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High Flow Nasal Oxygen Therapy: From Physiology to Clinic

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Abstract

High-flow nasal oxygen (HFNO) therapy has several physiological advantages over traditional oxygen therapy devices, including decreased nasopharyngeal resistance, washing out of the nasopharyngeal dead space, generation of positive pressure in the pharynx, increasing alveolar recruitment in the lungs, humidification of the airways, increased fraction of inspired oxygen and improved mucociliary clearance. Recently, the use of HFNO in treating adult critical illness patients has significantly increased, and it is now being used in many patients with a range of different disease conditions. However, there are no established guidelines to direct the safe and effective use of HFNO for critical patients. This review summarizes the positive physiological effects, mechanisms of action, and the clinical applications of HFNO with available published literatures.

Keywords: Critical care unit, high flow nasal oxygen, mechanisms, respiratory failure

INTRODUCTION

Oxygen support therapy should be given to the patients with acute hypoxic respiratory insufficiency in order to provide oxygenation of the tissues until the underlying pathology improves. The inspiratory flow rate requirement of patients with respiratory insufficiency varies between 30 and 120 L/min. Low flow and high flow conventional oxygen support systems produce a maximum flow rate of 15 L/min, and FiO_2 changes depending on the patient's peak inspiratory flow rate, respiratory pattern, the mask that is used, or the characteristics of the cannula. The inability to provide adequate airflow leads to discomfort in tachypneic patients. With high-flow nasal oxygen (HFNO) cannulas, warmed and humidified air matching the body temperature can be regulated at flow rates of 5–60 L/min, and oxygen delivery varies between 21% and 100%. When HFNO, first used in infants, was reported to increase the risk of infection, its long-term use was stopped. This problem was later eliminated with the use of sterile water, and its use has become a current issue in critical adult patients as well. Studies show that HFNO treatment improves physiological parameters when compared to conventional oxygen systems. Although there are studies indicating successful applications in different patient groups, there are also studies indicating that it does not create any difference in clinical parameters, but patient comfort is better in HFNO when compared with standard oxygen therapy and noninvasive mechanical ventilation (NIMV) (1-6). In this compilation, the physiological effect mechanisms of HFNO treatment and its use in various clinical situations are discussed in the light of current studies.

1. The Impact Mechanisms of High Flow Nasal Oxygen Therapy

The HFNO device consists of an air/oxygen mixer, an active heater, a humidifier, a unidirectional inspiratory circuit hose, and a soft nasal cannula that is slightly larger than the standard nasal cannula. In the air/

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oxygen mixer, FiO_2 can be increased from 21% (room air) to 100% (pure oxygen) depending on the flow (up to a maximum of 60 L/min). The oxygen is hydrated with water vapor by the active humidifier, and the oxygen can be heated to 37°C prior to delivery to the patient through the unidirectional inspiratory circuit hose (Figure 1) (7).

The physiological effects of HFNO therapy are summarized in Table 1. It was reported that by providing positive airway pressure, HFNO increases the end-expiratory lung volumes and functional residual capacity and decreases the inspiratory resistance. This leads to positive nasopharyngeal pressure and the elimination of CO_2 in the nasopharyngeal dead space. Thus, the metabolic load for gas exchange is reduced and it recovers oxygenation (8-11). These physiological effects suggest that HFNO may be useful in the treatment of respiratory failure, which can be caused by many different conditions.

1a. The Clearance of Nasopharyngeal Dead Space

The soft large nasal cannula creates positive nasopharyngeal pressure by causing resistance in expiration and reduces the total dead space by reducing the nasopharyngeal dead space. This is thought to improve alveolar ventilation. There are few studies showing that high flow cleans the dead space because it is difficult to dissect the pharyngeal airways and to measure the in vivo airflow. An animal study showed that HFNO is effective in CO_2 elimination and dead space washing. In this study, 13 neonatal piglets with acute lung injury were supported with HFNO at oxygen flow rates of 2–8 L/min. When a two-hole cannula fitting in both nostrils was used, its effect on the oxygenation was more pronounced, and when a single-hole cannula fitting in a single nostril was used, its effect on oxygen elimination was more pronounced (12). In a similar animal study, Möller et al. (13) randomly compared continuous airway pressures (CPAP, 2–6 cm H_2O), HFNO in which only a small leak was allowed, and HFNO in which a larger leak was allowed in 13 newborn and spontaneously breathing piglets with lung perforations. It has been found that the tracheal pressures of CPAP and HFNO are comparable. In low leakage and high leakage HFNO groups, PaO_2 showed a linear increase with the flow, and it was reported that gas exchange was corrected with the clearance of the nasopharyngeal dead space. With the development of newer technology, HFNO was shown to clear the pharyngeal dead space in the same study group consisting of 10 healthy volunteers and 3 tracheotomy patients by using radioactive 81mKr gas and a gamma camera. An increase was found in the O_2 inspired through HFNO and a decrease in the expired CO_2 (14). In 12 patients who underwent elective cardiac surgery, Parke et al. measured nasopharyngeal pressures when the mouth was open and closed at flow rates of 30, 40, and 50 L/min by inserting a nasopharyngeal catheter. With the mouth closed, the average airway pressure was found to be 1.93±1.25 cm-H_2O, 2.58±1.54 cmH_2O, and 3.31±1.05 cmH_2O at flow rates of 30, 40, and 50 L/min, respectively. There is a linear relationship between

