ORIGINAL ARTICLE

Physiologic Effects of High-Flow Nasal Cannula in Acute Hypoxemic Respiratory Failure

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Abstract

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

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

Methods: This was a prospective randomized crossover study in nonintubated patients with AHRF with $Pa_{O_2}/setFI_{O_2}$ less than or equal to 300 mm Hg admitted to the intensive care unit. We randomly applied HFNC set at 40 L/min compared with a standard nonocclusive facial mask at the same clinically set FI_{O_2} (20 min/step).

Measurements and Main Results: Toward 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, and we estimated changes in lung volumes and ventilation homogeneity by electrical impedance tomography. We enrolled 15 patients aged 60 ± 14 years old with $Pa_{O_2}/setFI_{O_2}$ 130 ± 35 mm Hg. 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 pressure time product ($P < 0.001$). 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 patients with AHRF, HFNC exerts multiple physiologic effects including less inspiratory effort and improved lung volume and compliance. These benefits might underlie the clinical efficacy of HFNC.

Keywords: high-flow nasal oxygen; electrical impedance tomography; esophageal pressure; acute lung injury

High-flow nasal cannula (HFNC) is a noninvasive 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 used in preterm infants and pediatric patients (2) and recent large randomized clinical trials have promoted its use in adults with acute hypoxemic respiratory failure (AHRF) (3). These trials demonstrated the potential of HFNC to improve clinical outcomes, such as reintubation rates and

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At a Glance Commentary

Scientific Knowledge on the Subject: High-flow nasal cannula (HFNC) is a noninvasive form of respiratory support that can reduce reintubation rates and mortality of patients with acute hypoxemic respiratory failure. The physiologic effects potentially underlying these clinical benefits are still largely undefined.

What This Study Adds to the Field: In patients with acute hypoxemic respiratory failure, 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.

90-day mortality (4–7). However, the physiologic mechanisms underlying the clinical benefits of HFNC are still poorly understood in adult patients with AHRF.

Basic clinical monitoring during HFNC therapy demonstrated rapid improvement of oxygenation and reduction of dyspnea in comparison with 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), whereas in another study in patients with chronic obstructive pulmonary disease electrical impedance tomography (EIT) (12) suggested an increase in end-expiratory lung volume. Reduced inspiratory effort and improved lung volume might be particularly important in AHRF, because they may prevent respiratory muscle exhaustion and lower the V_T/end-expiratory lung volume 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 patients with AHRF. 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 (MV), lung volume, 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 patients with AHRF 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, and $Pa_{O_2}/setFI_{O_2}$ less than or equal to 300 mm Hg while receiving additional oxygen by a standard facial mask, as per clinical decision. Exclusion criteria are listed in the online 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 enrollment, 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 FI_{O_2} for 20 minutes in computer-generated random order: standard nonocclusive oxygen facial mask with gas flow set at 12 L/min, and HFNC with gas flow 40 L/min.

Set FI_{O_2} during both phases was selected clinically by the attending physician before enrollment to achieve peripheral saturation between 90 and 95% on pulse oximetry during standard oxygen facial mask breathing. Set FI_{O_2} during both study phases was measured by a dedicated system (AIRVO 2; Fisher and 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 FI_{O_2} between 0.21 and 1.0 by connection to a wall supply. FI_{O_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 FI_{O_2}, obtained by modifying the additional oxygen wall supply. However, we could not avoid or verify lower tracheal and alveolar FI_{O_2} during the oxygen facial mask phase because of entrainment of room air.

At the end of each phase, we collected arterial blood gas analysis data, respiratory rates (RR), and hemodynamics. From the esophageal pressure waveforms recorded during the last 3–5 minutes of each phase we measured the following (21):

1. The average pressure time product over a minute (PTP_{min}), as a measure of the metabolic work of breathing per minute (*see* online supplement for detailed methods);
2. The per-breath PTP, as a measure of the metabolic work of breathing per single breath (*see* online 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 cm H_2O with the facial mask and 2.5 cm H_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 cm H_2O with the facial mask and 2.5 cm H_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:

1. The average global V_T and those distending nondependent and dependent lung regions ($V_{T_{glob}}$, $V_{T_{non\text{-}dep}}$, and $V_{T_{dep}}$, respectively).
2. The MV.
3. Corrected MV (MV_{corr}), defined as MV multiplied by the ratio of the patient's Pa_{CO_2} to 40 mm Hg (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 $\Delta EELI_{dep}$, respectively) (18).
5. Global inhomogeneity index, a measure of inhomogeneous distribution of tidal ventilation (24). The global inhomogeneity index gave a reliable and interpatient comparable synthetic assessment of inhomogeneous distribution of the V_T 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).

