Dual Oxygenation in the Treatment of Hypoxemic Respiratory Failure: A Retrospective Cohort Study

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ABSTRACT **Background:** At the beginning of the coronavirus disease 2019 (COVID-19) pandemic, many patients presented with acute hypoxemic respiratory failure, requiring ventilatory support. One treatment method was the addition of a reservoir mask to a high flow nasal cannula (HFNC) (dual oxygenation).

Objectives: To evaluate the clinical outcomes of combining reservoir mask on top of a high-flow nasal cannula.

Methods: A retrospective cohort of adult patients who were admitted due to COVID-19 during the first year of the pandemic to Rambam Health Care Campus. The primary endpoint was 30-day mortality. Secondary endpoints were incidence of invasive positive pressure ventilation initiation and admission to the intensive care unit (ICU). Patients who received positive pressure ventilation for reasons other than hypoxemic respiratory failure or who were transferred to another facility while still on HFNC were excluded.

Results: The final analysis included 333 patients; 166 were treated with dual oxygenation and 167 with HFNC only (controls). No significant differences in baseline characteristics were noted between the groups. The dual oxygenation group was slightly older (69.2 ± 14.8 years vs. 65.6 ± 15.5 years, $P = 0.034$). The 30-day mortality (24.1% vs. 36.5%, $P = 0.013$), rates of invasive positive pressure ventilation (47% vs. 59.3%, $P = 0.024$), and ICU admissions (41.6% vs. 52.7%, $P = 0.042$) were all significantly lower in the dual oxygenation group.

Conclusions: The addition of reservoir masks to HFNC may improve the oxygenation and overall prognosis in patients with severe hypoxemia due to COVID-19.

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KEY WORDS: coronavirus disease 2019 (COVID-19), dual oxygenation, high flow nasal cannula (HFNC), hypoxemia, reservoir mask

Hypoxemic respiratory failure is the leading cause for endotracheal intubation, intensive care unit (ICU) admission, and death in patients with coronavirus disease 2019 (COVID-19). Like other forms of acute lung injury, positive pressure ventilation (PPV) has long been accepted as the most effective way to improve oxygenation in these patients [1]. However, this therapeutic approach has several important drawbacks. Endotracheal intubation dramatically increases the risk of nosocomial infection and the potential harms of sedation. Non-invasive PPV is often not tolerated by patients, requires expertise in its operation (mask fitting, ventilation setting, monitoring), and could increase the risk of aspirations in certain populations. Both require relatively complex machinery and infrastructure [2].

Recent advances in high-flow delivery systems led to the widespread acceptance of high-flow nasal cannula (HFNC) as a non-invasive and easy to operate respiratory support, which is well tolerated by patients [3]. The effectiveness of this ventilatory method in preventing potential harm from invasive ventilations has been demonstrated in various critically ill populations [1,4,5]. However, application of HFNC was limited by the device's maximum configurations (typically a flow of 40–60 L/min with an FiO_2 of up to 100%). Patients who failed to improve under such settings were typically treated with other modes of PPV, with no other salvage option available [2,6].

The pre-vaccination COVID-19 pandemic was marked by increasing concerns regarding PPV, including potential infectiousness as well as staff and equipment shortages [7]. These concerns led to the quest for alternative approaches in patients who failed to adequately oxygenate under maximum HFNC support. One such method, applied in our tertiary care medical center, was the addition of a reservoir mask (RM) with HFNC, a method also known as dual oxygenation. Despite the widespread availability of this simple measure, to the best of our knowledge, the clinically relevant outcome of dual oxygenation has not been studied. In this study, we compared dual oxygenation to HFNC alone in the treatment of hypoxemic respiratory failure.

PATIENTS AND METHODS

This retrospective cohort study was conducted at Rambam Health Care Campus, Haifa, Israel. We accessed the electronic medical records of all patients hospitalized between 1 January 2020 and 31 March 2021 in any one of six dedicated COVID-19 wards.

