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REVIEW ARTICLE

APPLICATION OF THE HIGH-FLOW NASAL CANNULA IN PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME

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Abstract

Background: Acute respiratory distress syndrome (ARDS) is an acute inflammatory pulmonary process, which leads to protein-rich non-hydrostatic pulmonary oedema. It causes persistent hypoxemia, increases lung "stiffness" and impairs the lung's ability to excrete carbon dioxide. With the advent of the COVID-19 pandemic, many patients suffering from ARDS could not avoid falling ill. However, in many cases, the time from the onset of disease symptoms to the development of full-blown ARDS differed from that observed in ARDS caused by other underlying conditions. Based on the available data, ARDS associated with COVID-19 does not appear to exhibit a more rapid or severe progression of lung damage compared to ARDS from other causes.

Treatment approach: Supplemental oxygen therapy is one of the most commonly prescribed interventions used by clinicians when treating hypoxic acute care patients. This supplement often comes in the form of a low-flow nasal cannula (LFNC). The nasal cannula is an open system that provides low flow and low oxygen. Particularly in patients with COVID-19, HFNO has been shown to create a more uniform transmission of pressure and distribution of ventilation in the alveoli, compared to invasive mechanical ventilation.

Results: As a result, the probability of overdistension of open alveoli, together with the opening of closed alveoli, is reduced in a heterogeneous lung affected by SARS-COV-2. In normal breathing, about 1% of the air a person inhales is made up of the air exhaled in the previous breath. The result is that part of the exhaled CO2 is respired. However, the use of high-flow nasal oxygen (HFNO) facilitates the delivery of heated, humidified oxygen at high flow rates, effectively flushing out CO_2 from the anatomical dead space in the trachea and bronchi, thereby enhancing gas exchange. This reduces the anatomical dead space and respiration of CO2, promoting its elimination.

Conclusions As a result, HFNO has been shown to be effective in treating hypercapnia-induced respiratory failure. The purpose of the present study is to investigate the therapeutic effect after the application of the high-flow nasal cannula in patients with acute respiratory distress syndrome.

Keywords: Acute respiratory distress syndrome, high-flow nasal cannula.

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INTRODUCTION

The respiratory system enables gas exchange between the external environment and the body, thereby supporting aerobic metabolism. The inability of the respiratory system to perform the exchange results in respiratory failure.

Respiratory failure (RF) is a syndrome caused by a multitude of pathological conditions. According to a study conducted in the USA in 2017 reported an incidence of respiratory failure of 1,275 cases per 100,000 adults.[1] The epidemiology of respiratory failure largely depends on its underlying cause.

Common causes of respiratory failure are: Acute Myocardial Infarction (AMI-RF), Acute Respiratory Distress Syndrome (ARDS),[2] Coronavirus-Associated Acute Respiratory Failure (COVID-19),[3] Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD).[4] In the last three years, due to the COVID-19 pandemic, a relatively homogeneous population of patients with ARDS has been recorded. However, several subtypes of respiratory failure have been identified, indicating that it is not a single syndrome distinct from ARDS. Further progress in the care of ARDS will likely require an improved understanding of the epidemiology of this syndrome and its subtypes, as well as innovative trials of targeted therapies.[5] Given the syndrome's high mortality and long-term morbidity, continued study of the treatment and care of patients with ARDS is paramount.

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

The acute respiratory distress syndrome (ARDS) is an acute inflammatory pulmonary process, which leads to protein-rich non-hydrostatic pulmonary oedema, causes persistent hypoxemia, increases lung "stiffness" and impairs the lung's ability to excrete carbon dioxide. At the macroscopic level, computed tomography (CT) studies led to the concept of the "child's lung," suggesting a shift in perspective from a "stiff" to a "small" lung.[6]

Findings from CT scans related to the factor of gravity in the lungs when the patient is placed prone helped to give a clearer diagnostic picture of how the "baby lung" is not an anatomical concept, but a functional one, which is represented in a "sponge" sample.[7] A high fraction of dead space has been found to be associated with a significant mortality rate in people with ARDS.[8]

A number of factors as certain diagnostic methodologies followed, hospital admission protocols and the way medical emergencies are treated naturally influence the recognition of serious diseases.

