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Non-invasive ventilation or high-flow oxygen therapy: When to choose one over the other?

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ABSTRACT

It has been found that high-flow oxygen therapy (HFOT) can reduce mortality of patients admitted to intensive care unit (ICU) for de novo acute respiratory failure (ARF) as compared to non-invasive ventilation (NIV). HFOT might therefore be considered as a first-line strategy of oxygenation in these patients. The beneficial effects of HFOT may be explained by its good tolerance and by physiological characteristics including delivery of high FiO_2, positive end expiratory pressure (PEEP) effect and continuous dead space washout contributing to decreased work of breathing. In contrast, NIV should be used cautiously in patients with de novo ARF due to high tidal volumes promoted by pressure support and that may potentially worsen pre-existing lung injury. Although recent studies have reported no benefit and even deleterious effects of NIV in immunocompromised patients with ARF, the experts have recommended its use as a first-line strategy.

In patients with acute-on-chronic respiratory failure and respiratory acidosis, it has been clearly shown that NIV is the best strategy of oxygenation. However, HFOT seems able to reverse respiratory acidosis and further studies are needed to evaluate whether HFOT could represent an alternative to standard oxygen.

Although NIV is recommended to treat ARF in postoperative patients or to prevent post-extubation respiratory failure in ICU, recent large-scale randomized studies suggest that HFOT could be equivalent to NIV. While recent recommendations have been established from studies comparing NIV with standard oxygen, new studies are needed to compare NIV versus HFOT in order to better define the appropriate indications for both treatments.

Key words: high-flow oxygen therapy, hypercapnia, hypoxaemia, non-invasive ventilation, respiratory failure.

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INTRODUCTION

Respiratory failure is a condition in which the respiratory system fails in one or both of its gas exchange functions, that is oxygenation of and/or elimination of carbon dioxide from mixed venous blood.[1]

Acute hypoxaemic respiratory failure or de novo respiratory failure is characterized by acute hypoxaemia (usually defined by a PaO_2/FiO_2 ratio < 200 mm Hg) and high respiratory rate in patients without chronic lung disease and without cardiogenic pulmonary oedema. Breathing pattern results in high tidal volumes with hyperventilation, and hypercapnia is uncommon. Consequently, treatment is aimed at correcting hypoxaemia, unloading respiratory effort and finally avoiding intubation.[2] However, such a strategy should be conducted cautiously in view of avoiding delayed intubation, which may increase the risk of mortality.[3,4] Non-invasive ventilation (NIV) has shown conflicting results in this setting and it is therefore not recommended,[5] while use of high-flow nasal cannula oxygen therapy is currently spreading after having shown benefits in patients with hypoxaemic ARF.[6,7]

Acute hypercapnic respiratory failure occurs mainly in patients with underlying chronic lung disease, that is chronic obstructive pulmonary disease (COPD) exacerbation, obesity–hypoventilation syndrome or rib cage abnormalities. Up until now, the recommended treatment includes NIV, which provides ventilatory support, avoids intubation and decreases mortality.

In this review, we will discuss NIV and/or high-flow oxygen therapy (HFOT) applied only as a therapeutic measure to treat acute respiratory failure (ARF), while prophylactic applications designed to prevent respiratory failure will not be addressed.

CLINICAL STUDIES: WHY CHOOSE HFOT RATHER THAN NIV IN HYPOXAEMIC ARF?

The first observational study using HFOT was published in 2010 and compared clinical effects of HFOT versus standard oxygen in 20 hypoxaemic patients with ARF.[7] The authors found that patients under HFOT had

