Review Article

High-flow Nasal Cannula: COVID 19 and Beyond

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Abstract

Early case series have suggested that 20%–31% of COVID-19 patients will develop acute respiratory distress syndrome and require intensive care, potentially causing a nationwide shortage of mechanical ventilators. We present a review of the high-flow nasal cannula which presents several physiological benefits in acute respiratory failure. It is a safe treatment modality with low risk of exposure to aerosolized viral particles for health-care workers in the setting of negative-pressure or high-efficiency particulate air-filtered rooms and proper personal protective equipment.

Keywords: Acute respiratory distress syndrome, acute respiratory failure, COVID-19, high-flow nasal cannula, noninvasive positive-pressure ventilation

Introduction

Supplemental oxygen therapy is the first line in the treatment of hypoxemic respiratory failure. Factors that affect alveolar oxygen delivery include the fraction of inspired oxygen (FiO_2) delivered in supplemental flow, the device's interface with the patient, supplemental oxygen flow rate, and inspiratory demand.[1,2] Low-flow devices such as nasal cannulas, nonrebreathing masks, and bag valve masks can provide up to 15 L/min and 100% FiO_2. However, the inspiratory flow rates are approximately 30 L/min even during quiet breathing and exceed supplemental oxygen flow delivered by such devices.[3] This leads to entrainment of room air containing 21% oxygen to meet inspiratory demand and subsequent dilution of the total FiO_2 of the inspiratory flow. During times of respiratory distress, flows reach >100 L/min resulting in entrainment of much larger volumes of room air and resultant reduction in delivered FiO_2.[4]

Venturi mask is an intermediate-flow device that provides fixed FiO_2 but is also affected by this phenomenon.[5] When the FiO_2 requirements are low, this works well. When a higher FiO_2 is to be delivered, less room air is entrained to increase the ratio of supplemental oxygen to room air, but the maximum flow reduces. When the inspiratory demand increases, patients are forced to entrain increased amounts of room air around the mask and this causes the FiO_2 of the inspired flow to fall.

The high-flow nasal cannula (HFNC) overcomes flow limitations of low- and intermediate-flow devices and delivers up to 60 L/min of heated, humidified gas via nasal prongs [Figure 1].[6,7] Precise titration of FiO_2 is achieved via an oxygen blender connected to the circuit and ranges from 0.21 to 1.0 independent of the flow; room air entrainment is minimized by optimizing device flow to meet patient's inspiratory demand.[8] Over the past two decades, several studies have suggested that HFNC enhances patient comfort and oxygenation and is associated with improved clinical outcomes in critically ill patients.[6,9,10] Our review summarizes the contemporary literature on the use of HFNC in intensive care unit (ICU) patients.

Mechanism of action and clinical effects[11]

Physiological benefits of HFNC are summarized in Table 1. The prime clinical benefit of HFNC is its efficiency in delivering supplemental oxygen. It delivers flow-dependent FiO_2.[10] The greater the increase in flow, the more the FiO_2 is augmented. Chanques *et al*. showed that tracheal FiO_2 increases from 0.60 to 0.90 as the flow increases from 15 to 45 L/min.[8] HFNC

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minimizes room air entrainment by delivering flows that are higher than the inspiratory demand and hence results in a higher FiO_2 being delivered. Hence, maximum benefit of HFNC is obtained by matching flow to patient's inspiratory demand.[11]

HFNC washes carbon dioxide (CO_2) out of the upper airways, thereby reducing the anatomical dead space. Subsequently, the work of breathing is improved and respiratory rate lowered by reduction in anatomic dead space. Mauri *et al*. demonstrated this effect in their study of hypoxemic patients with arterial partial pressure of oxygen PaO2/FiO2 <300. They noted that HFNC set at 40 L/min significantly reduced work of breathing and respiratory metabolic demand compared with oxygen delivered by face mask at 12 L/min.[12] Subset analysis revealed that the patients with an elevated arterial partial pressure of carbon dioxide ($PaCO_2$) at baseline benefited the most. CO_2 production is further reduced by decreasing the work of breathing and respiratory metabolic demand. Hence, patients with combined hypoxic and hypercapnic respiratory failure are most likely to benefit from HFNC. Of note, maximal CO_2 washout is achieved by titrating up the high flow until complete washout of the nasopharyngeal dead space is achieved. Increasing flow from 15 to 45 L/min tripled reduction in anatomic dead space from 20 to 60 cc.[13] Hence, for both improving oxygenation and washing out CO_2, it is imperative that the flows be uptitrated to the highest tolerated by the patient to maximize benefits of HFNC.