In a detailed overview of the global incidence of critical illness in adults, a study by Rubenfeld et al. observed that there is a large difference in the number of available ICU beds provided in high-income countries compared to low-income ones. This disparity may lead to a different triage of acute critical diseases - such as ALI - due to a different approach to the care that will be offered and to a strong discrepancy in the evaluation of each case.[9]

ARDS EPIDEMIOLOGY

The current epidemiologic estimates of ARDS, following the Berlin conference in 2011 and the practical definition given to it, came from the multicentre LUNG SAFE study, which was conducted in Intensive Care Units in a total of 50 states. This study captures patient perspectives throughout the entire duration of their ICU stay. In particular, the occurrence of ARDS was estimated to reach 10.4% in all admissions made, while it doubled (23.4%) among patients who required mechanical ventilation. In a more detailed country-by-country analysis, the incidence of ARDS was highest in Oceania, at 0.57 cases/ICU bed/year, followed by Europe, North America, Africa, South America and Asia, with the lowest incidence of ARDS at 0.27 cases/ICU bed/year.[10]

One fact that was considered noteworthy was that from the totality of the specific patients, clinicians were unable to detect ARDS disease in 40% of these cases, despite having received specialized training for this purpose, which was available to researchers. Also, across the spectrum of ARDS severity, the diagnosis was not reached in at least 1 in 5 patients.

The same findings were reached by a study that estimated the under-diagnosis of ARDS by clinicians in up to 50% of cases, despite knowledge of the AECC criteria and staff training. Simultaneously, specific physiological markers were observed that correlate with patient characteristics and a higher likelihood of ARDS being diagnosed by clinicians in those receiving invasive mechanical ventilation.

Regarding this issue, the authors identified higher nurse-to-pa-

tient and physician-to-patient ratios. In essence, patients associated with lower ARDS underdiagnosis were very young, with lower body weight, higher SOFA score for non-pulmonary disease, lower PaO2/FIO2 ratio as well as pneumonia, pancreatitis and various other comorbidities, injury during the procedure of admission, absence of risk factors for ARDS and simultaneous presence of heart failure.[10]

ARDS PATHOLOGY

A key pathological feature underlying ARDS is diffuse alveolar damage (DAD), which leads to alveolar swelling. While an ideal definition of ARDS would encompass only those patients with confirmed DAD, avoiding false positives, which is not always the case. This discrepancy was evident in the initial observations by Ashbaugh et al. and was later corroborated by the findings of Vincent JL and colleagues.[11]

The same conclusions were reached by Guerin et al., who observed patients with persistant ARDS.[12] The authors found that a large proportion of patients with (DAD) experienced a significant impact from ARDS, which could not be alleviated, regardless of the severity level of the syndrome. The detection of DAD in a medical examination contributes greatly when recording the progress of the health of the patient suffering from ARDS.

In another study of lung biopsies for patients with ARDS, the occurrence of DAD was associated with higher mortality compared to ARDS without DAD.[13] ARDS is caused by various disorders of the body such as an infection, and usually occurs in people who are already seriously ill or have suffered some lung injuries. Clinically it can be classified as a direct lung attack or an indirect lung injury. With regard to the former, it is the classic "pulmonary ARDS" (ARDSp), while the latter is considered "extrapulmonary ARDS" (ARDSexp).

Common risk factors for the development of ARDS are: pneumonia, sepsis, inhalation/suction injury, trauma, burns, non-cardiac shock, drowning, and acute lung injury. However, chronic conditions such as obesity and diabetes are not as frequently associated with the onset of ARDS. Interestingly, a recent meta-analysis of the international literature found that obesity, in particular, is less strongly linked to ARDS than expected, an observation that contradicts common assumptions, as no clear pathophysiological mechanism has yet been established to explain this finding. With regard to diabetes, evidence suggests that it may exert a protective effect by enhancing the body's defense mechanisms against inflammatory insults. Another cause responsible for the occurrence of ARDS is excessive alcohol consumption, which is capable of leading to a significant reduction in the immune response involving alveolar macrophages.

The association between a positive fluid balance and increased mortality in patients with lung injury has been identified through studies primarily aimed at evaluating the impact of conservative fluid management or fluid removal strategies on outcomes in individuals with ARDS. Nevertheless, additional studies are necessary to confirm these results and determine their clinical significance.[14] This high impact has also been linked to various factors, including older patient age, non-Caucasian ethnicity, a range of genetic variations, and environmental exposures such as ozone. Observing patients with predisposing conditions for ARDS, several authors developed and validated the Lung Injury Prediction Score (LIPS) to assess the risk of progression to acute lung injury. However, the best LIPS cut-off score predicted ARDS with high sensitivity (69%) and specialty (78%).[15]

