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Is high flow nasal cannula superior to conventional oxygen therapies in COVID-19 induced hypoxia and other type II respiratory failures?

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Abstract: COVID-19 belongs to the severe acute respiratory syndrome (SARS) virus family, which includes virus strains that cause the common cold and flu, and directly affect the lungs by damaging the alveoli, thus impairing gaseous exchange. It creates a condition of silent hypoxia; although each person's symptoms of silent hypoxia may differ, the most typical ones are wheezing, sweating, confusion, and change of lips and skin colour. This silent hypoxia condition can potentially cause irreparable damage to vital organs if left untreated. So we need to oxygenate the patient at the earliest. The goal of oxygenation is to maintain the saturated partial pressure of oxygen (SpO2) level between 92-96%. For this, we used various assisted breathing devices (ABDs); the most used devices for covid-19 treatment were oxygen therapy devices, continuous positive air pressure (CPAP), bilevel positive airway pressure (BiPAP) devices and invasive ventilators. Where all conventional oxygen therapies are still effective, High Flow Nasal Cannula (HFNC) stands one step ahead and is a helpful aid during covid times. HFNC provides warm and humidified oxygen with a high flow rate of up to 60-80 L/min, compared to the 15 L/min flow of conventional oxygen therapies. Thus oxygenation not only got better, but the treatment also became simple and painless since it is a non-invasive technique (NIV) technique. In covid times, HFNC reached many small hospitals. Due to its increased availability, even more clinicians have access to it now. They are using it to treat patients with chronic obstructive pulmonary disease (COPD) and acute respiratory failure (ARF) and get good results. HFNC is becoming a better substitute for standard oxygen therapies and NIV to manage patients suffering from hypoxemic ARF. HFNC also has some drawbacks associated with it. However, despite its weaknesses, increasing evidence base advocates HFNC therapy as a new, advanced, state-of-the-art and efficient method for the initial management of patients with respiratory failure.

***Keywords*-** **Oxygen therapy, MV (Mechanical Ventilator), CPAP (Continuous Positive Air Pressure), HFNC (High Flow Nasal Cannula), NIV (Non-Invasive Ventilation), COVID-19, COPD (Chronic Obstructive Pulmonary Disease)**

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1. INTRODUCTION

COVID-19 belongs to the severe acute respiratory syndrome (SARS) virus family. So, unlike any other virus in the family, it affects the lungs by damaging the alveoli (tiny air sacs). The primary function of the alveoli is to exchange gases with the underlying capillaries [1]. The virus destroys the wall and the epithelial lining of the alveoli and capillaries. Following the destruction, the remains (plasma proteins) gather on the alveoli wall and start forming a clot in the lining. As the walls thicken, the oxygen (O_2) transfer to red blood cells (RBCs) decreases. With time, the O_2 transfer to the RBCs gets more complex, which causes trouble in the exchange of gases, and the body suffers a depletion of oxygen, thus creating a fall in the saturated partial pressure of oxygen (SpO_2) [2].

This way, the COVID-19 virus creates a condition of silent hypoxia because, despite suffering dangerously low levels of oxygen, the patients sometimes show no symptoms of shortness of breath or any breathing difficulty. Although each person's symptoms of silent hypoxia may differ, the most typical ones are- wheezing, coughing, a state of confusion, profuse sweating, change in the colour of lips and skin from natural tone to bluish. When O2 levels in the body are aberrantly low, such conditions can cause permanent damage to vital organs if left untreated. For example, acute respiratory distress syndrome (ARDS) is one of the severe and fatal consequences of Novel Coronavirus infection [3]. To avoid the further degradation of the ongoing silent hypoxic condition, we need to oxygenate the patient on a priority basis. The goal is to maintain the SpO_2 level in the patient between 92-96% [4]. For this, we used various assisted breathing devices (ABDs), e.g., Oxygen therapy devices, ventilators, and continuous positive air pressure (CPAP) devices. Data shows that even after the majority of people with COVID-19 had a moderate illness (40-45%), about 15 % of the patients were seriously ill, demanding oxygen therapy, and 5% were in critical condition, demanding intensive care unit (ICU) admission and care. Many of them also needed mechanical ventilation [5-7]. All severe COVID patients are suggested to get oxygen therapy, commencing at 5 L/min to 15 L/min, using various types of masks for adults and 1-2 L/min for children. After starting the oxygen therapy, now the focus should be on how much FIO_2 we can deliver with various devices instead of flow. e.g. nasal cannula can deliver 24%-44% at flows of 1-6 L/min, so we need to shift to a facemask which can provide up to 60% and then to a partial rebreathing mask (PRM) or non-rebreathing mask (NRM) that can provide 85-100%. Additionally, high-flow nasal cannula (HFNC) has superior flow rates and variable fractional oxygen concentrations compared to invasive/non-invasive ventilation (NIV) devices [8].

