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Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure

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At-a-glance commentary

Scientific knowledge on the subject. High-flow nasal cannula (HFNC) is a non-invasive form of respiratory support that can reduce re-intubation rates and mortality of acute

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hypoxemic respiratory failure patients. The physiologic effects potentially underlying these clinical benefits are still largely undefined.

What this study adds to the field. In acute hypoxemic respiratory failure patients, HFNC improves oxygenation, reduces the patient's effort, reduces the minute ventilation needed to obtain a physiologic arterial CO_2 level, increases the end-expiratory lung volume, and improves dynamic compliance, transpulmonary pressure and ventilation homogeneity. These beneficial effects might underlie the clinical efficacy of HFNC.

This article has an online data supplement, accessible from this issue's table of contents online at www.atsjournals.org

ABSTRACT

Rationale. High-flow nasal cannula (HFNC) improves the clinical outcomes of non-intubated acute hypoxemic respiratory failure (AHRF) patients.

Objectives. To assess the effects of HFNC on gas exchange, inspiratory effort, minute ventilation, end-expiratory lung volume, dynamic compliance and ventilation homogeneity in AHRF patients.

Methods. This was a prospective randomized cross-over study in non-intubated AHRF patients with $PaO_2/setFiO_2 \leq 300$ mmHg admitted to the Intensive Care Unit. We randomly applied HFNC set at 40 L/min compared to a standard non-occlusive facial mask at the same clinically set F_iO_2 (20 min/step).

Measurements and main results. Towards the end of each phase, we measured arterial blood gases; inspiratory effort and work of breathing by esophageal pressure swings (ΔPes) and pressure time product (PTP); lung volumes and ventilation homogeneity by electrical impedance tomography.

We enrolled 15 patients aged 60±14 years old with $PaO_2/setFiO_2$ 130±35 mmHg. Seven (47%) had bilateral lung infiltrates. Compared with the facial mask, HFNC significantly improved oxygenation ($p<0.001$) and lowered respiratory rate ($p<0.01$), ΔPes ($p<0.01$) and PTP ($p<0.001$). During HFNC, minute ventilation was reduced ($p<0.001$) at constant arterial CO_2 tension and pH ($p=0.27$ and $p=0.23$, respectively); end-expiratory lung volume increased ($p<0.001$), and tidal volume did not change ($p=0.44$); the ratio of tidal volume to ΔPes (an estimate of dynamic lung compliance) increased ($p<0.05$); finally, ventilation distribution was more homogeneous ($p<0.01$).

Conclusions. In AHRF patients, HFNC exerts multiple physiologic effects including less inspiratory effort and improved lung volume and compliance. These benefits might underlie the clinical efficacy of HFNC.

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INTRODUCTION

High-flow nasal cannula (HFNC) is a non-invasive respiratory support designed to deliver 30-60 L/min of a heated, humidified mixture of air and oxygen through specifically designed nasal prongs (1). HFNC was first employed in preterm infants and pediatric patients (2) and recent large randomized clinical trials have promoted its use in adult with acute hypoxemic respiratory failure (AHRF) (3). These trials demonstrated the potential of HFNC to improve clinical outcomes such as re-intubation rates and 90-day mortality (4-7). However, the physiologic mechanisms underlying the clinical benefits of HFNC are still poorly understood in adult AHRF patients.

Basic clinical monitoring during HFNC therapy demonstrated rapid improvement of oxygenation and reduction of dyspnea in comparison to a standard facial mask (8-9). Findings in other populations (10) indicate that advanced respiratory monitoring might demonstrate other specific physiologic effects. A study in pediatric patients with acute bronchiolitis treated with HFNC showed reductions in inspiratory effort, as measured by esophageal pressure swings (11), while in another study in patients with chronic obstructive pulmonary disease electrical impedance tomography (EIT) (12) suggested an increase in end-expiratory lung volume (EELV). Reduced inspiratory effort and improved lung volume might be particularly important in AHRF, as they may prevent respiratory muscle exhaustion and lower the tidal volume/EELV ratio, which are closely related to the need for intubation and the severity in these patients (13, 14).

The present study describes the effects of HFNC on specific advanced physiologic parameters that may be correlated with clinical outcomes of AHRF patients. Complementing standard clinical monitoring with the use of esophageal pressure and EIT, we assessed the effects of HFNC on: gas exchange, patients' inspiratory effort, minute ventilation, lung volume,

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dynamic compliance, transpulmonary pressure and ventilation homogeneity. Our hypothesis was that HFNC significantly improves these key physiologic parameters.

Some of the data reported here have already been presented in the form of an abstract (15).

METHODS

We enrolled 15 acute hypoxemic respiratory failure patients admitted to the general Intensive Care Unit of San Gerardo Hospital, Monza, Italy. Inclusion criteria were: new or acutely worsening respiratory symptoms following a known clinical insult lasting less than a week; $PaO_2/setFiO_2 \leq 300$ mmHg while receiving additional oxygen by a standard facial mask, as per clinical decision. Exclusion criteria are listed in the online data supplement. The ethical committee of San Gerardo Hospital approved the study (reference number: 432_2015bis) and informed consent requirements were met according to local regulations.

At enrolment, we collected the patients' main demographics and clinical data.

An esophageal balloon catheter was placed in the esophagus, as demonstrated by the appearance of cardiac artifacts and appropriate negative swings of pressure tracings during inspiration (16, 17). Esophageal pressure waveforms were continuously recorded by a dedicated data acquisition system throughout the study. An EIT dedicated belt was placed around each patient's chest and connected to a commercial EIT monitor. During the whole study, EIT data were registered at 20 Hz and stored for offline analysis by dedicated software (18).