Table 1. Summary of the effect mechanisms of high flow nasal oxygen therapy

Anatomical dead space is reduced by cleaning the nasopharyngeal area
A positive airway pressure is provided
The FiO_2 provided is higher and more stable
Heated and humidified air is supplied
Breathing workload is reduced

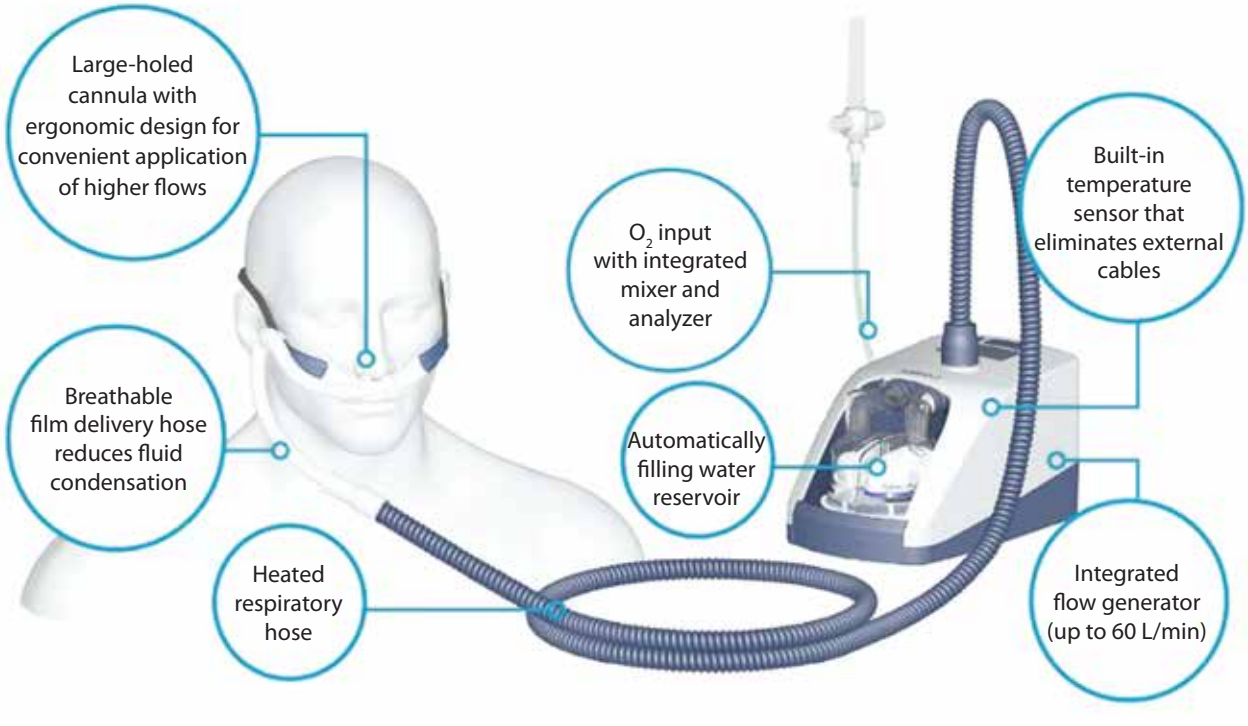

Figure 1. High-flow nasal oxygen cannula (Fisher & Paykel Optiflow®, New Zealand)

flow and pressure, and this relationship is more apparent when the mouth is closed (15). Corley et al. (16) measured airway pressures and end-expiration lung volumes (EELV) by using electrical impedance tomography in 20 patients who also underwent cardiac surgery. When compared with low-flow oxygen therapy, HFNO has been shown to increase both EELV and tidal volume, reduce the number of breaths, and improve oxygenation. This effect was more pronounced in obese patients with a higher body mass index.

1b. PEEP Effect and Alveolar Recruitment

Although nasopharyngeal pressure in HFNO has been shown to increase in many studies, it is unclear whether HFNO actually causes PEEP effect or recruitment in closed alveoli. In an investigation that they conducted with 10 healthy adults, Groves and Tobin (8) found that the average airway pressure was 7.1 cmH_2O at a flow rate of 50 L/min. Riera et al. (17) measured the global and regional end-expiratory lung impedance index (ΔEELI) in supine and prone positions with electrical impedance tomography in 20 healthy adults. EELI increased in both positions. While the ΔEELI distribution in the prone position was homogeneous, the ΔEELI change in the ventral areas in the supine position was found to be significantly higher. The average upper airway pressure was shown to increase when the mouth was closed and as the gas flow increased.