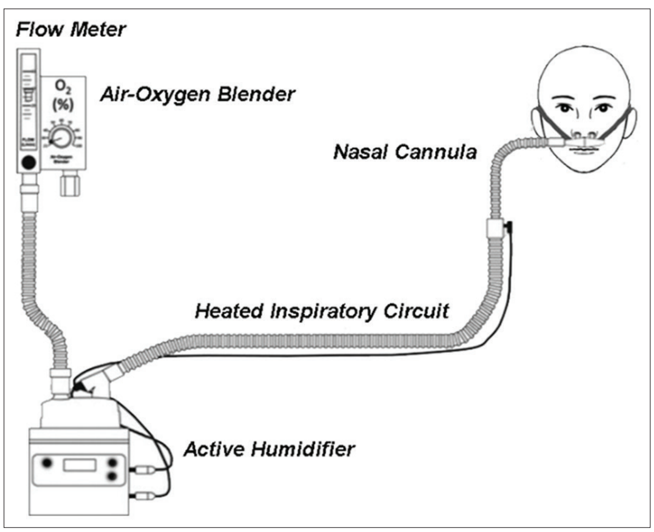

Figure 1: High-flow nasal cannula device.[11]

Table 1: Physiological benefits of high-flow nasal cannula
Improved oxygenation
Decreased anatomical dead space
Decreased metabolic demand of breathing
Decreased production of carbon dioxide
Superior comfort and improved work of breathing
Positive nasopharyngeal and tracheal airway pressure
Better secretion clearance

HFNC delivers optimally conditioned gas by warming and humidifying it to physiological conditions and hence further reduces the work of breathing. Such conditioning of the delivered gas is associated with better conductance and pulmonary compliance compared to dry and cooler gas.[14] It also renders several other benefits including improved mucociliary function, thereby facilitating secretion clearance, decreased risk of atelectasis, and improved ventilation/ perfusion ratio and oxygenation.[8] Thus, flows as high as 60 L/min are tolerated by patients.

HFNC also renders low-level positive pressure. This, in turn, increases lung volumes and improves gas exchange. Corley *et al*. demonstrated a substantially increased end expiratory lung volumes (EELVs) with HFNC compared to other low-flow devices.[15] This was later confirmed by Mauri *et al*.[12] Such an increase in EELV results in improved recruitment of alveoli and prevention of further alveolar collapse. While alveolar recruitment results from the positive airway pressure, the magnitude of this effect is variable and its clinical significance remains somewhat controversial.

At 35 L/min, the mean airway pressure measured with a nasopharyngeal catheter was 1.2 cm H_2O with mouth open, increasing up to 2.7 cm H_2O with mouth closed.[16] 45 L/min generated a mean pressure of 2 cm H_2O in the trachea with mouth closed but only 0.6 cm H_2O with the mouth open.[8] Similarly, 50 L/min produced a mean pressure of 3.3 cm H_2O with mouth closed and 1.7 cm H_2O with mouth open.[17] As most patients in respiratory distress breathe through the mouth, experts have argued that this positive effect of HFNC may be mitigated.

Noninvasive positive-pressure ventilation (NIV) is also commonly used to deliver positive pressure for alveolar recruitment. However, the NIV mask must be firmly secured to the patient's face which hinders secretion clearance, ability to maintain oral intake, and communication and hence is often not tolerated by patients. In these circumstances, HFNC is advantageous. While the patients are receiving HFNC, oral suctioning and expectoration can still occur. Furthermore, as previously mentioned delivery of heated, humidified gas enhances epithelial mucociliary function and hence improves airway clearance.[18,19]

High-Flow Nasal Cannula in Acute Respiratory Failure

HFNC is an attractive tool in the treatment algorithm of acute respiratory failure (ARF). Table 2 summarizes the key studies on the use of HFNC in ARF. These studies have small sample sizes and lack control groups and hence are unable to demonstrate its impact on strong primary outcomes such as reduction in mortality and freedom from intubation. However, they did lay the foundation for the large multicenter randomized FLORALI (Clinical Effect of the Association of Noninvasive Ventilation and High-Flow Nasal Oxygen Therapy in Resuscitation of Patients with Acute Lung Injury)