Each patient was entered in the two study phases with the same set FiO_2 for 20 minutes in computer-generated random order:

1. Standard non-occlusive oxygen facial mask with gas flow set at 12 L/min;
2. HFNC with gas flow 40 L/min.

Set FiO_2 during both phases was selected clinically by the attending physician before enrolment to achieve peripheral saturation between 90 and 95% on pulse oximetry during standard oxygen facial mask breathing. Set FiO_2 during both study phases was measured by a dedicated system (AIRVO™ 2, Fisher & Paykel Healthcare, Auckland, New Zealand) connected to the standard facial mask or the nasal cannula. This system can deliver airflows between 2 and 60 L/min with FiO_2 between 0.21 and 1.0 by connection to a wall supply. FiO_2 is continuously measured at the gas outlet of the system. In summary, in keeping with previous studies (12, 19-20), we set the gas delivery system at 12 L/min during the facial mask phase and at 40 L/min during HFNC with the same measured set FiO_2, obtained by modifying the additional oxygen wall supply. However, we could not avoid or verify lower tracheal and alveolar FiO_2 during the oxygen facial mask phase due to entrainment of room air.

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

From the esophageal pressure waveforms recorded during the last 3-5 minutes of each phase we measured (21):

1. The average pressure time product over a minute (PTP_{min}), as a measure of the metabolic work of breathing per minute (see the online data supplement for detailed methods);
2. The per-breath pressure time product (PTP), as a measure of the metabolic work of breathing per single breath (see the online data supplement for detailed methods);
3. The esophageal pressure swings during inspiration (ΔPes) as a measurement of the patient's inspiratory effort;
4. The dynamic end-expiratory transpulmonary pressure ($P_{L,ee}$), calculated as the difference between airway pressure (assumed to be 0 cmH_2O with the facial mask and

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2.5 cmH_2O (22) during HFNC) and the absolute Pes measured at the end of expiration (zero flow);

5. The dynamic end-inspiratory transpulmonary pressure ($P_{L,ei}$), calculated as the difference between airway pressure (assumed to be 0 cmH_2O with the facial mask and 2.5 cmH_2O during HFNC) and the absolute Pes measured at the end of inspiration (zero flow);
6. The driving transpulmonary pressure (ΔP_L), calculated as ($P_{L,ei}$ - $P_{L,ee}$).

During the last minutes of each phase, we measured the following EIT parameters too:

1. The average global tidal volume and those distending non-dependent and dependent lung regions ($V_{T,\ glob}$, $V_{T,\ non\text{-}dep}$ and $V_{T,\ dep}$, respectively);
2. The minute ventilation (MV);
3. Corrected minute ventilation (MV_{corr}), defined as MV multiplied by the ratio of the patient's $PaCO_2$ to 40 mmHg (23) (with lower values indicating improved CO_2 clearance, reduced CO_2 production, or both);
4. Global and regional changes in end-expiratory lung impedance (corresponding to end-expiratory lung volume) during the HFNC phase ($\Delta EELI_{glob}$, $\Delta EELI_{non\text{-}dep}$ and $\Delta EELI_{dep}$) (18);
5. Global inhomogeneity index (GI), a measure of inhomogeneous distribution of tidal ventilation (24). The GI index gave a reliable and inter-patient comparable synthetic assessment of inhomogeneous distribution of the tidal volume in the lungs (24). The risk of additional lung injury seems to increase linearly with inhomogeneous distribution of lung densities (25), which is correlated with ventilation inhomogeneity (26). Thus, any change in this index might be clinically significant. However, to our knowledge, no prospective clinical validation of specific thresholds has been done yet.

6. The global and regional peak inspiratory and expiratory airflows (PIF_{glob}, $PIF_{non\text{-}dep}$ and PIF_{dep}; PEF_{glob}, $PEF_{non\text{-}dep}$ and PEF_{dep}, respectively) (27);
7. From the EIT-derived airflow tracings, we also measured the inspiratory (Ti) and expiratory (Te) times, and the total cycle time (Ttot) (28).

We chose the sample size on the basis of previous studies (9-14, 16-20, 24). For the sake of clarity, EIT measures (e.g., $V_{T,\,glob}$) during HFNC were transformed from arbitrary units of impedance change to the percentage change from their baseline values during the oxygen facial mask phase. Normally distributed variables are expressed as mean ± standard deviations and were analyzed by a paired t-test. Non-normally distributed variables are expressed as medians [IQR] and were compared by Wilcoxon's signed rank test. Correlations were analyzed by Pearson's coefficient. A level of $p<0.05$ (two-tailed) was considered statistically significant.

Additional details on the method for this study are provided in an online data supplement.

RESULTS

Patients. Patients' main characteristics are reported in Table 1. Patients were 60±14 years old and 6 (40%) were women. At enrolment, all patients had $PaO_2/setFiO_2$ below 200 mmHg, with 3 (20%) lower than 100 mmHg. Seven patients (47%) had bilateral infiltrates on chest X-ray.

Effects of HFNC on inspiratory effort and work of breathing. During HFNC, the esophageal pressure swings (ΔPes) were significantly lower than with the standard non-occlusive oxygen facial mask ($p<0.01$) (Table 2 and Figure 1A), indicating that patients had less inspiratory effort. Interestingly, the $V_T/\Delta Pes$ ratio (i.e., an estimate of the dynamic lung compliance) was significantly higher during HFNC ($p<0.05$, Figure 3B), possibly indicating

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external "ventilation support" by the mandatory flow of HFNC during inspiration, improved lung mechanics, or both. PTP and PTP_{min} were both significantly lower with HFNC ($p<0.05$ and $p<0.001$), suggesting lighter metabolic work of breathing per breath and per minute (Table 2; Figure 1B).