ARDS DIAGNOSIS

The diagnosis of ARDS is based on the following criteria: Positive history of pulmonary or systemic risk factors, presence on chest X-ray of bilateral pulmonary infiltrates in clinical absence of left heart failure and PaO2/FiO2 aetiology less than 200 mmHg. It is further sub-classified into mild (PaO2/FiO2 200 to 300 mmHg), moderate (PaO2/FiO2 100 to 200 mmHg) and severe (PaO2/FiO2 less than 100 mmHg) subtype. Mortality and ventilator-free days increase with severity. Chest CT may be required in cases of pneumothorax, pleural effusions, mediastinal lymphadenopathy, or barotrauma to correctly identify infiltrates as pulmonary in their site.[16]

Assessment of left ventricular function may be required to differentiate or quantify the contribution of congestive heart failure to the overall clinical presentation. This assessment can be achieved through invasive methods, such as pulmonary artery

catheter measurements, or non-invasively, such as cardiac echocardiography or thoracic bio-impedance, or pulse contour analysis.

However, the use of pulmonary artery catheters (PACs) is controversial and should be avoided if clinically possible. Non-invasive assessment measures should be exhausted first. PAC use is discouraged by the new definition. The use of bronchoscopy may be required to evaluate for pulmonary infections and obtain material for culture.[16]

Other laboratory and/or x-ray tests shall be guided by the underlying disease process that has triggered the inflammatory process that has led to the development of ARDS. These patients are most likely to develop or be affected by associated multi-organ failure, including but not limited to renal, hepatic, and hematopoietic failure. Routine complete blood count with differential, comprehensive metabolic panel, serum magnesium, serum ionized calcium, phosphorus levels, blood lactate levels, coagulation factors, troponin, cardiac enzymes, and CKMB are recommended if clinically indicated.16 Regarding the differential diagnosis, this includes congestive heart failure, pulmonary infections with diffuse infiltrates on chest X-ray, and other rarer, non-infectious causes of acute respiratory failure accompanied by diffuse pulmonary infiltrates.[17]

CLINICAL MANAGEMENT OF ARDS

The use of a ventilator as well as the application of certain therapeutic practices to treat ARDS is worthy but not sufficient. It is estimated that almost 4 in 5 patients were treated with a PEEP level below 12 cmH2O.

Steady -state pressure- is considered a key contributor to ventilator use where it has been observed to be associated with mortality in these patients – it was estimated in only 40.1% of the ARDS population. Of a satisfactory number of subjects suffering from ARDS, approximately 1 in 3 patients did not receive mechanical ventilation, either with steady state pressure above 30 cmH2O or with a circulating volume above 8 mL/kg predicted body weight.

Although large tidal volumes are inconsistent with evidence-based respiratory care standards, reflexive clinical practices have persisted, partly due to the influence of findings from two recent randomized controlled trials. At the same time, these results indicate that clinicians show a greater preference for adjusting FiO2 rather than increasing PEEP for the treatment of hypoxemia. Finally, adjunctive measures such as recruitment manoeuvres and prone positioning were used in a minority of patients with ARDS (20.9% and 7.9%, respectively).[18]

ARDS MORTALITY

To date, mortality in patients with ARDS remains alarmingly high. The LUNG SAFE study notes 40% mortality within the hospital unit, with a noticeable increase in ARDS severity categories (34.9%, mild ARDS, 40.3% moderate ARDS, 46.1% severe ARDS). The results indicate that the application of specific diagnostic criteria enables physicians to reliably identify cases of ARDS. Laffey et al. studied the predictions associated with the findings in a secondary analysis of the Lung Safe study.

More specifically, a study examined approximately 2,377 patients with ARDS who received mechanical ventilation. It was found that lower ventilation pressures (peak, plateau, and driving pressure), higher levels of PEEP, and lower respiratory rates were associated with improved physiological stability. These parameters contributed to better health maintenance and were linked to increased survival times in patients with ARDS. These findings match corresponding elements from clinical trials that had already been identified. ARDS mortality rates were lower, which may be attributed to the improved treatments patients received, potentially contributing to increased life expectancy.