2. Oxygen therapy resources and Devices

Oxygen therapy consists of two basic systems, the oxygen system, which includes an oxygen source in a stored form or a production unit combined with storage. And a delivery system comprising devices like- face masks, nasal cannula, nasal catheters, and oxygen tubings is used to provide oxygen. [9] The oxygen source can be:- An Oxygen cylinder, where the compressed oxygen gas is kept in a tiny tank. Hospitals receive this pre-filled cryogenic distillation at an oxygen-producing facility or via pressure swing adsorption (PSA) at the hospital level. The oxygen is delivered on demand [10]. The second is a liquid oxygen tank, where the liquid oxygen is maximally produced by the cryogenic method and is generated off-site (not at Hospitals). Hospitals have huge liquid oxygen storage tanks that are refilled time-time. The tank is connected to a central pipe network via vaporizers laid inside the hospital, which can deliver gaseous oxygen directly to patients. The transport of liquid oxygen occurs by self-vaporization without any need for electricity. Since the oxygen is highly concentrated and then further pressurized to convert it into liquid form, more oxygen fits in a small, handy, portable, and refillable tank or dura cylinders [10]. Third, an Oxygen concentrator is a portable device that takes natural air in, removes other naturally occurring gases, leaves only the oxygen behind, concentrates it, and stores it in a reservoir. Oxygen is delivered from the reservoir by a tube to a conduit like an oxygen mask or nasal cannula. They are less expensive and do not require filling but can give a maximum flow rate of 5-8L/min, best for home care therapy [9-11].

3. Ventilator

A mechanical ventilator (MV) is a medical device that offers artificial respiration by moving oxygen in and carbon dioxide out of the lungs, thus providing breaths to a person who cannot breathe naturally or is breathing inefficiently. MV are hi-tech microprocessor-controlled devices. Since an MV forces air into the individual's lungs to assist with breathing, it can help a person breathe or assist them when they find it difficult or are incapable/insufficient of doing so on their own [12]. Mechanical ventilators were first used in 1929. There are two types; Negative-pressure ventilator, which sucks the air into the lungs through chest expansion and contraction, e.g. Tank or cuirass ventilators, and Iron lung ventilators. These were in use earlier but are not used these days. The second type, the Positive-pressure ventilator, forces the air into the lungs. These were developed at the beginning of the 1950s to treat polio patients having pulmonary paralysis. Air is blown into the person's lungs via a tube. Positive pressure ventilators can be invasive or non-invasive. For invasive ventilation, the patient has an endotracheal tube introduced into their windpipe, usually in the hospital ICU. Two processes can do invasive ventilation: Endotracheal intubation, where the tube is inserted through the patient's mouth or nose into their windpipe (trachea); or Tracheostomy, where an incision is made in the windpipe to introduce the tube [13,14].

Figure 1 shows the different components of an MV and their roles. The NIVs are equipped with masks and can be used at home without the supervision of medical staff. It is of three different types; the first one is Auto titrating (adjustable) positive windpipe pressure (APAP), where the air pressure adjusts automatically as the patient's breathing pattern varies. The second is Bilevel positive windpipe pressure (BiPAP), which allows for air delivery at different pressures separately for inspiration and expiration. And the third is CPAP, which delivers O_2 with constant flow and static pressure [15,16].

