Intensive Care Medicine

Optimum support by high flow nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates

--Manuscript Draft--

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Full Title:	Optimum support by high flow nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates	
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Abstract:	Purpose. Limited data exist on the correlation between higher flow rates of high flow nasal cannula (HFNC) and its physiologic effects in acute hypoxemic respiratory failure (AHRF) patients. We assessed the effects of HFNC delivered at increasing flow-rate on inspiratory effort, work of breathing, minute ventilation, lung volumes, dynamic compliance and oxygenation in AHRF patients. Methods. A prospective randomized cross-over study was performed in non-intubated AHRF patients with PaO_2/FiO_2 ≤300 mmHg. Standard non-occlusive facial mask and HFNC at different flow-rate (30, 45 and 60 l/min) were randomly applied maintaining constant FiO_2 (20 min/step). At the end of each phase, we measured arterial blood gases; inspiratory effort, by the esophageal pressure swings (ΔPes); work of breathing, by the esophageal pressure time product (PTP-Pes); lung volumes, by electrical impedance tomography. Results. We enrolled 17 AHRF patients. At increasing flow-rate, HFNC reduced ΔPes ($p<0.001$) and PTP-Pes ($p<0.001$), while end-expiratory lung volume (ΔEELV), tidal volume to ΔPes ratio (Vt/ΔPes, corresponding to dynamic lung compliance) and oxygenation improved ($p<0.01$ for all). Moreover, higher HFNC flow rate progressively reduced minute ventilation ($p<0.05$) without change in arterial CO_2 tension ($p=0.909$). The decrease of ΔPes, PTP-Pes and minute ventilation at increasing flow rates was better described by exponential fitting, while ΔEELV, Vt/ΔPes and oxygenation improved linearly. Conclusions. Increasing HFNC flow rate progressively decreases inspiratory effort and work of breathing, and improves lung aeration, dynamic compliance and oxygenation. Most of the effect on inspiratory workload and CO_2 clearance was already obtained at lowest flow rate.	
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Author Comments:	Dear Samir, Please find enclosed our revised manuscript and point-by-point answers to reviewers #1 and #3. We hope you will find these adequate for publication in Intensive Care Medicine. Thank you, Best, On behalf of the authors, Antonio Tommaso
Response to Reviewers:	Reviewer #1: The authors have greatly improved their manuscript and should be congratulated for their efforts. I have still a few questions. 1) In the results section, sentences such as "inspiratory effort as measured by ΔPes and PTPPes decreased significantly by application of HFNC at increasing flows ($p<0.001$ for both)" are a little misleading since they suggest that there might be a significant decrease of PTPes after each increase of flow, which is actually not the case. For most variables, there was only one significant change and a second significant change was observed for a few of them. I have not observed any variable with more than two significant changes. 1) We now clarified that in the results section we presented only the ANOVA fixed effects, while post-hoc statistical significances can be found in Table 4. We modified the text as follows (see page 11): “In this section, we will only present ANOVA fixed effects results, while actual values and flow-level post-hoc analyses are reported in Table 4.” 2) On page 12 (line 49), the authors write that "Thus, it might also be reasonable to simplify the clinical approach to selection of the highest flow tolerated by the patient starting from 60 l/min". This is an important assertion that could be relevant as the last sentence of the conclusion. Indeed, since physician have no tools to personalize flow at bedside, providing them with a simple rule is quite relevant. Could the authors add a few words in the conclusion? 2) We added the following as suggested (see page 16): “In the real-life ICU setting, time constraints could hinder accurate flow titration based on target physiologic parameter and a simplified approach with selection of the highest flow tolerated by the patient starting from 60 l/min might be a reasonable alternative.” 3) As suggested by Reviewer 2, one or two additional sentences explaining in more detail the Akaike's information criterion to the reader who is not familiar with would be a plus. 3) We added as requested the following sentences (see page 10): “The AIC is a statistical technique introduced to help identify the optimal representation of explanatory variables collected with an adequate number of parameters. AICc introduces an extra correction term to overcome the problem of overestimating the order of the model in case of small sample size. The individual AICc values are not easily interpretable so they are usually compared to the minimum AICc evaluated for the bulk of data collected. The model with the smallest value of AICc is considered the best model.”

4) Figure E1 adds some precious information. However, why expressing in the supplement PTPes as a proportion of baseline (oxygen) and in the main manuscript PTP as an absolute value?
4) Figure E1 refers to the best fitting analysis which was performed on change from baseline to limit the effects of different units of measure. This is now more clearly indicated in the statistical analysis section (see page 9): “To assess the best fitting describing the relative improvement of each variable at increasing flow rates and considering facial mask as baseline,”

5) I found interesting that VT did not change with flow, RR decrease in a linear way and MV (which is the produce of VT by RR) decrease exponentially. Could the authors comment?
5) As explained in the methods, minute ventilation was measured as sum of actual tidal volumes over 2-3 minutes divided by the number of minutes, rather than as multiplication between average tidal volume and respiratory rate (see page 9). Moreover, the difference between linear and exponential AICc for respiratory rate was <1 (Table E1 online), thus the two models can be considered almost equivalent.

Reviewer #3: The authors addressed all my comments.

I would still have 2 requirements:

1) To improve the non specialist reader's understanding of your discussion page 14, I strongly suggest adding the measurements details regarding airway pressure, when the effect of opening of the mouth is discussed:

Previous data in post-cardiac surgery patients without AHRF suggested that HFNC delivered at 35-50 l/min generates relatively low positive expiratory airway pressure (PEEP effect, around 3 cmH2O measured via a nasopharyngeal catheter) [28] and that this effect was not correlated with the patient keeping the mouth open or closed. However, another study, measuring the airway pressure via a transtracheal catheter, reported that the PEEP effect of HFNC delivered at 45 l/min was significantly reduced by asking the patient to breathe with the mouth open [18].
1) We changed the text as suggested (see page 14)

2) My previous comment regarding the patient's comfort has now been discussed but in opposition to "objective measurements". I agree with the authors that their objective was physiological. However, I don't want to oppose subjective (often considered as "not reliable") and objective ("reliable") measurements, but patient's preference (regarding a potential distress, which is subjective by nature) and intensive care therapies. Clinicians have to think comprehensively while caring for patients.