Patients in the study had a positive polymerase chain reaction test for COVID-19 performed within 2 weeks of hospital admission; presented with severe hypoxemia requiring the use of HFNC, defined as pulse oximetry saturation (SpO_2) persistently below 90% despite maximal flow (15 L/min) on RM; and were 18 years of age or older. Exclusion criteria included positive pressure ventilation (either noninvasive or invasive) initiated for any reason other than refractory hypoxemia (e.g., general anesthesia) or transfer to another facility while still on HFNC.

All patients were continuously monitored by pulse oximetry. For HFNC, a flow of 40 liters per minute heated to 37°C and humidified to 100% was used at an oxygen fraction (FiO_2) of 40–100% titrated to achieve capillary oxygen saturation (SpO_2) of 90–95%. RM was added via a non-rebreather mask at a fixed oxygen flow of 15 liters per minute at ambient temperature. Invasive mechanical intubation was performed at the attending physician's discretion, mostly because of decreasing oxygen saturation despite maximal non-invasive respiratory support.

The primary outcome was mortality within 30 days from the first application of HFNC. Secondary outcomes were the initiation of invasive positive pressure ventilation (IPPV) and admission to an ICU.

STATISTICAL ANALYSIS

Standard descriptive statistics were used to summarize population characteristics. We used a chi-square test for categorical variables, Mann-Witney U test for nonparametric variables, and Student's unpaired *t*-test for normally distributed continuous variables. Tukey's correction was applied when applicable to adjust for multiple comparisons. Categorical variables were described using proportions and percentages, non-parametric variables with mean and interquartile range, and normally distributed continuous variables as mean ± standard deviation. Survival analysis was performed using the Gehan–Breslow–Wilcoxon method. Cox regression was performed for multivariate survival analysis. We used the Pearson correlation coefficient to determine possible correlations between independent variables. Only variables not co-related ($P > 0.1$ on univariate analysis) were included in the model. A 2-sided $P < 0.05$ was considered statistically significant for all tests. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA).

ETHICS AND OTHER PERMISSIONS

This study was performed in accordance with the Declaration of Helsinki and was approved by Rambam Health Care Ethics Committee (approval 0228-21-RMC-D). Adult participant consent was waived by the ethics committee due to the retrospective nature of this study.

RESULTS

Of 1923 patients hospitalized with COVID during the study period, 341 (17%) were treated with HFNC. Three patients (0.9%) were excluded for being intubated for surgery and five (1.5%) were transferred to another facility while still requiring high flow oxygenation. In total, 333 patients were included in the final analysis: 166 patients (48.2%) were treated with the combination of HFNC and RM (dual oxygenation) and 167 (50.2%) were treated with HFNC alone (controls). Characteristics of both groups are presented in Table 1.

While patients treated with RM+HFNC were slightly older compared to controls (69.2 ± 14.8 years vs. 65.6 ± 15.5 years, *P*-value = 0.034), there were no significant differences in the incidence of chronic diseases, smoking status, or body mass index (BMI). Markers of disease severity at presentation including D-dimer, C-reactive protein (CRP), pulse, mean arterial pressure, absolute lymphocytes and neutrophil counts, and pulse oximetry were similar between the groups. There were no significant differences between the two groups in the lowest sequential organ failure assessment (SOFA) scores and highest lactate levels in the period before the first application of HFNC. There was no difference in the dosage of corticosteroids administered between the two groups. However, when looking at the entire hospitalization, including the period after the patient was put on HFNC, the maximal D-dimer was higher (mean deviation [Md] 624 ng/dl, $P = 0.035$) and pulse oximetry was lower (Md 4.3%, $P < 0.001$) in the dual oxygenation group. The number of patients treated with non-invasive positive pressure ventilation was similar in the two groups. Hospital stay was slightly longer in the dual oxygenation group (median stay 15.4 vs. 12.7 days), but this difference was not of statistical significance ($P = 0.065$).