Effects of HFNC on ventilation and gas exchange. Minute ventilation was significantly lower during HFNC ($p<0.001$) than with the standard non-occlusive oxygen facial mask (Table 2). This was due to changes in respiratory rate (RR) or V_T, which were inversely related ($\Delta RR \times \Delta V_T$: $R^2=0.74$, $p<0.001$). On average, RR decreased ($p<0.01$) while V_T did not differ in the two phases, at either the global or regional level. Despite the decrease in minute ventilation, HFNC significantly improved oxygenation ($p<0.001$) (Table 2 and Figure 2A), while $PaCO_2$ and pH did not change. MV_{corr} dropped significantly during HFNC ($p<0.001$) (Table 2; Figure 2B).

There was a significant correlation between the reductions in PTP and the changes of MV_{corr} during HFNC ($\Delta PTP \times \Delta MV_{corr}$: $R^2=0.46$, $p<0.01$), possibly indicating that enhanced CO_2 clearance by washout of the upper airways reduced the inspiratory work of breathing, that HFNC lowered CO_2 production, reducing the ventilation needs, or both. The relative reduction of PTP_{min} passing from the oxygen facial mask to HFNC was significantly larger than the reduction of MV_{corr} (32±12% vs. 18±15%, $p<0.05$). The relative reductions of PTP_{min} and RR passing from the mask to HFNC were not correlated ($p=0.147$, data not shown).

Effects of HFNC on lung volume, transpulmonary pressures, ventilation homogeneity and airflows. Lung volume, as measured by ΔEELI, significantly increased during HFNC, globally and in the dependent and non-dependent lung regions ($p\leq0.01$ for all) (Table 3 and Figure 3A). The increase in global gas content in the lungs was 51±57% of the baseline V_T. This suggests the generation of positive end-expiratory pressure by HFNC that might have improved oxygenation and, in the presence of unchanged V_T, reduced regional lung strain.

Similarly, end-expiratory and end-inspiratory transpulmonary pressures ($P_{L,ee}$ and $P_{L,ei}$) increased during HFNC ($p<0.05$) (Table 2) and became less negative, possibly indicating a lower tendency to alveolar collapse (21). Driving transpulmonary pressure fell during HFNC, though not significantly ($p=0.08$) (Table 2).

The global inhomogeneity ventilation index fell slightly but significantly during HFNC ($p<0.01$) (Table 3), indicating more homogeneous distribution of ventilation throughout the lungs, which might correspond to better distribution of lung densities (26).

Patients' PEF decreased significantly overall, by the reduction of PEF from the dependent lung regions (Table 3) and this might be regarded as an indirect sign of improvement of lung compliance in this region. PIF was reduced during HFNC, though not significantly ($p=0.07$) and this too might have contributed to improving oxygenation by giving higher alveolar FiO_2.

Finally, the Ti/Ttot ratio was lower during HFNC ($p<0.05$) (Table 3), which, in presence of lower inspiratory effort and unchanged maximal inspiratory pressure, suggests a lower tension-time index of the inspiratory muscles (28).

Variables associated with the efficacy of HFNC. There was a significant correlation between the reduction of inspiratory effort (ΔPes) and work of breathing (PTP) during HFNC and patients' baseline $PaCO_2$ ($R^2=0.433$, $p<0.01$ and $R^2=0.275$, $p<0.05$, respectively) (Figure 4 and 1 online). Baseline PaO_2 was not correlated with lowering of either of these variables ($p=0.42$ and $p=0.35$, data not shown).

DISCUSSION

The present study shows that in AHRF patients HFNC improves several key physiologic parameters including oxygenation, inspiratory effort, minute ventilation, respiratory rate and lung volume, dynamic lung compliance, transpulmonary pressure and homogeneity.

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Esophageal pressure swings and pressure-time product are validated, commonly used measures of patients' inspiratory effort and metabolic work of breathing, respectively (21). Previous studies described the reduction of work of breathing by HFNC in pediatric populations (11, 29). We found this was also true in adult AHRF patients, as measures of inspiratory effort and metabolic work of breathing significantly decreased during HFNC therapy. Our data, the physiological background and previous publications suggest that many factors contribute to reducing respiratory workload during HFNC. We observed better oxygenation, which reduced the patients' hypoxic drive. Higher arterial oxygenation during HFNC might have simply mirrored higher alveolar FiO_2: set FiO_2 might in fact have been significantly higher than tracheal and alveolar FiO_2 with the standard facial mask, due to entrainment of room air, while the higher external flow coupled with lower inspiratory airflow during HFNC might have permitted minimal differences between set and alveolar FiO_2 (8). Improved lung volume, indicating positive end-expiratory pressure, might have contributed to the increase in the $PaO_2/setFiO_2$ ratio and the lower hypoxic drive too (30). During HFNC, the minute ventilation needed to obtain normal arterial CO_2 tension was lower than with the facial mask and this might have followed enhanced CO_2 clearance by washout of upper airways (1, 8), leading to lower ventilation needs and work of breathing. However, lower CO_2 production from the respiratory muscles (8), linked to the decrease in minute ventilation, may also have helped reduce the inspiratory effort and ventilation needs. The possible improvement in dynamic lung compliance might have established more favorable working conditions during inspiration and unloading of the inspiratory muscles. Among all these factors, the relation between the reduction in MV_{corr} and changes in PTP suggests that better CO_2 clearance might have had a key role in reducing patients' work of breathing. However, this decrease was significantly larger than the reduction in MV_{corr}, possibly indicating that multiple mechanisms work to reduce the workload. As a sign to clinicians, in this study the

reduced inspiratory effort during HFNC positively correlated with higher baseline arterial CO_2 tension, suggesting HFNC was more effective in the presence of more severely impaired CO_2 clearance (e.g., in AHRF patients with higher dead space fraction) (31). The reduction of respiratory rate by HFNC was not related with that of PTP_{min}. Previous findings linked this reduction of the respiratory rate to clinical success (32) but our result suggests that mechanisms besides reduced work of breathing underlie the clinical benefits of HFNC. The causal link between acute reductions of respiratory workload, long-term prevention of respiratory decompensation, reduced need of intubation and improved survival seems reasonable but has yet to be proved.