Please delete the words "rather" and "objective", and rephrase page 15 for example, as follows:

Sixth, we didn't measure patients' comfort but assessed changes in physiological measures of patients' respiratory condition. Aside physiological effects of intensive care therapies, patients' comfort and preference need also to be taken into account regularly."
2) We changed the text as suggested (see page 15).

Optimum support by high flow nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates

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Authors' conflicts of interests: The authors declare that they have no conflict of interest related to the present study.

Short running title: High flow nasal cannula at increasing flow rates

Take-home message: In acute hypoxemic respiratory failure, high flow nasal cannula (HFNC) delivered at increasing flow rates induce significant improvement of patient's inspiratory effort, work of breathing, minute ventilation, lung volumes, dynamic compliance and oxygenation. However, most of the effect on inspiratory workload and CO_2 clearance was already obtained at lowest HFNC flow rate and personalized setting could be considered after careful evaluation of patient's condition and the individual response.

Tweet: Study on the beneficial effects of high flow nasal cannula delivered at increasing flow rates: linear vs. exponential improvements.

ABSTRACT

Purpose. Limited data exist on the correlation between higher flow rates of high flow nasal cannula (HFNC) and its physiologic effects in acute hypoxemic respiratory failure (AHRF) patients. We assessed the effects of HFNC delivered at increasing flow-rate on inspiratory effort, work of breathing, minute ventilation, lung volumes, dynamic compliance and oxygenation in AHRF patients.

Methods. A prospective randomized cross-over study was performed in non-intubated AHRF patients with $PaO_2/FiO_2 \leq 300$ mmHg. Standard non-occlusive facial mask and HFNC at different flow-rate (30, 45 and 60 l/min) were randomly applied maintaining constant FiO_2 (20 min/step). At the end of each phase, we measured arterial blood gases; inspiratory effort, by the esophageal pressure swings (ΔPes); work of breathing, by the esophageal pressure time product (PTP_{Pes}); lung volumes, by electrical impedance tomography.

Results. We enrolled 17 AHRF patients. At increasing flow-rate, HFNC reduced ΔPes ($p<0.001$) and PTP_{Pes} ($p<0.001$), while end-expiratory lung volume (ΔEELV), tidal volume to ΔPes ratio (Vt/ΔPes, corresponding to dynamic lung compliance) and oxygenation improved ($p<0.01$ for all). Moreover, higher HFNC flow rate progressively reduced minute ventilation ($p<0.05$) without change in arterial CO_2 tension ($p=0.909$). The decrease of ΔPes, PTP_{Pes} and minute ventilation at increasing flow rates was better described by exponential fitting, while ΔEELV, Vt/ΔPes and oxygenation improved linearly.

Conclusions. Increasing HFNC flow rate progressively decreases inspiratory effort and work of breathing, and improves lung aeration, dynamic compliance and oxygenation. Most of the effect on inspiratory workload and CO_2 clearance was already obtained at lowest flow rate.

Keywords. High-flow nasal oxygen; spontaneous breathing; electrical impedance tomography; esophageal pressure; acute lung injury; acute respiratory failure.

INTRODUCTION

Recent studies described that, in non-intubated adult patients with acute hypoxemic respiratory failure (AHRF), high flow nasal cannula (HFNC) improves oxygenation, lowers the respiratory drive, decreases desaturation during intubation, and prevents re-intubation of high- and low-risk patients [1-7]. Moreover, preliminary data suggest that HFNC might decrease mortality [4]. Physiologic mechanisms of HFNC, potentially underlying its clinical benefits, might include: reduced inspiratory effort and work of breathing, improved lung mechanics, increased end-expiratory lung volumes likely by positive end-expiratory pressure (PEEP) effect, lower minute ventilation [8], higher alveolar FiO_2 [9-10], increased CO_2 clearance by washout of anatomic dead space [11-12], and more efficient removal of secretions [2, 9].

In all these clinical and physiologic studies, the set HFNC flow rates were extremely heterogeneous, ranging between 15 and 100 l/min [2-11] and, to our knowledge, no study systematically compared different flow rates in AHRF patients. Thus, when caring for a AHRF patient, a key question remains open: what is the best flow rate during HFNC treatment?

Data from healthy adults, cardiac surgery and tracheotomised patients weaned from mechanical ventilation (i.e., in the non-acute phase) suggest that the increase in pharyngeal pressure (i.e., the PEEP effect) and the decrease of the respiratory rate induced by HFNC are correlated with the set flow rate [13-18]. These effects were enhanced by asking subjects to keep the mouth closed during breathing on HFNC, but this is not feasible in real-life long-term treatment of AHRF patients [13-14, 18]. Moreover, theoretically, application of HFNC at higher flow rates should exploit other physiologic benefits in AHRF patients (e.g., improved oxygenation by progressive reduction in difference between the set and the alveolar FiO_2).

To address the abovementioned question, we performed a physiologic randomized cross-over study aimed at measuring the following physiologic effects of HFNC at increasing flow rates in AHRF patients: oxygenation and gas exchange; respiratory rate, minute ventilation, lung mechanics, end-

expiratory lung volume (EELV), effort and work of breathing. To increase the clinical impact and reproducibility of the data, patients didn't receive any instruction regarding mouth opening/closing during any study phase. Aims of this study were: to describe whether the physiologic effects of HFNC improve by increasing flow rate; to assess the best model (i.e., linear vs. quadratic vs. exponential) to describe the correlation between each target physiologic variable and HFNC flow rate; to describe the optimum flow rate for each target physiologic variable, defined as the one obtaining maximum optimization in most patients.