Rates of IPPV (47% vs. 59.3%, $P = 0.024$), ICU admission (41.6% vs. 52.7%, $P = 0.042$), and mortality within 30 days of HFNC initiation (24.1% vs. 36.5%, $P = 0.013$) were all significantly lower in the dual oxygenation group.

Considering patients who died within 30 days from the first application of HFNC, median mortality was at 11 days for patients treated with RM and HFNC, compared with 7 days for patients treated with HFNC alone ($P = 0.005$). Considering patients who met criteria for secondary outcomes, median times to intubation and to ICU admission were 2 days for the dual oxygenation group vs. 1 day for controls ($P = 0.04$ and $P = 0.001$, respectively). The data are presented in [Figure 1].

To determine potential confounders, Cox proportional hazard model was constructed. Age, BMI, smoking history, chronic obstructive pulmonary disease, asthma, any malignancy diagnosed within the past 5 years, CRP, and D-dimer and SOFA score at presentation were included in the model. Dual oxygenation remained an independent predictor of 30-day mortality ($P = 0.018$) [Figure 2].

Table 1. Patient characteristics

Characteristics	HFNC alone (n=167)	RM + HFNC (n=166)	*P*-value
Age in years	**65.6 ± 15.5**	**69.2 ± 14.8**	**0.034**
BMI (kg/m²)	30.6 ± 5.6	29.5 ± 5.2	0.094
Female sex	59 (35%)	59 (35.5%)	1.00
Smoking status	156 (93.4%)	155 (93.4%)	0.988
Ethnic origin			
Jewish	73 (46%)	81 (52%)	0.31
Arab	86 (54%)	74 (48%)	
Marital status			
Widow	20 (12%)	23 (14%)	0.75
Divorce	17 (10%)	13 (8%)	
Married	116 (71%)	118 (73%)	
Single	11 (7%)	8 (5%)	
Pulmonary diseases			
COPD	14 (8.4%)	6 (3.6%)	0.067
Asthma	4 (2.4%)	6 (3.6%)	0.515
Interstitial lung disease	6 (3.6%)	2 (1.2%)	0.155
Solid malignancy diagnosed within 5 years	48 (28.7%)	52 (31.3%)	0.607
Cardiovascular diseases			
Ischemic heart disease	19 (11.4%)	21 (12.7%)	0.721
Heart failure	20 (12%)	22 (13.3%)	0.726
Atrial fibrillation	20 (12%)	14 (8.4%)	0.286
Other co-morbidities			
Hemodialysis	6 (3.6%)	14 (8.4%)	0.063
Diabetes mellitus	73 (43.7%)	77 (46.4%)	0.624
Hypertension	94 (56.3%)	100 (60.2%)	0.464
Hyperlipidemia	77 (46.1%)	88 (53%)	0.208
D-Dimer (ng/dl)			
On admission	1363 ± 1103	1655 ± 1389	0.068
Maximal	**2966 ± 2408**	**3590 ± 2462**	**0.035**
Pulse oximetry saturation [%]			
On admission	92.2 ± 7	91.7 ± 6.9	0.486
Lowest	**74.8 ± 10.8**	**70.5 ± 10**	**< 0.001**
C-reactive protein (mg/dl)			
On admission	15.3 ± 9.8	15.7 ± 9.5	0.693
Maximal	23.6 ± 11.7	24.6 ± 9.4	0.384
Maximal lactate	3.5 ± 2.6	3.6 ± 2	0.814
Maximal SOFA score during hospitalization	4 (2–6)	4 (2–6)	0.807
Length of hospitalization (days)	12.7 (7.2–21.2)	15.4 (8.9–25.5)	0.065
Noninvasive positive pressure ventilation	14 (8.4%)	13 (7.8%)	0.8
IPPV	**99 (59.3%)**	**78 (47%)**	**0.024**
ICU hospitalization	**88 (52.7%)**	**69 (41.6%)**	**0.042**
Death at 30 days from initiation of HFNC	**61 (36.5%)**	**40 (24.1%)**	**0.013**