Of interest, as early as the 1990s, Nolan et al reported a hospital mortality of 59% in mild and severe ARDS in a population-based study conducted in Australia.[19] Brun-Buisson et al. found almost identical results over the same period of time in a hospital-based survey of 78 ICUs in European countries, with 57.9% reporting even mild ARDS. Following this period, in-hospital mortality associated with ARDS demonstrated a consistent decrease of about 40%, including all ARDS categories. When considering only moderate-to-severe cases, the decline reached approximately 45%, as documented in the LUNG SAFE study.[18]

In addition, data from two high-quality studies conducted in Northern European countries further support these findings, which focused on patients with more severe ARDS (moderate

and severe ARDS), observed prolonged 90-day mortality between 38-41.2% even when calculated overall the ARDS, Linko et al. noted a 90-day mortality of 47%.

Nowadays, separate RCTs give much hope in terms of reducing mortality from ARDS. This is carefully evaluated in conjunction with a good study design strategy. Patients who take part in RCTs are selected according to strict criteria, and the generalizability of results from an RCT may be flawed if applied to the entire population.[19]

Viral infections such as the recent SARS-CoV-2 have been observed to negatively affect the already fragile health of patients suffering from ARDS. More specifically, since the onset of the COVID-19 pandemic in 2020, approximately 57,274,018 cases have been reported, resulting in around 1,368,000 deaths. A significant proportion of these cases progressed to ARDS, leading either to prolonged illness or death.[20]

However, the reported mortality rates for ARDS associated with COVID-19 vary widely, ranging from 3.4% to 88.3%, indicating significant heterogeneity across studies. These findings are influenced by various factors such as country and living conditions, the health system applied (length of hospital stay for each group of people), therapeutic approaches (due to the unprecedented situation of the pandemic, patients were given combinations of drugs to achieve treatment that were potentially harmful), and the institutional framework due to the pandemic led health systems to collapse. The rapid surge in cases, combined with a high burden of comorbidities, strained healthcare systems beyond capacity, limiting their ability to deliver appropriate care to all affected individuals, especially in vulnerable environments like nursing homes. For example, during the pandemic, hospitals faced a daily influx of patients requiring immediate care, far exceeding the available number of ICU beds. As a result, many individuals were at increased risk of death—not only due to the shortage of critical care resources but also because some healthcare teams lacked sufficient experience in managing ARDS. This was also evident in intensive care unit admissions, where a significant number of patients with acute respiratory distress syndrome (ARDS) ultimately died. In fact, some studies focusing on early mortality were practically difficult to have an overall picture of this condition and so could not include patients with no final outcome (discharge or death), so their estimates were not so clear and objective.[20]

In contrast to the possible dichotomy of "type L" (high complicity) and "type H" (low complicity) that was considered an important factor by some scholars in this case, the range of pulmonary complacency looks similar to that found in earlier studies of general ARDS. This investigation shows that several ARDS patients from COVID-19 had physiology similar to general ARDS that did not differ. This led to the conclusion that ARDS patients from COVID-19 are being treated with the same treatment regimen that existed before for ARDS in general.

Through the aforementioned study and based on the three phenotypes of severity (mild, moderate and severe) it is understood that ARDS resulting from COVID-19 has a high chance of improving by applying therapeutic approaches that failed in trials of patients with heterogeneous range of stimulators and endotypes. The efficacy and adequacy of steroid therapy in several (endless) trials, a treatment regimen for which trials in the general ARDS population often had conflicting data, may be an early example of this serious disease.[21]

Nowadays, a drug or innovative treatment for the complete treatment / prevention of ARDS has not yet been discovered. Treatment focuses primarily on addressing the underlying cause while providing oxygen and fluid therapy to prevent organ failure. Depending on the level of severity, treatment for ARDS should vary.[22]

TREATMENT APPROACH WITH HIGH-FLOW NASAL CANNULA

Supplemental oxygen therapy is one of the most commonly prescribed interventions used by clinicians in the treatment of hypoxic acute care patients. This supplement often comes in the form of a low-flow nasal cannula (LFNC). The nasal cannula is an open system that provides low flow and low oxygen. The cannulas deliver 100% oxygen at a rate of 0.5 to 6 litres per minute. Increasing the flow rate does not significantly increase FiO2 and could cause mucosal drying and patient discomfort. The amount of FiO2 depends on how poorly the patient is ventilated and how much air is entrained.

As a result, FiO2 cannot be accurately controlled. Peak tracheal oxygen concentration is unlikely to exceed 40 to 50%. High-flow oxygen therapy involves delivering oxygen flow through a nasal cannula, alone or mixed with air, over the patient's inspiratory flow.[17] The gas is humidified and heated close to body temperature.