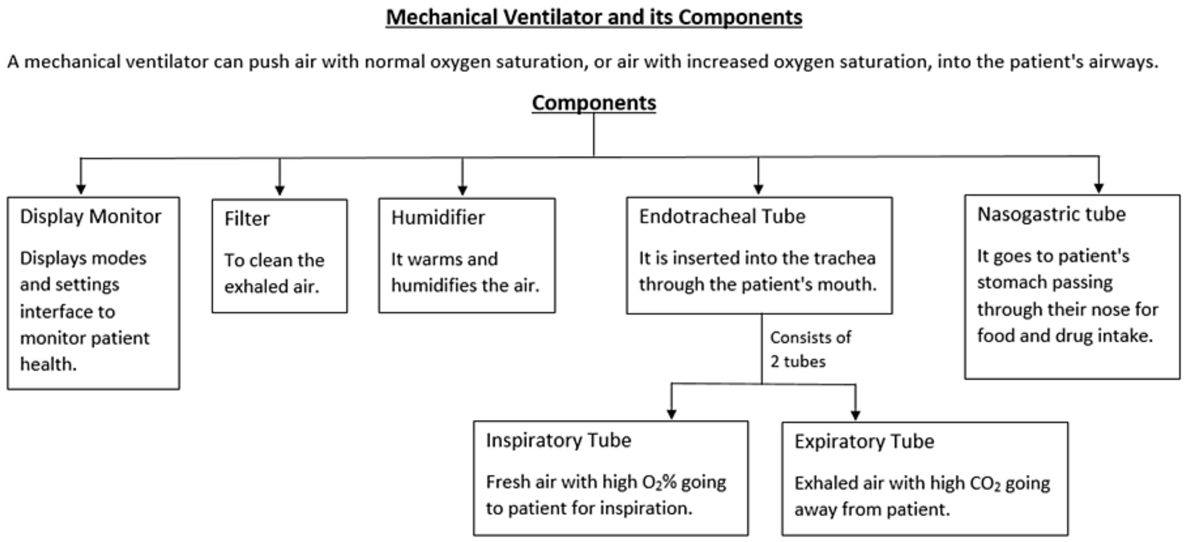

Figure 1: Mechanical ventilator and its components

Currently, CPAP/BiPAP ventilators are commonly being used in hospitals. They force the air inside the person's windpipe, but at the cost of gastric insufflation. The ventilator repeatedly blows and stops in fixed pre-set rounds allowing the lungs to accept oxygen and throw the carbon dioxide [16,17]. These can be operated with three different settings; the first is Volume-controlled. With this setting, the ventilator delivers a pre-set amount of air inside the person's windpipe even if it creates an increased airway pressure. After stopping the flow, the chest goes into recoil and throws the air out. The second is Pressure-controlled. With this setting, the ventilator supplies air till the airway pressure limit is touched on the upper hand, after which the valves open to throw the air out. The air volume may differ based on the windpipe resistance and pulmonary capacities. The third is Dual control, which combines the advantages of both of the above settings and provides airflow based on the need and response of the person [13]. Figure 2 shows a new CPAP device, which is even smaller and portable.