Another part of our findings suggests new hypotheses on the effects of HFNC on the physiologic determinants of ventilation-induced lung injury. We noted a decrease in driving transpulmonary pressure swings along inspiration. Additionally, absolute estimates of end-expiratory and end-inspiratory transpulmonary pressures were higher during the HFNC phase (as expected from the additional positive end-expiratory pressure effect), possibly resulting in a smaller tendency to lung collapse. As higher driving transpulmonary pressure and derecruitment (18, 21) potentially aggravate lung injury, HFNC might hypothetically lower this risk. Increased end-expiratory lung volume induced by HFNC with unchanged tidal volume might have reduced lung strain, which seems linearly correlated with the severity of ventilation-induced lung injury (14). Finally, the slight but significant decrease in the inhomogeneity of ventilation distribution indirectly suggests there may be fewer or smaller regional areas of alveolar collapse (26), potentially reducing the risk of focal multiplication of the alveolar wall tension and additional injury (25). In summary, our findings suggest that HFNC might affect key determinants of ventilation-induced lung injury such as lung stress, strain and inhomogeneity. There is lively debate on how to minimize the detrimental effects of spontaneous breathing on pre-existing lung injury (33-35) and the hypotheses on the

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potential role of HFNC in improving physiologic determinants of ventilation-induced lung injury may well merit further scrutiny.

Our study has several limitations. First, EIT imaging covers only part of the lungs (approximately 50%); it cannot detect an increase of lung volume along the vertical axis unless an abdominal belt is used, and most of the validation studies of EIT compared with other techniques were conducted in different settings (i.e. intubated patients or animals). However, previous studies have showed linear correlations between EIT measurements of lung volume changes and those obtained by other validated methods (36, 37), even in cases of significant changes in intra-thoracic pressure (38). Moreover, the randomized cross-over design of this study (with each patient compared with her/himself in the different phases) might have made the comparison of EIT measures more accurate. Second, the study phases were short; we aimed for the shortest time needed to equilibrate lung volumes and gas exchange given the difficulties of stable and reliable advanced respiratory monitoring in awake AHRF patients. Third, we assessed only objective rather than subjective measures of dyspnea and did not investigate patients' comfort; however, subjective indexes have already been extensively reported (1, 8). Fourth, we assessed PTP by analysing only the esophageal pressure tracings rather than the traditional PTPes that includes the chest wall static recoil pressure-time curve (39) because we lacked direct measure of chest wall compliance (Ccw) and absolute tidal volume. However, in the two study phases, Ccw was most probably unchanged and the Vt measured by EIT did not vary, so changes in PTP should have been linearly correlated with changes in PTPes. Moreover, we calculated PTPes by using standard formula for Ccw (21) and by calculation of absolute Vt through an arbitrary milliters/impedance units conversion factor derived from the lower PEEP phase of a previous study (38) and we found tight correlation with PTP (see the additional results section in the online data supplement). Fifth, the population was small and this might have explained the

lack of significance in some of the correlations. Sixth, we measured only set FiO_2 and not that delivered to the lower airways, which might have differed, especially during the facial mask phase due to entrainment of room air. Thus, we cannot know how much the difference between set and delivered FiO_2 could have influenced the study findings.

CONCLUSIONS

HFNC exerts various specific physiologic effects in AHRF patients including improved gas exchange, lower respiratory rate and effort, improved lung volume, dynamic compliance, transpulmonary pressures and homogeneity. All these physiologic benefits might positively affect the clinical outcome of AHRF patients.

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FIGURE LEGENDS

Figure 1. Reduction of inspiratory effort (A) and metabolic work of breathing (B) during treatment with high-flow nasal cannula (HFNC). In acute hypoxemic respiratory failure patients, HFNC delivered at 40 L/min reduced the negative swings of esophageal pressure (ΔPes, a measure of patients' inspiratory effort) as well as the esophageal pressure-time product (PTP, a measure of patients' per breath metabolic work of breathing) in comparison to a standard non-occlusive facial mask (Mask) at 12 L/min and the same set FiO_2.

Figure 2. HFNC improves oxygenation (A) and reduces minute ventilation (B) without affecting arterial CO_2 tension. In comparison to the standard non-occlusive facial mask (Mask), in acute hypoxemic respiratory patients, HFNC increased arterial O_2 tension (PaO_2) with no change in set FiO_2. During HFNC, the minute ventilation needed to obtain normal arterial CO_2 tension (i.e., corrected minute ventilation: $MV_{corr} = MV * PaCO_2/40$ mmHg) decreased, as if CO_2 removal was more effective, CO_2 production was reduced, or both.

Figure 3. HFNC increases lung volume (A) and raises the ratio of tidal volume to inspiratory effort (B). In comparison to a standard non-occlusive low-flow facial mask (Mask), in acute hypoxemic respiratory failure patients HFNC increased the lung volume at end-expiration as measured by electrical impedance tomography (ΔEELI, see text and the online data supplement for details), suggesting a positive end-expiratory pressure effect. HFNC also gave a higher ratio of tidal volume (V_T) to negative inspiratory pressure during inspiration (ΔPes), suggesting improvement in the mechanical properties of the respiratory system, external "ventilation support", or both. Average values were significantly different even though in five patients $V_T/\Delta Pes$ actually decreased.

Figure 4. Baseline arterial CO_2 tension is correlated with changes in inspiratory effort with the HFNC. Arterial CO_2 tension ($PaCO_2$) measured during the baseline standard oxygen

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facial mask phase (horizontal x axis) was correlated with the decrease in patient's effort (ΔPes) induced by the switch to high-flow nasal cannula (HFNC). Thus, HFNC might be particularly effective in unloading the respiratory muscles of acute hypoxemic respiratory failure patients with more impaired CO_2 clearance (i.e, those with higher dead space fraction).

TABLES

Table 1. Main characteristics of the study population.

