 GHz x 16, 126 GB of RAM and NVIDIA Quadro K5000 GPU). Segmentation of the aerated lung tissue from the CT images was performed using an iterative region growing algorithm[7]. Within the segmented lung, an aerated voxel was defined by a lung tissue density lower than the median of the density distribution plus two standard deviations: $\mu + 2\sigma$. An elastic 3D registration method was used to compute motion and deformation between inspiratory and expiratory lung images[8, 9].

For each voxel of the resulting registered image, the change in attenuation (Δ HU) between end-expiration and end-inspiration was computed for each image voxel. This parameter was the primary outcome of the study. Scattering of regional attenuation change was expressed as the coefficient of variation; CV- Δ HU: standard deviation (Δ HU)/mean (Δ HU). A regional lung displacement vector was computed for each voxel of the registered image. The modulus of this vector was used to compute the local lung displacement between expiration and inspiration. The median value for both lungs was defined as the median Lung Displacement (LD, mm). The inhomogeneity of LD was assessed as the coefficient of variation; CV-LD: standard deviation (LD) / mean (LD). Parametric response maps were computed based on Galban et al.[5]. These consist in classifying the lung voxels into 4 categories based on attenuation in registered inspiratory and expiratory images. Normal lung voxels were defined by an attenuation > -950 HU at total lung capacity (TLC) and > -856 HU at residual volume (RV) in the expiratory image and were expressed as a volume. Trapping was defined by an attenuation > -950 HU at TLC and < -856 HU at RV. Emphysema was defined by an attenuation < -950 HU at TLC and < -856 HU at RV. Lung voxels with an attenuation < -950 HU at TLC and > -856 HU at RV were categorized as: 'emptying emphysema'.

Statistical analysis

Data are presented as mean $\pm$ standard deviation. Following a Shapiro-Wilks normality test, one-way repeated-measures ANOVA with a Student-Newman-Keuls post-hoc multiple comparisons procedure was used to test differences between study conditions: Baseline, NHF and ERL. A p value < 0.05 was

considered as significant. All statistical analyses were performed with Sigmaplot V.13 software (Systat, Berkshire, UK).

Results

Baseline patient characteristics are presented in Table 1. One subject had a body mass index > 30. None of the patients were hypercapnic. All patients had a significant degree of gas trapping with an elevated residual volume.

Table 1
Subject characteristics.

n (F)	8 (3)
Age (yr)	62.6 ± 4.9
Height (cm)	170.8 ± 7.6
Weight (kg)	72.4 ± 17.8
BMI	24.6 ± 4.8
FEV1 (%Pred)	70.8 ± 16.9
FVC (%Pred)	98.6 ± 8.6
FEV1/FVC (%)	55.4 ± 10.2
TLC (%Pred)	121.3 ± 1.2
RV (%Pred)	173.7 ± 33.5
PO ₂	10.2 ± 1
PCO ₂	4.6 ± 0.2
pH	7.43 ± 0.02
HCO ₃ ⁻	23.1 ± 1.8
Data are mean ± standard deviation; <i>F</i> : female; <i>BMI</i> : body mass index; <i>FEV1</i> : forced expiratory volume in 1 second; <i>%Pred</i> : percent predicted value; <i>FVC</i> : forced vital capacity; <i>TLC</i> : total lung capacity; <i>RV</i> : residual volume.	

Sample 3D renderings of parametric maps of the various lung functional clusters (Normal; Trapping; Emphysema; Emptying Emphysema), ΔHU and LD in a representative patient are shown in Fig. 2. No major differences were observed between BL, NHF and ERL conditions in the lung functional clusters or ΔHU, however, LD showed regional reductions with NHF and ERL.

Averaged CT image-derived data are presented in Table 2. The volume changes from maximal expiration to maximal inspiration in the CT images tended to decrease with NHF and more so with ERL, however,

these changes did not reach statistical significance ($p > 0.05$). The volume of functional clusters defined based on expiratory-inspiratory attenuation change were not significantly different between baseline, NHF and ERL ($p > 0.05$). Regarding the other CT registration-based parameters, lung displacement significantly decreased with NHF and ERL compared to baseline ($p = 0.044$). There was a similar tendency to decline with ΔHU , however, the differences were again not statistically significant ($p > 0.05$).

Table 2
CT registration-based regional lung function data.