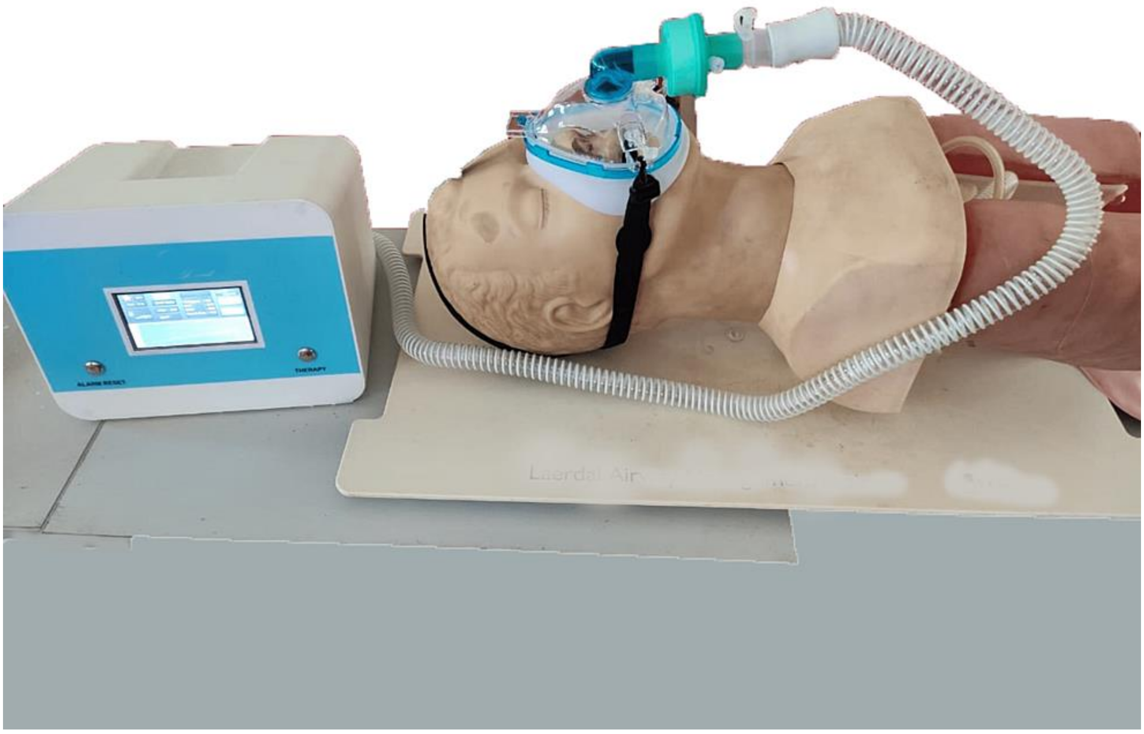

Figure 2: A portable continuous positive air pressure device

Mechanical ventilation every so often helps to save lives but sometimes can cause serious problems; since the air here is delivered at high pressures, the patients are at increased threat of developing pulmonary and cardiac complications. These can be linked directly to the physical effects of the high intra-thoracic pressures created by the ventilator, going up to alveolar and systemic inflammatory responses. Most side effects and complications of MV, such as Hemodynamic effects, oxygen toxicity, impact on respiratory muscles and respiratory infections, and ventilator-induced lung injury, can be avoided or minimized [17].

4. High Flow Nasal Cannula

Since the 1990s, NIV techniques have been primarily used in cardiogenic pulmonary oedema, and chronic obstructive pulmonary disease (COPD) to achieve great results but has debatable results in acute respiratory failure. NIV facilitates gaseous interchange and decreases respiratory exertion via positive pressure. However, good acceptance of NIV occasionally gets tough to accomplish because of the recurrent leaks around the mask, probably creating a lack in patient-ventilator concurrence and finally leading to the need for intubation. Also, it can further create other deadly complications due to the delay in intubation due to concealing the symptoms of respiratory distress, even barotrauma due to the increased tidal volume produced owing to the positive pressure. [18,19] Oxygen delivery via HFNC is a modern method that delivers warm and humidified oxygen with an increased flow rate. HFNC is a more effortless procedure than NIV and can become a better substitute treatment for hypoxemic acute respiratory failure (ARF). HFNC is easier to tolerate than NIV and also healthier for the patients. It supplies a high fraction of inspired oxygen (F_IO_2) and titratable F_IO_2, creates a low level of positive pressure, and offers a flush out of dead space in the upper windpipe, thus enhancing physical lung properties and decreasing the load on respiratory muscles during ARF. The gas is continuously supplied at high-flow rates to wash upper windpipes, creating a flush out of dead space and then throwing carbon dioxide (CO_2) out. This effect helps improve physical lung properties, reducing respiratory effort and minimal ventilation requirement [18,20].