High-flow nasal cannula (HFNC) treatment provides a liquid mixture of air, with or without oxygen, which is heated to a temperature between 31 °C and 37 °C. This system can provide a flow rate of 20 L/min to 40 L/min. If oxygen is added, it can be supplied at a rate of up to 15 L/min. The settings used depend on the patient's needs. Along with monitoring FiO2 delivery regulation, there are many advantages to this use.

The physiological mechanism of action and uses of the high-flow nasal cannula are explored. This activity examines the use of a high-flow nasal cannula and the role of the inter-professional team in the assessment and monitoring of patients receiving high-flow oxygen.[23]

Key components include a flow generator that provides gas flow rates up to 60 litres per minute, an air-oxygen mixer that achieves FiO2 scaling from 21% to 100% regardless of flow rates, and a humidifier that saturates the gas mixture. To minimize condensation, heated liquefied gas is passed through heated tubes through a wide-bore nasal tube.

In this system there are a number of physiological processes that take part to make the high flow nasal cannula more efficient. These factors include the effective clearance of waste gases such as carbon dioxide (CO_2) from anatomical dead space, a decreased respiratory rate, the application of positive end-expiratory pressure (PEEP), increased tidal volume, and elevated end-expiratory lung volume. Since High-Flow Therapy (HFT) improves ventilation, it helps patients breathe deeper, which helps remove secretions. Inhaling warm, humidified air leads to secretions that are more fluid and easier to clean. Together, these mechanisms increase patient comfort. HFT increases inspiratory flow, which reduces nasal resistance, while also introducing more fresh air into the airways, which reduces shortness of breath.

Oxygen administration improves systemic oxygenation, thereby enhancing energy levels through improved cellular function. It also contributes to upper airway clearance, optimizing ventilation efficiency by reducing dead space and promoting CO_2 elimination. A high-flow nasal cannula achieves a reduction in nasopharyngeal respiratory tract resistance, offering better ventilation and oxygenation through the application of positive pressure environment. The resistance of an airway follows the Hagen-Poiseuille law and is calculated as follows:

R = 8nl / 3,14 r4

Where l equals the length of the airway, n equals the dynamic viscosity of the air, and r equals the radius of the airway. Under normal conditions, the nasopharynx is a healthy part of the body that functions as a posterior extension of the nasal cavity and allows free passage between the nasal surface and the nostrils. By providing a positive pressure framework, the high-flow nasal cannula exerts a percentage of pressure from the inner path to the outer path. This widens the range of the respiratory passages of the nose, thereby significantly reducing the resistance to their flow, giving a great boost to the passage of ventilation and oxygen. Numerous studies converge to the conclusion that this mechanism significantly helps the better breathing process, reducing the speed of breathing and increasing the volume of breathing.[24]

High-flow oxygen therapy may reduce the need for invasive respiratory support (eg, intubation) and may have a clinical advantage over other therapies by preventing upper airway desiccation. However, for optimal efficiency when using high-flow nasal cannula (HFNC) therapy, patients are required to keep their mouths closed, with at least a 1 cm seal, in order to generate sufficient positive airway pressure at a flow rate of 10 liters per minute.[25]

It should be mentioned here that it is important that patients comply with the doctor's instructions regarding the use of the device, and this includes keeping their mouth closed as indicated when they have breathing difficulty. High-flow oxygen therapy is a non-invasive respiratory support that provides patients with heated, humidified and oxygen-enriched air.

Generally, this system sends cool, dry air providing more stable inspiratory oxygen concentrations. However, it may create some problems for patients such as drying of the mucous membrane, irritation and nosebleeds, which is unpleasant and annoying. The

most modern high-flow nasal cannula systems provide an integrated flow of gas that is humidified and heated in a controlled manner. Thus, the drying of the mucous membranes and the associated disadvantages are avoided. Only one source of oxygen and compressed air, as well as a heating/humidification framework is required, and this leads to better therapeutic results.[26]

CLINICAL CASES OF PATIENTS USING NASAL CANNULA

The study that validated the use of HFNO in adult medicine is referred to as the FLORALI clinical trial. This trial involved a randomized, multicentre study of 310 patients with acute hypoxemic respiratory failure who did not have hypercapnia (PaCO2<45 mmHg) and a PaO2:FiO2 ratio of 5300. These patients were randomly assigned to one of three groups: HFNO, conventional oxygen therapy with non-rebreather mask and non-invasive positive pressure ventilation (NIV). The primary objective was to determine the cumulative incidence of intubation up to day 28 from randomisation.

