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Review Article

THE PHYSIOLOGICAL EFFECTS AND CLINICAL USES OF HIGH FLOW NASAL CANNULA OXYGEN THERAPY: A REVIEW

Suresh Pariyar[1*], Geng Wan Ru[2] and Zhang Yan[3]

[1*]*School of Clinical Medicine, Inner Mongolia University for Nationalities, 538 West Huolin He Street, Horqin District, Tongliao city, Inner Mongolia, P.R.China.*

[2]*Department of Respiratory Medicine, Affiliated Hospital of Inner Mongolia University for Nationalities, 1742 Huolin He Street, Horqin District, Tongliao city, Inner Mongolia, P.R.China.*

[3]*Department of Pediatrics, Affiliated Hospital of Inner Mongolia University for Nationalities, 1742 Huolin He Street, Horqin District, Tongliao city, Inner Mongolia, P.R.China*

ABSTRACT

Supplemental oxygen delivery is the first line therapy for hypoxemic patients. Various conventional oxygen therapies (COT) have been used for many years. Because of many limitations and drawbacks in COT method, recently there has been introduced a novel and innovative method in alternative to COT, the heated humidified high flow nasal cannula oxygen therapy (HFNC). It comprises of an air blender, an active humidifier, a single heated circuit and a nasal cannula for appropriate size. It delivers heated (37^0c), humidified (100%) oxygen with high flow rates up to 60L/min. There are numbers of physiological properties of HFNC oxygen therapy such as; flushing of dead space, a positive expiratory pressure effect, control of FiO_2, heated and humidification of air, greater comfortable and well tolerated. HFNC oxygen therapy is being used in adult hypoxemic respiratory failure patients, airway obstructive disease, acute heart failure, post extubation, oxygenation for pre intubation, sleep apnea, do not intubate patients and others. HFNC oxygen therapy has been established and broadly studied in neonatal and pediatric setting. In this article we reviewed present existing literature of HFNC oxygen therapy in adult patients and reported its physiological effects and current evidence in clinical uses. The main point of this review is to guide clinicians towards evidence based clinical practice guideline.

Keywords: *high flow nasal cannula, conventional oxygen therapy, hypoxemia, acute respiratory failure, physiological effects, clinical uses*

INTRODUCTION

Administration of supplemental oxygen is the first line therapy for the respiratory failure patients to maintain adequate oxygenation and alveolar ventilation [1]. For many year's administration of oxygen has been provided by different devices such as nasal prongs, face masks. Depending on the rate of oxygen flow, the oxygen delivery devices are categorized as low flow devices (simple nasal cannula, simple face mask) which can deliver oxygen up to 6 L/min, Intermediate flow devices (ventury mask, non-rebreathing mask) which can deliver up to 15 L/min and high flow devices (heated humidified HFNC) which can deliver up to 60L/min [2]. The low flow and intermediate flow devices are collectively called conventional oxygen therapy (COT) method and have many limitations and drawbacks. Cold, dry and poorly humidified oxygen may have patient's complaints, such as dry nose, dry throat, nose pain, mask irritation and poor tolerance. Also the cold and dry oxygen increases airway resistance and known to reduce mucociliary clearance [3,4,]. Limitation in oxygen flow (up to 15L/min), these flow rates may be significantly lower than patients inspiratory flow rates and the oxygen is diluted as it is mixed with room air [5]. It is found that, in respiratory failure patients the inspiratory flow varies between 30 to 120 L/min [6]. The fraction of inspired oxygen (FiO_2) is not constant during conventional oxygen therapy.

Choosing a correct oxygen therapy method is very important to decrese rate of mechanical ventilation and mortality in hypoxemic patients and also making patients safety and comfortable. High flow nasal cannula (HFNC) oxygen therapy is being widely adopted innovative respiratory support for hypoxemic patients especially those with acute respiratory failure [7]. HFNC consists of an air blender, an active humidifier, a single heated circuit and a nasal cannula of appropriate size. It delivers adequately heated (37^0c) and humidified (100%) oxygen at high flow rate up to 60L/min [8]. HFNC has significant advantages in oxygenation and ventilation over conventional oxygen therapy. Constant supplement of high flow oxygen provides fixed FiO_2 and decrease oxygen dilution. It also washes out physiological dead space and generate positive end expiratory pressure (PEEP) that enhances ventilation [9,10]. The heated humidified air enhances clearance of secretion, decrease bronco spasm and maintain mucosal integrity. This device is very comfortable and compliance; patient can talk, eat, drink etc.

