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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 patients with acute hypoxemic respiratory failure (AHRF). 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 patients with patients AHRF and a PaO₂/FiO₂ (arterial partial pressure of oxygen/fraction of inspired oxygen) ratio of ≤ 300 mmHg. A standard non-occlusive facial mask and HFNC at different flow rates (30, 45 and 60 l/min) were randomly applied, while maintaining constant FiO₂ (20 min/step). At the end of each phase, we measured arterial blood gases, inspiratory effort, based on swings in esophageal pressure (ΔP_{es}) and on the esophageal pressure–time product (PTP_{Pes}), and lung volume, by electrical impedance tomography.

Results: Seventeen patients with AHRF were enrolled in the study. At increasing flow rate, HFNC reduced ΔP_{es} ($p < 0.001$) and PTP_{Pes} ($p < 0.001$), while end-expiratory lung volume ($\Delta EELV$), tidal volume to ΔP_{es} ratio ($V_T/\Delta P_{es}$, which corresponds to dynamic lung compliance) and oxygenation improved ($p < 0.01$ for all factors). Higher HFNC flow rate also progressively reduced minute ventilation ($p < 0.05$) without any change in arterial CO₂ tension ($p = 0.909$). The decrease in ΔP_{es} , PTP_{Pes} and minute ventilation at increasing flow rates was better described by exponential fitting, while $\Delta EELV$, $V_T/\Delta P_{es}$ and oxygenation improved linearly.

Conclusions: In this cohort of patients with AHRF, an increasing HFNC flow rate progressively decreased inspiratory effort and improved lung aeration, dynamic compliance and oxygenation. Most of the effect on inspiratory workload and CO₂ clearance was already obtained at the lowest flow rate.

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Take-home message: In acute hypoxemic respiratory failure, high-flow nasal cannula (HFNC) delivered at increasing flow rates induced a significant improvement of the patient's inspiratory effort, minute ventilation, lung volume, dynamic compliance and oxygenation. However, most of the effect on inspiratory workload and CO₂ clearance was already obtained at lowest HFNC flow rate. A personalized setting could be considered after careful evaluation of patient's condition and the individual response.

Keywords: High-flow nasal oxygen, Spontaneous breathing, Electrical impedance tomography, Esophageal pressure, Acute lung injury, Acute respiratory failure

Introduction

Recent studies have reported 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]. Preliminary data also suggest that HFNC may also decrease mortality [4]. The physiologic mechanisms of HFNC that potentially underlie its clinical benefits may include reduced inspiratory effort and work of breathing, improved lung mechanics, increased end-expiratory lung volumes, likely due to the positive end-expiratory pressure (PEEP) effect, lower minute ventilation [8], higher alveolar fraction of inspired oxygen (FiO_2) [9, 10], increased carbon dioxide (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 and cardiac surgery and tracheotomized 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 their mouth closed during breathing on HFNC, but this is not feasible in the real-life, long-term treatment of AHRF patients [13, 14, 18]. Moreover, theoretically, the application of HFNC at higher flow rates should exploit other physiologic benefits in AHRF patients (e.g. improved oxygenation by progressive reduction in the difference between the set and the alveolar FiO_2).

To address the question mentioned above on the best flow rate during HFNC treatment, 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. To increase the clinical impact and reproducibility of the data, patients did not receive any instruction regarding mouth opening/closing during

