EDITORIAL

High Flow, High Hope: HFNO in Acute Hypoxemic Respiratory Failure

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Since the late 18th century, supplemental oxygen has been utilized as a treatment, and its use for acute hypoxemia dates back to 1887.[1] In an acutely hypoxic patient, the benefit of offering supplemental oxygenation may be limited by a high inspiratory flow which results in entrainment of ambient air. In the last few years after the COVID pandemic, high-flow nasal oxygen (HFNO) has evolved, as the need for respiratory support during acute hypoxemic respiratory failure (AHRF) increased. HFNO by design is an interesting device providing the patient with heated and humidified oxygen at high flows.

High-flow nasal oxygen has several advantages over conventional supplemental oxygenation (Fig. 1):[2]

- Heated and humidified inhaled gases increase the clearance of secretions and decrease bronchoconstriction. By heating the inhaled oxygen to 37°C and humidifying it, the mucosal function in the airway is maintained. This helps maximize the mucus removal by the cilia without the risk of thermal injury.[3] Delivery of heated and humidified oxygen not only increases patient's comfort, but also decreases the risk of bronchoconstriction that occurs because of dry and cold gases.[4] In a study conducted by Roca et al., involving 20 patients, it was discovered that the use of HFNO resulted in improved comfort, reduced oxygenation rate, and enhanced oxygenation.[5]
- Dead space washout decreases minute ventilation requirements, thus decreasing respiratory rate and work of breathing. Because of its high flow, HFNO can continuously flush carbon dioxide (CO_2) from the upper airway increasing the FiO_2 and decreasing the fraction of inspired CO_2.[6]
- High inspiratory flow compensates for the increased peak inspiratory flow observed during respiratory distress, thereby decreasing entrainment of ambient air, hence providing a high fraction of inspired oxygen (FiO_2). However, open-mouth breathing leads to lower FiO_2 because of the mixing of room air with the inspired oxygen.[7]
- Positive airway pressure may result in the recruitment of atelectatic lung fields, thus enhancing the ventilation-perfusion (V/Q) ratio. Groves and Tobin were among the first to demonstrate positive airway pressure by using HFNO. They concluded that when the mouth is closed, the expiratory pressures are higher compared to when the mouth is open, and this is dependent on the flow.[8] Parke and McGuinness found that when the subjects kept their mouths closed while breathing, an increase of 10 L/min in the flow rate led to an increase of 0.69 cm H_2O in the mean airway pressure ($p < 0.01$). When subjects breathed with their mouths open, the same increase in flow rate led to a rise in mean airway pressure by 0.35 cm H_2O ($p < 0.03$).[9] The same group in a later study also found that expiratory pressures were higher compared to mean pressures.[10]

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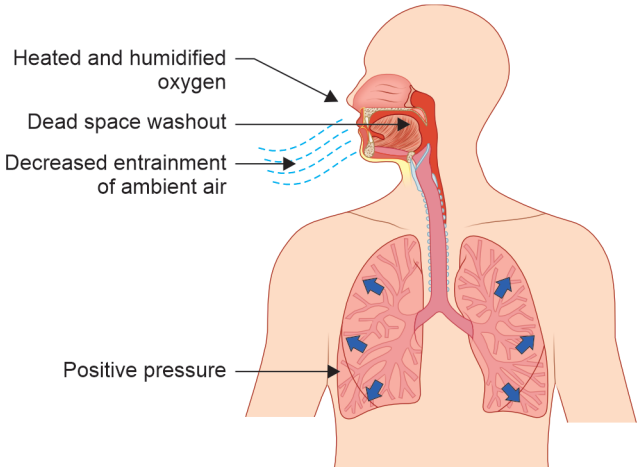

