Intensive Care Med (2011) 37:1780–1786
DOI 10.1007/s00134-011-2354-6

ORIGINAL

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# Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study

Received: 7 March 2011
Accepted: 2 September 2011
Published online: 27 September 2011


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**Electronic supplementary material**
The online version of this article (doi:10.1007/s00134-011-2354-6) contains supplementary material, which is available to authorized users.

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**Abstract** *Purpose:* To evaluate the efficiency, safety and outcome of high flow nasal cannula oxygen (HFNC) in ICU patients with acute respiratory failure. *Methods:* Pilot prospective monocentric study. Thirty-eight patients were included. Baseline demographic and clinical data, as well as respiratory variables at baseline and various times after HFNC initiation during 48 h, were recorded. Arterial blood gases were measured before and after the use of HFNC. Noise and discomfort were monitored along with outcome and need for invasive mechanical ventilation. *Results:* HFNC significantly reduced the respiratory rate, heart rate, dyspnea score, supraclavicular retraction and thoracoabdominal asynchrony, and increased pulse oxymetry. These improvements were observed as early as 15 min after the beginning of HFNC for respiratory rate and pulse oxymetry. $PaO_2$ and $PaO_2/FiO_2$ increased significantly after 1 h HFNC in comparison with baseline ($141 \pm 106$ vs. $95 \pm 40$ mmHg, $p = 0.009$ and $169 \pm 108$ vs. $102 \pm 23$, $p = 0.036$; respectively). These improvements lasted throughout the study period. HFNC was used for a mean duration of 2.8 days and a maximum of 7 days. It was never interrupted for intolerance. No nosocomial pneumonia occurred during HFNC. Nine patients required secondary invasive mechanical ventilation. Absence of a significant decrease in the respiratory rate, lower oxygenation and persistence of thoracoabdominal asynchrony after HFNC initiation were early indicators of HFNC failure. *Conclusions:* HFNC has a beneficial effect on clinical signs and oxygenation in ICU patients with acute respiratory failure. These favorable results constitute a prerequisite to launching a randomized controlled study to investigate whether HFNC reduces intubation in these patients.

**Keywords** Oxygen inhalation therapy · Heat · Humidity · Respiration, artificial · Non-invasive positive pressure ventilation

## Introduction

Supplemental oxygen administration is the first line treatment of acute respiratory failure. In patients who do not require immediate ventilatory support, significant drawbacks are associated with conventional oxygen therapy. These include the limited amount of oxygen supplied (15 l/min is usually the maximum flow

delivered via a facemask), the considerable imprecision regarding the exact amount of delivered $FiO_2$, and for many patients, the poor tolerance of both the facemask and oxygen because of insufficient heating and humidification, although the exact level of humidification required and the best way to deliver it remain unknown [1]. One further limitation with conventional oxygen administration is the substantial mismatch between the oxygen flow and the patient's inspiratory flow. One must indeed bear in mind that patient's peak inspiratory flows may vary between 30 and 120 l/min during respiratory failure [2]. This means that the proportion of humidified and oxygenated inspired gas can be very small (below 10%). Recently, an alternative to conventional oxygen therapy has received growing attention: heated, humidified high flow nasal cannula oxygen (HFNC) is a technique that can deliver up to 100% heated and humidified oxygen at a maximum flow of 60 l/min of gas via nasal prongs or cannula. This technique has been widely studied in the pediatric population [3, 4], where its beneficial effects are increasingly recognized. Most of the available data in adults concern physiological aspects of HFNC. Studies have shown that HFNC generates a low level of positive airway pressure [5, 6], reduces airway resistance [7] and flushes nasopharyngeal dead space [8], thus contributing to work of breathing reduction in COPD patients [9]. Data on ICU patients with respiratory failure are scarce [10, 11]. One physiological study reported a favorable effect of HFNC on comfort and oxygenation compared to the Venturi mask [10]. However, precise indications of HFNC, short- and long-term effects, tolerance and outcome of patients undergoing HFNC are unknown. Before launching a randomized controlled trial, we felt it was mandatory to have a pilot study evaluating the efficiency, safety and outcome of patients undergoing HFNC given through Optiflow®.

## Methods

### Design and setting

A prospective, observational study was conducted in a 12-bed university hospital ICU to investigate the effects of HFNC on respiratory parameters and outcome in patients with acute respiratory failure. The Ethics Committee of the French Society of Intensive Care (SRLF) approved the study and waived informed consent since use of HNFC is part of our common practice in these patients. All procedures were routine. Patients and/or family were, however, informed of the study, its purpose and our intention to publish its results.