Table 2: High-flow nasal cannula trials in medical patients

Trial	Design	Patient characteristics	Study arms	Outcomes
Tiruvoipati *et al*. (2010)[21]	Randomized crossover (*n*=42)	Successfully passed SBT	HFNC ->HFFM or vice versa 30L/min	No difference in RR or gas exchange; improved comfort with HFNC
Peters *et al*. (2013)[22]	Prospective (*n*=50)	DNI, in respiratory distress	HFNC 30-60 L/min, no control arm	HFNC improved RR and oxygenation
Maggiore *et al*. (2014)[23]	RCT (*n*=105)	PaO_2/FiO_2 ≤300 at time of extubation	HFNC 50 L/min versus Venturi Mask	HFNC reduced desaturations, reintubations, and NIV; improved comfort with HFNC
Lemiale *et al*. (2015)[24]	RCT (*n*=100)	>6 L/min COT or symptoms of respiratory distress	HFNC 40-50 L/min versus Venturi mask with 60% FiO2	No difference in intubations or comfort
Frat *et al*. (2015) FLORALI Trial[20]	RCT (*n*=310)	PaO_2/FiO_2 ≤300	HFNC 50 L/min versus COT or NIV	Fewer intubations with HFNC (38%) than with COT (47%) and NIV (50%); lower 90-day mortality with HFNC
Hernández *et al*. (2016)[25]	RCT (*n*=527)	Successfully passed SBT; low risk for reintubation	HFNC 30 L/min versus COT	Fewer intubations over 72 h with HFNC (4.9%) than with COT (12.2%); no difference in time to reintubation
Hernández *et al*. (2016)[26]	RCT (*n*=604)	Successfully passed SBT; high risk for reintubation	HFNC 50 L/min versus NIV	Similar intubation rates (22.8% in HFNC vs. 19.1% in NIV) over 72 h; less respiratory failure overall in HFNC (26.9% vs. 39.8%); more adverse events in NIV
Jones *et al*. (2016) HOT-ER Trial[27]	RCT (*n*=303)	SpO_2 ≤92% and RR ≥22 breaths/min admitted to ER	HFNC 40 L/min versus COT	5.5% of HFNC versus 11.6% of COT intubated within 24 h (*P*=0.053); no difference in 90 d mortality

SBT: Spontaneous breathing trial, HFNC: High-flow nasal cannula oxygenation, HFFM: High-flow face mask, RR: Respiratory rate, DNI: Do not intubate, RCT: Randomized control trial, NIV: Noninvasive ventilation, COT: Conventional low-flow oxygen therapy, ER: Emergency room, FiO_2: Fraction of inspired oxygen, SPO_2: Oxygen saturation measured on pulse oximetry

trial which addressed these outcomes by comparing HFNC with conventional low-flow oxygen and NIV.[20]

FLORALI trial randomized adults without preexisting lung disease presenting with a respiratory rate >25 breaths/minute, a PaO_2/FiO_2 ≤300 on 10 L/min or more of oxygen and a $PaCO_2$ <45 mmHg to either HFNC therapy (50 L/min with FiO_2 titrated to SpO_2 >92%), nonrebreather face mask (≥10 L/min for SpO_2 >92%) or NIV (inspiratory pressure titrated to 7–10 ml/kg tidal volume, expiratory pressure 2–10 mm H_2O, and FiO_2 titrated to SpO_2 >92%). The study found no difference between the three modalities as it pertains to its primary outcome of rates of intubation. However, there was a significant difference in ventilator-free days at day 28 and in mortality at 90 days in the HFNC arm. A question that still remained unanswered was if the severity of hypoxemia could limit the use of HFNC. A *post hoc* analysis of the FLORALI trial did show a significant reduction in rates of intubation in the HFNC therapy arm in the subgroup with a PaO_2/FiO_2 ≤200 and similar results were noted in another observational study as well.[28]

In contrast to the FLORALI trial, a different randomized trial investigating early HFNC therapy in the emergency room (ER) did not find it superior to conventional oxygen therapy. In the HOT-ER trial, patients presenting to the ER with hypoxemia (SpO_2 ≤ 92% on room air) were randomized to either HFNC (40 L/min with FiO_2 titrated to clinical need) or conventional oxygen therapy (1–15 L/min).[27] There was no significant difference in rates of intubation at 24 h and mortality at 90 days. There are several key differences in patient characteristics as well as study design between the two trials that could explain these results. The most common cause of ARF in the FLORALI trial was pneumonia, while only 25% of patients in the HOT-ER trial had pneumonia. Over half of HOT-ER patients presented with COPD, asthma, and heart failure; these patients were excluded from the FLORALI trial. Finally, flow was set on an average 10 L/min higher in the FLORALI trial compared to the HOT-ER trial. Patients in the FLORALI trial were required 48 h of uninterrupted HFNC, but in the HOT-ER trial, there was no set protocol for what happened once the patient left the ER.