HFNC oxygen therapy has been established and widely studied in neonatal and pediatric setting [11]. However, the use of HFNC oxygen therapy is being gaining attention in the adult patient with hypoxemic respiratory failure, post extubation, acute heart failure and so on. Also the HFNC has a role in treating hypercapnic respiratory failure as a rescue therapy when intubation and NPPV are contraindicated or NPPV is not tolerated or an alternative to NPPV and in do not itubate patients [12].

Physiological Mechanism:

HFNC delivers oxygen at flow rate up to 60 L/min, from an air/oxygen blender is which air is humidified with an active humidifier through a heated circuit. It is suggested that HFNC can provide several benefits. These include: reducing anatomical dead space, generating positive end-expiratory pressure (PEEP), maintaining constant FiO_2, improving mucociliary clearance and reducing respiratory work. Fully heated and humidified high flow gas can meet the flow demand of hypoxic patients. [13]. The key principle of HFNC oxygen therapy as follows,

- Flushed out anatomical dead space
- Constant PEEP
- Constant fraction of inspired oxygen (FiO_2)
- Heating, Humidification of inspired oxygen
- Nasopharyngeal Clearance
- Decrease work of breathing

Decrease in Anatomical Dead Space:

An important mechanism of HFNC oxygen therapy is to clear the dead space of nasopharyngeal cavity, thereby reducing the overall dead space and leading to oxygenation and alveolar ventilation. Thus, there is an advancement in the efficiency of respiratory strength in hypoxemic patients [14]. Since the HFNC delivers oxygen at high flow rates so washes out the expired volume of carbon dioxide (CO_2) from the airway and replacing it with oxygen. W Mollar et al. [15] demonstrated a study of two model, a simple tube and anatomically representative upper airway model, connected from segmental CT- scan image of a healthy volunteers. Both the models were filled with tracer gases, then oxygen was delivered via HFNC at rates of 15, 30, 45L/min. Dynamic infrared carbon dioxide spectroscopy and 81m kr gas radioactive gamma camera imaging were used to measure the clearance of tracer gases. Both model showed similar flow-dependent tracer gas clearance in the models. The tracer gas gap of the two models is related to the flow rate. There was complete tracer gas removal from the nasal cavity within 1 sec while using HFNC. This study concluded the fast occurring clearance of nasal cavities by HFNC oxygen therapy, which is capable of decreasing of dead space rebreathing. Same author conducted another randomized crossover study on 10 volunteers using scintigraphy with ^{81m}Krypton (^{81m}Kr) gas during a breath-holding maneuver with closed mouth and in 3 nasally breathing tracheotomized patients. The level CO_2 and O_2 in the upper airway were measure by volumetric capnography and oximetry and measured the inspired volume via inductance plethysmography [16]. Oxygen was delivered through HFNC at the rates of 15, 30, and 45 l/min. They found that, HFNC clears expired air (CO_2) from upper airways which reduces dead space by a decrease of rebreathing and making ventilation more effective. The flushing of dead space is flow and time dependent, and it can extend below the soft palate. Breathing rate is lower via HFNC oxygen therapy, where $PaCO_2$ and VT remain constant so the minute ventilation is lower. It is also likely that alveolar ventilation, along with $PaCO_2$ is constant. These evidences suggested the HFNC oxygen therapy reduces the dead space in upper airway.