	<i>BL</i>	<i>NHF</i>	<i>ERL</i>	<i>p</i>
Volume, Expiration [L]	4 ± 1.2	4.2 ± 1.3	4.1 ± 1.3	0.469
Volume, Inspiration [L]	6.6 ± 1.1	6.6 ± 1.2	6.2 ± 1.3	0.069
ΔVolume [L]	2.7 ± 0.5	2.4 ± 0.7	2.1 ± 0.7	0.178
PRM Clusters :				
Normal [%] (Green)	61.4 ± 27.1	60.7 ± 27.9	59.1 ± 27	0.568
Emptying Emphysema [%] (Blue)	2.1 ± 1.8	1.6 ± 1.7	1.5 ± 1.5	0.339
Trapping [%] (Orange)	29 ± 18.6	29.9 ± 19.2	31.9 ± 19.6	0.515
Emphysema [%] (Red)	7.6 ± 8.7	7.7 ± 9	7.5 ± 9.2	0.877
ΔHU [HU]	81.7 ± 28.8	77.3 ± 28.1	70 ± 26.7	0.164
CV-ΔHU	0.9 ± 0.3	1 ± 0.4	1 ± 0.3	0.457
LD [mm]	30.2 ± 12.7	$21.9 \pm 10.1^*$	$20.6 \pm 5.8^*$	0.044
CV-LD	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.661
Data are mean $\pm$ standard deviation; <i>BL</i> : Baseline; <i>NHF</i> : nasal high flow cannula at 25 L/min; <i>ERL</i> : positive expiratory pressure mask; <i>RR</i> : respiratory rate; Δ Volume: Volume change between the expiratory and inspiratory image; ΔHU : mean regional lung attenuation change in Hounsfield units; <i>CV-ΔHU</i> : coefficient of variation of ΔHU ; <i>LD</i> : mean regional lung displacement; <i>CV-LD</i> : coefficient of variation of LD. *: $p < 0.05$ vs. BL; §: $p < 0.05$ vs. NHF.				

Respiratory rate is shown in Fig. 3. Respiratory rate significantly decreased with NHF and further so with ERL (BL: 17.6 ± 2.9 ; NHF: 13 ± 3.6 ; ERL: 11.6 ± 2.8 bpm; $p < 0.001$).

Discussion

The goal of this study was to assess gas trapping and indices of regional lung function using CT image registration analysis in order to investigate the short-term effects of NHF in patients with stable COPD, under circumstances different than acute settings such as respiratory failure[10, 11]. We further compared NHF to ERL. Our main findings were that NHF reduced respiratory rate and tended to reduce lung volume change from maximal expiration to maximal inspiration, in turn reducing regional lung

displacement, but did not have a significant effect on gas trapping or the regional change in lung attenuation, an index of regional ventilation.

The assessment of traditional respiratory mechanical parameters in patients on NHF is challenging due to the technical difficulty of making measurements at the mouth, because of the high gas flow in the upper airways. It is currently thought that the mechanisms through which NHF improves respiratory function and decreases dyspnea and the work of breathing include: 1) generation of a higher flow rate compared to other oxygen delivery systems, exceeding the patient's peak inspiratory flow rate, which allows maintaining FiO_2 relatively constant by reducing the entrainment of room air; 2) washout of CO_2 from the anatomic dead space, allowing for an improved efficiency of gas exchange; 3) The high gas flow delivered with NHF, although through an open circuit, creates moderate positive nasopharyngeal pressures due to both upper airway resistance and turbulent flow regime, which could contribute to a reduced inspiratory upper airway resistance; 4) Previously, studies assessing alveolar aeration based on electrical impedance tomography (EIT) have suggested that small positive pressures generated by NHF can contribute to both an increase in lung volume and alveolar recruitment [12, 13], although at higher flow rates than in the present study. However, EIT is not a morphological imaging technique. It is therefore unclear how exactly positive pressure generated by NHF acts on the lung periphery to reduce the work of breathing.

In COPD patients, loss of lung parenchymal tethering causes small airways to collapse early on during expiration, resulting in dynamic compression of the airways, flow limitation and gas trapping [14]. This phenomenon has important implications with respect to mechanical efficiency, the sensation of dyspnea, and exercise limitation in these patients [15]. Pursed-lips breathing (PLB) is a technique whereby exhalation is performed through a resistance created by constriction of the lips [4]. Although the breathing maneuver is often spontaneously adopted by COPD patients, it is also routinely taught as a breathing-retraining exercise in pulmonary rehabilitation programs because it is thought to alleviate dyspnea [16]. However, the level of positive pressure induced by PLB is difficult to standardize. Alternatively, expiratory resistive loading (ERL) can be used in order to produce a graded and controlled amount of positive pressure, only during expiration, thus mimicking PLB [15].

Previous studies have measured modest positive airway pressures during NHF therapy, with a mean tracheal pressure of about 2 cmH_2O at 45 L/min [17] and 3.3 at 50 L/min [18], with the same device as ours and with a closed mouth. Because the positive pressure generated by NHF depends on the resistance of the air leak at the nares, it has been recently shown that a snug fit between the nasal prongs and the nares produces higher levels of upper airway positive pressure, using a bench top physical model [19]. However, even with a larger caliber nasal prong and a snug fit, the generated positive pressure is on the order of 3 cmH_2O at 25 L/min [19]. In this study, all patients had medium-sized nasal prongs during NHF therapy. Although upper airway pressure was not measured in this pilot study, it can be expected that the modest positive pressures generated by a flow rate of 25 L/min were insufficient to produce a measurable effect on small airway closure, gas trapping upon expiration, or lung recruitment.