### Patients

#### *Inclusion criteria*

All patients exhibiting acute respiratory failure requiring more than 9 l/min of oxygen output to achieve a $SpO_2$ of more than 92% (those achieving less than 92% were also included in the absence of criteria for immediate intubation, see below) or persistent signs of respiratory distress (defined when one or more of the following criteria were present: respiratory rate equal to or greater than 25 bpm, thoraco-abdominal asynchrony and supraclavicular retraction) despite oxygen administration were eligible.

#### *Exclusion criteria*

Patients requiring immediate endotracheal intubation (using commonly used criteria [12]) were excluded, as were those with hypercapnic respiratory failure (defined as a known history of COPD and hypercapnia on arterial blood gases).

### Device description

The HFNC device (Optiflow®, Fisher & Paykel, Auckland, New Zealand) consists of an air-oxygen blender with adjustable $FiO_2$ (21–100%) that delivers a modifiable gas flow (up to 60 l/min) to a heated chamber (Fisher & Paykel, MR 850 passover humidifier) where the gas is heated and humidified. The gas mixture is then routed through a high performance circuit (Fisher & Paykel, RT 310) containing 44 $mgH_2O/l$ water to be delivered at 37°C to the patient via short, wide bore binasal prongs. Conventional oxygen was given through a high-$FiO_2$, non-rebreathing facemask (Hudson RCI, Teleflex Medical, High Wycombe, UK).

### Registered variables

Baseline demographic and clinical data, as well as respiratory, hemodynamic and clinical variables at baseline and at various times after the beginning of HFNC and during 48 h, were recorded. Arterial blood gases were measured before and after 1 and 24 h of HFNC use. Noise and discomfort induced by the device were monitored throughout its use with a visual numeric scale (VNS) ranging from 0 to 10. For each patient, the attending physician was asked immediately upon initiating HFNC how he would have managed the patient had HFNC not been available. Three options were available: pursue conventional oxygen therapy, initiate non-invasive ventilation or intubate the patient.

### Statistical analysis

Results and figures are expressed as mean ± standard deviation. Changes over time of recorded variables were evaluated by one-way analysis of variance (ANOVA) for repeated measurements followed by Fisher's least significant difference test to detect differences between measurements. Categorical variables were compared by $\chi^2$ test and continuous variables by Student's $t$ test or Mann-Whitney as appropriate. A $p$ value <0.05 was considered significant.

## Results

### Patient characteristics

Thirty-eight patients were included during the study period (see electronic supplement, Figure E1). Patient characteristics are detailed in Table 1. Mean age was 54.2 ± 15.4 years old and mean SAPS II 39 ± 10. The main cause of respiratory failure was community-acquired pneumonia (15/38, 39%) (Table 1).

### Clinical parameters and oxygenation with HFCN

Before HFNC, patients were all under an estimated delivered $FiO_2$ of 100% with the conventional high $FiO_2$ facemask, with a mean flow of 14 ± 2 l/min. HFNC was set with a mean $FiO_2$ of 88 ± 16% and flow of 49 ± 9 l/min. Figure 1 shows changes over time in monitored parameters before and after initiation of HFNC. Use of HFNC was associated with a significant reduction in respiratory rate, heart rate, dyspnea score, supraclavicular retraction and thoracoabdominal asynchrony, and a significant improvement in pulse oxymetry. These improvements were seen as early as 15 min after the beginning of HFNC for respiratory rate and pulse oxymetry, 30 min for thoracoabdominal asynchrony, dyspnea score and supraclavicular retraction, and 6 h for heart rate. These improvements lasted throughout the study period (Fig. 1).

$PaO_2$ was significantly higher after 1 h of HFNC than before use of the device (141 ± 106 vs. 95 ± 40 mmHg, $p = 0.009$). The $PaO_2/FiO_2$ ratio was significantly improved at 1 and 24 h when compared with the value observed before use of HFNC (169 ± 108, 187 ± 86 and 102 ± 23 mmHg, respectively, $p = 0.036$ when tested with ANOVA). There was no significant increase in pH (respectively, 7.43 ± 0.09, 7.44 ± 0.07 and 7.41 ± 0.07 before, after 1 and 24 h of HFNC, $p = 0.87$) and $PaCO_2$ (respectively, 38 ± 11, 37 ± 11 and 38 ± 10 mmHg before, after 1 and 24 h of HFNC, $p = 0.77$) on arterial blood gases throughout the study period.