PEEP Effect:

Although HFNC is an open system, the high flow rate of nasal cannula can exert pressure on some expiratory resistance. Physiologically, the positive airway pressure produced by high flow oxygen provides a certain amount of pulmonary dilation pressure and alveolar recruitment. Parke et al. [17] performed a study in 15 human volunteers planned for elective cardiac surgery and demonstrated that high flow delivered via a

HFNC produced positive airway pressures in the nasopharynx. They delivered oxygen through HFNC at flow rates of 30, 40, 50 L/min in the patients with mouth open and closed. The pressure was measured over one minute of breathing. They found proportional relationship between flow and pressure i.e. the mean nasopharyngeal pressure during nasal high flow oxygen increases as flow increases. This effect has been studied in healthy persons by N Groves et al. [18]. In their study the volunteers were connected through a high flow nasal cannula with mouth closed. The pharyngeal pressures were measured with flows from 0 to 60 L/min. The median pressure of flow-dependent positive expiratory pressure was 7.4 cm H_2O recorded at a speed of 60 L/min during the mouth closure period. They recorded that the expiratory pressure of closing the mouth was higher than that of opening the mouth. In conclusion, this study shows that the mean nasopharyngeal pressure increases with the increase of nasal oxygen flow. The HFNC oxygen therapy depends on blood flow and whether the patient breathes with his mouth open or closed.

Constant FiO_2:

Actual FiO_2 is not stable with low-flow oxygen delivery and generally much lower than required [19]. At 1–6 L/min, FiO2 ranges from 0.26 to 0.54 during calm breathing and 0.24 to 0.45 during rapid breathing where at 6–15 L/min, FiO_2 ranges from 0.54 to 0.75 and 0.4 to 0.72 during calm and rapid breathing respectively [20]. HFNC can deliver oxygen adequately and support the respiratory system and hydrate the airways effectively. FiO_2 values are more stable and higher in patients treating via HFNC than those of standard oxygen delivery systems because it can deliver oxygen at high flow rates that can match or even exceed the patient's inspiratory flow demand. Also it reduces the entrainment of room air and dilution of administered oxygen [21]. However, HFNC delivers at high flow, so the actual FiO_2 is close to predicted FiO_2. Ritchie et al. [3] evaluated a study on healthy volunteer. Hypopharyngeal oxygraphy, capnography, and airway pressure were measured though hypopharyngeal catheter. Oxygen was transported through HFNC during rest and with exercise at rate of 10, 20, 30, 40 and 50l/min, of which FiO_2 is 60%. When the nose breathes more than 30 l/min at rest, the measured FiO_2 is always the same as the transported FiO_2.

Heat, Humidification and Nasopharyngeal Clearance:

The primary mechanical respiratory defence mechanisms are sneezing, coughing, gagging. Nasal hairs are natural filters and are responsible to trap inhaled contaminants. Mucociliary transport system is the second line defence mechanism which traps and neutralizes inhaled contaminants (in mucus) and expels them up and out of the airway, maintaining the lungs free from infection-causing agents, dust and allergens. Loss of humidity can be interfering in defense system. Conventional oxygen devices delivered dry and unwarmed air which are associated with, nasal dryness, oral dryness, mask discomfort, nasal and eye trauma, eye irritation, gastric distension, and aspiration [22,23]. Dr. Greenspan et al. [24] demonstrated a study in ventilated infants by delivering nonwarmed and nonhumidified ambient gas just for five minutes of respiration and resulted that there is a significant reduction in pulmonary compliance and conductance. Furthermore, Fontanari et al. [25] experimented on 22 normal volunteers and 18 asthmatic patients. Cold and dry air was delivered to them and observed that receptors in the nasal mucosa respond to cold and dry gas to show a protective bronchoconstrictor response in both normal subjects and asthmatics. On et al. [26] observed that the cool and dry triggered muscarinic receptors in the nasal mucosa and elicits the symptoms like bronchoconstriction.

HFNC delivers heated (37°C) and humidified air (100%) the respiratory system to saturation, especially in high flow rates (up to 60L/min), conventional oxygen delivery systems fail [27]. Saslow et al. [28] compared 6 cmH2O conventional CPAP using standard humidifier with heated and humidified HFNC oxygen therapy at flow rate of 5L/min in infants. Infants who used heating and humidified oxygen for 5 l/min high flow delivery had higher respiratory compliance. Warming and humidifying oxygen can reduce airway constriction and respiratory work. Chanques et al. [29] in their study, including 30 patients treated with HFNC oxygen therapy, the study showed that the humidity level of bubble humidifiers was low and was associated with significant discomfort; however, the use of heated humidifiers in patients treated with HFNC oxygen therapy was associated with a reduction in drying symptoms mediated by increased humidity levels and significant comfort. Heating and humidifying of the gas minimize airway constriction and reduce respiratory work. Active humidification improves mucociliary function, promotes secretion clearance, reduces atelectasis formation, and increases ventilation perfusion ratio and oxygenation. Through this mechanism, mucociliary function and secretion clearance were improved. A Hansai et al. [30] was conducted a study in patients with idiopathic bronchiectasis whose retention rate of inhaled tracers decreased before and after receiving warm and humid air through HFNC. Sztrymf et al. [31] reported the effect of high flow nasal cannula oxygen therapy in patients with acute respiratory failure in intensive care unit (ICU). Because of lower airway resistance and good mucosal clearance, HFNC oxygen therapy can improve patients comfort quality of life.