any phase of the study. The aims of this study were: (1) to describe whether the physiologic effects of HFNC improve by increasing flow rate; (2) 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; (3) 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 <1 week; PaO_2 (arterial partial pressure of oxygen)/ FiO_2 of ≤ 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 years; presence of tracheostomy; hemodynamic instability (hypotension with mean arterial pressure of <60 mmHg despite volume loads or vasoactive drugs); evidence of pneumothorax on chest X-ray or computed tomography 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 (Pes) 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, 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, $\text{PaO}_2/\text{FiO}_2$ 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 intragastric position was confirmed by the positive pressure deflections during spontaneous inspiration. The catheter was then withdrawn into the esophagus, as indicated by the appearance of cardiac artifacts and negative swings of pressure tracings during inspiration, and fixed [19–21]. The accuracy of esophageal pressure measurements relies 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 min at the end of each study phase and before starting the next one by a 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 applying small alternate electrical currents rotating around the patient's thorax at 20 Hz, so that tomographic data were acquired every 50 ms throughout all study phases and stored for offline analyses performed by dedicated software (Dräger EIT Data Analysis Tool and EITdiag; Dräger Medical GmbH) [22]. The esophageal pressure and EIT signals were synchronized 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 starting the EIT recordings and before beginning the study protocol, we recorded spirometry through a spirometer connected to a mouthpiece with occluded nostrils during spontaneous breathing for 30 s 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 milliliters and arbitrary units of impedance change was calculated and used to transform 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. EIT calibration was not repeated after the start of the first study phase as this

step would have altered the physiologic breathing pattern and prolonged duration of an already long study (>1.5 h).

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, with each phase lasting 20 min:

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

HFNC was delivered through specific nasal prongs of medium or large size (Fisher and Paykel Healthcare, Auckland, New Zealand) to fit the size of the nares. The set FiO_2 was clinically chosen by the attending physician before patient enrolment to target a peripheral saturation of 90–96% on pulse oximetry during standard oxygen facial mask breathing and was kept constant during all phases. The set FiO_2 during each phase was measured using a dedicated system (AIRVO™ 2; Fisher and Paykel Healthcare) connected to the standard facial mask or the HFNC. The system can deliver air flows of between 2 and 60 l/min with a set FiO_2 (continuously measured at the gas outlet of the system) of 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 increasing or decreasing the additional oxygen wall supply in increments. Patients did not 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 data on the arterial blood gas analysis, respiratory rate and hemodynamics.

Esophageal pressure data

From the esophageal pressure waveforms analyzed 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 esophageal pressure waveform during inspiration over a period of 2–3 min divided by the number of minutes, as a measure of patient's effort over 1 min [21, 23]. PTP_{PES} represents a modification of the classic computation of the pressure–time product that requires measurement of the passive elastic recoil of the chest wall.

However, chest wall elastance cannot be measured in non-intubated patients and the addition of passive elastic recoil of the chest wall to PTP_{Pes} in the four study phases would not modify our results as tidal volume did not change (see below) and lung elastance would be assumed to be equal.

2. The average esophageal pressure swings during inspiration (ΔP_{es}), defined as the difference between end-expiratory and end-inspiratory esophageal pressure 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 esophageal pressure 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 ($V_{T, glob}$, $V_{T, non-dep}$ and $V_{T, dep}$, respectively);
2. The minute ventilation (MV), measured as the sum of all tidal volumes over two to three representative minutes divided by the number of minutes, which may represent a more precise measure of MV than multiplication of average tidal volume by average respiratory rate (RR);
3. Corrected minute ventilation (MV_{corr}), defined as MV multiplied by the ratio of the patient's $PaCO_2$ (partial pressure $CO_2/40$ mmHg (i.e. $MV_{corr} = MV \times [actual PaCO_2/40 \text{ mmHg}]$) [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 ($\Delta EELV_{glob}$, $\Delta EEL \times V_{non-dep}$ 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 arbitrary units (a.u.) during HFNC phases and multiplied these by the calibrating ml/a.u. factor.

Finally, esophageal pressure and EIT data were combined and used to calculate the dynamic compliance of the lung as $V_{T, glob}/\Delta P_{es}$, to evaluate the effects of HFNC on lung mechanics.

Statistical analysis

Sample size was based on previous studies [8, 13–18, 21–23]. Normally distributed variables were expressed as the mean \pm standard deviation (SD), while median and interquartile range 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 model describing the relative improvement of each variable at increasing flow rates and considering the facial mask as baseline, we applied three different statistical models to the variations between phases: linear, quadratic and exponential. We then 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 the 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 which obtained the highest change from the facial mask phase of each parameter in most patients was indicated as the optimum flow. A level of $p < 0.05$ (two-tailed) was considered to be 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

The patient population consisted of 17 patients, nine (53%) of whom were women, with a mean age (\pm SD) of 62 ± 10 years. Severity of clinical condition was relevant, as indicated by SAPS II at ICU admission of 48 ± 13 and SOFA score of 11 ± 3 . Eight patients (47%) had pulmonary etiology of AHRF and nine (53%) presented a non-infectious cause. The number of days since recognition of AHRF in the ICU were 2 ± 1 (range 1–3). Twelve patients (70%) presented bilateral infiltrates on chest X-ray. The patients' characteristics are listed in Table 1.