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better comfort and improved respiratory rate and blood oxygenation compared with standard oxygen.[7] While few physiological studies had been conducted to understand the potentially beneficial effects of HFOT, a first large-sample randomized controlled including 310 non-hypercapnic patients with de novo ARF (respiratory rate above 25 breaths per minute and PaO_2/FiO_2 < 300 mm Hg) was conducted to compare three strategies of oxygenation: standard oxygen, HFOT and HFOT with NIV sessions delivered through face mask.[6] The hypothesis at the time of the study design was that HFOT with NIV could be the best strategy as compared to standard oxygen. The major result was that 90-day mortality was significantly lower in patients treated by HFOT alone (12%) than by HFOT with NIV (28%) or by standard oxygen (23%) (P = 0.02). Although intubation rates did not differ among the three groups, risk of intubation was significantly lower with HFOT in patients with PaO_2/FiO_2 < 200 mm Hg.[6] This study questioned the use of NIV in patients with de novo respiratory failure and suggested that HFOT might be considered in this setting as the first-line therapy. For the first time, a large-scale randomized controlled trial (RCT) showed a decreased mortality rate compared to standard oxygen. Concerning NIV, given the uncertainty of evidence, the recent European/American clinical practice guidelines were unable to offer a recommendation.[5] Although NIV may decrease the risk of intubation as compared with standard oxygen, no significant difference in terms of mortality was found in analysis of all the RCT (Table 1).[6,8–16]

PHYSIOLOGICAL EFFECTS OF HFOT: HOW ARE THE BENEFITS OF HFOT TO BE EXPLAINED?

HFOT is a simple system consisting in an air–oxygen blender directly connected to a flow meter (set up to 70 L/min) or in more recent systems in a turbine connected to an oxygen flow meter. The gas mixture containing up to 100% of oxygen is routed to a heated humidifier delivering gas conditioned at 37°C and completely saturated with water (relative humidity: 100%). Gases are delivered to the patient through a simple specific interface, nasal prongs or cannula, which are configured to provide high flow and to limit water condensation.[17] Currently, most intensive care unit (ICU) ventilators offer an option enabling HFOT, but they need to be connected to the heated humidifier and circuit as described above. The constant high flow rate of gas in the HFOT system in the upper airway promotes physiological effects including delivery of high FiO_2, positive end expiratory pressure (PEEP) effect and washout of dead space flushing out carbon dioxide.[17]

Oxygenation and PEEP effect

The hallmark of hypoxaemic ARF is an inspiratory effort leading to a high peak inspiratory flow reaching a mean of 30–40 L/min.[18] The high flow generated by the HFOT system is able to deliver high FiO_2 that in most cases exceeds the patient's peak inspiratory flow rate and thereby limits the dilution of inhaled gas with room air. In a physiological study, FiO_2 was measured during oxygen delivery in the pharynx of healthy subjects with several devices including a standard mask, a non-rebreathing mask and HFOT.[19] With a standard mask, FiO_2 was less than 0.6 despite a flow of 12 L/min, and dropped below 0.5 when ARF was simulated by thoracic light compression bandages. Although the non-rebreathing mask avoided such a FiO_2 drop during simulated ARF, the highest FiO_2 obtained was less than 0.7, while it reached 0.85 using HFOT set with a flow rate of 40 L/min.[19]

The second effect of the HFOT system is to generate a low level of positive pressure in the upper airway directly proportional to the gas flow delivered, thereby possibly improving oxygenation. However, due to air

Table 1 Summary of proposals for first-line therapies in acute respiratory failure

	NIV	High-flow nasal cannula oxygen therapy	Comment
Acute hypoxaemic respiratory failure	–	++	A randomized controlled study has reported benefits of HFOT versus NIV and standard oxygen
Immunocompromised patients	++	+	NIV is recommended by the recent European/American guidelines. However, studies are ongoing to determine the place of HFOT
COPD exacerbation with acute respiratory acidosis	++++	?	NIV is strongly recommended by the recent European/American guidelines
Acute respiratory failure after planned extubation	–	?	NIV was associated with either an absence of impact on outcomes or an increased mortality rate
Post-operative patients with acute respiratory failure	+++	+	NIV is recommended by the recent European/American guidelines. In cardiothoracic post-operative patients, HFOT can be an alternative to NIV

COPD, chronic obstructive pulmonary disease; HFOT, high-flow oxygen therapy; NIV, non-invasive ventilation. ++++, high recommendation; +++, moderate recommendation; ++, low recommendation; +, very low recommandation; -, probably not to be used; ?, not enough data.