Decreased Work of Breathing:

It is not clear whether HFNC reduces the work of breathing, but some studies have shown that it does. It is not clear whether HFNC oxygen therapy reduces the work of breathing, but some studies have shown that it has role to reduce work of breathing in hypercapnic patients. Itagaki et al. [32] evaluated 40 patients in ICU. Low flow oxygen (up to 8L/min) was given through the oronasal mask for 30 minutes, and followed HFNC at flow rates of 30-50L/min was given. The thoracic and abdominal movements were measured by breath induction plethysmography and the synchronization between thorax and abdomen was observed. They found that HFNC had better chest-abdominal synchronization than mask delivery. Corley et al. [4] investigated 20 patients of post-cardiac surgery by comparing low flow oxygen with HFNCs. They believe that HFNCs are more beneficial to patients with high BMI by increasing both EELV and tidal volume to reduce respiratory rate and improve oxygenation. All these data suggest that HFNC oxygen therapy reduces respiratory work in patients with hypoxemia.

Clinical uses HFNC:

The HFNC oxygen therapy is a very versatile and useful oxygen supplement method. It can be used in low-monitoring environment and requires little knowledge of mechanical ventilation. However, the majority of patients receiving HFNC treatment are extremely hypoxemic, which raises the important question of whether it should be used in this situation. In order to overcome these problems, several potential clinical applications have emerged in recent years. These include acute hypoxic respiratory failure or respiratory distress syndrome (ARDS), respiratory failure caused by heart failure and respiratory support in patients with respiratory failure after extubation. In this review, we also use HFNC as an adjunct to airway instrumentation, for patients with impaired immune function, do not intubate patients and as a means of reducing suffering at the end of life.

Acute hypoxemic respiratory failure:

Conventional oxygen therapy (COT) is a first-line supportive therapy for patients with hypoxic acute respiratory failure (ARF). Unfortunately, in these systems, the flow, heating and humidification of inhaled oxygen, as well as the increase of entrainment of indoor air, are limited at the patient's high inspiratory flow rate, resulting in oxygen dilution and FiO2 reduction [33]. Sztrymf et al. [34] studied the efficacy, safety and outcome of immediate HFNC oxygen therapy in patients with hypoxic ARF intensive care unit (ICU) without any time limit. The use of HFNC was associated with significant decreases in respiratory frequency, heart rate, dyspnea score, supraclavicular contraction and thoracoabdominal asynchrony, and significant improvements in Spo2. These improvements were evident in the first 15-30 minutes after the application of high nasal flow and continued throughout the study period without any unintended side effects. More than 75% of patients avoided intubation. Therefore, the authors concluded that HFNC oxygen therapy has a good effect on clinical signs and oxygenation in patients with severe ARF. In a prospective observational study of ARF patients with community-acquired pneumonia and sepsis, the same group of authors further confirmed these positive results [31]. Roca et al. [35] evaluated the respiratory and oxygenation parameters of 20 patients in intensive care unit (ICU). They found that clinical and physiological parameters improved significantly after 30 minutes of HFNC oxygen therapy compared with standard mask oxygen therapy. It is worth noting that the median duration of routine treatment before the start of HFNC is more than 4 days, which excludes any conclusion that HFNC has an immediate effect on ARF. In addition, HFNC is only used for 30 minutes, so data on the long-term effects of the device cannot be obtained. Parke et al. [36] assessed whether patients with mild to moderate hypoxic respiratory failure in cardiothoracic ICU had better tolerance to HFNC and fewer treatment failures than traditional mask delivery for the HFNC group, flow was 35 L/min, and FIO2 were titrated to maintain SpO2 at ≥95%; therapy failed for 3 of 29 (10%) in the HFNC group and 12 of 27 (44%) in the conventional group. Rello et al. [37] applied HFNC to acute hypoxic respiratory failure caused by influenza A (H1N1). Of the 35 patients, 5 received conventional oxygen therapy and 10 needed immediate intubation. The remaining 20 patients were unable to maintain SpO2 above 92% when the oxygen supply was more than 9 l/min: 9 patients were successfully treated with HFNC, avoiding intubation, and the remaining 11 patients were subsequently intubated. The results showed that the patients in the HFNC treatment group improved significantly without intubation. In a recent randomized controlled trial conducted by Frat et al. [38], in patients with hypoxic ARF admitted in ICU receiving HFNC oxygen therapy, NIV and standard oxygen therapy (SOT) were evaluated to their effects on tracheal intubation and to compare the results. NIV and SOT did not decrease the intubation rate in the whole study population. However, the intubation rate of HFNC group was significantly lower in the subgroup with severe respiratory insufficiency ($PaO_2/FiO_2 \leqslant 200$). Even after adjusting the simplified acute physiology score II (SAPS II) and the history of cardiac insufficiency, there were more days without ventilators (if intubated) and better survival rates.