Please note that all the lung volumes (e.g., V_T) mentioned above were not measured but rather we assumed that the changes in chest electrical impedance reflect changes in lung volumes. 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 ± SD and were analyzed by a paired Student's *t* test. Nonnormally distributed variables are expressed as medians (interquartile range) and were compared by Wilcoxon signed rank test. Correlations were analyzed by Pearson coefficient. A level of *P* less than 0.05 (two-tailed) was considered statistically significant.

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

Results

Patients

Patients' main characteristics are reported in Table 1. Patients were 60 ± 14 years old and six (40%) were women. At enrollment, all patients had $Pa_{O_2}/setFI_{O_2}$ less than 200 mm Hg, with three (20%) less than 100 mm Hg. Seven patients (47%) had bilateral infiltrates on chest radiograph.

Effects of HFNC on Inspiratory Effort and Work of Breathing

During HFNC, ΔPes were significantly lower than with the standard nonocclusive oxygen facial mask ($P < 0.01$) (Table 2, 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 ($P < 0.05$), possibly indicating 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

MV was significantly lower during HFNC ($P < 0.001$) than with the standard nonocclusive oxygen facial mask (Table 2). This was caused by changes in 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 ($P < 0.01$), whereas V_T did not

Table 1. Main Characteristics of the Study Population

Patient	Sex	Age (*yr*)	SAPS II at ICU Admission	Number of Organs Dysfunction	Etiology of Acute Respiratory Failure	$Pa_{O_2}/setFI_{O_2}$ (*mm Hg*)	Bilateral Infiltrates on Chest Radiograph
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, noninfectious	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, noninfectious	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
Total or mean ± SD	6 F/9 M	60 ± 14	38 ± 9	1 ± 2	13 primary/2 extrapulmonary; 13 infectious/2 noninfectious	130 ± 35	7 yes/8 no

Definition of abbreviations: ICU = intensive care unit; SAPS II = Simplified Acute Physiology Score II.

Table 2. Effects of HFNC on Work of Breathing, Ventilation, Gas Exchange, and Hemodynamics

Variable	Oxygen Facial Mask	HFNC	*P* Value*
ΔPes, cm H_2O	9.9 ± 4.2	8.0 ± 3.4	<0.01
PTP, cm $H_2O \times s$	9.5 (5.7 to 12.1)	7.4 (4.1 to 9.4)	<0.01
PTP_{min}, cm $H_2O \times s/min$	216.3 ± 100.5	154.8 ± 84.8	<0.001
$P_{L,ee}$, cm H_2O	−10.1 ± 5.0	−7.5 ± 5.2	<0.001
$P_{L,ei}$, cm H_2O	−3.6 ± 4.9	−2.6 ± 4.5	0.16
ΔP_L, cm H_2O	5.7 ± 3.4	4.3 ± 2.9	0.08
RR, bpm	24 (20 to 27)	22 (17 to 24)	<0.01
V_T (change from facial mask), %	—	−5 ± 32	0.44
$V_{Tnon\text{-}dep}$ (change from facial mask), %	—	3 ± 49	0.59
V_{Tdep} (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 $F_{I_{O_2}}$	0.60 (0.50 to 0.75)	0.60 (0.50 to 0.75)	1.00
Pa_{O_2}, mm Hg	72 (68 to 75)	98 (78 to 131)	<0.001
$Pa_{O_2}/setF_{I_{O_2}}$, mm Hg	130 ± 35	184 ± 53	<0.001
Pa_{CO_2}, mm Hg	40.7 ± 5.7	41.1 ± 5.9	0.27
pH	7.45 ± 0.02	7.44 ± 0.03	0.23
SBP, mm Hg	141 ± 25	137 ± 27	<0.05
MAP, mm Hg	90 ± 15	88 ± 16	0.11
CVP, mm Hg	4.6 ± 5.2	5.8 ± 4.7	<0.05
HR, bpm	85 ± 9	84 ± 9	0.44