Best model for the correlation between physiology and HFNC flow rates

The AICc analysis indicated that linear correlation better described variations of $\Delta EELV_{glob}$ and $\Delta EELV_{dep}$, $V_{T/}$

ΔP_{es} , RR and PaO_2/FiO_2 with increasing HFNC flow rates [Table 2; Electronic Supplementary Material (ESM) Table E1, Figs. E1A, E1B). On the other hand, exponential fitting better matched the decrease of ΔP_{es} , $PTP_{P_{es}}$, MV and MV_{corr} at higher flow (Tables 1, 2; ESM Figs. E2A, E2B), 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. ΔP_{es}).

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 ΔP_{es} , $PTP_{P_{es}}$, $\Delta EELV_{glob}$, $\Delta EELV_{dep}$, $V_T/\Delta P_{es}$, RR and PaO_2/FiO_2 ; 45 l/min for none of the physiologic

parameters and 30 l/min for MV and MV_{corr} (Table 3). However, we must note that the flow associated with the 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 (ESM Table E2).

Patients' drive and effort at increasing HFNC flow rates

Only the results of the fixed-effects ANOVA model are presented in this section; the 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 the facial mask. Similarly, the inspiratory effort as measured by ΔP_{es} and $PTP_{P_{es}}$ decreased significantly by application of HFNC at increasing flows ($p < 0.001$ for both) (Table 4; Fig. 1a; ESM Fig. E3).

Table 1 Main characteristics of the study population

Patient no.	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	Male	75	44	11	Septic shock (leg erysipelas)	165	No
2	Female	66	46	13	Severe sepsis (peritonitis)	96	No
3	Male	53	40	13	Pneumonia	244	No
4	Female	65	74	9	Postoperative respiratory failure	148	Yes
5	Female	54	19	12	Pneumonia	190	No
6	Male	39	47	10	Pneumonia	238	Yes
7	Male	65	36	9	Postoperative respiratory failure	168	Yes
8	Female	68	43	12	Pneumonia	163	Yes
9	Male	59	41	12	Chest trauma	158	Yes
10	Female	70	68	16	Postoperative respiratory failure	140	Yes
11	Male	49	65	13	Pneumonia	73	Yes
12	Female	68	49	9	Postoperative respiratory failure	218	Yes
13	Female	55	37	13	Postoperative respiratory failure	193	No
14	Male	61	45	8	TRALI	133	Yes
15	Female	66	54	6	Pneumonia	162	Yes
16	Male	76	55	8	Postoperative respiratory failure	207	Yes
17	Female	63	49	8	Postoperative respiratory failure	142	Yes
Total or mean \pm SD	9 Female/8 male	62 \pm 10	48 \pm 13	11 \pm 3	8 pulmonary/ 9 extra-pulmonary; 8 infectious/ 9 non-infectious	167 \pm 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/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)

Correlation of flow rate with physiologic parameters ^a	Best model ^b		
	Linear	Quadratic	Exponential
ΔP_{es}	×	×	✓
$PTP_{P_{es}}$	×	×	✓
$\Delta EELV_{glob}$	✓	×	×
$\Delta EELV_{dep}$	✓	×	×
MV	×	×	✓
MVcorr	×	×	✓
$V_{T, glob}/\Delta P_{es}$	✓	×	×
RR	✓	×	×
PaO_2/FiO_2	✓	×	×

✓ indicates best fitting model

Only variables with significant differences at increasing flow rates were included