Patient*	Sex	Age (years)	SAPS II at ICU admission	Number of organs dysfunction	Etiology of acute respiratory failure	$PaO_2/setFiO_2$ (mmHg)	Bilateral infiltrates on chest X-ray
1	M	60	40	2	Primary, infectious	119	no
2	M	55	36	2	Primary, infectious	134	yes
3	M	53	34	3	Primary, infectious	193	no
4	F	43	26	1	Primary, infectious	97	no
5	F	66	56	2	Primary, infectious	121	yes
6	M	68	43	1	Primary, infectious	107	yes
7	M	47	33	2	Extrapulmonary, non-infectious	114	no
8	F	56	26	1	Primary, infectious	117	no
9	F	47	42	1	Primary, infectious	158	yes
10	F	78	43	1	Primary, infectious	146	no
11	M	70	44	2	Extrapulmonary, non-infectious	171	no
12	M	49	51	1	Primary, infectious	68	yes
13	M	95	26	1	Primary, infectious	83	yes
14	M	47	35	1	Primary, infectious	144	yes
15	F	74	48	1	Primary, infectious	180	no
Mean ± SD	6 F/9 M	60 ± 14	38 ± 9	1 ± 2	13 primary / 2 extra-pulmonary; 13 infectious / 2 non-infectious	130 ± 35	7 yes/8 no

*SAPS II, simplified acute physiology score II; ICU, intensive care unit; $PaO_2/setFiO_2$, oxygen partial arterial pressure on set oxygen inspired fraction ratio.

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Table 2. Effects of HFNC on work of breathing, ventilation, gas exchange and hemodynamics.

Variable*	Oxygen facial mask	High-flow nasal cannula	P-value#
ΔPes (cmH_2O)	9.9 ± 4.2	8.0 ± 3.4	<0.01
PTP (cmH_2O*s)	9.5 [5.7-12.1]	7.4 [4.1-9.4]	<0.01
PTP_{min} (cmH_2O*s/min)	216.3 ± 100.5	154.8 ± 84.8	<0.001
$P_{L,ee}$ (cmH_2O)	-10.1 ± 5.0	-7.5 ± 5.2	<0.001
$P_{L,ei}$ (cmH_2O)	-3.6 ± 4.9	-2.6 ± 4.5	0.16
ΔP_L (cmH_2O)	5.7 ± 3.4	4.3 ± 2.9	0.08
RR (bpm)	24 [20-27]	22 [17-24]	<0.01
V_T (change from facial mask, %)	-	-5 ± 32	0.44
$V_{T, non-dep}$ (change from facial mask, %)	-	3 ± 49	0.59
$V_{T, dep}$ (change from facial mask, %)	-	-5 ± 33	0.54
Minute ventilation (change from facial mask, %)	-	-19 ± 16	<0.001
Corrected minute ventilation (change from facial mask, %)	-	-18 ± 15	<0.001
Set FiO_2	0.60 [0.50-0.75]	0.60 [0.50-0.75]	1.00
PaO_2 (mmHg)	72 [68-75]	98 [78-131]	<0.001
$PaO_2/setFiO_2$ (mmHg)	130 ± 35	184 ± 53	<0.001
$PaCO_2$ (mmHg)	40.7 ± 5.7	41.1 ± 5.9	0.27
pH	7.45 ± 0.02	7.44 ± 0.03	0.23
SBP (mmHg)	141 ± 25	137 ± 27	<0.05
MAP (mmHg)	90 ± 15	88 ± 16	0.11
CVP (mmHg)	4.6 ± 5.2	5.8 ± 4.7	<0.05
HR (bpm)	85 ± 9	84 ± 9	0.44

*ΔPes, inspiratory esophageal pressure swing; PTP, pressure-time product per breath; PTP_{min}, pressure time product per minute; PL,ei : dynamic end-inspiratory transpulmonary pressure; PL,ee: dynamic end-expiratory transpulmonary pressure; ΔPL: driving transpulmonary pressure; RR respiratory rate; V_T, tidal volume; $V_{T, non-dep}$, tidal volume distending non-dependent regions; $V_{T, dep}$ tidal volume distending dependent regions; Set FiO_2: inspired O_2 fraction clinically set before enrollment to obtain 90-95% peripheral oxygen saturation with standard facial mask. As the delivered flow was significantly higher during high-flow therapy, entrainment of room air was more likely with the standard facial mask and the FiO_2 reaching the trachea and conducting airways might have been higher during this phase; PaO_2, oxygen partial arterial pressure; $PaO_2/setFiO_2$, oxygen partial arterial pressure/set oxygen inspired fraction ratio; $PaCO_2$, carbon dioxide partial

arterial pressure; SBP, systolic arterial blood pressure; MAP, mean arterial pressure; CVP, central venous pressure; HR, heart rate. Normally distributed variables are expressed as mean ± standard deviation, non-normal ones as median [interquartile range].

P-value by paired t-test or by Wilcoxon's signed rank test, as appropriate.

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Table 3. Effects of HFNC on lung aeration, homogeneity and respiratory pattern.