BMI = body mass index, COPD = chronic obstructive pulmonary disease, HFNC = high flow nasal cannula, ICU = intensive care unit, IPPV = invasive positive pressure ventilation, SOFA = sequential organ failure assessment

Bold signifies significance

Figure 1. Kaplan Mayer's survival curves

HFNC = high flow nasal cannula, ICU = intensive care unit, IPPV = invasive positive pressure ventilation, RM = reservoir mask

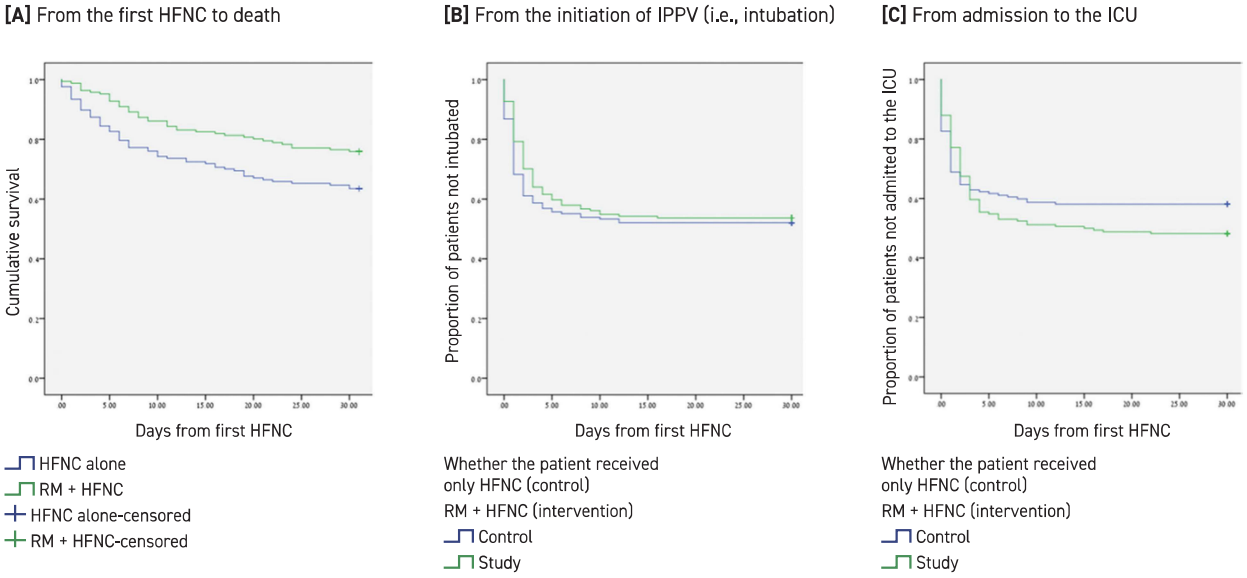
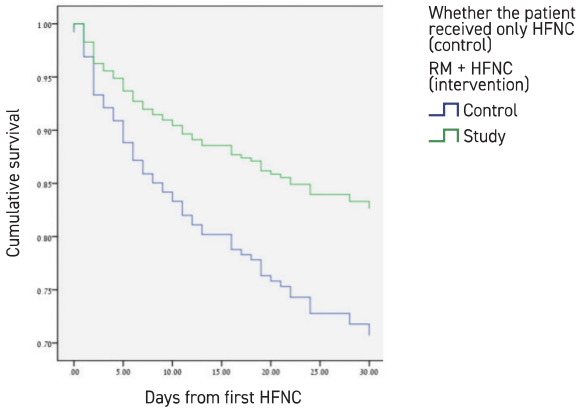


Figure 2. Cox regression for 30-day survival accounting for age, BMI, history of smoking, COPD or asthma, malignancy diagnosed within the past 5 years and SOFA score, D-Dimer, and CRP at presentation