Acute Hypercapnic Respiratory Failure:

There is abundant evidence that HFNC oxygen therapy is a very promising treatment for some hypercapnic respiratory failure. Nilius et al. [39] studied the effect of HFNC on 17 chronic obstructive pulmonary disease patients with chronic hypercapnia respiratory failure. After mixing 20 l/min indoor air and 2 l/min oxygen through nasal cannula, via both or one nostrils were introduced for 45 minutes. Individuals respond differently to HFNC, but some have lower respiratory rate and some have lower $PaCO_2$. The results showed that high flow nasal intubation could improve respiratory efficiency and could be used as an adjuvant therapy for low flow oxygen to prevent hypercapnia respiratory failure in patients with severe chronic obstructive pulmonary disease. Jens Bräunlich et al. [40] conducted an interventional clinical study on 54 patients with severe chronic obstructive pulmonary disease. All patients received 20, 30, 40 and 50 l/min of oxygen through hfnc. The parameters such as flow-dependent changes in mean airway pressure, breathing volume, respiratory frequency and reduced partial pressure of carbon dioxide ($PaCO_2$) were evaluated. They concluded that HFNC can improve the respiratory effect of COPD patients, reduced $PaCO_2$, reduce work of breathing and rapid shallow breathing index as indicators of work load of breathing. Helene Vogelsinger et al. [41] studied a single cohort of 77 patients with clinically stable hypoxemia who had indications for long-term oxygen therapy (LTOT). They received COT and HFNC oxygen therapy for 60 minutes, including oxygen adaptation, and were separated through a 30-minute washout period, regardless of whether they had hypercapnia or not. All patients can tolerate HFNC well. $PaCO_2$ decreased significantly during the oxygen adaptation of HFNC, and the increase of PaO_2 was consistent with that of SpO_2 during the treatment. They concluded that short-term use of HFNC oxygen is safe in normal and hypercapnic COPD patients. Lower oxygen levels can effectively correct hypoxic respiratory failure and reduce hypercapnia, thereby reducing oxygen consumption. Chatila et al. [42] studied of exercise-breathing ability of chronic obstructive pulmonary disease patients with unloaded bicycle ergometer and found that exercise ability increased after using HFNC to improve oxygenation compared with spontaneous breathing. Eun Sun Kim et al, [7] studied a retrospective study included acute respiratory failure patients with hypercapnia in the medical intensive care unit (MICU) from April 2011 to February 2013, who required HFNC oxygen therapy for hypoxemia. Respiratory parameters were recorded and arterial blood gas analyses conducted before, and at 1 and 24 h after initiation of HFNC oxygen therapy. Oxygen therapy with sufficient to maintain a normal partial pressure of arterial oxygen and significantly reduced in acute respiratory failure patient with hypercapnia. Eun Sun Kim et al. [7] studied a retrospective study involving patients with acute respiratory failure with hypercapnia in the intensive care unit (MICU) from April 2011 to February 2013 who treated with HFNC oxygen therapy to correct hypoxemia. Respiratory parameters were recorded and arterial blood gas was analyzed before, 1 and 24 hours of HFNC oxygen treatment. In patients with hypercapnia and acute respiratory failure, there were sufficient FiO_2, maintained normal arterial partial pressure of oxygen (PaO_2) and significantly reduce $PaCO_2$ by HFNC oxygen therapy.