**Table 1** Patient characteristics

| | |
|---|---|
| Age (years) | 54.2 ± 15.4 |
| Sex (f/m) | 18/20 |
| Comorbidities | |
| Ongoing malignancy | 5 |
| HIV infection | 8 |
| Non-HIV immunodeficiency | 4 |
| Chronic respiratory failure | 6 |
| Diabetus mellitus | 3 |
| Chronic cardiac failure | 2 |
| SAPS II | 39 ± 10 |
| ODIN score | 2 ± 1 |
| Etiology of respiratory failure | |
| Community-acquired pneumonia | 15 |
| H1N1 influenza infection | 5 |
| Cardiogenic pulmonary edema | 5 |
| *Pneumocystis jiroveci* pneumonia | 2 |
| Pulmonary embolism | 2 |
| Postoperative atelectasis | 2 |
| Aspiration pneumonia | 2 |
| Self-extubation-associated respiratory failure | 1 |
| Meprobamate drug overdose | 1 |
| Pancreatitis | 1 |
| Bronchiectasis infection | 1 |
| Gemcitabine-associated interstitial pneumonia | 1 |
| ICU length of stay (days) | 7.3 ± 7.9 |
| Length of HFNC use (days) | 2.8 ± 1.8 |

*f/m* female to male ratio, *SAPS II* Simplified Acute Physiology Scale score, *ODIN* Organ Dysfunction and/or Infection score

### Duration and tolerance of HFNC

The nasal discomfort or noise disturbances induced by the device, when evaluated by a VNS, did not change between the beginning and the end of the study, with average values of 3 ± 3 and 4 ± 3, respectively (Figure E2). Intolerance was never a cause HFNC cessation. No unexpected side effect was reported. Optiflow was used for an average of 2.8 ± 1.8 days (maximum 7 days). None of the patients developed nosocomial pneumonia during HFNC.

### Patient outcome and prediction of intubation

Nine patients required secondary intubation and invasive mechanical ventilation. Intubation was performed in a median time of 4.0 h after beginning HFNC (minimum 1 h, maximum 48 h). Patients were all intubated while still under HFNC.

In order to identify predictors of HFNC failure, we compared respiratory parameters of these nine patients to those of the rest of the study population. They exhibited a higher respiratory rate 30 min (29.1 ± 3.8 vs. 24.6 ± 5.8, $p = 0.05$) and 45 min (30.4 ± 5.2 vs. 24.1 ± 5.9, $p = 0.012$) after the beginning of HFNC (Fig. 2), a lower $SpO_2$ 15, 30 and 60 min after beginning HFNC (respectively, 92.7 ± 10.1 vs. 98.4 ± 2.2, $p = 0.007$; 94.2 ± 7.8