BMI = body mass index, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, HFNC = high flow nasal cannula, SOFA = sequential organ failure assessment, RM = reservoir mask



DISCUSSION

We showed decreased 30-day mortality and longer median survival in patients treated with the addition of RM to HFNC. This association remained unchanged after accounting for multiple potential confounders, including BMI, smoking status, underlying diseases (and particularly chronic lung diseases) and severity at presentation as reflected by SOFA scores, D-Dimer, and CRP levels. These findings, beyond the proven efficacy of HFNC in COVID respiratory failure [2,6], could be explained by several physiological mechanisms.

First, the addition of the physical barrier of the RM probably improves the effectiveness of nasal HFNC. This is similar to the addition of a surgical mask with HFNC, which has been shown to improve oxygenation (increasing PaO_2 from 59 ± 6 to 79 ± 16 mmHg), $P < 0.001$) in a previous small, controlled study of 25 ICU patients [7]. These results are echoed in another small, controlled study to assess the effect of an oxygen mask (with no additional flow) placed on top of HFNC. After 30 minutes, arterial hemoglobin saturation was higher in all patients (Md 24 mmHg, 95% confidence interval 16–32) [8].

Various mechanisms have been suggested to explain these findings, including shifts to the hemoglobin dissociation curve [9] and the rise of $PaCO_2$ [10]. However, it seems the most likely mechanism is the decrease of room air entrainment in the presence of a physical barrier. This explanation is supported by several corroborative findings. PaO_2 was significantly increased, explaining the improvement in hemoglobin saturation, and $PaCO_2$ did not differ significantly [7]. In a study including healthy volunteers subjected to strenuous exercise to simulate the increased ventilation in severe respiratory failure, the authors found that positive airway pressure was reached only when the participants breathed with their mouth closed [11]. This finding might

explain why adding RM to HFNC improved oxygenation in the current study. A meta-analysis of studies evaluating HFNC found actual FIO_2 delivery to decrease significantly in severe respiratory failure, a finding attributed to room air entrainment [12]. Exercise tolerance and hemoglobin saturation were increased when surgical masks were added to HFNC in a study evaluating patients with idiopathic pulmonary fibrosis [13]. The addition of other barriers (e.g., surgical mask) to a device delivering flow to the mouth (such as an oxygen mask) does not seem to improve oxygenation [14]. It seems the simple barrier of the RM helps funnel the high flow from the nasal prongs to the mouth, contributing especially to patients in severe respiratory distress who are more likely to breathe with their mouth open.

Flow addition might be of importance. While most available HFNC devices support minute flow of up to 60 L/min, O_2 infrastructure in our hospital that was used during the study period only allowed for up to 40 L/min flow of pure oxygen. Patients with early respiratory failure in general, and COVID in particular, tend to have very high peak inspiratory flow (PIF). One report found patients hospitalized with severe COVID to have PIF of 42.8 ± 23.2 L/min on average, with maximal reported peak flows of over 120 L/min [15]. This finding means that the addition of the typical RM flow rate of 15 L/min, increasing the actual pure oxygen minute flow of HFNC by 37.5%, should be meaningful in preventing room air dilution in patients with severe hypoxemic respiratory failure. The importance of increasing O_2 flow from 40 L/min to 60 L/min, particularly in the presence of high PIF, was demonstrated in a recent laboratory model [16] and in a small, controlled trial [17]. This situation could also explain why such a benefit was not shown in earlier studies comparing HFNC with high flow face masks [18].

Added expired oxygen-enriched dead space (in the form of the reservoir bag and masked area) should further decrease room air entrainment (and thus increase delivered FIO_2) during high flows of peak inspiration. This result has been shown in a small, controlled study assessing the double trunk mask (DTM), a device designed to retain expired flow. The addition of DTM to HFNC increased PaO_2 from 68 ± 14 mmHg to 85 ± 22 mmHg ($P < 0.001$) [19].