To manage COVID, the Government of India (GOI) created a task force that guided to treat moderate and severe cases COVID patients first with HFNC. And intubation should only be introduced in patients facing high breathing efforts or who are intolerant to HFNC and NIV [21]. HFNC use also reduces the needed stay days in the hospital by reducing the need for intubation. Thus HFNC proves helpful in situations with limited numbers of MVs and helps a patient get early treatment. With HFNC, there was a prevalent risk of aerosol generation. To address this, GOI guided all hospitals to advise patients to cover the cannula with N-95 masks, or hospitals can even use an incubation box for patients. GOI recommended HFNC settings: Start at a flow rate of 20 to 30 litres per minute and an F_IO_2 of 40%; titrate flow rate up to a maximum of 60 litres per minute with slowly increasing 5-10 L/min as indicated by respiratory rate, effort in breathing and SpO_2. F_IO_2 should be raised in 5-10% increments, up to 100%, if increasing flow alone is ineffective in achieving the desired SpO_2 level [22].
It has been demonstrated that in newborns, the conductance and pulmonary compliance can significantly decrease within just 5 minutes of the direct delivery of ambient oxygen to the trachea. In comparison, sufficiently acclimatized oxygen has minimal effect on the physical properties of the lungs. Saslow, et al. have found increased respiratory compliance in newborns when HFNC delivered acclimatized oxygen at just 5 L/min of high-flow rate compared to 6 cmH_2O of a standard CPAP. The findings showed that humidification and heating of the oxygen minimize broncho-constriction and facilitate effortless breathing. The acclimatized oxygen improves mucociliary function, eases clearing of discharge, and reduces atelectasis, which ensures a better ventilation/perfusion ratio and oxygenation [23].

The success rate of NIV methods also relies on acceptance and patient compliance. Despite a higher airflow rate, HFNC is getting more approval than NIV and conventional oxygen therapies. The heater and humidifier in HFNC help to make the physiological conditions similar to that found in alveolus with absolute humidity of 44 mg/L of water. Whereas the conventional oxygen therapies, which are given using face masks, deliver non-humidified or under-humidified cold oxygen, which directly hits the upper windpipe and causes dehydration, which leads to broncho-constriction and brings discomfort to the patient. This problem arises even after using a bubble humidifier in the conventional oxygen therapies. Many studies have been conducted on patients, and reviews have been taken from patients, to evaluate the comfort provided by HFNC therapy. They stated that patients feel better relief and less dyspnoea feeling by HFNC than conventional oxygen therapies via a mask or NIV, subsequently improving acceptance [23,24]. HFNC appears to be a better substitute for standard oxygen therapy and NIV to manage patients suffering from hypoxemic ARF. Its better acceptance, physiological effects comprising high F_IO_2, Positive end-expiratory pressure (PEEP) effect, and flushing of dead space leads to reduced exertion upon respiration and helps minimize lung strain [24].

5. Limitations to HFNC

Salvador, et al. described the discomforts of a patient from HFNC. The heated and high-flow oxygen near the nose irritates the nostrils. Problems can get serious if the patient suffers from rhinitis, nasal mucus, or epistaxis. The patient can even face oral dryness due to the high flow rate if the oxygen is inadequately humidified. The continuous flow causes strain in expiration due to its undue resistance from the expired air. The patient can manifest this as a feeling of suffocation. The constant chest pressure can further lead to patients' discomfort. Since one cannot move the setup, it limits patient mobility, including going to the washroom and waning their quality of life. The patient does not know the concept of HFNC therapy as he does not know that he needs to be in a prone position throughout the therapy, and the treatment will not be helpful if the oxygen comes out via the mouth. Thus patient needs to be well informed about HFNC therapy. These discomforts may seem small, but they play a significant role in the acceptance and usage of these devices [25].