Although no significant difference was observed in the overall study population (p=0.17), the subgroup of patients with PaO2:FiO2<200 (which included 80% of all patients) showed that HFNO resulted in approximately 35% fewer intubations compared to conventional oxygen therapy and NIV (p=0.009). Regarding secondary objectives, patients in the HFNO arm had lower ICU (p=0.047) and 90-day (p=0.02) mortality rates and were found to have more off-ventilator days (p =0.02).[27]

In 2019, a meta-analysis was performed, which included randomized trials with a total of 2093 patients. The analysis concluded that the use of high-flow nasal oxygen (HFNO) did not reduce mortality rates, or ICU or hospital length of stay, or relieved patient-reported discomfort and dyspnoea. However, there was a significant reduction in the probability of intubation with a hazard ratio of 0.85 and a 95% confidence interval ranging from 0.74 to 0.99.[28] Shortly before COVID-19 became a global pandemic in 2020, a panel of experts from the European Society of Intensive Care Medicine strongly recommended the use of HFNO to treat respiratory failure resulting from hypoxemia. In addition, they conditionally recommended the use of HFNO after extubation or after cardiac or thoracic surgery in high-risk and/or obese patients.[29]

RESULTS FROM THE USE OF A NASAL CANNULA

Humidification and heating of the supplied gas mixture produce a first set of beneficial mechanisms of action. Unlike conventional oxygen therapy that provides dry and cold oxygen, HFNO does not dry out the mucous membranes. On the contrary, it reduces the viscosity of the mucus, enhances its water content and improves the function of the cilia. The result is better mobilization and clearance of bronchial secretions. In addition, HFNO reduces inflammation, epithelial damage, atelectasis, and bronchospasm. It also reduces the metabolic cost of the respiratory process. Patients with tachypnea consume a significant amount of calories to humidify and warm the inhaled air.[30]

High flow is also related to a second set of beneficial mechanisms of action. To minimize dilution of O2 with ambient air, it is important to compensate for patients' increased inspiratory flow. The normal inspiratory-expiratory volume is about 15 litres per minute, but in cases of acute respiratory failure, ventilation per minute can reach 30-120 litres per minute.

Accordingly, if a patient with an inspiratory flow of 30 litres per minute receives oxygen through a simple nasal cannula with a peak flow of 6 litres per minute, theoretically the delivered FiO2 would be 0.45, since for every 1 litre per minute the FiO2 increases by 0.04 over 0.21.

However, the flow rate of 6 litres per minute cannot compensate for the inspiratory flow of 30 litres per minute. Therefore, a patient will inhale the remaining 24 litres per minute of ambient air in the room, causing dilution. As a result, the actual FiO2 inspired by the patient will be significantly lower than the calculated value.

On the other hand, if a patient is given HFNO at a flow rate of 30 litres per minute, any increase in inspiratory rate will be compensated for, keeping dilution with ambient air to a minimum and ensuring that the actual inspired FiO2 remains nearly the same, such as that provided by the device, which may reach up to 1.0.[31] While a Venturi mask offers a more accurate predetermined FiO2 (which can be as high as 0.6) than a nasal cannula, it is also subject to the same limitation as the maximum O2 flow capacity is limited to 15 litres per minute.

Patient inspiratory flow beyond this value will cause the mixture

to mix with ambient air, which enters through holes in the sides of the mask to remove exhaled CO2. In contrast, the non-rebreather mask uses valves to prevent the supplied oxygen from mixing with ambient air, but its maximum flow rate is also limited to 15 litres per minute.[32] In summary, HFNO alone can address the increased inspiratory rate of a patient experiencing acute respiratory failure and can provide flows up to 60 litres per minute while maintaining FiO2 levels up to 1.0.

Continuous Positive Airway Pressure (CPAP) is known to reduce resistance to inhalation. The Hagen-Poiseuille law is used to calculate the resistance of an airway through the formula: R=8nl/3.144. This formula takes into account the dynamic viscosity of the air, the length and radius of the airway. By applying positive inspiratory pressure, the airways are dilated using high-flow nasal oxygen therapy (HFNO), which increases their diameter and therefore decreases inspiratory resistance.[33]

Positive End Expiratory Pressure (PEEP) is a function of HFNO exerting positive pressure on the airways during all phases of breathing. This pressure is most significant at the end of expiration, resulting in a proportional increase in PEEP ranging from 2.7 to 7.4 cm H2O per 10 litres per minute increase in flow. Because of PEEP, functional residual capacity increases by approximately 25%, leading to an increase in end-expiratory volume and alveolar recruitment, including non-ventilated alveoli the walls of which have collapsed. In this way, oxygenation is enhanced.30 Furthermore, PEEP has a more significant effect in patients with higher body mass indices (BMI).[34]