Variable*	Oxygen facial mask	High-flow nasal cannula	P-value#
$\Delta EELI_{glob}$ (change from facial mask, % of baseline V_T)	-	51 ± 57	<0.001
$\Delta EELI_{non\text{-}dep}$ (change from facial mask, % of baseline V_T)	-	29 ± 36	≤0.001
$\Delta EELI_{dep}$ (change from facial mask, % of baseline V_T)	-	26 ± 33	≤0.01
GI index	0.50 [0.49-0.57]	0.47 [0.43-0.60]	<0.01
PIF_{glob} (change from facial mask, %)	-	-15 ± 23	0.07
PEF_{glob} (change from facial mask, %)	-	-27 ± 22	≤0.001
$PIF_{non\text{-}dep}$ (change from facial mask, %)	-	-11 ± 29	0.29
PIF_{dep} (change from facial mask, %)	-	-20 ± 19	<0.01
$PEF_{non\text{-}dep}$ (change from facial mask, %)	-	-19 ± 32	0.07
PEF_{dep} (change from facial mask, %)	-	-34 ± 18	<0.001
Ti (sec)	1.2 ± 0.2	1.2 ± 0.3	0.84
Te (sec)	1.3 ± 0.2	1.5 ± 0.6	<0.05
Ti/Ttot	0.5 ± 0.0	0.4 ± 0.0	<0.05

*$\Delta EELI_{glob}$, global change of end-expiratory lung impedance; V_T, tidal volume; $\Delta EELI_{non\text{-}dep}$, change of end-expiratory lung impedance in non-dependent regions; $\Delta EELI_{dep}$, change of end-expiratory lung impedance in dependent regions; GI index, global inhomogeneity index; PIF, peak inspiratory flow; PEF, peak expiratory flow. Normally distributed variables are expressed as mean ± standard deviation, non-normal ones as median [interquartile range]

P-value by paired t-test or by Wilcoxon's signed rank test, as appropriate.

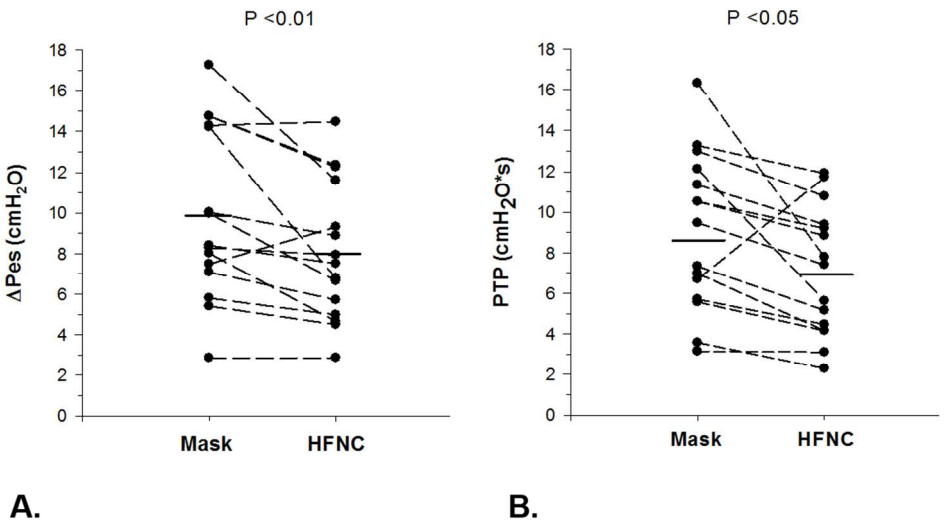

Figure 1
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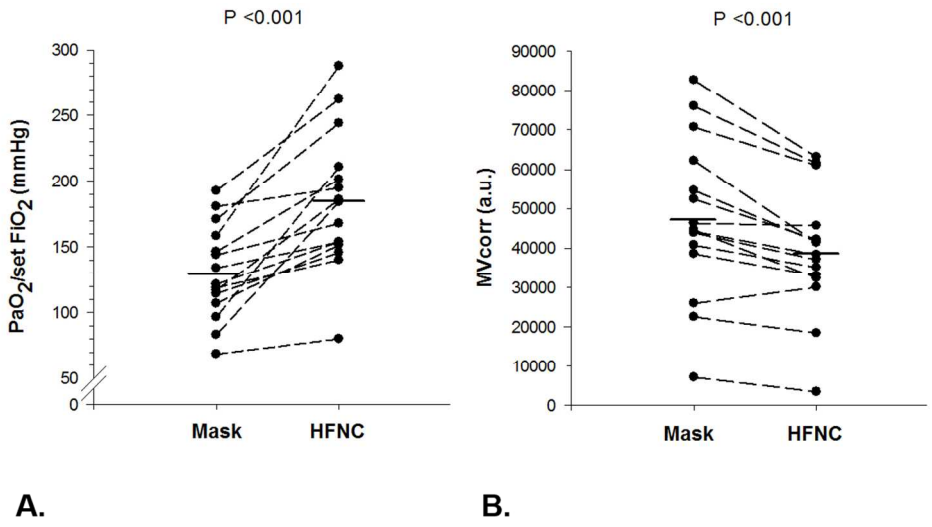

Figure 2
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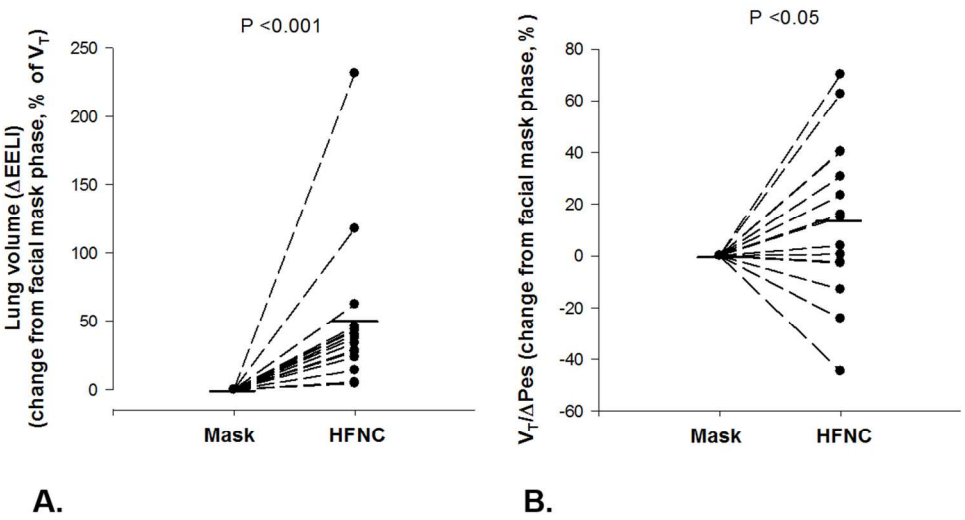