The significant drawbacks of HFNC include; Since HFNC provides oxygen with high flow, it consumes more oxygen which became a limiting factor during the Covid period. An oxygen crisis arose as the demands rose and the production did not meet the consumption demands. HFNC cannot be suggested to patients with severe hypoxemic respiratory failure (HRF) because it has yet to confirm that it ensures a positive pharyngeal pressure because high flow via an HFNC encounters resistance from patient expiration and pharyngeal pressure increases. Some critical questions like the indication to start the therapy and timing criteria for activating the therapy, ending the therapy, and accelerating the treatment, if needed, remain unanswered. The large scale randomized clinical trials are yet to be conducted to prove its wide clinical applications [23]. HFNC is not just a device that only needs to be powered on and off. Proper training of health workers and patient guidance is essential to help them take advantage of the technique with due safety [26].

6. Other Prospects

Generally, oxygen does not humidify at low flow rates, and if such oxygen is given to a patient, the patient chiefly complains of dry nose, dry throat, and nasal pain. Inadequate heat and humidification lead to decreased acceptance of oxygen therapy. Where standard devices limit oxygen flow to 15 L/min, with HFNC, we can smoothly achieve flow rates up to 60 L/min; thus, the oxygen is adequately humidified in HFNC. While the performance of humidifiers largely determines the humidification, it is also influenced by the patient's respiration patterns. Chikata, et al. evaluated the performance of commonly used HFNC systems. They established that, irrespective of patient minute volume (VT), the HFNCs deliver adequately warm and humidified oxygen when the flow rate is above 40 L/min [23,27].

The latest studies also show a similar intubation rate with a decreased death rate in persons cured via HFNC compared to those treated via NIV or conventional oxygen therapies. HFNC reduces the nasopharyngeal and oro-pharyngeal dead space by a flush-out effect and maintains PEEP. The flush-out of nasopharyngeal dead space is linked with a better gaseous exchange at the alveoli level, which allows the patient to breathe more comfortably. This can also help us use the HFNC to provide respiratory care free of or with supplemental O_2 administration. Since HFNC has a heater and humidifier, warm and humidified O_2 can be given at high flow rates and delivered with titrated, supplemental oxygen therapy [18,26].

The inspiratory flow fluctuates broadly between 30-100 L/min in Hypoxemic Respiratory Failure (HRF) patients. Where conventional devices limit oxygen flow to 15 L/min, the gap between patient inspiratory flow and delivered flow becomes significantly huge since FIO2 is inconstant and often lower than needed. HFNC can solve this quickly and thus has received extra attention in treating mild to moderate HRF and is being considered a substitute to conventional oxygen therapies. It also seems helpful for treating hypercapnic respiratory failure [28,29]. Also, there are emerging pieces of evidence that support the use of HFNC in patients suffering from COPD, ARF, and those getting palliative treatment. HFNC is comfortable, has good acceptance, and thus is safe to manage breathlessness even in malignancy patients. Also, we can provide high-flow oxygen via face masks to patients with Covid-19 infection, which eases the load on critical care resources. Also, HFNC is used in non-intubated thoracoscopic surgery, reducing procedure-related injury and increasing post-operative recovery for early lung cancer [30,31]. The evidence base for HFNC is promptly developing and offers assurance in dismissing bothersome symptoms and for patients getting palliative treatment [30].

7. DISCUSSION

Different methods and NIV have previously been tried to prevent intubation in persons with hypoxemic ARF. These days HFNC is being used more and more in persons with hypoxemic ARF and has shown improved relief, with reduced dyspnoea, along with significantly less/no mouth and windpipe dehydration compared to conservative standard oxygen therapy [18]. HFNC has been proven more useful than CPAP in avoiding intubations and ventilation days. HFNC is expected to provide methods to help in efficient breathing beyond just applying CPAP, because HFNC clears the dead space in the upper windpipe (nasopharynx region), thus improving oxygenation and CO_2 elimination. With HFNC, CO_2 levels are brought down in a flow-dependent method free of leaks, while the oxygenation and tracheal pressures increase similarly in a flow-dependent form [32]. Table 1 shows a comparison between HFNC and Conventional oxygen therapies.