leakage the pressure levels are quite variable. Consequently, positive pressure is markedly reduced when the patient opens his mouth. Parke *et al.* measured nasopharyngeal pressure in post-operative patients at different levels of flow using HFOT.[20] The pressure recorded during spontaneous breathing on HFOT correlated linearly with administered flow rate and was significantly higher when subjects breathed with their mouths closed: exceeding 3 cm H_2O with a gas flow rate of 50 L/min with mouth closed, and less than 2 cm H_2O with mouth open.[20] In physiological studies assessing pulmonary volumes with electrical impedance tomography after cardiac surgery or during hypoxaemic ARF, increased end-expiratory lung volume was found with HFOT as compared to standard oxygen therapy, suggesting alveolar recruitment reflecting a PEEP effect.[21,22]

Comparing HFOT and NIV, clinical studies have shown less improvement in oxygenation with HFOT, probably due to lower impact of the PEEP effect with HFOT than with NIV.[6,23] In a pilot study successively applying standard oxygen, HFOT and NIV in patients with ARF, PaO_2 increased from standard oxygen to HFOT while PaO_2/FiO_2 ratios remained similar.[23] This suggests that oxygenation improvement was mainly due to increased FiO_2. By contrast, PaO_2 further increased with NIV with a significant increase in PaO_2/FiO_2 ratio reflecting a probable PEEP effect favouring alveolar recruitment.

Ventilatory support

Respiratory muscle activity in hypoxaemic ARF is especially high due to high respiratory drive.[18] However, the spontaneous breathing could be deleterious as recently elucidated by Brochard *et al.* in the concept of patient self-inflicted lung injury (P-SILI); it could lead to an aggravation of lung injury through changes in global or regional pressure, even without any ventilatory support.[24–26]

HFOT seems able to decrease work of breathing and consequently may mitigate lung injury. Many authors have shown that patients with ARF were treated first by standard oxygen through a non-rebreathing mask, and subsequently by HFOT, a decrease in work of breathing under HFOT assessed by variation of oesophageal pressure (diminution of pressure time produced during inspiration).[22,27] Mauri *et al.* assumed that better working conditions could be partially due to improvement of inspiratory effort and pulmonary compliance.[22] Otherwise, the high-flow rate of continuously delivered gas may flush the upper airways, generating a washout of dead space and then flushing out carbon dioxide.[28,29] This effect associated with mechanically improved thoracic properties results in reduced inspiratory effort and minute ventilation requirement. This is consistent with the common finding of decreased respiratory rate and work of breathing with HFOT.[22,27]

Comfort and humidification

Despite a high oxygen flow rate, HFOT is better tolerated than NIV and standard oxygen. The heated humidifier of HFOT provides the same physiological conditions as those found in alveoli with absolute humidity of 44 mg/L of water.[30] An in vitro study showed that exposure of human epithelial cells to HFOT avoided the effects of low humidity, including reduced epithelial cell function and increased inflammation.[31] In clinical practice, standard oxygen through face mask provides non-humidified or underhumidified cold gas that dries the upper airway and reduces patient comfort, even when a bubble humidifier is used.[32] However, it has yet to be proven that heating and humidification of inspired gas may prevent thick secretions, potential dysfunction of mucociliary clearance, atelectasis facilitation and clinical impact.[33]

FROM DELETERIOUS EFFECT OF NIV TO 'PROTECTIVE-NIV' IN HYPOXAEMIC ARF

As it has been found that mortality may be lower with HFOT alone than with HFOT and NIV session, these findings suggest that NIV may be deleterious for patients with hypoxaemic ARF.[6] Moreover, time to intubation was not significantly different between the three groups, a finding suggesting that the poor outcomes observed under standard oxygen and NIV treatments could be mainly due to oxygenation strategy and not delayed intubation.

Suboptimal NIV: Role of high tidal volumes?

The harmfulness of NIV may result from a suboptimal use. Indeed, in our study, NIV has been delivered during short intermittent sessions, using low levels of PEEP (5 ± 1 cm H_2O), and overly high pressure support (8 ± 3 cm H_2O) generating high tidal volumes (9.2 ± 3 mL/kg of predicted body weight, PBW).[6] However, these settings closely approximate those reported in previous studies: pressure support varying from 9 to 11 cm H_2O and PEEP from 4 to 7 cm H_2O.[9–12,34,35] Lastly, NIV was delivered continuously and not by intermittent sessions as in most studies.