HFNC should be considered first-line therapy for patients in acute hypoxemic respiratory failure, especially in light of a meta-analysis of over 3,000 patients, where it reduced the need for endotracheal intubation (ETI) compared to conventional oxygen therapy and NIV (odds ratio: 0.60; 95% confidence interval: 0.41–0.86).[29] On the other hand, there continues to remain paucity of literature on the use of HFNC as first-line therapy in acute hypercapnic respiratory failure.

High-Flow Nasal Cannula in Immunosuppressed Patients

Mortality is particularly high among immunosuppressed patients requiring mechanical ventilation.[30,31] Hence, respiratory management that prevents intubation and invasive mechanical ventilation is of particular interest. NIV is often considered first-line therapy based on older studies that suggested that NIV reduces intubations and subsequently mortality in contrast to conventional oxygen therapy.[32-34] However, emerging data have raised concerns about NIV in this patient population.[24,35] In addition, in a *post hoc* analysis of the FLORALI trial, it was noted that NIV increases rates of intubations and mortality compared with HFNC or conventional oxygen therapy among immunosuppressed patients.[35]

A retrospective analysis of cancer patients found HFNC use to lower 28-day mortality compared to conventional oxygen therapy and/or NIV (35% vs. 57%).[36] Furthermore, in a separate prospective observational study, HFNC was noted to reduce intubations (35% vs. 55%) and also lower mortality (20% vs. 40%) when compared to NIV.[37] HFNC is also beneficial in lung transplant patients as it reduces intubations (59% vs. 89%) and lowers mortality (50% vs. 83%) in comparison to face mask oxygen therapy.[38] Timing of HFNC is also critical for its success. It is ineffective when used as a rescue therapy after NIV or conventional oxygen therapy failure; it renders greatest benefits when applied early.[39] HFNC reduces dyspnea and respiratory rates and hence it can provide effective palliative therapy patients who do not wish to be intubated.[22,40]

High-Flow Nasal Cannula Preceding Endotracheal Intubation

The most frequent complication associated with ETI for ARF is severe desaturation under 80%.[41] Preoxygenating prior to ETI is a crucial step that allows delaying desaturation. Oxygenation through a high-flow facial bag mask is usually recommended and NIV has been shown to be useful although has never been studies in a large multicenter RCT.[42] Both of these fail to completely prevent desaturation during ETI as their use is interrupted during laryngoscopy. HFNC can be delivered uninterrupted and hence has been proposed a potentially superior modality. It was indeed found to be superior to nonrebreathing bag reservoir facial mask in achieving a higher median SpO_2 (100% vs. 94%, $P < 0.0001$) and lowering rates of desaturation (80%) events (2% vs. 14%, $P = 0.03$) during ETI.[43] Patients with severe hypoxemia were excluded from this study and subsequent studies have also failed to demonstrate this benefit among severely hypoxemic patients.[44,45] Despite several intuitive benefits of HFNC in preoxygenating prior to ETI, the literature lacks a clear indication and further larger trials are needed to settle this question.

High-Flow Nasal Cannula Following Extubation

Atelectasis and residual oxygenation impairment can last up to 24–48 h after extubation following anesthesia and paralysis even in healthy patients.[46] Owing to its positive effects, HFNC improves postextubation atelectasis and oxygenation in both ICU and postsurgical patients. In the ICU population, HFNC decreases dyspnea score, respiratory rate, and heart rate postextubation compared to nonrebreathing mask.[47] In a retrospective analyses of 67 ICU postextubation comparing HFNC and nonrebreathing mask, the authors found better oxygenation in the high-flow arm; no differences in $PaCO_2$, respiratory rate, mean arterial pressure, and heart rate. Furthermore, the use of HFNC was associated with greater ventilator-free days and lower reintubation rates.[48]