METHODS

Study population. We enrolled 17 non-intubated AHRF patients admitted to the Intensive Care Unit (ICU) of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. Inclusion criteria were: new or worsening respiratory symptoms (e.g., dyspnea, shortness of breathing) following a known clinical insult (e.g., pneumonia) lasting less than one week; $PaO_2/FiO_2 \leq 300$ while receiving additional oxygen as per clinical decision; evidence of pulmonary infiltrates on chest X-ray performed on the day of the study. Exclusion criteria were: age <18 year-old; presence of tracheostomy; hemodynamic instability (hypotension with mean arterial pressure <60 mmHg despite volume loads or vaso-active drugs); evidence of pneumothorax on chest x-ray or CT scan; respiratory failure explained by cardiac failure or fluid overload; severe chronic obstructive pulmonary disease; history of nasal trauma and/or deviated nasal septum; altered mental status; contra-indication to electrical impedance tomography (EIT) (e.g., patient with implantable defibrillator); impossibility to position the EIT belt (e.g., wound dressings or chest drains); impossibility to position the esophageal pressure catheter (e.g., esophageal surgery). The Ethical Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy approved the study (reference number: 1628/2015) and informed consent was obtained from each patient according to local regulations.

Demographic data collection. At enrolment, the following variables were collected: sex, age, predicted body weight (PBW), Simplified Acute Physiology Score (SAPS) II at ICU admission, Sepsis-related Organ Failure Assessment (SOFA) score, days since recognition of AHRF by ICU physician, etiology of the AHRF, PaO_2/FiO_2 by arterial blood gas analysis and presence of bilateral infiltrates on chest X-ray (both performed for clinical reasons the same day of the study).

Esophageal pressure and EIT monitoring. A nasogastric tube equipped with an esophageal balloon (Nutrivent Sidam, Mirandola (MO) Italy) was advanced through the nose for 50-55 cm to reach the stomach and inflated by the recommended volume (4 ml). The intra-gastric position was confirmed by the positive pressure deflections during spontaneous inspiration. Then the catheter was withdrawn into the esophagus, as indicated by the appearance of cardiac artifacts and negative swings of pressure tracings during inspiration and fixed [19-21]. Accuracy of esophageal pressure measurement relied on standardized careful positioning and on the visual inspection of tracings, as calibration against airway pressure swings during occlusion is technically challenging in non-intubated patients. Waveforms of the esophageal pressure were recorded for 5 minutes at the end of each study phase and before starting the next one by dedicated data acquisition system (Colligo Elekton, Milan, Italy). An EIT dedicated belt containing 16 equally spaced electrodes, was placed around each patient's thorax at the fifth or sixth intercostal space and connected to a commercial EIT monitor (PulmoVista® 500, Dräger Medical GmbH, Lübeck, Germany). During the study, EIT data were generated by application of small alternate electrical currents rotating around the patient's thorax at 20 Hz, so that tomographic data were acquired every 50 msec throughout all study phases and stored for offline analyses performed by dedicated software (Dräger EIT Data Analysis Tool and EITdiag, Dräger Medical GmbH, Lübeck, Germany) [22]. The Pes and EIT signals were synchronised offline with specific markers indicating relevant time-points created online during each study phase.

In three patients, esophageal pressure monitoring could not be obtained for technical reasons (e.g., poor quality of the recorded tracings or technology failure).

Calibration of EIT. After beginning of the EIT recordings and before the start of the study protocol, we recorded spirometry through a spirometer connected to a mouthpiece with occluded nostrils during spontaneous breathing for 30 seconds for offline calibration of the EIT measures. Briefly, 3-5 representative tidal volumes were selected on spirometry and EIT tracings and the average ratio between millilitres and arbitrary units of impedance change was calculated and used for transformation of impedance changes into lung volume variations during all study phases. After the calibration phase, the mouthpiece and spirometer were removed and the patients could breathe freely. We didn't repeat EIT calibration after start of the first study phase as it would have altered the physiologic breathing pattern and would have prolonged duration of an already long study (>1.5 hours).

Study protocol. Patients were kept in semi-recumbent position without sedation. A calm environment was ensured around the patients throughout the study. Each patient underwent four study phases in computer-generated random order, each lasting 20 minutes:

1. Standard non-occlusive oxygen facial mask with gas flow set at 12 l/min;
2. HFNC with gas flow 30 l/min;
3. HFNC with gas flow 45 l/min;
4. HFNC with gas flow 60 l/min.

HFNC was delivered through specific nasal prongs of medium or large size (Fisher & Paykel Healthcare, Auckland, New Zealand) to fit the nares size. Set FiO_2 was clinically chosen by the attending physician before enrolment to target peripheral saturation 90-96% on pulse oximetry during standard oxygen facial mask breathing and was kept constant during all phases. Set FiO_2 during each phase was measured by a dedicated system (AIRVO^{TM} 2, Fisher & Paykel Healthcare, Auckland, New Zealand) connected to the standard facial mask or the HFNC. The system can deliver airflows between 2 and 60 l/min with set FiO_2 (continuously measured at the gas outlet of the system) between 0.21 and 1.0 by connection to a wall oxygen supply. During all phases, we reached the same measured set FiO_2 by incrementing or decrementing the additional oxygen wall

supply. Patients didn't receive any instruction regarding mouth opening or closing during any study phase (i.e., during data collection the patients could breathe with the mouth open, closed, or alternating both).

At the end of each study phase, we collected arterial blood gas analysis, respiratory rate and hemodynamics.