Figure 3
324x173mm (96 x 96 DPI)

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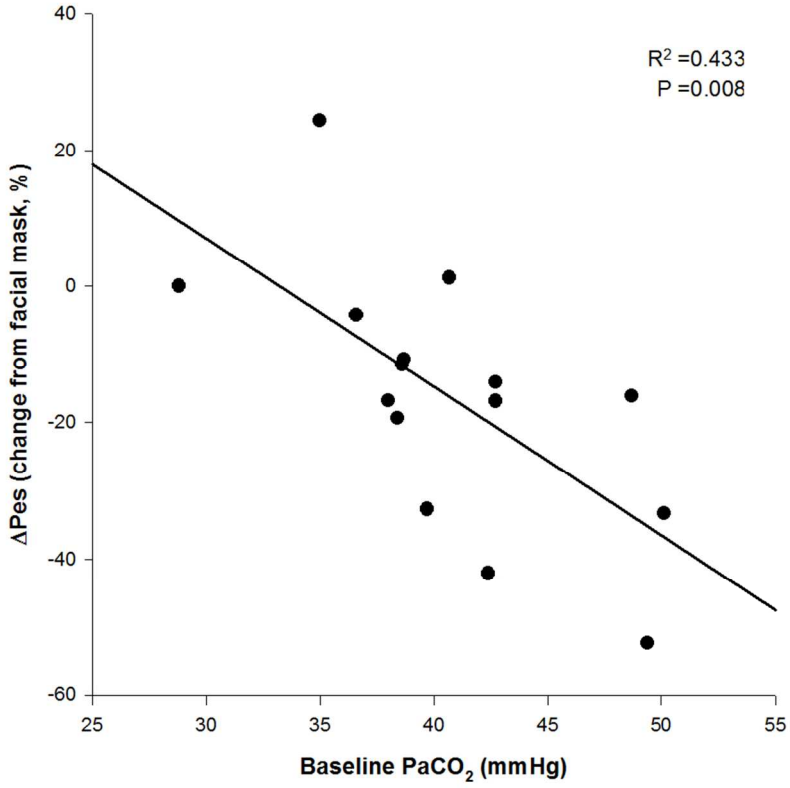

Figure 4
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Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure

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ONLINE DATA SUPPLEMENT

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DETAILED METHODS

Study population. We enrolled 15 non-intubated acute hypoxemic respiratory failure (AHRF) adults admitted to the general Intensive Care Unit (ICU) of San Gerardo Hospital, Monza, Italy. Inclusion criteria were: new or worsening respiratory symptoms following a known clinical insult lasting less than a week; $PaO_2/setFiO_2 \leq 300$ mmHg while receiving additional oxygen by standard facial mask as per clinical decision. Exclusion criteria were: age <18 years; intubation or tracheostomy; pregnancy or breast-feeding; hemodynamic instability; pneumothorax; acute cardiogenic pulmonary edema; history of chronic obstructive pulmonary disease (COPD); history of nasal trauma and/or deviated nasal septum; contraindication to EIT use (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 San Gerardo Hospital ethics committee approved the study (reference number: 432_2015bis) and informed consent was obtained from each patient according to local regulations.

Data collection at enrolment. At enrolment, we collected sex, age, height, SAPS II score, number of organ failures, etiology of the acute respiratory failure, $PaO_2/setFiO_2$ obtained on clinical settings, and bilateral infiltrates on chest X-ray (E1).

Advanced respiratory monitoring. An esophageal balloon catheter (Cooper Surgical, Trumbull, CT) was advanced through the nose for 50-55 cm to reach the stomach and inflated to the recommended volume (E2). 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 (E3). Esophageal pressure waveforms were continuously recorded by a dedicated data acquisition system throughout the study (Powerlab AD Instruments, Colorado Springs, CO). 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 frequency, so that tomographic data were acquired every 50 msec and stored for offline analysis by dedicated software (Dräger EIT Data Analysis Tool and EITdiag, Dräger Medical GmbH, Lübeck, Germany), as previously described (E4). The Pes and EIT signals were synchronised offline with markers positioned online at the beginning and end of each study phase.

Study protocol. Patients were positioned in a semi-recumbent position for both study phases and the RASS score was around 0 without sedation. A calm environment was ensured around the patients throughout the study. Each patient completed the following two phases with the same set FiO_2 for 20 minutes in computer-generated random order:

1. Standard non-occlusive oxygen facial mask with air/oxygen flow set at 12 L/min;
2. HFNC with heated (37°C), humidified air/oxygen flow set at 40 L/min.

Set FiO_2 during both phases was clinically chosen by the attending physician before enrolment to achieve peripheral saturation between 90 and 95% on pulse oximetry during standard oxygen facial mask breathing. Set FiO_2 during both phases was measured by a dedicated system (AIRVO^{TM} 2, Fisher & Paykel Healthcare, Auckland, New Zealand) connected to the standard facial mask or the nasal cannula. This system can deliver airflows between 2 and 60 L/min with FiO_2 between 0.21 and 1.0 by connection to a wall supply. FiO_2 is continuously measured at the gas outlet of the system. In summary, in keeping with previous studies we set the gas delivery system at 12 L/min during the facial mask phase and 40 L/min during HFNC with the same measured set FiO_2, obtained by modification of the additional oxygen wall supply. However, we could not avoid or verify lower tracheal and alveolar FiO_2 during the facial mask phase because of entrainment of room air.