1c. Oxygen Presentation

The oxygen delivered to the patient depends on the peak inspiratory flow rate of the patient, the pattern of respiration, the characteristics of the cannula or mask that is used, and the flow rate of the central oxygen system. The FiO_2 provided in low-flow oxygen systems is not constant and is usually lower than estimated. In these systems, FiO_2 can be given between 26% and 54% in calm breathing and between 24% and 45% in fast breathing at a flow rate of 1–6 L/min. At higher flow rates of 6–15 L/min, FiO_2 can be given between 54% and 75% in calm respiration and between 49% and 72% in fast respiration (18, 19). Higher FiO_2 can be given with a higher flow in HFNO that produces flow-dependent FiO_2. When the oxygen flow is increased from 15 L/min to 45 L/min, the FiO_2 in the trachea can be increased from 60% to 90%. While oxygen is given through a conventional nasal cannula and face mask, the room air often dilutes the given oxygen. The oxygen delivered with high flow in HFNO reduces the entrance of room air and its diluent effect. When the patient's respiratory effort and respiratory rate change in devices delivering oxygen at low flow rates, the oxygen delivery to the patient also changes. When the flow rate is adjusted according to the patient's breathing effort and the severity of respiratory failure, the FiO_2 given in HFNO is less affected by the change in the patient's inspiratory effort (20, 21). The FiO_2 that is measured, especially at the high flow rates in HFNO, is closer to the delivered FiO_2, and this is more evident when the mouth is closed. In their study in which they measured pharyngeal pressures with hypopharyngeal oxygraphy and capnography, Ritchie et al. (22) found that the FiO_2 measured over 30 L/min during nasal respiration (mouth closed) while resting was close to the FiO_2 delivered.

1d. Humidification

In clinical practice, the natural humidification is distorted when the oxygen is delivered from an artificial supply source or when it is delivered directly to the lungs by bypassing the upper respiratory tracts using an endotracheal tube/tracheostomy cannula. The air that is given dry and unheated with conventional oxygen support devices causes nasal dryness, dry mouth, eye irritation, gastric distention, and aspiration. Cold air is known to induce bronchospasm. Thus, heating the air reduces bronchoconstriction and breathing workload. In addition, mucociliary functions improve and the cleaning of secretions become easier. This reduces atelectases and improves gas exchange by correcting the ventilation/perfusion ratio. The heated-humidified air provides more efficient distribution of oxygen to the lungs. This benefit is important, especially for patients with a problem of secretion, such as chronic obstructive pulmonary disease (COPD). Because the HFNO provides air with a high flow, if humidification is not sufficient during HFNO, it may carry the same adverse effects as in NIMV (23, 24).

1e. Its Effect on Respiratory Parameters

Thanks to the above-mentioned physiological effects, HFNO has been shown to reduce respiratory effort, the respiratory rate and to be more comfortable than traditional oxygen delivery systems and NIMV. Vargas et al. (25) investigated the effects of HFNO on respiratory muscle effort, gas exchange, dyspnea score, and patient comfort. In the study they conducted with 12 critical ICU patients with acute hypoxic respiratory insufficiency, measurements were made at four different periods. Oxygen was given through a non-rebreather mask (NRM) in the first period, through HFNO and a 5 cmH_20 CPAP randomly in the second and third periods, and through a simple face mask in the last period. In this study in which each period lasted for 20 minutes, there was no significant difference between HFNO and CPAP in the respiratory effort and number. Itagaki et al. (26) compared low oxygen given through a face mask and HFNO applied at rates of 30–50 L/min (up to 8 L/min) in ICU patients with mild-moderate hypoxic respiratory failure in reference to the respiratory inductance plethysmography. Compared with the face mask, thoracoabdominal synchronization with HFNO was better and the number of respirations was lower (it decreased from 25 breaths/min to 21 breaths/min, $p<0.001$) and the phase angle was found to have significantly improved ($p=0.047$). $PaCO_2$ and VT remained stable because the respiratory rate decreased while the VT was stable and ventilation per minute decreased. This supports the fact that the dead space is smaller. When low-flow oxygen delivery systems were compared with HFNO, a rapid decrease in the number of breaths was observed in HFNO (7-10).

2. High Flow Nasal Oxygen Therapy in Different Clinical Situations

2a. Its Use in Acute Hypoxemic Respiratory Failure

High-flow nasal oxygen therapy has often been studied in acute hypoxic respiratory failure. Studies have generally compared conventional oxygen support systems and NIMV. NIMV is recommended as an initial treatment option for acute COPD exacerbations, acute cardiogenic pulmonary edema, hypoxic respiratory failure in immunosuppressed patients, and for weaning COPD patients from the mechanical ventilation (27-30). However, the benefit of NIMV in de novo acute hypoxic respiratory failure is not clear. In the case of hypoxic respiratory failure occurring in patients without a chronic lung disease or underlying cardiac disease, there is a high likelihood of failure, and NIMV failure is a factor that increases mortality in ICU (31, 32).

The major studies on the use of HFNO in acute hypoxic respiratory failure are presented in Table 2. The primary endpoint of most initial studies in which the number of patients was limited and in which

the control groups were absent was the correction in the physiological parameters and the rate of intubation. Its effect on mortality was examined in subsequent studies. Nevertheless, the initial studies formed the basis of the FLORALI study, which is a large, multicenter, randomized controlled study. The FLORALI study (High flow oxygen therapy for resuscitation of patients with acute lung injury) is an important randomized controlled trial examining the patients with hypoxic respiratory failure of varying severity who are likely to benefit from HFNO. Patients without acute hypoxia and hypercapnia were randomized to HFNO, standard oxygen therapy, or NIMV treatments. In the post hoc analyzes of 238 patients with initially severe hypoxemia ($PaO_2/FiO_2 \leq 200$ mmHg), the intubation rate was significantly lower in the HFNO group compared to the other two groups (p=0.009). When the entire cohort was taken into consideration, HFNO significantly increased the number of days without a ventilator and decreased the 90-day mortality in comparison to the standard oxygen therapy and NIMV. When compared with the other two methods and evaluated in terms of patient comfort, besides the fact that HFNO leads to less discomfort in patients, it reduces the feeling of shortness of breath (6). Although the FLORALI study suggests that HFNO treatment is superior to standard oxygen therapy and NIMV in patients with non-hypercapnic hypoxic respiratory insufficiency, there are some limitations. The number of patients undergoing NIMV is low in the study. In all three groups, the vast majority of patients had pneumonia (approximately 75%). There were bilateral infiltrates compatible with acute respiratory distress syndrome (ARDS) at the same rate, and the use of NIMV in ARDS patients is unclear and controversial. It is indicated that pneumonia is a risk factor for the failure of NIMV (33, 34).