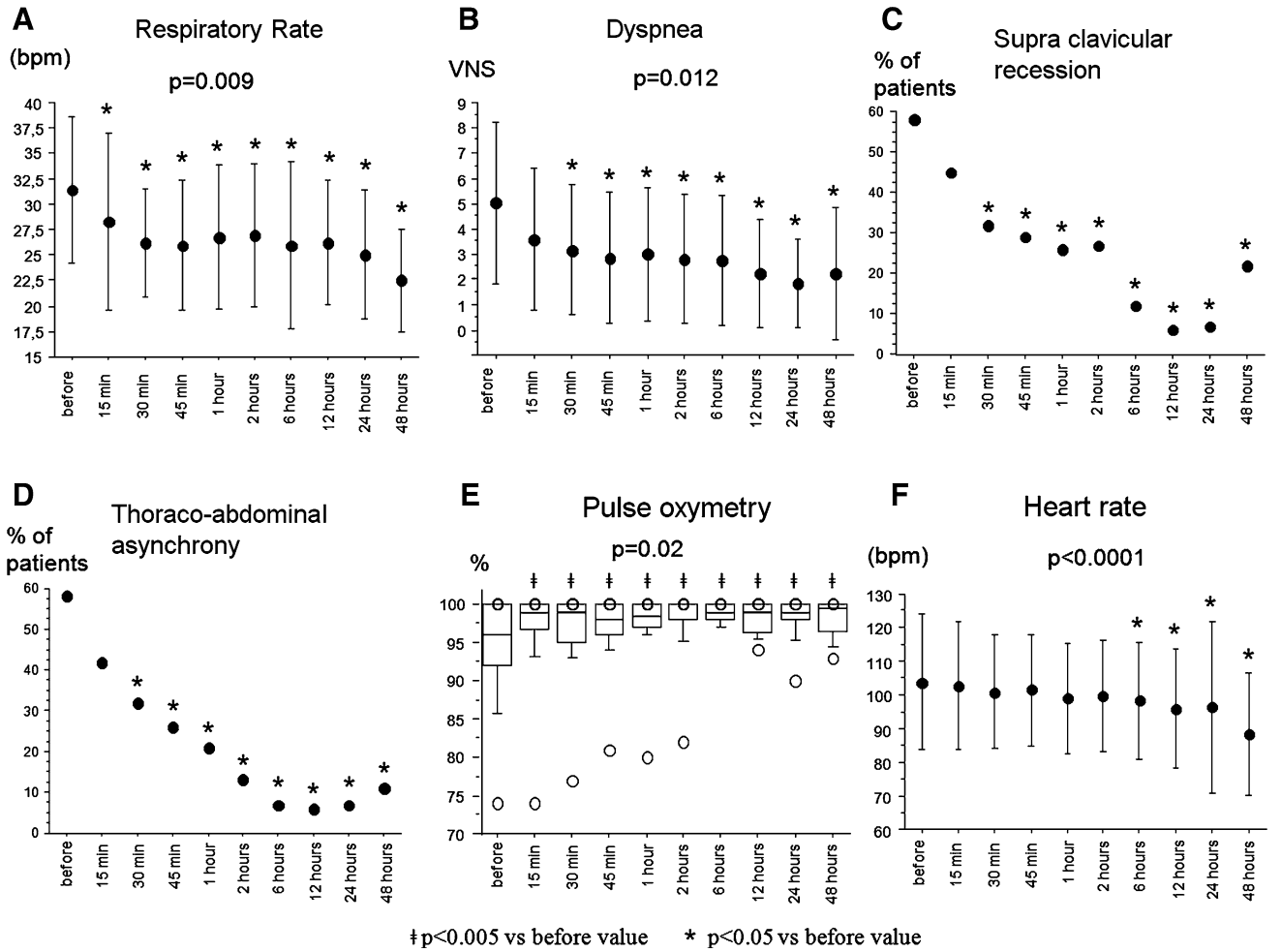


**Fig. 1** Evolution of clinical patterns. Results are expressed as mean ± standard deviation except for pulse oxymetry expressed as a box plot with median, interquartile and maximum values (*open circles*). A significant improvement is observed concerning respiratory rate, pulse oxymetry, dyspnea score, clinical signs of respiratory distress and heart rate. $^{*}p < 0.05$ versus before value, $^{\ddagger}p < 0.005$ versus before value

vs. 97.8 ± 2.6, $p = 0.0035$; 95.7 ± 6.7 vs. 98.4 ± 1.5, $p = 0.039$) and a lower $PaO_2$ and $PaO_2/FiO_2$ ratio 1 h after beginning HFNC (respectively, 82.1 ± 29.5 vs. 165.3 ± 116.8, $p = 0.046$ and 90.7 ± 33.1 vs. 200.6 ± 111.7, $p = 0.008$). The percentage of patients exhibiting thoraco-abdominal asynchrony at 15 (43.7% vs. 9%, $p = 0.04$), 30 (50% vs. 11.5%, $p = 0.02$), 60 (75% vs. 10%, $p = 0.0007$) and 120 min (80% vs. 15.6%, $p = 0.009$) after the beginning of HFNC was also significantly greater in patients requiring intubation (Fig. 2). Finally, all but three patients were discharged alive.

## Discussion

Our study evaluated immediate and long-term effects of high flow humidified nasal oxygen in patients with severe acute respiratory failure. Its main results are the following: (1) HFNC exerted early and sustained favorable effects on clinical parameters and oxygenation; (2) HFNC was well tolerated; (3) the respiratory rate appeared to be an early predictor of HFNC failure; (4) HFNC may have avoided mechanical ventilation (including invasive and non-invasive mechanical ventilation) in a significant proportion of patients. Taken together, results from our pilot study provide sufficient data to launch a randomized trial to confirm whether or not the beneficial effects observed in our study and in others [10] translate into less intubation of patients with hypoxemic respiratory failure treated with HFNC.