In patients with COVID-19, HFNO has been shown to create a more uniform transmission of pressure and distribution of ventilation in the alveoli, compared to invasive mechanical ventilation. As a result, the probability of over-distension of open alveoli, together with the opening of closed alveoli, is reduced in a heterogeneous lung affected by SARS-COV-2.[35]

In normal breathing, about 1% of the air a person inhales is made up of the air exhaled in the previous breath. The result is that part of the exhaled CO2 is respired. However, the use of high-flow nasal oxygen (HFNO) introduces pure oxygen directly into the trachea and bronchi, flushing out the CO2 that is there. This reduces the anatomical dead space and respiration of CO2, promoting its elimination. As a result, HFNO has been shown to be effective in treating hypercapnia-induced respiratory failure.[30]

All of the above can achieve beneficial results even at low flow rates (up to 40 litres per minute). However, higher flow rates are required for PEEP to have a significant impact. The resulting benefits include a reduction in respiratory rate, fine ventilation, inspiratory effort, and respiratory work. The decrease in ventilation per minute is due to the decrease in respiratory rate, while the tidal volume remains constant and/or increases.

It is important to note that while alveolar ventilation remains unchanged or increases, dead space ventilation decreases, resulting in a decrease in total ventilation per minute. This reduction in respiratory rate, inspiratory effort, and breathing also protects the lung from P-SILI (Patient Self-Inflicted Lung Injury) caused by increased trans-pulmonary pressures and tissue stress.[36]

Following are the practical benefits and drawbacks associated with HFNO. One advantage is the ease of application and handling, as well as its ability to allow patients to eat, drink and communicate with their environment without causing claustrophobia. However, regarding its disadvantages, rarely, it can cause irritation to the nasal mucosa or a feeling of heat in the nose, as well as an unpleasant odour.[37]

When cannulas are used it is important that the nasal protuberances do not completely occlude the nasal passages. Nevertheless, it is equally important that they are not too small in diameter, as this would result in loss of positive pressure in the airways. Therefore, it is important to make the right size choice. For the procedure, the temperature is set at 37°C.

Initially, low flow rates of 30-40 litres/minute are administered and gradually increased to compensate for the patient's inspiratory flow. In addition, the FiO2 of the administered mixture is increased until the desired SaO2 is reached. Both flow and FiO2 are then adjusted based on the patient's clinical response. Continuous electronic monitoring and recording of heart rate, respiratory rate and SaO2 by oximetry (SpO2) are required during the procedure.

To withdraw the HFNO from the patient, a reverse methodology is used. This involves a gradual decrease in both flow rate and FiO2. A 5-10% reduction in FiO2 and 5 L/min in flow rate is made at each stage until flows of 25 L/min and FiO2 levels below 0.40

are achieved. This allows for gradual discontinuation of the high-flow oxygen nasal cannula.[37]

In patients with COVID-19, high-flow nasal oxygen delivery reduces the need for intubation and time to recovery.[38] Despite the possible reduction in the probability of intubation, however, there is no clarity regarding how high-flow nasal oxygen can affect recovery time.[39,40]

COMPLICATIONS

Researchers in Italy have found that when a patient with COVID-19 wears a standard surgical mask over their nasal cannula for high-flow oxygen therapy, all oxygenation parameters demonstrate significant improvement. This includes PaO2, which increased from 59 (±16) to 79 (±16) mmHg ($p<0.001$), PaO2:FiO2, which increased from 83 (+22) to 111 (±38) ($p< 0.001$) and SaO2, which increased from 91% (±1.5) to 94% (±1.6). Placing the mask over the nasal cannula helps prevent oxygen from diluting or mixing with ambient air. Improvements in oxygenation indices have also been observed in patients with COVID-19 by adding a 50% Venturi mask over the nasal cannula during HFNO therapy.[41]

In general, for patients, the measured SaO2 may demonstrate a drastic decrease as a result of technical difficulties with the device itself. These issues may include, but are not limited to, running out of distilled water or a blockage in the tube that carries it to the humidification bottle, a blocked or displaced nasal cannula, and a malfunctioning or worn filter. It is vital to carry out thorough tests to address these concerns. In addition, the device must be disinfected after each use to ensure its reliability. Furthermore, nasal congestion may hinder the effectiveness and/or tolerance of the technique, necessitating periodic demucosation and/or topical corticosteroid administration.[42]

In some patients, inhalation of high-temperature gas mixtures may cause concern. A study of 40 patients revealed that patients experienced increased discomfort when the temperature of the mixture was increased from 31°C to 37°C, while the flow remained constant. In contrast, there was no increase in discomfort when the flow increased with constant temperature.[43] Therefore, it may be appropriate to start treatment at a lower temperature when applying HFNO and gradually increase to the desired target of 37°C. This goal is necessary and must be achieved in order to reap the beneficial physiological effects of heated gas.