When HFNO therapy is used in patients with hypoxic respiratory insufficiency, the question arises whether the intubation will be delayed and whether or not the mortality will increase. In the study of Kang et al. (35), the ICU mortality according to the intubation time, the weaning time from the ventilator, the 14-day and 28-day mortality, and the duration of stay in the ICU were evaluated in the group of patients in whom HFNO failed. The patients were divided into six groups, including those with acute de novo respiratory failure (i.e., pneumonia and acute respiratory distress syndrome), acute-on-chronic lung disease (i.e., chronic obstructive pulmonary disease and tuberculosis destroyed lung), cardiogenic pulmonary edema, pulmonary edema due to renal failure, septic shock other than respiratory infection, and after extubation. In this study, despite HFNO treatment, intubation was required in 28.4% of patients. The intubated patients were divided into those who were intubated within the first 48-hour period and those who were intubated after the first 48-hour period. Although there were more diabetic patients (33.9% vs. 15.6%, p=0.020) in the early intubation group, the SOFA (Sequential Organ Failure Assessment) score was higher (median 10.0 vs. 7.0, p=0.007), the ICU mortality was lower, the extubation success was increased, and the number of days without ventilation was increased in this group. There was no difference between early and late intubation groups in terms of 14-day and 28-day mortalities or the duration of stay in the ICU. Overall ICU mortality was found to be lower in the early intubation group. It was emphasized in the results for the propensity corrected scores and matched analysis that intubation in the first 48-hour period was associated with decreased ICU mortality, greater extubation success, more successful weaning from a ventilator, and more days without a ventilator. It has been concluded that delayed intubation in patients with failed HFNO may result in respiratory muscle fatigue and cardiac dysfunction and could worsen hospital outcomes (Table 2) (36-39).

2b. Its Use during Preoxygenation in Intensive Care

Desaturation is the most common complication during life-threatening hypoxemia intubation in ICUs, and desaturations are often seen despite preoxygenation. In critical patients, there are many factors that reduce the effectiveness of preoxygenation, including obesity, cardiovascular disease, anemia, low cardiac output, hypermetabolic state, and ventilation/perfusion mismatch. In addition, difficult intubation is encountered more frequently in severe cases. The risk of apnea and desaturation increases in patients in whom intubation is tried more than twice. The improvement of preoxygenation during emergency intubations in the ICU is necessary to reduce intubation-related morbidities (40, 41). In the ICU, the efficiency of oxygenation with a conventional face mask is limited in order to prevent desaturation during the intubation. In this regard, the effectiveness of NIMV has been researched. Baillard et al. (42) showed that the effectiveness of NIMV in preoxygenation was greater than the face mask. The desaturation rate (SpO2 <80%) in their studies decreased from 46% to 7% with NIMV. However, NIMV is not a commonly used application for preoxygenation in ICUs. There are no large and randomized controlled trials showing the superiority of NIMV in preoxygenation. Baillard et al. (42) reported spontaneous NIMV use as 42%. The superiority of HFNO treatment compared to other preoxygenation methods (such as NIMV and reservoir facial mask) was investigated, and it was concluded that HFNO was easier to apply than NIMV (Table 3). Miguel-Montanes et al. (43) compared HFNO with NRM in the study they conducted with patients having mild-moderate hypoxemia in the ICU. Before intubation, 50 patients were preoxygenated with an NRM and 51 patients were preoxygenated with HFNO. The decrease in SpO2 during intubation was found to be greater in the NRM group. The difference between the two groups was maintained when correction was made according to the basal variables [basal SpO2, presence of diabetes mellitus, difficulty in intubation (using an Eschmann tube changer), successful intubation according to the Cormack score after two or four attempts by the assistant, intubation reasons, atrial fibrillation, gender, chronic respiratory failure, and the presence of coronary artery disease] (94 vs. 99, difference 5%, p=0.007). The SpO2 decrease during intubation was examined with the linear effect model, and the difference retained its significance. The prevalence of severe hypoxemia was found to be lower in the HFNO group. HFNO use during intubation was found to be an independent protective factor for the development of severe hypoxemia. Considering the frequent occurrence of hypoxemia during intubation in the ICU, the results of Miguel-Montanes et al. (43) appear to suggest the clinical feasibility of the use of HFNO. However, the results of that study were not supported by subsequent randomized controlled trials. In a randomized controlled trial conducted by Vourch et al. (44), ICU patients with severe hypoxemia were preoxygenated with HFNO and NRM, but there was no difference between the two groups in terms of desaturation. In the study of Semler et al. (45), standard oxygen was randomized to HFNO during laryngoscopy. There was no difference between the two groups in terms of the lowest values of SpO2 in the two minutes after the intubation procedure. In terms of the desaturation incidence (SpO2 <90%), no difference was found

Table 2. Studies conducted with HFNO in patients with hypoxic respiratory failure