Despite long-standing use of HFNC in neonates, use of this technique in adults has only recently received attention. In addition to the washout of the pharyngeal deadspace, a decrease in inspiratory resistance and a better matching of the patient's inspiratory flow, it has been

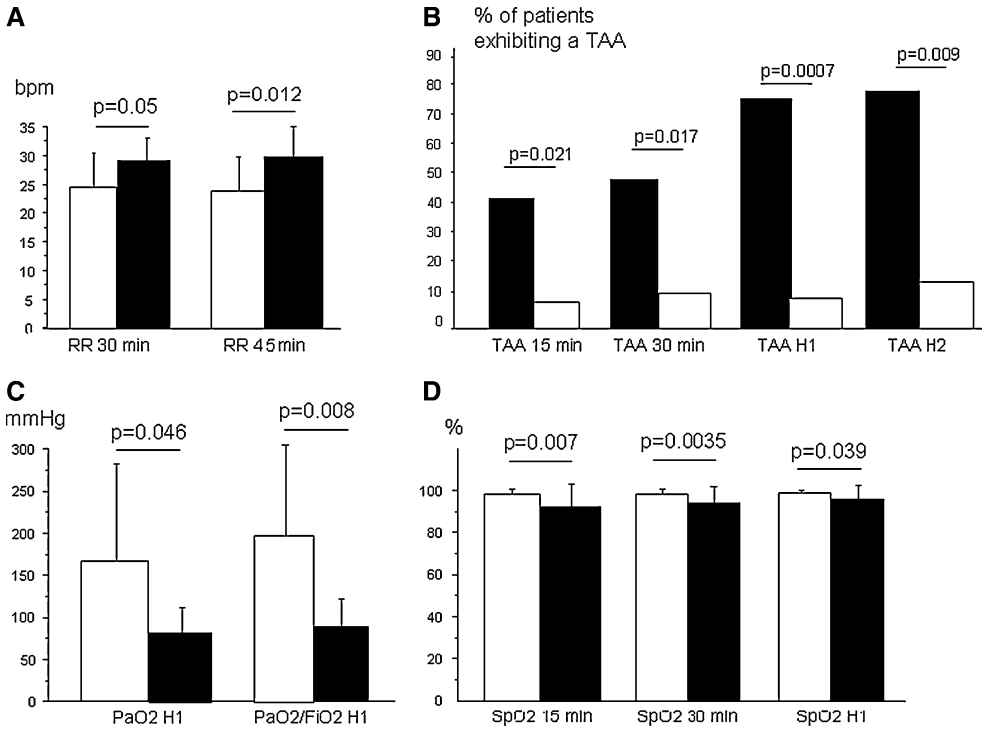


**Fig. 2** Differences between patients that eventually required mechanical ventilation (*black bars*) and the patients that did not (*white bars*). *TAA* thoraco-abdominal asynchrony, *RR* respiratory rate. Results are expressed as mean ± standard deviation. The respiratory rate 30 and 45 min after the beginning of HFNC (Fig. 2a), as well as the percentage of patients exhibiting thoraco-abdominal asynchrony (Fig. 2b) 15, 30, 60 and 120 min after the beginning of HFNC, is significantly higher in patients requiring invasive mechanical ventilation as compared to the others. The $PaO_2$ and $PaO_2/FiO_2$ ratio 1 h after the beginning of HFNC (Fig. 2c), as well as $SpO_2$ 15, 30 and 60 min after the beginning of HFNC (Fig. 2d) is significantly lower in patients requiring invasive mechanical ventilation as compared to the others

shown (both in healthy volunteers [5] and in patients recovering from cardiac surgery [6]) that HFNC delivers a low level of positive airway pressure, thus further contributing to improving oxygenation and decreasing the work of breathing [13]. During acute respiratory failure, Roca et al. [10] found a significant improvement in respiratory parameters and arterial blood gases after 30 min of HFNC in comparison to 30 min conventional facemask oxygen therapy. We confirm and expand these results by showing a similar improvement in respiratory rate and oxygenation, but additionally, and for the first time, long-term effects of HFNC with a sustained improvement in respiratory parameters and data on the outcome of adult patients continuously treated with HFNC. Improvement in oxygenation was not as significant as alleviation of respiratory distress. This is not in itself surprising for at least three reasons: (1) the majority of patients were included because of community-acquired pneumonia, which does not resolve in a couple of hours; (2) despite the fact that patients requiring immediate intubation were not included, oxygenation was severely impaired in our patients; (3) finally, and contrary to the study by Roca et al., our patients were treated with HFNC very early in the course of their respiratory failure (often immediately upon ICU admission), meaning that others treatments, such as antibiotics, fluid loading, etc., did not yet have time to be effective. Outcome results from our study indicate that the success rate of HFNC (i.e., avoidance of intubation) in our patients was over 75%. Another—admittedly indirect and potentially biased—hint of this beneficial effect of HFNC in avoiding intubation lies in the next step physicians would have made had HFNC not been available, with intubation being much more often declared than actually occurring (ESM Fig. 3).