A newer study has shown HFNC (50 L/min for 48 h postextubation) to improve oxygenation, lower $PaCO_2$ and respiratory rate, greater patient comfort, and less need for any mechanical ventilation (including NIV) in postextubation patients when compared to entrainment masks.[23] Similarly, 24 h of HFNC at 30 L/min following extubation reduced reintubations in comparison to conventional oxygen (4.9% vs. 12.2%) in low-risk patients (number needed to treat = 14). It also improved secretions.[25] Among high-risk patients, HFNC delivered at 50 L/min following extubation was similar to NIV in preventing reintubation. In addition, it was better tolerated by patients. High-risk patients were described being older than 65 years and having at least one of the following: (1) heart failure related respiratory failure, (2) moderate-to-severe COPD, (3) ≥2 comorbidities, (4) APACHE II score >12, (5) body mass index >30 kg/m^2 (6) limited airway patency, (7) inability to manage secretions, or (8) mechanical ventilation >7 days.[26] A multicentered randomized controlled trial (RINO trial) is currently under way comparing the use of HFNC to entrainment mask in reducing failure rates among patients with moderate hypoxemia postextubation (ClinicalTrials.gov: NCT02107183).

Postoperative respiratory failure increases mortality.[49] NIV is recommended in postoperative patients based on prior studies.[50] HFNC may have a similar benefit, especially among cardiothoracic surgery and lung resection patients.[51,52] The evidence on use of HFNC in abdominal surgery patients remains equivocal.[53] Table 3 summarizes recent prospective trials evaluating HFNC in surgical patients.

Predictors of High-Flow Nasal Cannula Failure

Early prediction/recognition of progressive respiratory failure despite HFNC therapy is critical. Delaying intubation beyond 48 h when on HFNC increases mortality and results in prolonged mechanical ventilation.[58] Persistently elevated respiratory rates, worsening hypoxemia, thoracoabdominal asynchrony, and the presence of nonpulmonary organ failure may also indicate failure of HFNC therapy.[9,10] Roca *et al*. proposed the respiratory rate oxygenation (ROX) index in patients with ARF from pneumonia.

ROX index is defined as the ratio of SPO_2/FiO_2 to respiratory rate. ROX index > 4.88 after 12 h of HFNC therapy suggested that patient was unlikely to need mechanical ventilation (PPV of 89%). In contrast, ROX index did not help predict who would need to be intubated. Currently, clinical judgment remains the best measure to identify patients who may need escalation of support beyond HFNC.[59]

Table 3: High-flow nasal cannula oxygenation trials in surgical patients

Trial	Design	Patient Characteristics	Study Arms	Outcomes
Thoracic surgery				
Ansari *et al*. (2016)[51]	RCT (*n*=59)	Postlung resection	HFNC 20-50 L/min versus LFO	HFNC reduced hospital LOS; No difference in 6MWT on POD2
Yu *et al*. (2017)[52]	RCT (*n*=110)	Postlobectomy; high risk for reintubation	HFNC 35-60 L/min versus LFO	HFNC reduced reintubations and hypoxemia
Abdominal surgery				
Futier *et al*. (2016)[53]	RCT (*n*=220)	High risk for reintubation	HFNC 50-60 L/min versus LFO	No difference in reintubations, in-hospital mortality or hypoxemia
Cardiac surgery				
Parke *et al*. (2011)[54]	RCT (*n*=60)	Surgical ICU patients	HFNC 35 L/min versus LFO	Lower NIV use (10% vs. 30%) and desaturation events with HFNC
Parke *et al*. (2013)[55]	RCT (*n*=340)	Surgical ICU patients	HFNC 45 L/min versus UC	No difference in SPO_2/FiO_2 on POD 3; fewer escalations in respiratory support in HFNC
Corley *et al*. (2015)[56]	RCT (*n*=55)	BMI ≥30 kg/m^2	HFNC 35-50 L/min versus LFO	No difference in SPO_2/FiO_2 after 24 h; no difference in atelectasis on POD 5
Stephan *et al*. (2015)[57]	RCT (*n*=830)	Previously failed extubation or high risk for reintubation	HFNC 50 L/min versus NIV	No difference in reintubations or ICU mortality; higher skin breakdowns with NIV

HFNC: High-flow nasal cannula oxygenation, LFO: Low-flow oxygenation, RCT: Randomized control trial, LOS: Length of stay, POD: Postoperative day, UC: Usual care, BMI: Body mass index, FiO_2: Fraction of inspired oxygen, SPO_2: Oxygen saturation measured on pulse oximetry, NIV: Noninvasive ventilation