Study	Study Design	Number of patients	Patient Population	Method	Primary Termination Point	Secondary Termination Point	Main Result	Side effect
Roca et al. (2010) (4)	Prospective, crossover	20	Hypoxic ARI	HFNO (Starting flow 20–30 L/min) vs. simple face mask	Patient comfort (dyspnea, mouth dryness, comfort)	Respiratory parameters Blood gases Hemodynamic parameters	Increase in comfort, Decrease in oxygenation, decrease in respiratory rate No difference in heart rate, TA.	Cervical-thoracic discomfort Excess gas temperature Nasal discomfort
Sztrymf et al. (2011) (11)	Prospective, observational	38	Severe hypoxic ARI (39% community-acquired pneumonia)	49±9 L/min vs. simple face mask	Clinical parameters and oxygenation Patient Comfort	Intubation rate, Duration until intubation, Risk factors for HFNO failure	Decrease in thoracoabdominal asynchrony in clinical findings Improvement in oxygenation Intubation rate 23.7% (9/38) Median time until intubation 4 hours Increased respiratory rate after HFNO started Low PaO_2/FiO_2, continuation of thoracoabdominal asynchrony	Well-tolerated
Sztrymf et al. (2012) (36)	Prospective, observational	20	Severe hypoxic ARI (55% pneumonia, 15% sepsis, 30% unknown cause)	Median HFNO duration 26.5 (17–121) hours HFNO 20–30 L/min vs. simple face mask	Respiration rate, Oxygen saturation	Intubation rate ICU mortality	Decrease in respiratory rate Increase in oxygen saturation and PaO_2 Intubation rate is 30% (6/20) ICU mortality 15% (3/20)	-
Rello et al. (2012) (37)	Post-hoc analyses of single-centered cohort studies	25	Influenza A/H1N1 infection severe ARI	HFNO	Treatment success Improvement in PaO_2/FiO_2	The factors affecting HFNO failure	Desaturation rate Success rate 45% Risk factors for failure include vasopressor use, low PaO_2/FiO_2	No secondary infection or nosocomial infection.
Parke et al. (2011) (15)	Prospective randomized controlled	60	Elective cardiac surgery, mild-moderate hypoxia	HFNO vs. face mask Starting HFNO flow 35 L/min	Treatment success	NIMV ratio	Higher treatment success (26/29 vs. 15/27) Less need for NIMV (10% vs. 30%) Lower desaturation rate No difference in terms of PaO_2/FiO_2 recovery rate No difference between the ICU leaving time and the hospital leaving time	Better patient comfort and tolerance

Table 2. Studies conducted with HFNO in patients with hypoxic respiratory failure (continued)

Frat et al. (2015) (6)	Multi-centered, open-label, randomized controlled FLORALI Study	310	Nonhypocapnic hypoxic ARI (PaO_2/FiO_2 ≤300 mmHg)	HFNO (50 L/min, with double-hole nasal cannula), Standard oxygen NIMV	28-day intubation rate	Number of days without ventilator 90-day mortality	Intubation rate; HFNO group: 38% Face mask: 47% NIMV: 50% (p=0.18) Number of days without ventilator is less in HFNO Risk for 90-day mortality; 2.01 (Standard oxygen vs. HFNO, p=0.046) 2.5 (NIMV vs. HFNO, p=0.006).	Patient comfort and tolerance good in HFNO No difference in terms of cardiac arrhythmia, cardiopulmonary arrest, or nosocomial pneumonia.
Messika et al. (2015) (38)	Observational, single-centered	45	ARDS (33% Severe, 38% Moderate, 29% Mild ARDS) (the cause is pneumonia in 80%)	Starting flow 60 L/min	Intubation rate	Causes of HFNO failure	Intubation rate is 40% SAPS II elevation, hemodynamic impairment, low PaO_2/FiO_2 ratio	-
Kang et al. (2015) (35)	Retrospective, observational	175 unsuccessful HFNO patients	130 (74.3%) early-intubated 45 (25.7%) late intubated	ARI-de novo (n=58, 33.1%) Patients with chronic disease and ARI (n=53, 30.3%) Cardiogenic pulmonary edema (n=14, 8%) Pulmonary edema due to renal insufficiency (n=6, 3.4%) Pulmonary edema due to septic shock except lung infection (n=15, 8.6%) ARI after extubation (n=29, 16.6%)	Total ICU mortality	Weaning from ventilator 14^{th} and 28^{th} day mortality Length of Stay at YBU	Lower ICU mortality (39.2% vs. 66.7%, p=0.001) No difference between the 14^{th} and 28^{th} day mortality and the duration of stay in ICU. In the early-intubated group, higher extubation success (37.7% vs. 15.6%, p=0.006), higher ventilator weaning, higher number of days without ventilator (8.6±10.1 vs. 3.6±7.5, p=0.001)	-
Gaunt et al. (2015) (39)	Retrospective	145	Medical and trauma patients 35 (24.1%) MV before HFNO 21 (14.5%) MV after HFNO 89 (61.3%) no MV	Up to 80 L/min (FiO_2: 21%–100%) Median flow rate 50 L/min	The effect of early HFNO onset on the VAP incidence and on admission of unplanned ICU	Length of stay in ICU Duration of stay after ICU	Unplanned ICU Admission 20% VAP rate 7% MV application before HFNO extends the duration of stay in ICU and after ICU.	-

ARDS: Acute respiratory distress syndrome; ARI: acute respiratory insufficiency; HFNO: high flow nasal oxygen; ICU: intensive care unit; MV: mechanical ventilation; NIMV: noninvasive mechanical ventilation; VAP: ventilator associated pneumonia

between the groups in terms of the rate of SpO2 lower than 80% or in terms of a decrease in SpO2 more than 3%. These results do not support the routine use of HFNO during intubation of hypoxic patients in the ICU. However, there are ongoing studies investigating the efficacy of HFNO in preoxygenation.