## Predicting failure

The obvious concern with such a technique is to not delay intubation, as with non-invasive ventilation where NIV failure (and thus delayed intubation) is associated with increased mortality in patients with de novo respiratory failure [14]. Although most of our patients had de novo respiratory failure, noticeable differences exist between our setting and that of non-invasive ventilation. First of all, patients that required secondary intubation were intubated relatively shortly after HFNC (median 4 h), suggesting that little or no delay was taken in these patients in comparison with much longer delays with NIV. Second, all patients were intubated while still under HFNC. This provided remarkable intubation conditions. Indeed, our own (unpublished) experience with intubation under Optiflow® indicates that this technique offers major advantages. First of all, and most importantly, the same device is used all the way through, from initial management of respiratory failure right until per-intubation oxygenation. Second, the high constant flow probably provides sufficient oxygen to the alveoli during apnea, as previously described in a similar setting [15] and recently showed during intubation in an experimental study [16].

Obviously only a randomized study will give definite answers to these different questions. We were able to identify, however, early, simple indicators of HFNC failure. Indeed, patients that were secondarily intubated exhibited no decrease in respiratory rate, contrary to those successfully treated with HFNC, and thoracoabdominal asynchrony was significantly more frequent in patients secondarily intubated. Thus, our results may provide the following useful message to the clinician wishing to use HFNC: in the absence of a clear reduction in respiratory rate and persistent thoracoabdominal asynchrony, intubation should be considered. This may seem obvious, basic clinical judgment, but the exact timing of the decision to intubate is not that easy during acute respiratory failure in the absence of overt signs of impaired consciousness or hemodynamic instability.

### Indications

Over 70% of patients received HFNC because of lung infection-related respiratory failure, including patients with overt immunosuppression. Indeed, 12 of our patients had a previously known immunosuppression state, 8 of whom were HIV patients. Only two of these patients required secondary invasive mechanical ventilation, and all of them had a favorable outcome. These results suggest that HFNC could be a useful tool in the management of acute respiratory failure in immunocompromised patients, with possibly similar results as those reported with non-invasive ventilation [17, 18]. Five patients with pandemic H1N1 flu pneumonia were managed with HFNC. This might be an interesting therapeutic option in case of a massive outbreak of respiratory failure during a flu pandemic in instances of limited or exceeded capacity of invasive ventilation. Another potential field of application of HFNC that was not tested in the present work is that of do-not-intubate patients [19, 20], where the use of non-invasive ventilation is debated. Boyer et al. [21] recently reported the benefit of HFNC in this setting in a patient with pulmonary fibrosis.

Our study has several limitations. First of all, it was not a randomized controlled study. However, it seemed difficult (and a matter of ethical debate) to undergo a RCT with a technique for which—at that time—no data in adults requiring ICU admission for acute respiratory failure were available. Thus, our study was designed as a pilot study for a RCT. A multicenter randomized trial, FLORALI-REVA, is about to begin in France. Second, actual delivered $FiO_2$ was not measured in our study; it is thus difficult to ascertain that $FiO_2$ with the facemask was similar to that with HFNC. Given the characteristics of our facemask (use of a reservoir) and the oxygen flow rates used, we believe that most if not all of the patients had the highest obtainable $FiO_2$ with the facemask. $PaO_2/FiO_2$ ratios should nonetheless be interpreted with caution, given that—like in many studies comparing oxygen therapy via facemasks with NIV—$FiO_2$ was not measured but solely estimated. It is possible that a noticeable part of the improvement in oxygenation seen in our patients with HFNC may be due to greater $FiO_2$. However, several beneficial effects have been reported with HFNC, which all contribute to patients' respiratory status improvement [13]. Our study was not designed to identify the individual contribution of these effects.

## Conclusion

Our results show a favorable effect of HFNC on clinical signs and oxygenation in critical care patients with acute respiratory failure. We identified an early lack of decrease in respiratory rate and persistence of thoraco-abdominal asynchrony as early and simple indicators of HFNC failure. Taken together, our study constitutes a good prerequisite to launch a randomized controlled study to investigate the potential reduction of intubation with HFNC in patients with hypoxemic acute respiratory failure.

**Acknowledgments** Authors wish to thank Mr Nathan Samis for his technical assistance.

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