Esophageal pressure data. From the esophageal pressure waveforms analysed offline we measured:

1. The average pressure time product of esophageal pressure over a minute (PTP_{Pes}), defined as the sum of the areas subtended by the Pes waveform during inspiration over a period of 2-3 minutes divided by the number of minutes, as a measure of patient's effort over a minute [21, 23]. PTP_{Pes} represents a modification from classic computation of pressure time product, which requires measurement of the passive elastic recoil of the chest wall; however, chest wall elastance can't be measured in non-intubated patients and the addition of passive elastic recoil of the chest wall to PTP_{Pes} in the 4 study phases wouldn't modify our results as tidal volume didn't change (see below) and lung elastance would be assumed as equal.
2. The average esophageal pressure swings during inspiration (ΔPes), defined as the difference between end-expiratory and end-inspiratory Pes in the same series of representative breaths used to measure PTP_{Pes}, divided by the number of breaths, as a measurement of the patient's inspiratory effort [21, 23];

EIT data. The raw EIT data recorded during the Pes recordings were analyzed offline. We divided the EIT lung-imaging field into two regions of interest: from halfway down we identified the dependent dorsal lung region, while the other half represented the non-dependent ventral region. We measured the following EIT parameters:

1. The average global tidal volume as well as those distending non-dependent and dependent lung regions in a series of representative breaths, divided by the number of breaths ($V_{T, glob}$, $V_{T, non\text{-}dep}$ and $V_{T, dep}$, respectively);

2. The minute ventilation (MV), measured as the sum of all tidal volumes over 2-3 representative minutes divided by the number of minutes, which might represent a more precise measure of MV than multiplication of average tidal volume by average respiratory rate;

3. Corrected minute ventilation (MV_{corr}), defined as MV multiplied by the ratio of the patient's $PaCO_2$/40 mmHg (i.e. MV_{corr} = MV*[actual $PaCO_2$/40 mmHg]) [24], with lower values indicating enhanced CO_2 clearance, less CO_2 production, or both;

4. Global and regional changes in lung aeration during the HFNC phase ($\Delta EELV_{glob}$, $\Delta EELV_{non\text{-}dep}$ and $\Delta EELV_{dep}$), as previously described [22]. Briefly, considering the facial mask phase as baseline, we measured global and regional changes in end-expiratory lung impedance expressed as a.u. during HFNC phases and multiplied those by the calibrating ml/a.u. factor.

Finally, combination of Pes and EIT data was used to calculate the dynamic compliance of the lung (C_L) as $V_{T, glob}/\Delta Pes$, to evaluate the effects of HFNC on lung mechanics.

Statistical analysis. We chose the sample size based on previous studies [8; 13-18; 21-23]. Normally distributed variables were expressed as mean ± standard deviation, while median and interquartile range [IQR] were used to report non-normally distributed variables. Differences between variables across different HFNC flow rates obtained during each study phase were tested by one-way analysis of variance (ANOVA) for repeated measures, or by one-way repeated measures ANOVA on ranks, as appropriate. Post hoc correction for multiple comparisons was performed using Bonferroni comparison. To assess the best fitting describing the relative improvement of each variable at increasing flow rates and considering facial mask as baseline, we

applied three different statistical models to the variations between phases: linear, quadratic and exponential. Then, we estimated the accuracy of each model for every variable by the Akaike's information criterion (AIC) value, corrected for finite sample size (AICc). The AIC is a statistical technique introduced to help identify the optimal representation of explanatory variables collected with an adequate number of parameters. AICc introduces an extra correction term to overcome the problem of overestimating the order of the model in case of small sample size. The individual AICc values are not easily interpretable so they are usually compared to the minimum AICc evaluated for the bulk of data collected. The model with the smallest value of AICc is considered the best model. Finally, the flow rate obtaining the highest change from facial mask phase of each parameter in most patients was indicated as optimum flow. A level of $p < 0.05$ (two-tailed) was considered statistically significant. Statistical analyses were performed with SigmaPlot 12.0 (Systat Software Inc., San Jose, CA) and JMP PRO 12 (SAS Institute Inc., Cary, NC).

RESULTS

Patient population. Patients were 62±10 years old and 9 (53%) were women. Severity of clinical condition was relevant as indicated by SAPS II at ICU admission of 48±13 and SOFA of 11±3. Eight patients (47%) had pulmonary etiology of AHRF and 9 (53%) presented non-infectious cause. Days since recognition of AHRF in the ICU were 2±1 (range 1-3). Twelve patients (70%) presented bilateral infiltrates on chest X-ray. Patients' characteristics are listed in Table 1.

Best model for the correlation between physiology and HFNC flow rates. AICc analysis indicated that linear correlation better described variations of $\Delta EELV_{glob}$ and $\Delta EELV_{dep}$, $V_T/\Delta Pes$, RR and PaO_2/FiO_2 with increasing HFNC flow rates (Table 2 and Table E1 online, Figure E1A and E1B online). On the other hand, exponential fitting better matched the decrease of ΔPes, PTP_{Pes}, MV and MV_{corr} at higher flow (Table 2 and Table 1 online, Figure E2A and E2B online), possibly indicating that most of the effects of HFNC on effort and CO_2 wash-out/production were already

obtained at 30 l/min. However, we must acknowledge that differences in AICc were relatively small for some variables (e.g., ΔPes).

Optimum flow rate during HFNC treatment. Optimum flow, defined as the HFNC flow rate obtaining maximum optimization of each physiologic parameter (i.e., absolute reduction or increase from facial mask, as appropriate) in most patients, was: 60 l/min for ΔPes, PTP_{Pes}, $\Delta EELV_{glob}$, $\Delta EELV_{dep}$, $V_T/\Delta Pes$, RR and PaO_2/FiO_2; 45 l/min for none; 30 l/min for MV and MV_{corr} (Table 3). However, we must notice that the flow associated with largest improvement showed significant variability between patients: for example, considering $\Delta EELV_{dep}$ (optimum flow = 60 l/min), in 37% of patients the highest increase was obtained at 30 or 45 l/min (Table E2 online).