Fig. 1: Advantages of high-flow nasal oxygen

The scientific evidence on the use of HFNO in AHRF started with some anecdotal reports of improved patient comfort and oxygenation. In an early prospective observational study, Sztrymf et al. compared clinical parameters and arterial blood gas in patients on conventional facemasks and HFNO having AHRF. With the use of HFNO, researchers observed a notable reduction in the respiratory

rate, along with an elevation in both oxygen saturation (SpO_2) and the partial pressure of oxygen (PaO_2).[11] In a multicenter RCT, Frat et al. studied 310 patients with AHRF and compared the effectiveness of high-flow oxygen therapy, standard oxygen therapy via a face mask, and non-invasive ventilation (NIV). They found that while there was no significant difference in intubation rates between the groups, the HFNO group had a significantly higher number of ventilation-free days at day 28 (24 ± 8 days) compared to the standard oxygen-by-face mask group (22 ± 10 days) and the NIV group (19 ± 12 days), with a *p*-value of 0.02 for all comparisons. There was a notable difference in the 90-day mortality rate, with the HFNO group showing more favorable results. The primary endpoint of the study was underpowered because the study was designed with the assumption that the intubation rate among standard oxygen would be 60%, but the actual rate was found to be 47%.[12] A later meta-analysis of 9 RCTs of 2093 patients with AHRF found results contrary to that of the trial by FLORALI study group. The meta-analysis found a decreased risk of intubation with HFNO or escalation of oxygen therapy. They also found that HFNO has no impact on intensive care unit (ICU) length of stay (LOS), hospital LOS, patient comfort, or patient-reported dyspnea.[13] The COVID pandemic expanded the use of HFNO outside of ICUs. In a prospective observational trial, 608 patients from the ward and ICU who were started on HFNO were compared. The intubation rates between the two groups were not different. The rate of mortality between the two groups was similar. Significantly more ICU-free days were seen in patients in whom HFNO was started in the ward.[14] The ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate is defined as the ROX index.

$$\text{ROX index} = \frac{SpO_2 / FiO_2}{RR}$$

where RR, respiratory rate; SpO_2/FiO_2, ratio of pulse oximetry/fraction of inspired oxygen

Roca et al. found that at 12 hours the ROX index had the best prediction accuracy. ROX score of 4.88 or more after 12 hours of initiating HFNO was associated with a reduced risk of mechanical ventilation.[15] In a subsequent study, it was discovered that the ROX index's ability to predict outcomes improved over time, as indicated by the increasing area under the receiver operating characteristic curve at 2 hours (0.679), 6 hours (0.703), and 12 hours (0.759). Additionally, a ROX index of 4.88 or more at 2, 6, or 12 hours was consistently linked to a reduced likelihood of requiring mechanical ventilation.[16]

Magdy in their RCT on early initiated HFNO in patients with pneumonia presenting with AHRF included 160 patients. They have compared HFNO to NIV. The primary outcome was similar to the FLORALI study group i.e., the number of patients who need intubation. They found that the intubation rate between HFNO (15%) and NIV(18.7%) was not statistically different. However, they found that for the 48-hour time period, in the HFNO group, the partial pressure of oxygen (PaO_2)/FiO_2 ratio was significantly higher. Also observed was a significantly lower respiratory rate with HFNO at 48 hours [HFNC 20.1 ± 3.4, NIV 23.4 ± 4.2, mean difference 3.3 (95% CI 1.38–4.2, $p = 0.01$)]. There was no significant difference in the length of stay in the ICU or hospital between the two groups. It was concluded that ROX index value below 5.4 at the 12-hour mark was consistently linked to an increased likelihood of intubation.[17]

Conclusion

So we conclude that HFNO is relatively a new device with a limited number of RCTs. Though the device has been extensively used during the COVID pandemic and thereafter, evidence for prevention of intubation, mortality benefit, or LOS is inconsistent. The largest RCT was underpowered in this regard. The use of HFNO outside the ICU is also an area that can change the outcome of patients and prevent ICU admission. There is no doubt that HFNO is here to stay because of its physiological benefits and patient comfort, but the exact outcome gain requires more research.

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