PEEP levels may appear relatively low as many patients have met the criteria for acute respiratory distress syndrome (ARDS). Indeed, around three-quarters of patients with de novo ARF had PaO_2/FiO_2 ratio < 300 mm Hg and bilateral pulmonary infiltrates.[6,36] It has even been found that patients breathing spontaneously under HFOT or standard oxygen could be considered at an early stage as having ARDS with a pattern of inflammatory biomarkers similar to that of ARDS patients under invasive mechanical ventilation.[37,38] Deleterious impact of NIV in hypoxaemia could be the consequence of high tidal volumes and low levels of PEEP that could provoke ventilator-induced lung injury (VILI).

High tidal volume: Consequence of treatment or sign of severity?

In our sub-analysis, patients who were intubated were more likely to generate large tidal volumes at NIV initiation than those who did not, although patients did not differ in terms of NIV settings, severity score or

respiratory rate.[39] The factors associated with intubation were hypoxaemia and tidal volume exceeding 9 mL/kg of PBW.[39] Similarly, an observational study found that nearly half of the patients with hypoxaemic ARF treated with NIV had a tidal volume exceeding 10 mL/kg of PBW despite a target tidal volume between 6 and 8 mL/kg of PBW.[40,41] These two studies suggest that high tidal volumes could be a marker of high respiratory drive due to hypoxaemia and that they could reflect the severity of the underlying respiratory disease. However, settings may also have an impact on tidal volumes in patients with hypoxaemic ARF. A physiological study showed that inspiratory work of breathing decreased significantly after pressure support was applied above PEEP, as compared to continuous positive airway pressure (PEEP alone) or standard oxygen.[42] However, the increased pressure support resulted in a significant increase of tidal volumes, regardless of the levels of PEEP.[42]

Consequently, tidal volumes might vary with the severity of hypoxaemic ARF due to inspiratory effort and also with preset level of pressure support that together can lead to alveolar overdistension.[41,43,44]

An alternative way to apply NIV: Protective-NIV?

In a recent monocentre RCT, Patel *et al.* found that NIV delivered via helmet reduced intubation rates in patients with ARDS as compared to NIV delivered via facial mask, from 61% to 18%, respectively, in facemask and helmet groups.[45] Obviously, the interface may have an important effect, but above all, ventilator settings were significantly different between groups: patients treated with helmet had higher PEEP and lower pressure support levels. The lower pressure support levels in the helmet group (around 8 cm H_2O) are surprising, given the results of a previous physiological study suggesting that pressure support levels had to be increased by 50% when using the helmet to achieve physiological effects comparable to those recorded with face mask.[46] Unfortunately, measurement of tidal volumes under helmet is not routinely feasible and was not provided in the Patel *et al.*'s study. However, the low level of pressure support reported may have contributed to reduction of transpulmonary pressure and potential lung injury (VILI) by decreasing ventilator assistance and tidal volumes.

Otherwise, NIV delivered through helmet yielded higher PEEP levels than under facemask (8 vs 5 cm H_2O) with nearly half of the patients under helmet having a PEEP level of 10 cm H_2O.[45] Several studies have revealed better tolerance with helmet than with face mask, a finding that could favour possible continuous prolonged application of NIV during longer periods of time with higher PEEP levels.[47,48]

One way to potentially optimize NIV delivery could involve changes in ventilator settings[6,9–12,35] including reduced pressure support and increased PEEP levels and changes in interface that would improve comfort through use of the helmet.[47,48] However, RCT are needed to compare such a potential protective-NIV with HFOT in the management of hypoxaemic ARF patients.