Patients' drive and effort at increasing HFNC flow rates. In this section, we will only present ANOVA fixed effects results, while actual values and flow-level post-hoc analyses are reported in Table 4. Patients' drive, as assessed by respiratory rate, progressively decreased ($p<0.01$ by ANOVA) during HFNC in comparison to facial mask. Similarly, the inspiratory effort as measured by ΔPes and PTP_{Pes} decreased significantly by application of HFNC at increasing flows ($p<0.001$ for both) (Figure 1A and E3 online, Table 4).

Lung volumes, mechanics and oxygenation at increasing HFNC flow rates. In this section, we ANOVA fixed effects results, while actual values and flow-level post-hoc analyses are reported in Table 4. Global and regional tidal volume didn't change during HFNC in comparison to standard facial mask (Table 4). EELV, instead, significantly increased during treatment with HFNC in comparison to facial mask, globally and in the dependent lung region, indirectly suggesting PEEP effect and recruitment ($p<0.01$ for both) (Figure 2A and E3 online, Table 4). $EELV_{non\text{-}dep}$ remained stable in comparison to facial mask, likely indicating minimal additional risk of lung hyperinflation. HFNC significantly reduced minute ventilation and corrected minute ventilation ($p<0.01$ for both) in comparison to facial mask, possibly indicating enhanced CO_2 clearance from the nasopharyngeal dead space, decreased CO_2 production, or both (Figure 1B, Table 4). More favourable mechanical characteristics of the lung, as indicated by increased $V_T/\Delta Pes$ ratio, became evident during HFNC

compared to standard facial mask ($p<0.01$). Finally, PaO_2/FiO_2 increased at higher flow rates ($p<0.001$, Figure 2B), while $PaCO_2$ and pH didn't vary (Table 4).

DISCUSSION

The study main findings are: in AHRF patients, HFNC at increasing flow rates improved inspiratory drive and effort, oxygenation, efficiency of minute ventilation, end-expiratory lung volume and lung mechanics; improvement of oxygenation, end-expiratory lung volume and mechanics showed linear correlation with flow rates, with nearly constant improvement at increasing flow; correlations between flow rates, effort and minute ventilation, instead, were better described by exponential fitting and most of the improvement was already obtained at 30 l/min; finally, optimum flow for each studied physiologic variable didn't always correspond to the highest (i.e., 60 l/min) with considerable variability between patients, and personalized bedside titration of HFNC flow rate (possibly starting from the highest) seems warranted.

We observed that optimum flow (i.e., the flow obtaining highest improvement from baseline in most patients) can be different for each target variable, and this should be considered when attempting to individualize HFNC settings. Indeed, considering averaged results, to obtain the highest improvement in oxygenation, one might set the flow rate at 60 l/min (or at the highest value tolerated by the patient). On the other hand, maximal reduction in effort and work of breathing might be achieved in most patients by setting a lower flow rate (e.g., 30 l/min). In few subjects, further reduction in the work of breathing could be obtained at higher flow rates. Our data suggest that individualized settings of HFNC might be of key importance to fully exploit the clinical benefits. However, in clinical practice, time constraints may limit the possibility of assessing serial variations of target physiological variables at different flow rates to identify the "personalized" optimum flow. Thus, it might also be reasonable to simplify the clinical approach to selection of the highest flow tolerated by the patient starting from 60 l/min.

In this study, we enrolled adult AHRF patients within a few days from diagnosis in the ICU and we explored the effects of HFNC randomly delivered at increasing flow rates on drive and effort, lung volumes, mechanics and oxygenation [8]. Previous study by Vargas et al. measured patient's drive, effort and gas exchange in a population of AHRF patients admitted to the ICU describing significant physiologic improvements during HFNC in comparison to facial mask. In that study, the PTP_{Pes} was measured with the same method and showed similar variations. However, HFNC was delivered only at a single flow rate of 60 l/min and no monitoring of lung volumes (either tidal or end-expiratory) was implemented [25]. To date, only few studies described the effects of increasing HFNC flow rates and all were conducted only on healthy subjects, post-cardiac surgery and weaned patients after long-term ventilation without actual acute respiratory failure [13-18]. These studies described increased hypo-pharyngeal and tracheal pressures and improved EELV at increasing flow rates (both suggesting PEEP effect), decreased respiratory rate (possibly indicating decreased respiratory drive) and higher arterial oxygenation (likely by better matching of patient's alveolar and set HFNC FiO_2) [13-18, 10]. However, none of these studies assessed the physiologic effects of HFNC delivered at increasing flow rates in patients with AHRF.

A key beneficial effect of HFNC might be the reduction of inspiratory drive and effort induced by: improved CO_2 clearance, improved lung mechanics, external respiratory support, decreased hypoxic respiratory drive [12, 25-26]. In this study, we observed that inspiratory Pes swings and pressure time product, that are accepted measures of patient's effort, decreased during HFNC and that their improvement correlated (albeit non-linearly) with increasing flow rates. Indeed, optimum flow distribution for ΔPes was more skewed among patients (i.e., 43% had highest reduction at 30 l/min or 45 l/min) than it was for lung volume or oxygenation. These findings might suggest that, in AHRF patients, most of the reduction in effort and work of breathing can already be obtained at the lowest flow rate of 30 l/min. A possible explanation could be that CO_2 might be effectively washed-out from the upper respiratory tract already at 30 l/min, as shown also in previous study [27], together with similar decay of the minute ventilation needed to maintain physiologic $PaCO_2$; we

could also speculate that "physical" barriers (e.g., anatomical conformation of the glottis) might preclude higher HFNC flows to reach the trachea, thus impeding further improvement in the efficiency of CO_2 wash-out at 45 l/min and 60 l/min. The preliminary nature of our data precludes definitive conclusions on the correlation between increasing HFNC flow rates and inspiratory effort, work of breathing and CO_2 wash-out. Further studies measuring CO_2 tension in the upper airways during HFNC at increasing flow rates in AHRF patients might help to clarify the underlying mechanisms.