Acute Heart Failure:

It is common to find patients with acute heart failure (AHF) who, after being stabilized, maintain a level of dyspnea or hypoxemia which does not improve with conventional oxygenation systems. Various oxygenation methods are used for treating respiratory failure occurring with acute heart failure [43]. Nuttapol Rittayamai et al. [44] investigated the physiological effects of HFNC compared to conventional in subjects with acute dyspnea and hypoxemia in congestive heart failure and found that, HFNC improved dyspnea and comfort level in patients. Jose Manuel Carratala Perales et al. [45] experimented five CHF patients due to acute pulmonary edema and treated with COT (Venturi mask, 15L/m) for 24 hrs and then after 24 hrs treated with HFNC oxygen therapy. The clinical and gasometric parameters and degree of dyspnea showed significant improvement after 24 hrs treatment with HFT system. Takahito Itoh et al. [46] conducted experiment on four cases with refractory hypoxemia due to congestive heart failure, successfully treated with HFNC oxygen therapy instead of invasive ventilation. Mean duration of the therapy was 6-9 days without relapse of respiratory distress. Roca O, at el. [47] administered high flow oxygen through nasal cannula to 10 admitted patients with NYHA class III and left ventricle ejection fraction 45% or less and found decrease in respiratory rate and inspiratory collapse inferior venacava is significantly decreased. Onalk Makdee at el. [48] assigned patients aged 18 years and older with cardiogenic pulmonary edema to receive either conventional oxygen therapy or HFNC in emergency department. They found high flow nasal cannula therapy decreases the severity of dyspnea during the first hour of treatment. CHEN Zhi-peng et al. [49] explore the clinical effect of high-flow oxygen and noninvasive positive-pressure ventilation in patients with acute left heart failure in acute left heart failure in ICU and found that HFNC can improve oxygenation obviously in patients with acute left heart failure,is more comfortable and tolerable than NIV.

Post-extubation:

High flow oxygen therapy is a routine treatment for hypoxic respiratory failure in patients with ICU after extubation. Traditionally, this treatment is performed through a mask rather than a nasal cannula because of the flow limitation of the traditional nasal cannula and the trend of breathing through the mouth in patients with dyspnea [50]. Re-intubation is associated with increased ICU, longer hospital stays and mortality [51]. The failure rate of extubation in ICU ranged from 6% to 47%. Respiratory failure is the most common cause. Its morbidity and mortality are more than twice that of successful extubation. Tiruvoipati et al. [52] compared the efficacy of high flow oxygen intubation and high flow face mask (HFFM) in 50 patients after extubation. All patients were randomly divided into scheme A (HFFM followed by HFNC) and scheme B (HFNC followed by HFFM) 30 minutes after extubation. The results showed that HFNC was an effective method of oxygen transfusion, and the tolerated to extubated patients who requiring large flow of oxygen and significantly better than that of HFFM. Maggiore et al. [53] randomly selected common ICU patients with hypoxemia risk ($PaO2/FiO2 < 300$ before extubation) to use HFNC (n = 53) or venturi inner mask (n = 52). The PaO2/FiO2 ratio was higher and the interface displacement was smaller in HFNC patients.

They are also highly saturated, received fewer re-intubations and required less ventilator support. Meanwhile, Parke et al. [54] were randomly assigned to receive HFNC (45 l/min) or conventional delivery after cardiac surgery. Oxygen therapy was started after extubation and lasted until the second day. There was no significant difference in oxygenation between the two groups. $PaCO_2$ in HFNC group was lower at 4 hours after extubation and in the morning of the second day. The number of patients requiring increased respiratory support in HFNC group decreased significantly. Moccaldo A, [22] conducted a randomized study of 109 patients who received Venture mask oxygen or high flow nasal cannula oxygen. All analysis parameters (respiratory rate, oxygenation, device displacement, comfort) were support the use of HFNC. The frequency of re-intubation in HFNC group (3.5%) was significantly lower than that in Venturi mask group (21%), although it may be thought that the latter seemed to be unusually high. Nevertheless, this study clearly demonstrates the potential benefits of this technique in improving post-extubation comfort and oxygenation. Hernandez et al. [55] conducted a randomized clinical trial of 527 patients with low risk of respiratory failure after extubation who were randomly treated with HFNC oxygen therapy or standard oxygen therapy (SOT). Compared with SOT, HFNC oxygen therapy resulted in lower respiratory failure (14.4% to 8.3%) and re-intubation rate (12.2% to 4.9%) after extubation.