ARF IN IMMUNOCOMPROMISED PATIENTS: NIV IS STILL RECOMMENDED

Recent European/American guidelines recommend early NIV for immunocompromised patients with ARF.[5] In the early 2000s, two RCT reported lower intubation rates and mortality with NIV than with standard oxygen.[35,49] However, the largest RCT carried out to date, including 374 patients, did not confirm the potential benefits of NIV, and found similar outcomes in immunocompromised patients with ARF treated with NIV or with oxygen alone.[50]

Other studies focusing exclusively on immunocompromised patients found better outcomes with HFOT alone than with NIV,[51,52] thereby suggesting potential deleterious effects of NIV. The application of HFOT has been increasing and in a prospective international observational study focusing on immunocompromised patients, the first-line strategy of oxygenation was standard oxygen in 54% of the patients, NIV in 26% and HFOT in 20%.[53] After adjustment, HFOT was associated with a decreased risk of intubation without effect on mortality, whereas NIV had no impact on intubation or mortality. Although NIV remains the standard care for these patients, future studies will assess which is the best strategy: NIV sessions interspaced with standard or high-flow oxygen versus HFOT alone (Table 1).

POST-EXTUBATION RESPIRATORY FAILURE

Several studies have illustrated the beneficial effects of NIV in post-operative patients.[54,55] Indeed, NIV has been found to decrease the risk of intubation in patients with ARF after abdominal and thoracic surgery as compared to standard oxygen, and recent European/American clinical practice guidelines have suggested NIV as first-line therapy for these patients.[5] However, one multicentre, randomized non-inferiority study of 830 patients after cardiothoracic surgery compared HFOT with NIV for prevention or resolution of ARF.[56] Around 60% of patients presented with ARF, and HFOT was not inferior to NIV in terms of reintubation for mechanical ventilation or switch to the other treatment, 27.8% and 27.4% for NIV and HFOT, respectively.[57]

In contrast, NIV should not be applied in ICU patients who develop ARF after planned extubation.[5] Two RCT compared NIV versus standard oxygen and reported either an absence of impact on outcomes or an increased mortality rate using NIV.[58,59] Few patients with underlying COPD or cardiogenic pulmonary oedema were included and whether NIV is beneficial in treatment of post-extubation respiratory failure in this population remains uncertain (Table 1).

NIV AS FIRST-LINE TREATMENT FOR ACUTE RESPIRATORY ACIDOSIS DUE TO COPD EXACERBATION

NIV has shown benefits for patients with an acute exacerbation of COPD in terms of need for intubation or

mortality.[5,60,61] The recent European/American guidelines on NIV for ARF recommend NIV for patients with ARF leading to acute respiratory acidosis (pH ≤7.35) due to COPD exacerbation.[5] There is a strong evidence base to support the use of NIV in patients with a pH of 7.25–7.35.[5,62,63] NIV improves pH and respiratory rate, most of the time within the first 1–4 h, which are good predictors of successful outcomes using NIV.[5,63] NIV reduces the sensation of dyspnoea and the need for intubation, and all in all, it improves survival. Benefits may also include decreased risk of nosocomial pneumonia.[2] Experts have recommended an NIV trial in severe patients with profound acidosis (pH <7.20),[64] or hypercapnic coma,[65] who are considered as requiring intubation and invasive ventilation, except in cases of immediate deterioration.[5] Indeed, even in this population, NIV decreases mortality and the need for intubation. However, NIV is not recommended in patients with hypercapnia who are not acidotic or as a means of preventing the development of respiratory acidosis in cases of COPD exacerbation.[5]

Physiological effects of HFOT in COPD exacerbation

Ventilatory support is the main physiological effect expected from treatment during a COPD exacerbation. HFOT contributes to reduced respiratory efforts by the PEEP effect[66] and by the reduction of functional dead space through washout in the upper airways[28,29,67] contributing to partial pressure of CO_2 (pCO_2) reduction.[68,69] Increased tidal volume and decreased respiratory rate are other physiological effects of HFOT favouring a reduction in the work of breathing in acute hypercapnic respiratory failure.[70–74]

Many physiological studies have reported that pCO_2 decreased under HFOT in stable COPD patients. They showed this reduction to be flow-dependent.[71] Surprisingly, pCO_2 reduced to normal values, despite a decrease in minute volume suggesting it was most likely achieved by washout of the respiratory tract and functional reduction in dead space.[71] In another physiological study of 36 stable COPD patients, the washout effect was correlated with increased leakage and airflow.[67] A randomized cross-over study (long-term oxygen therapy versus HFOT at 30 L/min with room air) confirmed that HFOT reduced CO_2 rebreathing, and also showed that it increased tidal volume and improved breathing pattern with a reduction of respiratory rate without any change in minute ventilation.[73] Similar results have been reported, even in patients with acute exacerbation of COPD.[75]

Is there a place for HFOT?