High-Flow Nasal Cannula as a Palliative Care Measure

Among other populations, HFNC has been shown to be feasible and effective in achieving good comfort and relief in dyspnea in "do not intubate" patients during their end of life care.[22,59,60] It has been shown that NIV may help reduce the amount of opiates needed and allow sensorium to be much more preserved. Hence, HFNC allows patients to communicate better while still maintaining an adequate comfort level at the end of life.[61]

High-Flow Nasal Cannula in the Era of COVID-19 Pandemic

In December 2019, cases of severe respiratory illness were described from Wuhan, capital of Hubei Province in China. As of mid-April 2020, the world has seen over 2 million cases with more than 150,000 deaths worldwide. To date, the largest number of cases are in the USA, with New York as the epicenter. In the reports from China, up to half of the patients in respiratory failure were managed by noninvasive means, HFNC or NIV. In a case series from Wuhan, of the 191 cases, 54% had respiratory failure and a third had ARDS.[62] In another report, 60%–70% of patients admitted to ICU had ARDS.[63] Relief of hypoxemia being the highest priority, mild-to-moderate respiratory failure was managed with supplemental oxygen with nasal cannula and if no response, escalated to nonrebreather mask. In the report by Zhou *et al*., 21% of the patients were managed with HFNC.[62]

Advantages of Using High-Flow Nasal Cannula

Two phenotypes of acute hypoxemic respiratory failure and ARDS are recognized. The Type I ("L" type) has low lung elastance and normal lung compliance. The Type II ("H" type) presents with high elasticity, low compliance, increased extravascular lung water and the classic ARDS with recruitable lung bases. Both present with hypoxemic respiratory failure. The relative dissociation between compliance and the hypoxemia observed in the L type is attributed to ventilation perfusion abnormalities due to loss of pulmonary vasoconstriction due to the viral pneumonia.

HFNC has a role in both phenotypes although the "L" type may respond better. The transition from the Type I to Type II seems to depend on the extreme negative respiratory swings in the hypoxic extremely dyspneic patient.[64,65] The ability of the HFNC to deliver heated humidified oxygen from 21% to 100% up to 60 L/min makes it comfortable for the airways to tolerate. The high flows are more likely to meet the higher demands of the dyspneic hypoxemic patient and therefore may reduce the need for intubation.

Safety/Risk of Using High-Flow Nasal Cannula

HFNC and noninvasive ventilation are considered aerosol-generating interventions with risk of viral aerosolization, and in order to reduce the risk to the health-care workers, few precautions can be observed:

1. Preferably use in negative-pressure room with the patient wearing a surgical mask. If not available, the patient should be in a single room with high-efficiency filtration system with a surgical mask over the nasal cannula with droplet/contact isolation and health-care workers in proper personal protective equipments (PPEs)
2. Use snug fitting nasal cannula
3. Some recommend a high limit of 30–40 L/min to reduce the risk of droplet travel distance at rest which increases with cough, but if the health-care workers have adequate

PPE protection, and the patient is in the negative-pressure room, higher flows may be considered
4. Turn off the flow when adjusting the nasal cannula on the patient.

In the WHO guidelines statement, the use of HFNC is placed prior to intubation in the overall plan of management.[66] Similarly, the surviving sepsis guidelines of SCCM recommends use of HFNC when conventional oxygen therapy fails (recommendation 25) and preferentially over noninvasive ventilation (recommendation 26).[67] Experience from the front lines also seems to echo the usefulness of HFNC.[68] Although initial report from China suggested HFNC was helpful in the treatment algorithm, initial recommendations in USA cautioned against its use and to go from nonrebreather mask to intubation.[69] However, with more experience in USA, recognition that when used with adequate precautions, HFNC can get patients through the respiratory failure and avoid intubation is increasingly recognized.[11] It is critical to monitor indicators of improvement including oxygen saturation, oxygen percentage requirement, reduction in respiratory rate, reduced/resolved use of accessory muscles of respiration as indicators of response, and improvement. One important caution is not to delay intubation if HFNC is not meeting the goals.

Conclusion

HFNC oxygenation provides several physiological benefits that make it an effective treatment modality in select patients with hypoxemia and ARF. Future studies will continue to help guide how this treatment modality can be best delivered (i.e., optimal device settings, duration of therapy, and patient selection).

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Conflicts of interest

There are no conflicts of interest.

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