2c. Its Use After Extubation in Intensive Care

Oxygen therapy after extubation in ICUs is an indispensable treatment in high-risk patients, especially in terms of extubation failure. In recent years, the superiority of HFNO treatment over standard oxygen treatments has been investigated in extubated patients. Its

effects on oxygenation of patients, patient comfort, and clinical outcomes (such as extubation failure, re-intubation rate, and mortality) were investigated in the studies. HFNO can form PEEP between 1.5 and 7 cmH_2O. Due to the positive pressure that it creates in the airways, HFNO has been thought to improve oxygenation by improving the atelectases and increasing the functional residual capacity (46). Stéphan et al. (47) assessed NIMV and HFNO as a primary failure of treatment in cardiac surgery patients who had risk factors for the development of post-extubation respiratory failure, who had risk factors for the failure of spontaneous respiratory trial, or who had extubation failure after successful spontaneous respiratory trial. While the risk of treatment failure was less in the HFNO group, the period between the beginning of the treatment and the failure of treatment, the re-intubation rate, and the rates of transition to other treatments were similar between the two groups, and early termination of the treatment was more frequent in the NIMV group. No difference was found between NIMV failure and HFNO failure in heavier hypoxemic patients (24.8% vs. 27.5%, p=0.50). During the first 72 hours, respiratory support was given to 153 patients in the NIMV group and 151 patients in the HFNO group. Although PaO_2/FiO_2 increased in both groups from the first to the third day, this increase was significantly higher in the NIMV group; the respiratory rate was higher in the NIMV group from the first to the third day; PaO_2/FiO_2 values were similar in both groups; and no difference was found in terms of ICU mortality. There were no differences in terms of dyspnea score, comfort score, skin injury score, the number of unplanned nurse interventions, or the number of bronchoscopies. In the randomized and crossover study conducted by Tiruvoipati et al. (48), the patients who were intubated and extubated due to respiratory insufficiency were randomized to NRM and HFNO after a 30 min stabilization period. The patients were switched to HFNO and NRM for the next 30 min. In the maintenance of gas exchange, there was no difference in terms of the respiratory rate or the hemodynamic parameters. Patient tolerance and comfort were reported to be better with HFNO. In a similar crossover study, a portion of the patients were oxygenated with NRM and a portion of them were oxygenated with HFNO in the first 30 min after extubation. A decrease in the respiration rate and heart rate was detected first in the HFNO group. Dyspnea scores 30 min after the start of treatment were found to be lower in the HFNO group, and an increase in patient comfort was also noted (49). In the study comparing the clinical effects of HFNO and NRM after extubation, the mean PaO_2/FiO_2 ratio was significantly increased in the HFNO group and a faster recovery (270 vs. 183 mmHg, p<0.0001) was observed in oxygenation with HFNO. Although there was no difference between the two groups in terms of respiration rate, mean blood pressure, or heart rate, there was an increase in the number of days without a ventilator and a decrease in the rate of intubation in the HFNO group (50). The results of the RINO study (ClinicalTrials.gov: NCT02107183) in which face mask and HFNO were compared in patients with moderate hypoxemia in terms of extubation failure after multicenter randomized controlled extubation will provide more evidence-based data on the place of HFNO in preventing extubation failure.

In the study in which patients with low risk for re-intubation were randomized to HFNO or nasal oxygen therapy, the patients with low risk for re-intubation were defined as the patients who were younger than 65 years of age, who had an APACHE II score lower than 12 on the day of extubation, whose BMI was <30 kg/m^2, who had an adequate cough reflex, who could easily be weaned, who had no or only one comorbidity, who had no heart failure, who had no moderate-severe COPD or airway problems, and who had no prolonged MV. The rate of re-intubation in the first 72 hours after the extubation and the extubation failure in HFNO group was lower and there was no difference in terms of the time until re-intubation (51). In patients with low risk for extubation failure in the ICU, HFNO appears to reduce the re-intubation rate. In a study conducted in a group of patients with high risk for extubation failure in the ICU, it was investigated whether HFNO was as effective as NIMV in preventing extubation failure. Those at high risk for re-intubation were the patients who were over 65 years of age, who had an APACHE II score above 12 on the extubation day, who had a BMI over 30 kg/m^2, who could not control secretions, who had one or more comorbidities, who had difficult or prolonged weaning, who had heart failure as the primary indication for MV, who had moderate to severe COPD, who had airway integrity problems, or who were connected to MV for a long time. While no difference was found between the two groups in terms of re-intubation rate, post-extubation respiratory insufficiency, or time until re-intubation, the rate of mortality was lower in the HFNO group. Side effects causing the treatment to be discontinued were not observed in the HFNO group, while treatment was terminated in 42.9% of the patients in the NIMV group due to side effects (p<0.001) (Table 3) (52).