Indeed, previous studies showing potential benefits of HFOT in ARF did not include patients with hypercapnia. Up until now, only a few smaller studies[76,77] and case reports[78,79] with hypercapnic patients have been published. However, studies conducted in emergency departments comparing HFOT with standard oxygen or NIV included larger samples of patients with ARF of various causes and, especially, COPD exacerbation.[80–84] One RCT compared HFOT with NIV in 204 patients with respiratory failure admitted to emergency departments and requiring NIV.[81] The most common condition treated was COPD (39% of patients). The primary outcome was treatment failure rate defined by the need for intubation and decision to apply alternate therapy within 72 h. The principal findings showed that HFOT was not inferior to NIV.[81] Although the included patients did not meet specific criteria of COPD exacerbation with acute respiratory acidosis at baseline, they had hypercapnia and an indication (accepted by the investigators) to be treated by NIV. One interesting point is that tolerance of HFOT appeared to be higher than tolerance of NIV. Results of this study suggest that HFOT could be an alternative option when NIV tolerance compromises continuation of treatment. A retrospective study including 33 COPD patients with hypoxaemia and hypercapnia showed that the application of HFOT after failure of standard oxygen, NIV or intolerance to NIV resulted in improvement of pCO_2 after 1 and 24 h of treatment initiation.[76] In another observational study, Lee *et al.* evaluated the impact of HFOT as compared to NIV in 88 patients with severe exacerbation of COPD with acute respiratory acidosis. HFOT was set for a gas flow of 45–60 L/min and NIV with a PEEP of 5 cm H_2O and pressure support aimed at obtaining tidal volume of 7–10 mL/kg.[77] There was no difference between the two strategies concerning pCO_2 or partial pressure of oxygen (pO_2) improvement, and intubation and mortality rates were similar in both groups, approximating 26% and 17%, respectively.[77]

These results do not justify application of HFOT alone in treatment of patients with COPD exacerbation or acute respiratory acidosis. However, HFOT should be evaluated as an alternative to standard oxygen in these settings. Future studies should be conducted to assess potential strategies associating HFOT with NIV in view of decreasing NIV and hospital stay duration as compared to NIV alone (Table 1).

CONCLUSION

There exist highly valid evidences to apply NIV as the first-line therapy in COPD exacerbation with acute respiratory acidosis. NIV is also recommended in postoperative patients having respiratory failure after abdominal and thoracic surgery, whereas in postoperative cardiothoracic surgery patients, HFOT seems as efficient as NIV. NIV is not recommended in ICU patients after planned extubation to treat respiratory failure due to it being associated with a risk of mortality. Similarly, its benefits are uncertain in patients with hypoxaemic ARF, whereas HFOT seems to be more efficient in terms of mortality and need for intubation in severe hypoxaemic patients. Paradoxically, NIV remains recommended early in the management of immunocompromised patients with respiratory failure, even though recent results have proven controversial. Further studies are needed to assess the potential benefits of HFOT applied in the place of standard oxygen in association with NIV or HFOT alone in immunocompromised patients with acute respiratory and COPD exacerbation with respiratory acidosis.

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Abbreviations: ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; FiO_2, fraction of inspired oxygen; HFOT, high-flow oxygen therapy; ICU, intensive care unit; NIV, non-invasive ventilation; PaO_2, partial pressure of arterial oxygen; PBW, predicted body weight; pCO_2, partial pressure of CO_2; PEEP, positive end expiratory pressure; RCT, randomized controlled trial; VILI, ventilator-induced lung injury.

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