Pre-intubation:

Endotracheal intubation in critically ill patients is associated with life-threatening complications, about 20% of which are mainly due to hypoxemia [56]. Hypoxemia and hemodynamic instability in ICU patients were the main causes of hypoxia and severe desaturation during laryngoscopy. During the whole process, preoxidation was interrupted, even for a short period of time [57]. Non-invasive ventilation can be used to enhance oxygenation before endotracheal intubation, but masks must be removed during laryngoscopy, which will deprive patients of oxygen during procedure [[58]. In these cases, nasal cannulas do not interfere with laryngoscopy, and HFNC can be used to deliver oxygen during apnea due to its high flow rate and constant FiO_2 content. In addition, the high flow rate of NHF forms a huge oxygen reservoir in the nasopharyngeal region. Together with the elimination of carbon dioxide by flushing dead zone [16] and CPAP [3-8cmH_2O], nasal high flow becomes a promising oxygenation device during intubation, which maintains oxygenation without rapidly and dangerously increasing carbon oxide concentration [59]. Miguel Montanes et al. [60] studied a clinical trial involving 101 patients, comparing preoperative and intraoperative oxygenation with non-breathing bag mask and HFNC during tracheal intubation in ICU patients. The lowest median oxygen saturation was 94% in non-breathing bag mask intubation and 100% in HFNC intubation. The authors conclude that HFNC significantly reduces the incidence of severe hypoxemia and that it can improve patient safety during ICU intubation. Fewer data have been published, so the potential benefits of HFNC during intubation should be further evaluated in clinical studies. However, for ethical reasons, this study cannot be designed as a randomized controlled trial [6]. It is immoral to compare HFNC with traditional mask oxygen in a randomized controlled study because the published data clearly show the advantages of HFNC.

Use of HFNC in the Emergency Department:

Dyspnea and hypoxemia are one of the most common complaints of patients in the emergency department (ED). According to current guidelines, oxygen therapy is one of the first treatments available. Depending on the severity of respiratory distress, it can be delivered through a mask or nasal cannula. The rapid relief of dyspnea and the correction of hypoxemia are not always achieved by conventional oxygen. Limited oxygen supply must be added to conventional oxygen, which is quite inaccurate for the exact amount of FiO2transported. Owing to insufficient heating and humidification, some patients have poor tolerance to oxygen. Lenglet H et al. [61] evaluated a prospective observational study in the emergency department of a university hospital. The potential benefits and feasibility of HFNC in 17 patients with acute respiratory failure who still need more than 9 l/min of oxygen after oxygen therapy or who have persistent clinical symptoms of respiratory distress were studied. Patients were treated with HFNC after routine oxygen treatment through mask. The rate of dyspnea before and 15, 30 and 60 minutes after the onset of HFNC was measured by Borg scale, visual analogue scale (VAS), respiratory rate (RR) and pulse oxygen saturation (SpO_2). The new device was associated with a significant reduction in dyspnea scores (Borg score dropped from 6 to 3, VAS from 7 to 3, RR from 28 to 25, Spo2 from 90% to 97%). HFNC can rapidly and significantly improve dyspnea scores and other parameters. Compared with traditional mask oxygen therapy, HFNC also has good tolerance, comfort and ease of use. These results suggest that HFNC can be used as a first-line treatment for ARF patients. However, more studies are needed to prove whether early use of hFnc can prevent emergency patients with ARF from being admitted to ICU.