^a ΔP_{es} Inspiratory esophageal pressure swing, $PTP_{P_{es}}$ 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, MV minute ventilation, MVcorr corrected minute ventilation; $V_{T, glob}/\Delta P_{es}$ dynamic compliance of the lung, RR respiratory rate, PaO_2/FiO_2 oxygen partial arterial pressure/oxygen inspired fraction ratio

^b Best fitting was defined as the model associated with lowest Akaike's information criterion corrected for finite sample size (AICc). See the "Methods" section for details and Electronic Supplementary Material Table E1 for actual values

Table 3 Identification of the optimum flow for each of the studied physiologic parameters

Targeted physiologic variable	Optimum flow rate ^a		
	HFNC 30 l/min	HFNC 45 l/min	HFNC 60 l/min
ΔP_{es}	×	×	✓
$PTP_{P_{es}}$	×	×	✓
$\Delta EELV_{glob}$	×	×	✓
$\Delta EELV_{dep}$	×	×	✓
MV	✓	×	×
MVcorr	✓	×	×
$V_{T, glob}/\Delta P_{es}$	×	×	✓
RR	×	×	✓
PaO_2/FiO_2	×	×	✓

Only variables with significant improvement at increasing flow rates were included in the analysis

✓ indicates optimum flow

HFNC High-flow nasal cannula

^a Optimum flow was defined as the flow associated with the largest number of patients obtaining the highest improvement from the baseline facial mask phase. The proportion of patients obtaining the highest improvement from baseline face mask at each flow rate is reported in ESM Table E2

Lung volumes, mechanics and oxygenation at increasing HFNC flow rates

The results of the fixed-effects ANOVA model are reported in this section; actual values and flow-level post

hoc analyses are reported in Table 4. Global and regional tidal volume did not change during HFNC in comparison to standard facial mask (Table 4). In contrast, EELV increased significantly during treatment with HFNC in comparison to facial mask, both globally and in the dependent lung region, indirectly suggesting PEEP effect and recruitment ($p < 0.01$ for both) (Table 4; Fig. 2a; ESM Fig. E3). $EELV_{non-dep}$ remained stable in comparison to the 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 the facial mask, possibly indicating enhanced CO_2 clearance from the nasopharyngeal dead space, decreased CO_2 production, or both (Fig. 1b; Table 4). More favorable mechanical characteristics of the lung, as indicated by increased $V_T/\Delta P_{es}$ ratio, became evident during HFNC compared to standard facial mask ($p < 0.01$). Finally, PaO_2/FiO_2 increased at higher flow rates ($p < 0.001$; Fig. 2b), while $PaCO_2$ and pH did not vary (Table 4).

Discussion

The main findings of this study are that 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. The improvement of oxygenation, end-expiratory lung volume and mechanics showed a linear correlation with flow rates, with nearly constant improvement at increasing flow. In contrast, correlations between flow rates, effort and minute ventilation were better described by exponential fitting, with most of the improvement in these variables already obtained at 30 l/min. Finally, optimum flow for each physiologic variable studied did not always correspond to the highest flow rate (i.e. 60 l/min), with considerable variability between patients, indicating that personalized bedside titration of HFNC flow rate (possibly starting from the highest working downwards) seems warranted.

We observed that optimum flow (i.e. the flow rate at which the highest improvement from baseline achieved by most patients) can be different for each target variable; this variability 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 a few subjects, an even 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

Table 4 Effects of high-flow nasal cannula 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
ΔP_{es} (cmH ₂ O)	9.4 (6.8–12.2)	7.9 (5.9–11.8) ^a	8.1 (5.7–9.5) ^a	6.8 (5.1–9.3) ^a	<0.001*
$PTP_{P_{es}}$ (cmH ₂ O s/min)	254.3 (160.2–359.5)	173.5 (126.4–256.4) ^a	168.9 (110.3–217.2) ^a	151.4 (111.8–195.6) ^a	<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 ^a	<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 ^a	<0.05*
MV (l/min)	9.1 ± 4.0	7.0 ± 2.8 ^a	7.0 ± 2.9 ^a	6.9 ± 2.1	≤0.001*
Corrected MV (l/min)	8.7 ± 4.2	6.5 ± 2.7 ^a	6.6 ± 3.0 ^a	6.6 ± 2.4	<0.01*
$V_{T, glob}/\Delta P_{es}$ (ml/cmH ₂ O)	42 (28–80)	52 (33–81)	57 (34–81)	55 (35–80) ^a	<0.01*
RR (bpm)	24 ± 8	20 ± 7	19 ± 7 ^a	18 ± 7 ^{a, b}	<0.001*
PaO ₂ (mmHg)	70.0 (64.5–77.5)	81.0 (74.5–88.3) ^a	89.0 (80.5–101.0) ^a	97.4 (84.5–115.5) ^{a, b}	<0.001*
PaO ₂ /FiO ₂ (mmHg)	151 ± 60	177 ± 74 ^a	187 ± 67 ^a	205 ± 61 ^{a, b}	<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