CONCLUSIONS

HFNO has been associated with contraindications such as partial nasal obstruction, airway abnormalities such as laryngeal injury, mucosal disruption, or tracheal rupture. It is also contraindicated in people who have undergone laser or diathermy procedures due to the risk of fire. Contagious respiratory infections, such as tuberculosis, as well as age, such as children under 16 years of age, are also relevant contraindications. Additionally, HFNO has been associated with absolute contraindications such as decreased level of consciousness, hemodynamic instability, skull base fracture, cerebrospinal fluid leak, nasal-intracranial space communication, and facial trauma, significant pneumothorax not treated by chest tube placement, complete nasal or other airway obstruction and active epistaxis. It is important that the attending physician takes into account the above contraindications before proceeding with HFNO therapy.

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ANNEX

TABLE 1. Distribution of Sociodemographic Characteristics of Celiac Adolescents

Sociodemographic Characteristics	**Mean± SD (Min-Max)**	
Age	16.44±1.17 (15-18)	
Height	163.92±9.92 (145-188)	
Weight	52.48±14.08 (36-93)	
BMI (percentile)	33.85±28.09 (5-88)	
	n	**%**
Gender		
Female	40	74.1
Male	14	25.9
Diagnosis duration		
0-6 month	8	14.8
6-12 month	6	11.1
1-3 years	8	14.8
3 years and over	32	59.3
Family's income Level		
Income<Expense	26	48.2
Balanced (equal)	24	44.4
Income>Expense	4	7.4
Current symptom		
No symptom	40	74.1
Yes (abdominal swelling, nausea, abdominal pain, diarrhea, other)	14	25.9
Additional chronic disease		
Yes	42	77.8
No	14	22.2

TABLE 2. Leves of CDPQOL with sub-dimensions and THLS-32

		Mean	SD	Min-Max
Limitations		8.22	2.65	3-12
Isolation		7.96	4.38	0-16
Uncertainty		8.0	2.62	2-12
Social		17.25	6.32	5-27
CDPQOL total score		41.44	14.33	18-65
THLS-32	% 3.7 inadequate levels of HL % 40.7 limited levels of HL % 33.3 adequate levels of HL % 22.2 excellent levels of HL	35.06	7.11	21.88-49.48

Note. CDPQOL= Celiac Disease-Specific Pediatric Quality of Life; THLS-32= Turkish Health Literacy Scale; HL=Health Literacy.

TABLE 3. Correlations between sub-dimensions of THLS-32, BMI, diagnosis duration and CDPQOL: Pearson Correlation Analysıs

	r	**p**
THLS-32	0.137	0.325
Access to health-related information	0.325	0.295
Understanding health-related information	0.158	0.255
Using/applying health-related information	0.011	0.939
Evaluating health-related information	0.139	0.315
BMI	**-0.376**	0.005
Diagnosis duration	**-0.602**	0.000

Note. THLS-32= Turkish Health Literacy Scale; BMI= Body Mass Index.

TABLE 4. Effect of sub-dimensions of THLS-32, BMI and age on CDPQOL: Multiple linear regression model

	Unstandardized Coefficients		Standardized Coefficients			% 95 Confidence Interval for B	
	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
Constant	36.322	35.525		1.022	0.312	-35.145	107.788
Access to health-related information	0.33	0.604	0.014	0.055	0.956	-1.182	1.249
Understanding health-related information	1.103	0.668	0.436	1.652	0.105	-0.241	2.447
Using/applying health-related information	-1.002	0.754	-0.269	-1.330	0.190	-2.519	0.514
Evaluating health-related information	-0.165	0.504	-0.092	-0.327	0.745	-1.178	0.849
Age	0.731	1.807	0.060	0.405	0.688	-2.905	4.367
BMI	-0.218	0.069	-0.426	-3.130	**0.003**	-0.357	-078

Note. R=0.471; R^2= 0.222; Adjusted R^2=0.123; BMI= Body Mass Index.