Definition of abbreviations: CVP = central venous pressure; HFNC = high-flow nasal cannula; HR = heart rate; MAP = mean arterial pressure; ΔPes = inspiratory esophageal pressure swing; ΔP_L = driving transpulmonary pressure; $P_{L,ee}$ = dynamic end-expiratory transpulmonary pressure; $P_{L,ei}$ = dynamic end-inspiratory transpulmonary pressure; PTP = pressure-time product per breath; PTP_{min} = pressure time product per minute; RR = respiratory rate; SBP = systolic arterial blood pressure; set $F_{I_{O_2}}$ = $F_{I_{O_2}}$ clinically set before enrollment to obtain 90–95% peripheral oxygen saturation with standard facial mask (because the delivered flow was significantly higher during high-flow therapy, entrainment of room air was more likely with the standard facial mask and the $F_{I_{O_2}}$ reaching the trachea and conducting airways might have been higher during this phase); V_{Tdep} = tidal volume distending dependent regions; $V_{Tnon\text{-}dep}$ = tidal volume distending nondependent regions. Normally distributed variables are expressed as mean ± SD, nonnormal ones as median (interquartile range).

**P* value by paired *t* test or by Wilcoxon signed rank test, as appropriate.

differ in the two phases, at either the global or regional level. Despite the decrease in MV, HFNC significantly improved oxygenation ($P < 0.001$) (Table 2, Figure 2A), whereas Pa_{CO_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 nondependent lung regions ($P \leq 0.01$ for all) (Table 3, 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, $P_{L,ee}$ 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, although 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, although not significantly ($P = 0.07$) and this too might have contributed to improving oxygenation by giving higher alveolar $F_{I_{O_2}}$. 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 ΔPes and PTP during HFNC and patients' baseline Pa_{CO_2} ($R^2 = 0.433$, $P < 0.01$ and $R^2 = 0.275$, $P < 0.05$, respectively) (Figure 4; *see* Figure E1 in the online supplement). Baseline Pa_{O_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 patients with AHRF, HFNC improves several key physiologic parameters including oxygenation, inspiratory effort, MV, RR and lung volume, dynamic lung compliance, transpulmonary pressure, and homogeneity.

Esophageal pressure swings and PTP are validated, commonly used measures of patients' inspiratory effort and metabolic work of breathing, respectively (21).