Previous data in post-cardiac surgery patients without AHRF suggested that HFNC delivered at 35-50 l/min generates relatively low positive expiratory airway pressure (PEEP effect, around 3 cmH_2O measured via a nasopharyngeal catheter) [28] and that this effect was not correlated with the patient keeping the mouth open or closed. However, another study, measuring the airway pressure via a trans-tracheal catheter, reported that the PEEP effect of HFNC delivered at 45 l/min was significantly reduced by asking the patient to breathe with the mouth open [18]. In our study, we didn't measure hypo-pharyngeal pressure as estimate of airway pressure, nor we instructed the patients to keep the mouth closed to maximize PEEP effect. Nonetheless, PEEP effect was indirectly suggested by an increase in EELV during HFNC (which hardly finds an alternative explanation to increased end-expiratory transpulmonary pressure) and lack of instructions on mouth opening/closing greatly enhance clinical translation of our findings. Lower EELV values measured during HFNC in few patients might correspond to breathing with the mouth open coupled with decreased dynamic driving transpulmonary pressure (i.e., ΔPes), possibly inducing alveolar de-recruitment. EIT monitoring suggests that EELV increase was mainly due to linear improvement of the regional end-expiratory volume in the dependent zones. Improvement of dependent lung volume was associated with increase in dynamic lung compliance and peripheral arterial oxygenation in similarly linear fashion. It has been shown that alveolar recruitment induced by the application of higher PEEP levels is mostly located in the gravitationally dependent lung regions [29] and that it is associated with improved lung mechanics and reduced intrapulmonary shunt fraction. These

observations generate the hypothesis that the PEEP effect obtained by HFNC might increase with the set flow rate (which seems reasonable as the PEEP induced by HFNC should be related to increased expiratory resistance) and that this PEEP effect might induce regional recruitment. Optimum flow value of 60 l/min for all these variables supports this reasoning. On the other hand, we must acknowledge that oxygenation might have improved at higher flow rates by better matching between delivered HFNC flow and inspiratory flow of dyspneic AHRF patients, which increases the alveolar FiO_2 for a given set FiO_2 [10].

Our study has several limitations. First, study phases were short; however, based on previous studies, twenty minutes should be enough to obtain a stable effect on effort, lung volumes and gas exchange. Second, EIT images approximately display half of the lungs, cannot measure lung volume changes along the vertical axis and most of the validation studies of EIT compared with other techniques were conducted in different settings (e.g., intubated patients or animals model). However, previous studies showed good agreement between the findings of EIT and other reference methods that measure whole lung volume [30-31]. Third, albeit in line with previous studies, sample size was small, which might have precluded the observation of significant differences. This could be even more relevant for our study, that was designed as a physiologic study but generates a number of information with the potentiality to change clinical practice regarding selection of HFNC flow rate. Fourth, we included AHRF patients with both mono- and bilateral infiltrates on chest X-ray, which might have introduced some heterogeneity. Fifth, we didn't record whether patients' mouth was open or closed during data collection, potentially missing a physiologic explanation for some findings (e.g., decreased EELV at higher HFNC flow rate). Sixth, we didn't measure patients' comfort but assessed changes in physiological measures of patients' respiratory condition. Aside physiological effects of intensive care therapies, patients' comfort and preference need also to be considered regularly. Seventh, optimum flow rate was selected as the one inducing the highest absolute change from baseline of each physiologic parameter in most patients. Thus, even small

differences with apparently limited clinical relevance might have contributed to the definition of optimum flow.

CONCLUSIONS

In AHRF patients, HFNC delivered at increasing flow rates linearly improves respiratory drive, end-expiratory lung volume, lung mechanics and oxygenation, while effort and minute ventilation decreases in an exponential way, with most of the effects already obtained at 30 l/min. Individual improvements might be highly heterogeneous and HFNC optimum flow rate should ideally be personalized, rather than being based on average population values. In the real-life ICU setting, time constraints could hinder accurate flow titration based on target physiologic parameter and a simplified approach with selection of the highest flow tolerated by the patient starting from 60 l/min might be a reasonable alternative.

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TABLES

Table 1. Main characteristics of the study population.

Patient #	Sex	Age (years)	SAPS II at ICU admission	SOFA score	Cause of acute hypoxemic respiratory failure	PaO_2/FiO_2 (mmHg)	Bilateral infiltrates on chest X-ray
1	M	75	44	11	Septic shock (leg erysipelas)	165	no
2	F	66	46	13	Severe sepsis (peritonitis)	96	no
3	M	53	40	13	Pneumonia	244	no
4	F	65	74	9	Postoperative respiratory failure	148	yes
5	F	54	19	12	Pneumonia	190	no
6	M	39	47	10	Pneumonia	238	yes
7	M	65	36	9	Postoperative respiratory failure	168	yes
8	F	68	43	12	Pneumonia	163	yes
9	M	59	41	12	Chest trauma	158	yes
10	F	70	68	16	Postoperative respiratory failure	140	yes
11	M	49	65	13	Pneumonia	73	yes
12	F	68	49	9	Postoperative respiratory failure	218	yes
13	F	55	37	13	Postoperative respiratory failure	193	no
14	M	61	45	8	TRALI	133	yes
15	F	66	54	6	Pneumonia	162	yes

16	M	76	55	8	Postoperative respiratory failure	207	yes
17	F	63	49	8	Postoperative respiratory failure	142	yes
Total or mean ± SD	9 F / 8 M	62 ± 10	48 ± 13	11 ± 3	8 pulmonary / 9 extra-pulmonary; 8 infectious / 9 non-infectious	167 ± 46	12 yes / 5 no

* SAPS II, simplified acute physiology score II; ICU, intensive care unit; SOFA score, sequential organ failure assessment score; PaO_2/FiO_2, oxygen partial arterial pressure on oxygen inspired fraction ratio; TRALI, transfusion-related acute lung injury.