The reduction in respiratory rate observed in this study is in agreement with several previous studies that have described significant decreases in breathing rate and changes in the pattern of breathing during NHF [20, 21]. Our data show that this reduction in respiratory rate was not explained by an improvement in regional lung function in these stable COPD patients, a mechanism often proposed in the literature [1, 2, 22] which has been attributed to positive expiratory pressure induced by NHF. Indeed, an improvement in regional lung ventilation would be expected to increase the change in lung attenuation (ΔHU) as well the local lung displacement, between expiration and inspiration. However, our data show that not only ΔHU was not increased, LD actually significantly decreased. Other mechanisms such as the washout of CO_2 from the anatomic dead space, or a drop in upper airway inspiratory resistance may have contributed to the reduction in the work of breathing and respiratory drive with NHF, leading to a reduced respiratory rate. However, we cannot confirm these mechanisms based on the findings of the present study, that focused on regional lung function. The decrease in respiratory rate was concomitant with a 0.2 L increase in end-expiratory lung volume, which could explain the decrease in LD based on CT image registration. We observed similar changes with ERL both regarding respiratory rate and the somewhat smaller increase in the end-expiratory lung volume based on the corresponding CT image. These findings are also in agreement with previous data in the literature[23], although the involved mechanisms may be different from that of NHF.

The present study had several limitations. Because the standard deviation of the outcome parameters was not known beforehand, a formal sample size estimation was impossible. The small number of enrolled subjects reduced the statistical power. Despite this, we were able to detect significant changes based on which we can confidently reject any improvement in regional lung function with NHF at 25 L/min in COPD patients who presented significant gas trapping. Only a single flow rate was tested because of radiation exposure due to CT imaging. We chose to investigate a flow rate which would be applicable to stable COPD patients without exacerbation or acute respiratory failure. For the same reason as above, a single nasal prong size was assessed. Therefore, the findings of this study, do not exclude the possibility that regional lung function could be improved with larger nasal prong calibers and higher NHF flow rates.

In conclusion, our data show that neither NHF at 25 L/min administered through medium-sized nasal prongs, nor ERL significantly improved the regional lung ventilation of patients with stable COPD with gas trapping, assessed based on the registration of expiratory and inspiratory CT images. Further study is needed to evaluate higher flow rates of NHF.

List Of Abbreviations

NHF: Nasal high flow.

COPD: chronic obstructive pulmonary disease.

FiO_2 : fraction of inspired oxygen.

PLB: pursed-lips breathing.

CT: computed tomography.

ERL: expiratory resistive loading.

Δ HU: change in attenuation between end-expiration and end-inspiration.

LD: Lung Displacement.

TLC: total lung capacity.

RV: residual volume.

EIT: electrical impedance tomography.

Declarations

Ethics approval and consent to participate: Patients included in this study were part of a COPD cohort of 77 patients attending Grenoble University Hospital (Grenoble, France). This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Comité de Protection des Personnes, Grenoble - approval: 2018-A00363-52. The study's clinical trial registration number is NCT03821311 - registered with <https://clinicaltrials.gov/>. Participant registration took place from Jan-2019 to Dec-2019. All adult participants provided written informed consent to participate in this study.

Consent for publication: Not applicable.

Availability of data and materials: The datasets analyzed in the current study are available from the corresponding author upon reasonable request.

Competing interests: SB has received funding to his institution for carrying out this work. JLP has received grants and research funds from: Air Liquide Foundation; Agiradom; AstraZeneca; Fisher and Paykel; Mutualia; Philips; Resmed; Vitalaire; Boehringer Ingelheim; Jazz pharmaceutical; Night Balance; Sefam. All other authors declare no competing interests.

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Author Contributions: JC, RT, JP, GF and SB conceived the study; JC, GF, SB performed image acquisition; JC, LB, MM, SB analysed image data; JC and SB performed statistical analysis; JC, RT, JP, GF, SB interpreted the findings; SB drafted the manuscript. All authors have seen and edited the submitted manuscript.

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Figures

Figure 1

Image processing workflow. Inspiratory and expiratory CT images were segmented using a region growing algorithm. The segmented expiratory image is warped using elastic image registration software to match the inspiratory image. The indices of regional lung ventilation are computed based on the registered and inspiratory images.

Figure 2

3D rendering of computed regional lung function indices in a sample COPD patient. PRM: parametric response maps; Δ HU: regional attenuation changes from maximal expiration to maximal inspiration; LD: lung displacement; NHF: nasal high flow; ERL: expiratory resistive loading.

Figure 3

Respiratory rate in each of 8 COPD patients; BL: baseline; NHF: nasal high flow cannula; ERL: expiratory resistive loading.

Supplementary Files

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