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

Esophageal pressure data. The esophageal pressure waveforms recorded during the last minutes of each phase were analysed offline to measure:

1. The average pressure time product over a minute (PTP_{min}), 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 the metabolic work of breathing per minute;
2. The average per-breath pressure time product (PTP), defined as the area subtended by the Pes waveform during inspiration in a series of representative breaths divided by the number of breaths (at least ten), as a measure of the metabolic work of breathing per single breath (E5);
3. The average esophageal pressure swings during inspiration (ΔPes) defined as the absolute differences between end-expiratory and end-inspiratory Pes in the same series of representative breaths used to measure PTP, divided by the number of breaths, as a measurement of the patient's inspiratory effort (E6);
4. The dynamic end-expiratory transpulmonary pressure ($P_{L,ee}$), calculated as the average difference between airway pressure (assumed to be 0 cmH_2O with the facial mask and 2.5 cmH_2O with the HFNC) and the absolute Pes measured at the end of expiration (zero flow) in a selected series of breaths;
5. The dynamic end-inspiratory transpulmonary pressure ($P_{L,ei}$), calculated as the average difference between airway pressure (assumed to be 0 cmH_2O with the facial mask and 2.5 cmH_2O with the HFNC) and the absolute Pes measured at the end of inspiration (zero flow) in a selected series of breaths;
6. The driving transpulmonary pressure (ΔP_L), calculated as ($P_{L,ei}$ - $P_{L,ee}$).

EIT data. We analysed raw EIT data recorded during the last minutes of each study phase offline. We divided the EIT lung-imaging field into two region 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, as the absolute number of arbitrary units (a.u.) of lung impedance change during inspiration 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), defined as the sum of all consecutive tidal impedance changes expressed in a.u. of lung impedance over 2-3 representative minutes, divided by the number of minutes;

3. Corrected minute ventilation (MV_{corr}), defined as MV multiplied by the ratio of the patient's $PaCO_2$ to 40 mmHg (i.e. MV_{corr} = MV*[actual $PaCO_2$/40]) (E7), with lower values indicating better CO_2 clearance, less CO_2 production, or both;

4. Global and regional changes in lung aeration during the HFNC phase ($\Delta EELI_{glob}$, $\Delta EELI_{non\text{-}dep}$ and $\Delta EELI_{dep}$), as previously described (E8). 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 treatment;

5. Global inhomogeneity index (GI), a measure of regional inhomogeneous distribution of tidal ventilation, measured as previously described (E9);

6. Global and regional peak inspiratory and expiratory airflows (PIF_{glob}, $PIF_{non\text{-}dep}$ and PIF_{dep}; PEF_{glob}, $PEF_{non\text{-}dep}$ and PEF_{dep}, respectively) measured as previously described (E10). Briefly, we calculated instantaneous flows as the slope of the change in global

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or regional impedance over 50 msec, divided by the same time, and considered the maximum values along inspiration and expiration as PIF and PEF (E10), respectively.

7. From the EIT-derived airflow tracings, we also measured the inspiratory (Ti) and expiratory (Te) times, as well as the total cycle time (Ttot). Briefly, Ti was defined as the time from the zero flow point at the beginning of inspiration to the zero flow point at end-inspiration; Te was the time from the zero flow point at the beginning of expiration to the zero flow point at the beginning of a new inspiration, and Ttot was the time from the zero flow point at the beginning of inspiration to the zero flow point at the beginning of a new inspiration, all averaged over a series of representative breaths.

Calculation of esophageal pressure-time product (PTPes) from Pes and EIT data. In an effort to make our results more comparable to the literature, we calculated also the PTPes as the area subtended by Pes and the chest wall static recoil pressure-time curve over Ti (E11). The latter curve was drawn as the instant-by-instant Vt variation (calculated as impedance change multiplied by an average arbitrary milliliters/impedance units conversion factor measured during the lower PEEP phase in a population of intubated AHRF patients enrolled in previous study [E12]) divided by the chest wall compliance (obtained as 4% of calculated vital capacity/cmH_2O [E5]).

Statistical analysis. We chose the sample size on the basis of previous studies (E12-E16), with the aim of measuring fine physiologic effects by advanced respiratory monitoring rather than broad-spectrum clinical outcomes. For the sake of clarity, EIT measures during HFNC were transformed from arbitrary units of impedance change to percentage change from their baseline values during the facial mask phase. Normally distributed variables were expressed as mean ± standard deviation and analyzed by a paired t-test. Non-normally distributed variables were expressed by median and interquartile range and compared by Wilcoxon's

signed rank test. Correlations were analyzed by Pearson's coefficient. A level of $p < 0.05$ (two-tailed) was considered statistically significant. Statistical analyses were done with SigmaPlot 12.0 (Systat Software Inc., San Jose, CA).

ADDITIONAL RESULTS

Correlation between measured PTP and the calculated PTPes. Calculation of PTPes confirmed the results obtained by considering PTP: HFNC significantly reduced PTPes in comparison to facial mask (7.5±2.8 vs. 9.4±3.9 cmH_2O*s, p=0.03). Moreover, PTP and PTPes didn't differ during any study phase (8.5±3.2 vs. 9.4±3.9 cmH_2O*s during facial mask, p=0.32; 6.8±2.9 vs. 7.5±2.8 cmH_2O*s during HFNC, p=0.25) and they were tightly correlated (R^2=0.77, p<0.001).

Factors correlated with reduction of minute ventilation during HFNC. There was a significant negative correlation between the decrease in MV_{corr} during HFNC and patients' height (R^2=0.25, p=0.05). As height might be correlated with anatomic dead space (E17), hypothetically the relative amount of dead space washed of CO_2 by HFNC might play a role in lowering the patient's workload.

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Figure 1 online. Baseline arterial CO_2 tension is correlated with changes in the inspiratory work of breathing with the high-flow nasal cannula. Arterial CO_2 tension ($PaCO_2$) measured at baseline during the oxygen facial mask phase was correlated with the decrease in patient's work of breathing (PTPes) induced by the high-flow nasal cannula (HFNC).