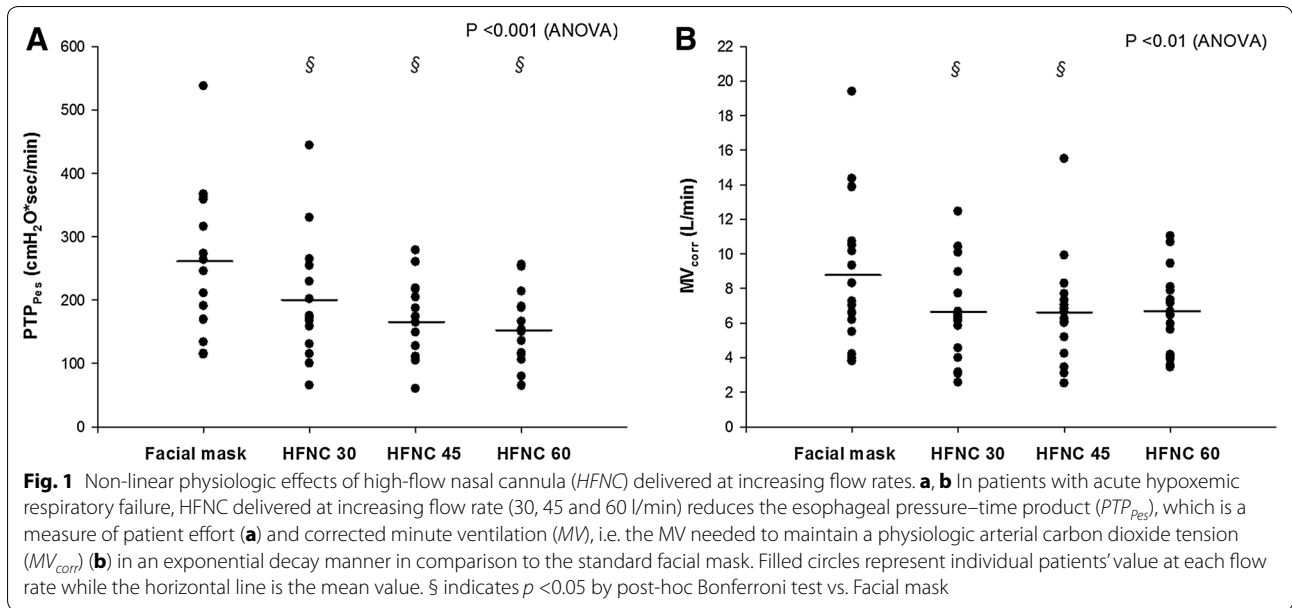
$V_{T, glob}$ tidal volume, PBW predicted body weight, $V_{T, non-dep}$ tidal volume distending non-dependent lung regions, $V_{T, dep}$ tidal volume distending dependent regions, $\Delta EELV_{non-dep}$ change of end-expiratory lung volume in non-dependent regions, PaCO₂ carbon dioxide partial arterial pressure, SBP systolic arterial blood pressure, MAP, mean arterial pressure, HR, heart rate. See Table 2 for all other abbreviations