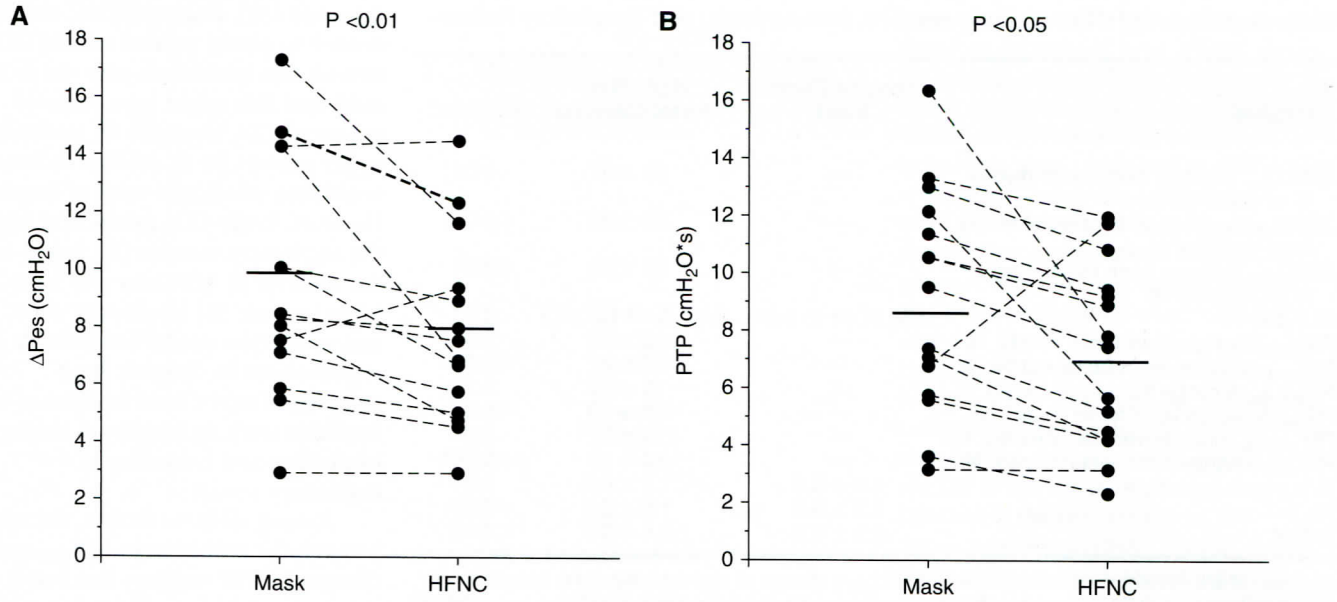

Figure 1. Reduction of inspiratory effort (*A*) and metabolic work of breathing (*B*) during treatment with high-flow nasal cannula (HFNC). In patients with acute hypoxemic respiratory failure, HFNC delivered at 40 L/min reduced the negative swings of esophageal pressure (a measure of patients' inspiratory effort) and the esophageal pressure-time product (a measure of patients' per breath metabolic work of breathing) in comparison with a standard nonocclusive facial mask at 12 L/min and the same set $F_{I_{O_2}}$. *Horizontal bars* represent mean values. ΔPes = inspiratory esophageal pressure swing; PTP = pressure-time product.

Previous studies described the reduction of work of breathing by HFNC in pediatric populations (11, 29). We found this was also true in adult patients with AHRF, because measures of inspiratory effort and metabolic work of breathing significantly decreased during HFNC therapy. Our data, the physiologic 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 $F_{I_{O_2}}$: set $F_{I_{O_2}}$ might in fact have been significantly higher than tracheal and alveolar $F_{I_{O_2}}$ with the standard facial mask, because of entrainment of room air,

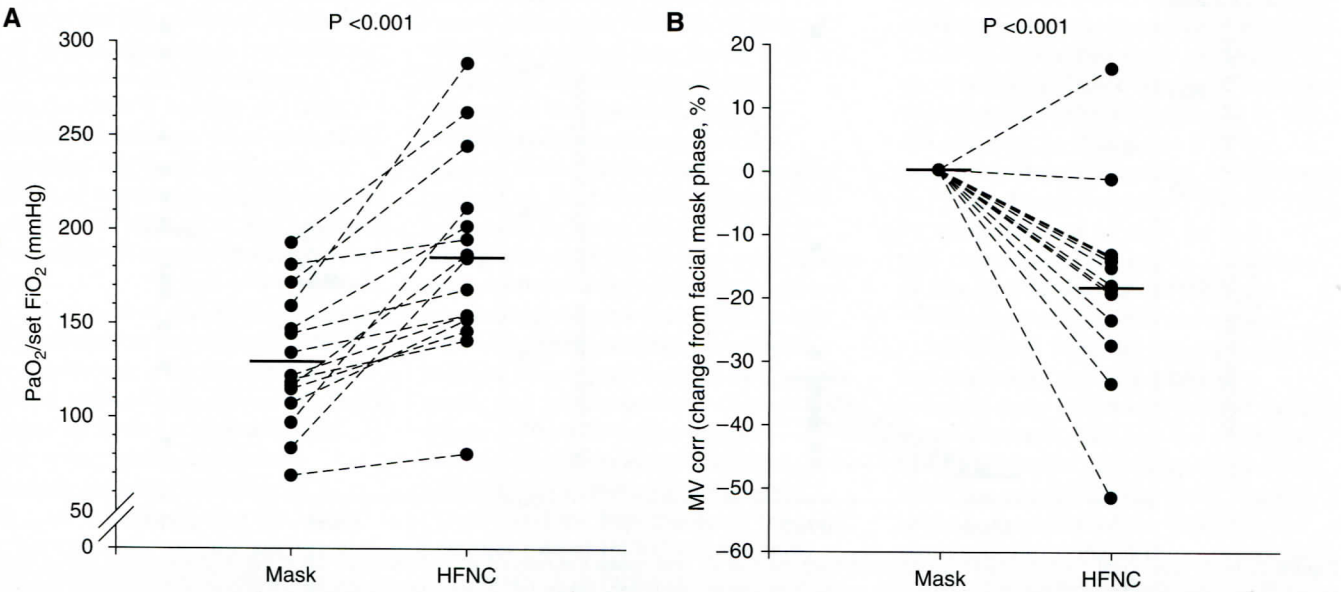

Figure 2. High-flow nasal cannula (HFNC) improves oxygenation (*A*) and reduces minute ventilation (*B*) without affecting arterial CO_2 tension. In comparison with the standard nonocclusive facial mask, in patients with acute hypoxemic respiration, HFNC increased Pa_{O_2} with no change in set $F_{I_{O_2}}$. During HFNC, the minute ventilation (MV) needed to obtain normal arterial CO_2 tension (i.e., corrected MV = MV * Pa_{CO_2}/40 mm Hg) decreased, as if CO_2 removal was more effective, CO_2 production was reduced, or both. *Horizontal bars* represent mean values. MV_{corr} = corrected minute ventilation.