3. Its Use for the Other Special Cases in Intensive Care

Although NIMV is accepted as the first treatment option in hypercapnic respiratory insufficiency developing due to acute exacerbation of COPD, it cannot be applied in some patients due to reasons such as mask intolerance. Although there are studies conducted with HFNO in patients with hypoxic respiratory insufficiency, there are no large series and randomized controlled studies conducted with HFNO in hypercapnic patients. In a study conducted by Nillius et al. (53) in 17 patients with severe COPD and hypercapnic respiratory failure, HFNO was administered with a two-nasal-hole or a partial-hole cannula delivering 2 L/min O_2 at a flow rate of 20 L/min for 45 min. Although there was a decrease in respiratory rate with HFNO compared to baseline, a patient-based change was observed in respiratory pattern. While a decrease in respiratory rate was observed in some patients, a decrease of 8 mmHg in $PaCO_2$ values was observed in some patients without a change in respiratory rate. In addition to the respiratory effects of HFNO treatment, it has been proposed that it can also improve hemodynamic parameters by reducing the load on the heart. Roca et al. (54) applied HFNO (FiO_2: 21%) to 10 patients who were New York Heart Association (NYHA) Class III and whose ejection fraction was 45% or less. ECHOs were performed at the beginning and at HFNO 20 L/min, 40 L/min, and at the end of HFNO. The presence of more than a 20% collapse in the inferior vena cava (IVC) in the inspirium was considered clinically significant. There was a significant decrease in the inspirium IVC from the basal value (37%) at HFNO 20 L/min and 40 L/min (p<0.05). The hypothesis that the positive pressure that HFNO produces in the airways reduces upper airway obstruction and recovers the ventilation has been examined by McGinley et al. (55) in patients with obstructive sleep apnea. HFNO was administered to 11 patients with moderate-severe OSA (BMI 30.5±4.3 kg/m^2) with a flow rate of 20 L/min. A decrease in the apnea-hypopnea index (28±5 vs. 10±3, p<0.01) and in the arousal index (18± vs. 8±2, p<0.01) was found. Fiber optic bronchoscopy (FOB) can be performed in the ICU for critical patients to look for atelectasis and infection, and hypoxemia is frequently observed during FOB. The effectiveness of HFNO to prevent hypoxemia during FOB was evaluated by Miyagi et al. (56) in five patients with hy-

Table 3. Studies on the use of high-flow nasal oxygen therapy in preoxygenation and post-extubation in intensive care

Study	Study design	Number of patients	Patient population	Comparison	Primary and secondary endpoints	Results
Use for preoxygenation in intensive care						
Miguel-Montanes et al. (2015) (43)	Prospective, semi-experimental pre-post study	101	Patients requiring intubation in ICU	Non-rebreather mask (NRM) vs. HFNO	The lowest median SpO_2 during intubation SpO_2 after oxygenation Number of patients with SpO_2 <80%	The lowest median SpO_2 92% (83%–98.59%) vs. 100% (95%–100%), p<0.0001. Severe hypoxic episode 14% vs. 2%, p=0.03 Independent protective factor before the use of HFNO preoxygenation: odds ratio, 0.146; 95% Cl, 0.01–0.90; p=0.037.
Vourc'h et al. (2015) (44)	Multi-centered, randomized-controlled, parallel, open-label PREOXYFLOW Work	124	Acute hypoxemic respiratory failure PaO_2/FiO_2 & lt; 300 mmHg	Face mask: 4 min, 15 L/min FiO_2 vs. HFNO: 4 min, 60 L/min, FiO_2: 100%	Lowest desaturation during intubation Intubation-related complications, duration of stay in ICU, ICU mortality, 28-day mortality	The lowest SpO_2 value 91.5% (80%–96%) vs. 89.5% (81%–95%), p=0.44 No significant difference in any of the secondary endpoints.
Semler et al. (2016) (45)	Randomized, open-label, parallel group FELLOW Study	150	intensive care patients requiring intubation	HFNO (n=77), 15 L/min, 100% FiO_2 etc. Nasal Oxygen (n=73) 15 L/min	The lowest SpO_2 two minutes after the induction and intubation Hypoxemia (SpO_2 <90%), Severe hypoxemia (SpO_2 <80%) and desaturation (more than 3% reduction in SpO_2), duration of stay in MV and ICU, Hospital mortality	The lowest SpO_2% 92 [IQR 84%–99% vs. 90% [IQR 80%–96%] (p=0.16) No difference in terms of secondary and tertiary endpoints
Use after extubation in intensive care						
Tiruvoipati et al. (2010) (48)	Randomized, crossover study	50	Patients undergoing planned extubation in ICU	N=25 High-flow face mask first, then HFNO N=25 HFNO first, then high flow face mask	Maintenance of gas exchange in arterial blood gases Effect on heart rate, respiratory rate, blood pressure Effect on patient comfort and tolerance	No difference in gas exchange and hemodynamic parameters Better HFNO tolerance (p=0.01), there is a tendency toward more comfort (p=0.09).
Brotfain et al. (2014) (50)	Retrospective	67	ICU patients ready for extubation	HFNO (n=34) vs. non-rebreather mask (NRM) (n=33)	Recovery in oxygenation Number of days without a ventilator Re-intubation rate Length of stay at ICU Mortality	Better PaO_2/FiO_2 in the HFNO group (222 mmHg vs. 270 mmHg, p<0.05) Similar hemodynamic parameters before and after extubation No difference in respiratory rate and $PaCO_2$ Higher number of days without ventilator in the HFNO group (4.2±2.2 vs. 3.0±2.0, p=0.03), lower rate of intubation 2.9% vs. 18.2% (p=0.04)
Corley et al. (2015) (46)	Randomized-controlled study	155	ICU patients with a BMI ≥30 kg/m^2 who underwent cardiac surgery	HFNO (n=81) 35 L/min flow (max. 50 L/min) vs. Standard oxygen (n=74)	Atelectasis score in lung graphy the PaO_2/FiO_2 ratio after 24 Hours of extubation, Respiratory rate, dyspnea score	No difference in terms of the 1st and 5th day Atelectasis scores and PaO^2/FiO^2, Treatment change in in 3 patients in the HFNO group and 5 patients in the standard