Bronchoscopy and other invasive procedure:

In bronchoscopy, gas exchange is usually impaired due to a mismatch between sedation and ventilation. Hypoxemia is common in bronchoscopy because PaO_2 usually decreases by about 20 mHg during procedure, and the most serious decrease occurs during bronchoalveolar lavage (BAL) [62]. In order to avoid hypoxemia caused by bronchoscopy, oxygen can be supplied through low or high gas flow interfaces. Another successful method is noninvasive ventilation during bronchoscopy in high-risk patients. HFNC as an assistant airway instrument was studied in airway operations (such as bronchoscopy and intubation) in patients with low and high risk (such as hypoxemia and morbid obesity). Lucangelo et al. [63] compared the use of HFNC (40 or 60 l/min) or Venturi mask to deliver 50% oxygen before and during bronchoscopy in stable patients (SaO2 > 90% when breathing indoor air). Fifteen patients in each group were given data at baseline (when breathing in indoor air), at the end of bronchoscopy (during which they received 50% oxygen using the prescribed treatment) and 10 minutes after bronchoscopy (when they received 35% oxygen through venturi tube masks). Patients treated with HFNC for 60 L / min maintained high PaO_2 value, high arterial and alveolar oxygen tension and high PaO_2 / FiO_2 ratio during and after operation.

Others:

The HFNC oxygen therapy can be use in various conditions such as; sleep apnea, palliative care, immunocompromize patients and most importantly in DNI patients. McGinley et al. [64] found that HFNC delivery in patients with obstructive sleep apnea was more likely to lead to upper respiratory obstruction. HFNC with 20 l/min flow was used in both children and adults. In children, this reduces inspiratory flow restrictions and awakening and apnea Index. HFNC also lowered the awakening and apnea Hypopnea Index in adults. Epstein et al. [65] searched a hospital database and identified 183 cancer patients, 55% of whom received no attempt to resuscitate (DNR) orders. These patients received HFNC treatment (median treatment time was 3 days): 41% improved, 44% remained stable, and 15% worsened during treatment. The total mortality rate was 55%.

Coudroy et al. [66] reviewed the archives of respiratory failure patients with impaired immune function (i.e., shortness of breath or respiratory distress, PaO2/FiO2 ≤ 300). Patients received either HFNC (n = 60), alternate treatment of NIV and HFNC (n = 30) or conventional oxygen therapy (25 cases). The intubation rate and mortality rate in NIV group were higher than those in HFNC group. Recently, Peters et al. [67] confirmed that 50 patients with hypoxic and mild hypercapnic respiratory distress had not been intubated (DNI) or resuscitated (DNR), who had been admitted to ICU and received HFNC treatment before NIV. The patients were diagnosed as pulmonary fibrosis (15), pneumonia (15), chronic obstructive pulmonary disease/COPD (12), cancer (7), hematological malignancies (7) and congestive heart failure/CHF (3). At the beginning of HFNC treatment, the average FiO_2 was 0.67, the flow rate was 42.6 L/min, the average oxygen saturation increased from 89.1% to 94.7% ($p < 0.001$), and the respiratory rate was 30.6-24.7/min ($p < 0.001$). It is noteworthy, however, that despite the overall severity of the disease, only 18% of patients progressed to NIV, while 82% remained unchanged in HFNC with a median duration of 30 hours. This study is observational, but it should be prospective.

CONCLUSION

For the decades use of heated humidified HFNC oxygen therapy has been getting attention of clinicians on hypoxemic patients as alternative to COT. As compared to COT, HFNC seems more comfortable and well tolerated by patients. Since HFNC is heated and humidified, it reduces airway resistance, enhances mucociliary clearance, reduces work of breathing and improves quality of life. Patients can talk, eat and drink during the treatment. HFNC has many beneficial effects HFNC flushes dead space, exerts PEEP effect, maintain FiO_2. Physicians have been using HFNC in variety of patients with respiratory failure, post extubation , cardiac surgery and so on. Also it can be used in preoxygenation during endotracheal intubation and bronchoscopy. It is much more effective in patients who are contraindicated to mechanical ventilation, intolerated COT and NIV, do-not resuscitate and immune compromised patients. Despite this there are some important issues remains to be resolved, like absolute indication of HFNC, criteria for timing to start and stopping of HFNC and for escalating treatment. However, the HFNC oxygen therapy is being innovative and widely accepted oxygen therapy at present time.

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