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 VT	—	51 ± 57	<0.001
$\Delta EELI_{non\text{-}dep}$ (change from facial mask), % of baseline VT	—	29 ± 36	≤0.001
$\Delta EELI_{dep}$ (change from facial mask), % of baseline VT	—	26 ± 33	≤0.01
GI index	0.50 (0.49 to 0.57)	0.47 (0.43 to 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, s	1.2 ± 0.2	1.2 ± 0.3	0.84
Te, s	1.3 ± 0.2	1.5 ± 0.6	<0.05
Ti/Ttot	0.5 ± 0.0	0.4 ± 0.0	<0.05

Definition of abbreviations: dep = dependent; $\Delta EELI_{dep}$ = change of end-expiratory lung impedance in dependent regions; $\Delta EELI_{glob}$ = global change of end-expiratory lung impedance; $\Delta EELI_{non\text{-}dep}$ = change of end-expiratory lung impedance in nondependent regions; GI index = global inhomogeneity index; glob = global; HFNC = high-flow nasal cannula; non-dep = non-dependent; PEF = peak expiratory flow; PIF = peak inspiratory flow; Te = expiratory time; Ti = inspiratory time; Ttot = total cycle time. Normally distributed variables are expressed as mean ± SD, nonnormal ones as median (interquartile range).

**P* value by paired *t* test or by Wilcoxon signed rank test, as appropriate.

whereas the higher external flow coupled with lower inspiratory airflow during HFNC might have permitted minimal differences between set and alveolar $F_{I_{O_2}}$ (8). Improved lung volume, indicating positive end-expiratory pressure, might have contributed to the increase in the $Pa_{O_2}/setF_{I_{O_2}}$ ratio and the lower hypoxic drive too (30). During HFNC, the MV 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 MV, 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