Table 2. Best fitting (linear, quadratic and exponential statistical models) (✓) to describe the improvement of target physiologic variables between study phases (12-30-45-60 l/min). Only variables with significant differences at increasing flow rates were included.

Correlations - Flow rate with*:	Best model**		
	Linear	Quadratic	Exponential
ΔPes	✗	✗	✓
PTP_{Pes}	✗	✗	✓
$\Delta EELV_{glob}$	✓	✗	✗
$\Delta EELV_{dep}$	✓	✗	✗
MV	✗	✗	✓
MVcorr	✗	✗	✓
$V_{T,\,glob}/\Delta Pes$	✓	✗	✗
RR	✓	✗	✗
PaO_2/FiO_2	✓	✗	✗

*ΔPes, inspiratory esophageal pressure swing; PTP_{Pes}, esophageal pressure-time product per minute; $\Delta EELV_{glob}$, global change of end-expiratory lung volume; $\Delta EELV_{dep}$, change of end-expiratory lung volume in dependent regions; MVcorr, corrected minute ventilation; $V_{T,\,glob}/\Delta Pes$, dynamic compliance of the lung; RR, respiratory rate; PaO_2/FiO_2, oxygen partial arterial pressure on oxygen inspired fraction ratio.

** Best fitting was defined as the model associated with lowest Akaike's information criterion corrected for finite sample size (AICc). See methods for details and Table E1 online for actual values.

Table 3. Identification of the optimum flow (✓) for each of the studied physiologic parameter. Optimum flow was defined as the one associated with the largest number of patients obtaining highest improvement from baseline facial mask phase. Only variables with significant improvement at increasing flow rates were included.

Target physiologic variable*	Optimum flow**		
	HFNC 30 L/min	HFNC 45 L/min	HFNC 60 L/min
ΔPes	✗	✗	✓
PTP_{Pes}	✗	✗	✓
$\Delta EELV_{glob}$	✗	✗	✓
$\Delta EELV_{dep}$	✗	✗	✓
MV	✓	✗	✗
MVcorr	✓	✗	✗
$V_{T,\,glob}/\Delta Pes$	✗	✗	✓
RR	✗	✗	✓
PaO_2/FiO_2	✗	✗	✓

* ΔPes, inspiratory esophageal pressure swing; PTP_{Pes}, esophageal pressure-time product per minute; $\Delta EELV_{glob}$, global change of end-expiratory lung volume; $\Delta EELV_{dep}$, change of end-expiratory lung volume in dependent regions; MVcorr, corrected minute ventilation; $V_{T,\,glob}/\Delta Pes$, dynamic compliance of the lung**;** RR, respiratory rate; PaO_2/FiO_2, oxygen partial arterial pressure on oxygen inspired fraction ratio.

** Proportions of patients obtaining highest improvement from baseline face mask at each flow rate are reported in Table E2 online.

Table 4. Effects of HFNC delivered at increasing flow rate on target physiologic variables.

Variable*	Facial mask 12 L/min	HFNC 30 L/min	HFNC 45 L/min	HFNC 60 L/min	P-value
ΔPes (cmH_2O)	9.4 [6.8-12.2]	7.9 [5.9-11.8]§	8.1 [5.7-9.5]§	6.8 [5.1-9.3]§	**<0.001**
PTP_{Pes} (cmH_2O*sec/min)	254.3 [160.2-359.5]	173.5 [126.4-256.4]§	168.9 [110.3-217.2]§	151.4 [111.8-195.6]§	**<0.001**
$V_{T, glob}$ (ml/Kg PBW)	7.2 ± 4.6	7.2 ± 5.0	7.1 ± 4.8	7.0 ± 4.7	0.154
$V_{T, glob}$ (ml)	443 ± 302	437 ± 314	435 ± 307	429 ± 301	0.840
$V_{T, non-dep}$ (ml)	257 ± 228	258 ± 244	259 ± 242	275 ± 232	0.896
$V_{T, dep}$ (ml)	186 ± 126	180 ± 117	176 ± 120	175 ± 112	0.428
$\Delta EELV_{glob}$ (ml)	baseline	74 ± 174	115 ± 142	230 ± 237§	**<0.01**
$\Delta EELV_{non-dep}$ (ml)	baseline	53 ± 183	64 ±133	128 ± 185	0.121
$\Delta EELV_{dep}$ (ml)	baseline	31 ± 119	59 ± 121	93 ± 150§	**<0.05**
Minute Ventilation (L/min)	9.1 ± 4.0	7.0 ± 2.8§	7.0 ± 2.9§	6.9 ± 2.1	**≤0.001**
Corrected Minute Ventilation (L/min)	8.7 ± 4.2	6.5 ± 2.7§	6.6 ± 3.0§	6.6 ± 2.4	**<0.01**
$V_{T, glob}$/ΔPes (ml/cmH_2O)	42 [28-80]	52 [33-81]	57 [34-81]	55 [35-80]§	**<0.01**
RR (bpm)	24 ± 8	20 ± 7	19 ± 7§	18 ± 7§°	**<0.001**
PaO_2 (mmHg)	70.0 [64.5-77.5]	81.0 [74.5-88.3]§	89.0 [80.5-101.0]§	97.4 [84.5-115.5]§°	**<0.001**
PaO_2/FiO_2 (mmHg)	151 ± 60	177 ± 74§	187 ± 67§	205 ± 61 §°	**<0.001**
$PaCO_2$ (mmHg)	38.2 ± 5.0	38.0 ± 5.4	38.1 ± 5.7	38.3 ± 5.4	0.909
pH	7.46 ± 0.05	7.46 ± 0.06	7.46 ± 0.05	7.46 ± 0.06	0.997
SBP (mmHg)	133 ± 26	129 ± 24	130 ± 21	130 ± 23	0.208
MAP (mmHg)	77 [62-102]	77 [62-100]	81 [64-100]	76 [60-101]	0.258
HR (bpm)	86 ± 21	84 ± 22	85 ± 21	85 ± 22	0.705