Table 1- Comparison between Conventional Therapies and HFNC

Problems with MV	Solution with HFNC	References
MV's deliver dry and unwarmed gas, and this cold gas induces broncho-constriction, causing patient discomfort.	A heater and a humidifier are fundamental components in HFNC, which eliminates these problems, and this acclimatizing of oxygen lessens the broncho-constriction and eases the effort for breathing.	[32,34]
It includes endotracheal intubation, an invasive process, and the patient cannot talk or swallow after intubation. A nasogastric tube (Ryles tube) is inserted and is used to give drugs, liquid, and liquid food.	HFNC is among the several modalities of NIV and provides non-invasive oxygenation. No intubation is needed, so it is painless. Even patients can talk and eat food and take medicines normally.	[35]
Most humidification occurs naturally in the upper airway. However, with endotracheal intubation and tracheostomy, the tube bypasses the upper airway, which presents with mask uneasiness, nasal dryness, oral dryness, and eye irritation.	With no requirement of intubation and invasion, the provision of initial humidity in HFNC prevents dehydration of the airway, thus helping avoid the inflammatory response due to drying of the mucosa, leading to increased patient comfort.	[36]
The vocal cord can get damaged from the intubated endotracheal tube, affecting air passage into the lungs, especially in young children with smaller airways.	HFNC is a non-invasive method, and no intubation is needed; thus, there is no chance of vocal cord damage.	[33]
In patients with Hypoxemic Respiratory Failure (HRF), maintaining the desired oxygenation relies on managing the Fraction of inspired air (F_IO_2) and PEEP. With conventional oxygen therapy, oxygen delivery is limited to 15 L/min, creating a significant amid between patient inspiratory flow and delivered flow F_IO_2 values.	HFNC plays an important role here by doing its primary job, which is to provide oxygen at a great flow rate of 60 L/min while maintaining the PEEP effect continuously. With this, HFNC does provide a higher flow, and actual F_IO_2 values are generally close to the delivered F_IO_2, thus proving to be more beneficial for patients with mild to moderate HRF.	[37]
Critical COVID-19 patients frequently show poor prognosis after MV and develop problems like- ventilator-associated pneumonia; deep-vein thrombosis.	HFNC prevents intubation in the patients. Thus these complications can be avoided.	[29]
Atelectasis is a condition in which the lung or some of its areas do not expand fully. Since the alveoli are not in continuous use, there are chances of airway collapse.	It reduces the probability of airway collapse by continuous involvement of alveoli by the PEEP (positive end-expiratory pressure) effect.	[33]
These complications considerably extend the length of ICU stay.	Since the complications here are minimized, the patient does not need an extended ICU stay. And Patients have the satisfaction of taking oral feeds earlier, which also helps in recovery.	

8. Conclusions

The existing data suggest that HFNC therapy could be used as a paramount preference over conventional CPAP support. HFNC offers better washout of arterial CO_2, while CPAP also does but not as proficiently, and that too independent of the alterations in minute ventilation. Compared to standard oxygen therapies, HFNC provides higher oxygenation and enhances respiratory physiology by decreasing the load on the lungs, improving mucociliary clearance, and increasing dead space flush-out. This flush-out effect aids in a better gaseous exchange at the alveoli level, allowing the patient for comfortable and effortless breathing. Thus HFNC helps in adequate oxygen supply to the lungs, which is vital for persons with discharge problems, such as COPD patients. So, HFNC can be seen as an actual NIV therapy for ventilator care. And as we discussed above, instead of the discomforts and drawbacks of HFNC, it proved to be of great help in Covid-19 and gave excellent results even in severely ill patients with COPD complications and Hypoxemic ARF. Thus we can consider HFNC therapy as a new, advanced, state-of-the-art, and efficient method for the initial management of respiratory failure patients related to various underlying diseases and disorders.

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11. Conflicts of Interest
The authors declare that there are no conflicts of interest.

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