While tolerability and discomfort were not assessed in this study, it is our experience that HFNC, with or without RM, is relatively well tolerated by patients, particularly when compared with positive pressure support, such as nasal invasive positive pressure ventilation (NIPPV) and IPPV. Pressing masks, the relative ease of communication, and the ability to eat and drink without assistance, which are all important in the isolated and resource strained setting of dedicated COVID-19 wards, may contribute. This finding is also in consonance with previous studies evaluating the tolerability of HFNC [12,20].

LIMITATIONS

This study has several important limitations. First, the retrospective design inherently raises the risk of biases, particularly since no randomization was performed and no strict protocol detailing the criteria for adding RM to HFNC was followed. As a result, criteria for adding RM or ICU admission varied greatly among physicians and during various phases of the pandemic. Similarly, no unified criteria for intubation or indeed ICU admission were accepted. Some of these concerns could be addressed by accumulating additional observational data from other medical centers and using a longer time frame to include newer SARS-CoV-2 variants.

Most patients included in our analysis were hospitalized before the introduction of vaccines. Further evaluation is needed to validate these findings in vaccinated patients and with clinically distinct natural history of emerging variants of concern.

Last, relatively few patients (8.4%) were put on BiPAP, probably due to concerns regarding potential aerosolization with the use of NIPPV. Since these concerns have largely been debunked and the use of BiPAP gained popularity in patients with COVID-19, it would be interesting to compare this modality to RM and HFNC, especially in view of previous evidence suggesting the benefits HFNC might have over NIPPV [21].

CONCLUSIONS

We found potential efficacy with the addition of RM to HFNC in COVID-19 patients with severe hypoxemia. Adding RM to HFNC resulted in improved 30-day mortality and decreased the need for intubation and ICU transfer. This cheap, widely available, and safe treatment warrants further, large scale randomized studies. Indications could include progressing hypoxemia ($SpO_2 < 90\%$) despite maximal HFNC support when positive pressure ventilation is not planned. Possible contraindications may include potential airway complications and hypercarbia. Pending empirically rigorous proof, formal guidelines could standardize the use of this readily accessible approach.

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What wisdom can you find that is greater than kindness?

Jean Jacques Rousseau (1712–1778), Genevan philosopher, writer, and composer

Capsule

Gene therapy in patients with the Crigler–Najjar syndrome

Patients with the **Crigler–Najjar** syndrome lack the enzyme uridine diphosphoglucuronate glucuronosyltransferase 1A1 (UGT1A1), the absence of which leads to severe unconjugated hyperbilirubinemia that can cause irreversible neurologic injury and death. Prolonged, daily phototherapy partially controls the jaundice, but the only definitive cure is liver transplantation. **D'Antiga** and colleagues reported the results of the dose-escalation portion of a phase 1–2 study evaluating the safety and efficacy of a single intravenous infusion of an adeno-associated virus serotype 8 vector encoding UGT1A1 in patients with the Crigler–Najjar syndrome who were being treated with phototherapy. Five patients received a single infusion of the gene construct (GNT0003). Two received 2 × 1012 vector genomes (vg) per kilogram of body weight and three received 5 × 1012 vg per kilogram. No serious adverse events were reported. The most common adverse events were headaches and alterations in liver-enzyme levels. Alanine aminotransferase increased to levels above the upper limit of the normal range in four patients, a finding potentially related to an immune response against the infused vector. These patients were treated with a course of glucocorticoids. By week 16, serum bilirubin levels in patients who received the lower dose of GNT0003 exceeded 300 µmol per liter. The patients who received the higher dose had bilirubin levels below 300 µmol per liter in the absence of phototherapy at the end of follow-up: mean ± standard deviation baseline bilirubin level, 351 ± 56 µmol per liter; mean level at the final follow-up visit (week 78 in two patients and week 80 in the other), 149 ± 33 µmol per liter.

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