*ΔPes, inspiratory esophageal pressure swing; PTP_{Pes}, esophageal pressure-time product per minute; $V_{T, glob}$ tidal volume; PBW predicted body weight; $V_{T, non-dep}$, tidal volume distending non-dependent lung regions; $V_{T, dep}$ tidal volume distending dependent regions; $\Delta EELV_{glob}$, global change of end-expiratory lung volume; $\Delta EELV_{non-dep}$, change of end-expiratory lung volume in non-dependent regions; $\Delta EELV_{dep}$, change of end-

expiratory lung volume in dependent regions; $V_{T, glob}/\Delta Pes$, dynamic compliance of the lung**;** RR, respiratory rate; PaO_2, oxygen partial arterial pressure; PaO_2/FiO_2, oxygen partial arterial pressure on oxygen inspired fraction ratio; $PaCO_2$, carbon dioxide partial arterial pressure; SBP, systolic arterial blood pressure; MAP, mean arterial pressure; HR, heart rate. Normally distributed variables are expressed as mean ±standard deviations, non-normal ones are expressed as median [interquartile range].

§ $p<0.05$ vs. facial mask by post-hoc Bonferroni test; ° $p<0.05$ vs. HFNC 30 L/m post-hoc Bonferroni test; no other between-phases post-hoc comparison was significant.

FIGURES LEGEND

Figure 1. Non-linear physiologic effects of high flow nasal cannula (HFNC) delivered at increasing flow rates. In acute hypoxemic respiratory failure patients, HFNC delivered at increasing flow rate (30, 45 and 60 l/min) reduces esophageal pressure time product (PTP_{Pes}, a measure of patient's effort, panel A) and corrected minute ventilation, i.e. the minute ventilation needed to maintain a physiological arterial carbon dioxide tension (MV_{corr}, panel B) in an exponential decay manner in comparison to standard facial mask.

Figure 2. Linear physiologic effects of high flow nasal cannula (HFNC) delivered at increasing flow rates. In acute hypoxemic respiratory failure patients, HFNC delivered at increasing flow rates of 30, 45 and 60 l/min induces significant changes in the dependent end-expiratory lung volumes ($\Delta EELV_{dep}$, panel A) and improves oxygenation (PaO_2/FiO_2 ratio, panel B) in a linear fashion in comparison to standard facial mask oxygen.

Figure 1

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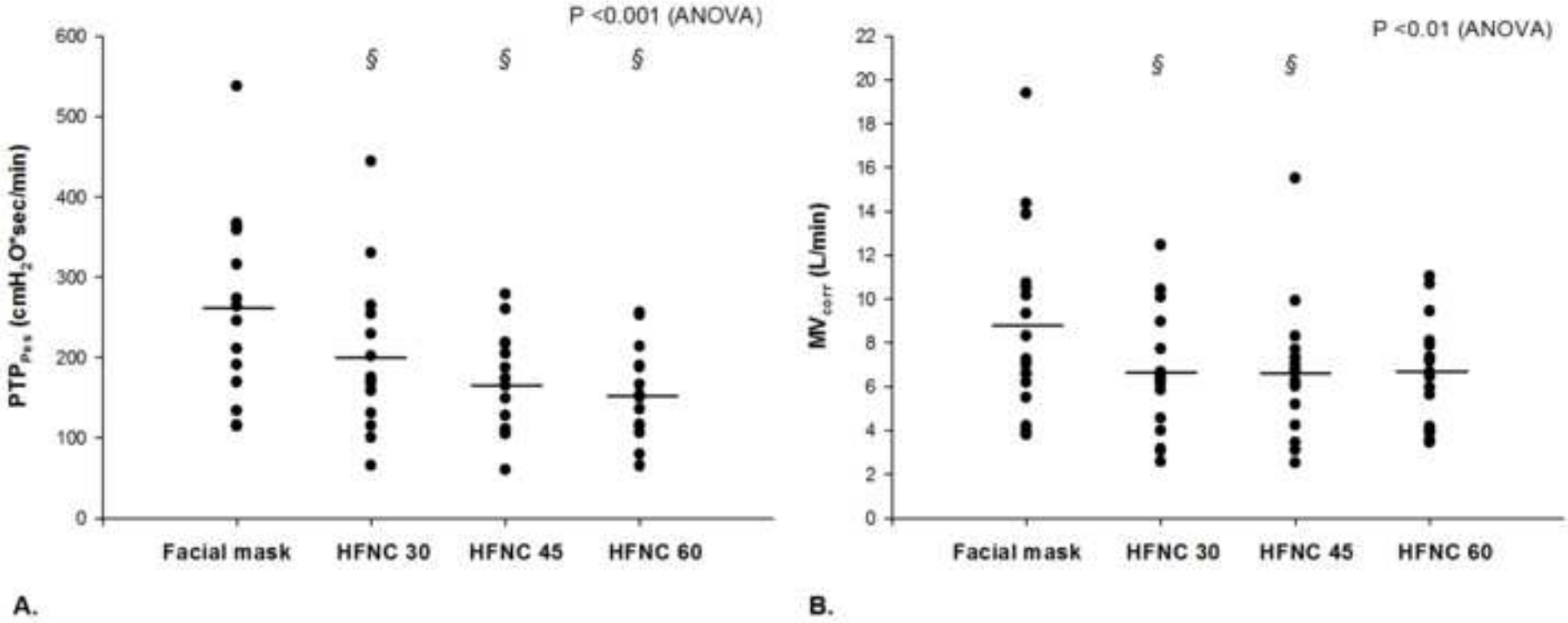

Figure 2