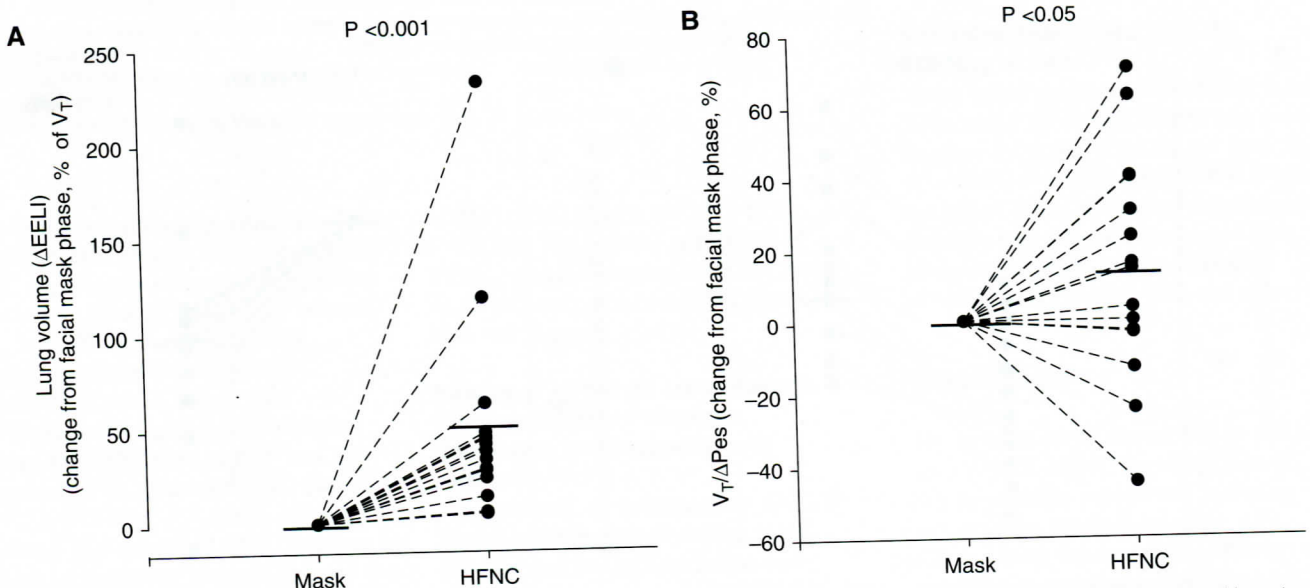

Figure 3. High-flow nasal cannula (HFNC) increases lung volume (*A*) and raises the ratio of VT to inspiratory effort (*B*). In comparison with a standard nonocclusive low-flow facial mask, in patients with acute hypoxemic respiratory failure HFNC increased the lung volume at end-expiration as measured by electrical impedance tomography (see text and the online supplement for details), suggesting a positive end-expiratory pressure effect. HFNC also gave a higher ratio of VT 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 VT/ΔPes actually decreased. *Horizontal bars* represent mean values. ΔEELI = change of end-expiratory lung impedance.

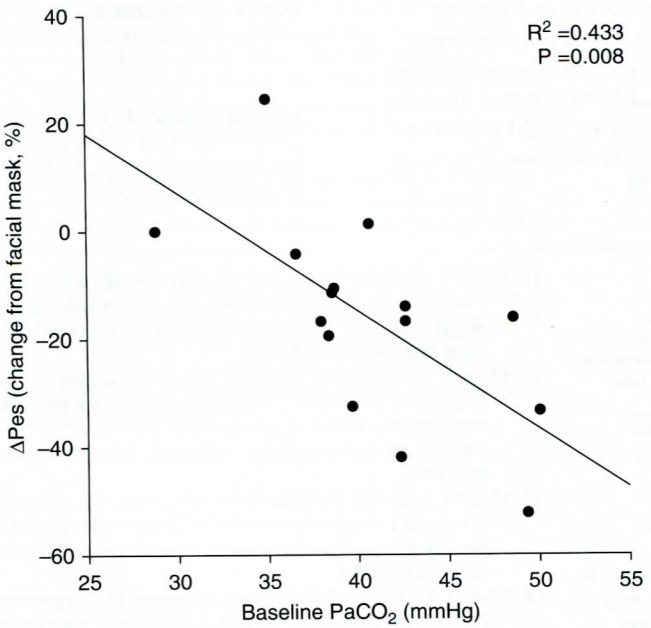

Figure 4. Baseline arterial CO_2 tension is correlated with changes in inspiratory effort with the high-flow nasal cannula (HFNC). Pa_{CO_2} measured during the baseline standard oxygen facial mask phase (*x-axis*) was correlated with the decrease in patient's effort induced by the switch to HFNC. Thus, HFNC might be particularly effective in unloading the respiratory muscles of patients with acute hypoxemic respiratory failure with more impaired CO_2 clearance (i.e., those with higher dead space fraction). The *solid line* represents the regression line. ΔPes = inspiratory esophageal pressure swing.

severely impaired CO_2 clearance (e.g., in patients with AHRF with higher dead space fraction) (31). The reduction of RR by HFNC was not related with that of PTP_{min}. Previous findings linked this reduction of the RR 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 $P_{L,ei}$ and $P_{L,ee}$ 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 V_T 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 preexisting lung injury (33–35) and the hypotheses on the 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 intrathoracic pressure (38). Moreover, the randomized crossover design of this study (with each patient compared with herself or 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 patients with AHRF. 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 analyzing 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 and absolute V_T. However, in the two study phases, chest wall compliance was most probably unchanged and the V_T 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 chest wall compliance (21) and by calculation of absolute V_T through an arbitrary milliliter/impedance unit conversion factor derived from the lower positive end-expiratory pressure phase of a previous study (38) and we found tight correlation with PTP (*see* the additional results section in the online supplement). Fifth, the population was small and this might have explained the lack of significance in some of the correlations. Finally, we measured only set $F_{I_{O_2}}$ and not that delivered to the lower airways, which might have differed, especially during the facial mask phase because of entrainment of room air. Thus, we cannot

how how much the difference between set nd delivered FI_{O_2} could have influenced e study findings.

onclusions

FNC exerts various specific physiologic ffects in patients with AHRF including improved gas exchange, lower RR and effort, improved lung volume, dynamic compliance, transpulmonary pressures, and homogeneity. All these physiologic benefits might positively affect the clinical outcome of patients with AHRF. ■

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