Table 3. Studies on the use of high-flow nasal oxygen therapy in preoxygenation and post-extubation in intensive care (continued)

				2–4 L/min nasal cannula or 6 L/min simple face mask	Length of Stay at ICU Treatment change; transition to HFNO, NIMV or NIMV in the standard oxygen group, switching to NIMV or IMV for the HFNO group	oxygen group (Odds ratio 0.53, (95% CI 0.11, 2.24), p=0.40].
Rittayamai et al. (2015) (49)	Randomized, crossover study	17	Patients undergoing planned extubation in ICU	n=9 first HFNO (35 L/d), then NRM (6–10 L/min, SpO_2 ≥94%) n=8 First NRM then HFNO	Severity of shortness of breath, respiratory rate, heart rate, blood pressure, oxygen saturation Patient comfort	Reduced shortness of breath Decrease in respiratory rate (19.8±3.2 vs. 23.1±4.4 respiration/min, p=0.009), decrease in heart rate (89.5±9.5 vs. 95.4±10.4 beats/min p=0.006), Lower dyspnea score; 1.6±1.2 vs. 2.9 1.5 (p=0.04) Most of the patients (88.2%) stated that they would prefer HFNO (p=0.07)
Hernandez et al. (2016) (51)	Multi-centered, randomized-controlled	527	Patients at low risk for extubation failure in ICU	HFNO (n=264) vs. Nasal Oxygen (n=263)	Re-intubation rate 72 hours after extubation Extubation failure Time until re-intubation	Lower re-intubation in HFNO No difference in HFNO 4.9% vs. 12.2% (p=0.004) Reduce extubation failure 8.3% vs. 14.4% (p=0.03) No difference in terms of the time until re-intubation 19 hours (12–28 hours) vs. 15 hours (9–31 hours)
Stephan ve ark (2015) (47)	Multi-centered, Randomized Noninferiority study	830	The patients underwent cardiothoracic surgery (coronary artery by-pass grafting, valvular repair, pulmonary thromboendarterectomy)	NIMV (n=416) (Whole face mask, PS: 8 cm H_2O, PEEP: 4 cm H_2O, FiO_2: 50% etc. HFNO (n=414) (50 L/min, FiO_2: 50%)	Treatment failure Increase in PaO_2/FiO_2 ratio on the 1st and 3rd days ICU mortality Secondary endpoints: dyspnea score, comfort score, skin injury score, number of unplanned nurse interventions, number of bronchoscopies	NIMV 416/91 (21.9%) (95% CI 18.0%–26.2%), HFNO 414/87 (21.0%, %95 CI 17.2%–25.3%) Risk difference 0.9% (95% CI 4.9%–6.6%, p=0.003). Increase in the rate of PaO_2/FiO_2 160→187 (95% CI, 149–170) (95% CI, 173–202), HFNO group 136→157 (95% CI, 127–145) (95% CI, 145–169) (p<0.001). Respiratory rate is higher in NIMV group (p<0.001). ICU mortality 5.5% (95% CI 3.6%–8.3%) vs. 6.8% (95% CI 4.6%–9.7%) (p=0.46).
Hernandez et al. (2016) (52)	Multi-centered, randomized-controlled, noninferiority study	604	Patients at risk for extubation failure in ICU	NIMV (n=314) vs. HFNO (n=290)	Extubation failure in the first 72 hours after extubation Post-extubation respiratory failure Time until re-intubation Respiratory infections, sepsis, multiple organ failure Duration of stay and mortality in ICU Side effects	Re-intubation rate 22.8% vs. 19.1% (absolute difference 3.7%) Post-extubation respiratory failure 26.9% vs. 39.8% (absolute difference 3.7%) No difference in time until re-intubation (26.5 vs. 21.5 hours) Duration of the stay in ICU is shorter in HFNO (3 days vs. 4 days, p=0.048) No side effects in HFNO group, treatment were terminated in 42.7% of the patients in NIMV group.

CI: Confidence interval; HFNO: high flow nasal oxygen; ICU: intensive care unit; IQR: interquartile range; MV: mechanical ventilation; NIMV: noninvasive mechanical ventilation; NRM: non-rebreather mask

poxic respiratory failure (HFNO, flow 30–50 L/min, FiO_2: 50%–95%). In this case series, in which bronchoalveolar lavage was obtained from all patients, one patient needed NIMV after FOB, but HFNO was continued in the other patients for another 30 min after FOB. No FOB procedure was interrupted due to hypoxia or patient discomfort.

In conclusion, HFNO, which has been widely used in critical patients in recent years, seems to be effective at preventing extubation failure and in achieving preoxygenation during intubation and seems to be especially effective at enhancing patient comfort. Studies on the clinical use of HFNO are still continuing.

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