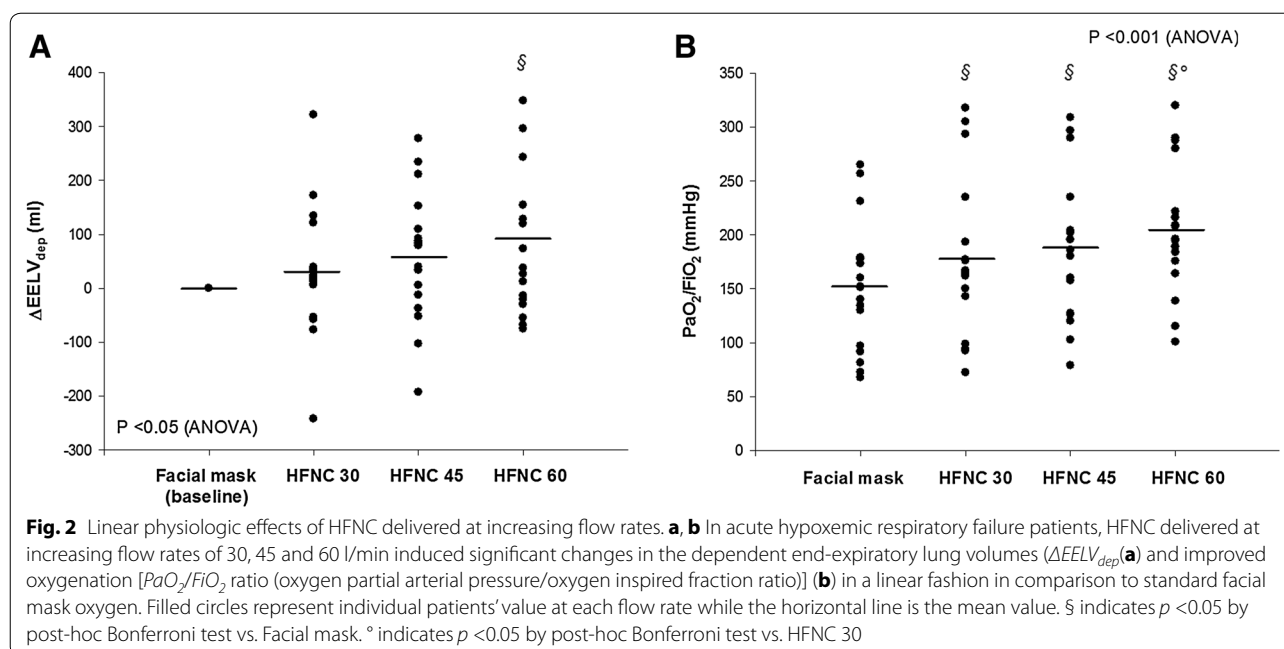
Normally distributed variables are expressed as the mean ± standard deviation; non-normal distributed variables are expressed as median with the [interquartile range] in parenthesis. Unless indicated otherwise, the post hoc comparison of variables revealed no between-phase significance for the variables compared

*p < 0.05

^a Significant at p < 0.05 vs. facial mask by post hoc Bonferroni test

^b Significant at p < 0.05 vs. HFNC 30 l/min post hoc Bonferroni test





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 the selection of the highest flow tolerated by the patient, starting from 60 l/min.

The patient cohort in this study comprised adult patients with AHRF who were diagnosed within a few days in the ICU. We explored the effects of HFNC randomly delivered at increasing flow rates on drive and effort, lung volumes, mechanics and oxygenation on these patients [8]. Vargas et al. measured patient's drive, effort and gas exchange in a population of patients with AHRF who had been admitted to the ICU and described significant physiologic improvements during HFNC in comparison to the facial mask. In that study, the PTP_{Pes} was measured with the same method used in our study 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 a few studies have described the effects of increasing HFNC flow rates, and all were conducted only on healthy subjects and on post-cardiac surgery and weaned patients after long-term ventilation without actual acute respiratory failure [13–18]. The authors of these studies describe increased hypo-pharyngeal and tracheal pressures and improved EELV at increasing flow rates (both results suggesting a PEEP effect), decreased respiratory rate (possibly indicating decreased respiratory drive) and higher arterial

oxygenation (likely by the better matching of patient's alveolar and set HFNC FiO_2) [10, 13–18]. 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 and decreased hypoxic respiratory drive [12, 25, 26]. In our study, we observed that swings in the inspiratory esophageal pressure and pressure–time product, both accepted measures of a patient's effort, decreased during HFNC and that improvement in these variables correlated (albeit non-linearly) with increasing flow rates. Indeed, among patients, optimum flow distribution for ΔP_{es} was more skewed (i.e. 43% had highest reduction at 30 or 45 l/min) than was lung volume or oxygenation. These findings may suggest that, in AHRF patients, most of the reduction in the effort and work of breathing can be obtained at even the lowest flow rate of 30 l/min. A possible explanation may be that CO_2 might be effectively washed-out from the upper respiratory tract already at 30 l/min, as shown also in a 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 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

CO₂ wash-out. Further studies measuring CO₂ tension in the upper airways during HFNC at increasing flow rates in AHRF patients may help to clarify the underlying mechanisms.

Data on post-cardiac surgery patients without AHRF suggest 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 is not correlated with the patient keeping the mouth either open or closed. However, in another study, which measured the airway pressure via a trans-tracheal catheter, Chanques et al. 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 did not measure hypo-pharyngeal pressure as an estimate of airway pressure, nor did we instruct the patients to keep the mouth closed to maximize the PEEP effect. Nonetheless, the PEEP effect was indirectly suggested by an increase in EELV during HFNC (for which it is difficult to find an alternative explanation for increased end-expiratory transpulmonary pressure), and the lack of instructions on mouth opening/closing greatly enhance the clinical translation of our findings. Lower EELV values measured during HFNC in a few patients may correspond to breathing with the mouth open coupled with decreased dynamic driving transpulmonary pressure (i.e. ΔP_{es}), possibly inducing alveolar de-recruitment. EIT monitoring suggests that the increase in EELV was mainly due to linear improvement of the regional end-expiratory volume in the dependent zones. Improvement of dependent lung volume was associated with an increase in dynamic lung compliance and peripheral arterial oxygenation in a similar 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. An optimum flow value of 60 l/min for all these variables supports this reasoning. On the other hand, we must acknowledge that oxygenation may have improved at higher flow rates by better matching between delivered HFNC flow and inspiratory flow of dyspneic AHRF patients, which increases the alveolar FiO₂ for a given set FiO₂ [10].

Our study has several limitations. First, the study phases were short; however, based on previous studies,

20 min should be a sufficiently long time period to obtain a stable effect on effort, lung volumes and gas exchange. Second, EIT images display approximately one-half the area of the lungs and therefore cannot be used to measure lung volume changes along the vertical axis. In addition, most of the validation studies of EIT compared with other techniques have been conducted in different settings (e.g. intubated patients or animal models). However, previous studies have shown 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, our sample size was small, which may have precluded the observation of significant differences. This could be even more relevant in our study, which was designed as a physiologic study but which generates a lot of information with the potential to change clinical practice regarding the selection of HFNC flow rate. Fourth, we included AHRF patients with both mono- and bilateral infiltrates on chest X-ray, which may have introduced some heterogeneity. Fifth, we did not record whether the patient's mouth was open or closed during data collection, potentially missing a physiologic explanation for some of the findings (e.g. decreased EELV at higher HFNC flow rate). Sixth, we did not measure patients' comfort but assessed changes in physiologic measures of patients' respiratory condition. In addition to the physiologic effects of intensive care therapies, patients' comfort and preference also need to be considered regularly. Seventh, optimum flow rate was selected as the flow rate inducing the highest absolute change from baseline of each physiologic parameter in most patients. Thus, even small differences with apparently limited clinical relevance may have contributed to the definition of optimum flow.

Conclusions

In patients with AHRF, 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 a flow rate of 30 l/min. Individual improvements may be highly heterogeneous, and ideally the HFNC optimum flow rate should 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 the target physiologic parameter, and a simplified approach with selection of the highest flow rate tolerated by the patient, starting from 60 l/min, may be a reasonable alternative.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-017-4890-1) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflict of interest related to the present study.

Ethical approval and consent to participate

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.

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