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RESEARCH LETTER

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High flow nasal oxygen as a "second-line" therapy for COVID-19 patients intolerant to noninvasive ventilation. A retrospective cohort study

1 | INTRODUCTION

The role of noninvasive ventilation (NIV) in reducing the risk of mortality and endotracheal intubation (ETI) in patients with hypercapnic acute respiratory failure (hARF) across a variety of aetiologies is well established.[1] Its efficacy nevertheless seems to be affected by patient intolerance caused by agitation or uncooperativeness.[2] Indeed, despite the judicious use of sedation, poor tolerance is one of the major causes of NIV failure leading to the need for ETI and intensive care unit (ICU) admission.[3]

High-flow nasal oxygen (HFNO) is increasingly utilized to correct severe, refractory hypoxemia in patients with acute respiratory distress syndrome due to a variety of causes.[4] Several studies have reported improved patient comfort with HFNO which appears to have a significant advantage over NIV as far as patient tolerance is concerned.[5,6] Moreover, although the current body of evidence is still limited, an increasing number of studies suggests that HFNO may be an effective, safe alternative to NIV that reduces the need for ETI and improves survival in subjects with mild to moderate hypercapnia.[5,7,8]

The limited availability of ICU resources during the COVID-19 pandemic led the authors to use HFNO as a "second-line" therapy for patients with hARF and poor tolerance to NIV in the attempt to diminish the need for ETI and, ultimately, the demand for ICU care. Due to the scarcity of data on this therapeutic approach, the authors were prompted to retrospectively investigate the outcomes of patients who failed to tolerate NIV and were switched to HFNO, in the effort to answer the question whether HFNO may be an effective alternative to NIV.

2 | METHODS

The clinical course of an unselected group of consecutive hARF patients admitted to the study centre SARS-CoV-2 Intermediate Respiratory Care Unit (IRCU) between December 1st, 2020 and July 31st, 2022 who failed to tolerate NIV and were switched to HFNO (the HFNO group) was retrospectively evaluated and compared with that of the patients who tolerated NIV (the NIV group). Patients admitted since the beginning of the pandemic to November 30th, 2020 could not be considered due to the lack of availability of clinical records. On August 1st, 2022 the SARS-CoV-2 IRCU was closed.

This retrospective cohort study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University/City Hospital of Padova (29.06.2021/No 0042076).

All the patients signed informed consent forms releasing their medical records for review.

Baseline demographic and clinical data and clinical, laboratory and blood gas data on IRCU admission are outlined in Table 1. Arterial blood gas (ABG) data were also recorded at the patient's discharge from IRCU.

Patients presenting with CO_2 retention ($PaCO_2 \geq 45$ mmHg) and signs of respiratory muscle fatigue (i.e., dyspnea, tachypnea, and/or abdominal paradox) generally received NIV and were included in the study. NIV was delivered through an oronasal mask using a portable ventilator set on the pressure support ventilation mode. The patients showing intolerance to NIV received a maintenance dose of dexmedetomidine (between 0.2 and 0.5 mcg/kg/h by IV infusion) to achieve adequate sedation that would not compromise their respiratory status. Exclusion criteria for NIV were as follows: recent facial or cranial trauma or surgery, facial abnormalities, high risk of aspiration, and inability to clear sputum. Intermittent NIV was attempted in patients showing intolerance, but it was terminated if they continued to demonstrate discomfort, agitation or uncooperativeness.[3] Patients intolerant to NIV who did not meet the criteria for emergency ETI were prescribed HFNO therapy which was delivered using an AIRVO2 respiratory humidifier (Fisher & Paykel Healthcare). HFNO was initially used at a 60 L/min gas flow rate and a F_IO_2 of 1.0; it was then adjusted to provide the minimum F_IO_2 necessary to maintain a $SaO_2 \geq 92\%$. Titration was determined according to ABG values. Patients were considered intolerant to HFNO if it was terminated due to discomfort (i.e., paradoxical suffocation and/or "chest pressure"), agitation or uncooperativeness. Complications

TABLE 1 Patients' baseline demographic and clinical characteristics, clinical and laboratory data at Intermediate Respiratory Care Unit admission and clinical outcomes.

	Overall (*n* = 29)	HFNO group (*n* = 10)	NIV group (*n* = 19)	*p* value
Baseline demographic and clinical data				
Age, years	81 (49–94)	80 (49–94)	82 (60–94)	0.23
Female, *n* (%)	11 (37.9)	6 (60)	5 (26.3)	0.11
Smokers, *n* (%)	8 (27.6)	2 (20)	6 (31.6)	0.67
Body mass index, kg/m^2	26.53 (18.2–34.6)	22.48 (18.2–31.13)	27.22 (23.53–34.6)	0.06
Pts with comorbidities, *n* (%)				
o metabolic disorder (diabetes, obesity)	14 (48.3)	4 (40)	10 (52.6)	0.70
o respiratory disease (asthma, COPD, OSA)	19 (65.5)	5 (50)	14 (73.7)	0.24
o hemato-oncology disease	0 (0)	0 (0)	0 (0)	>0.99
o cardiac disease (cardiac arrhythmia, previous MI, angina pectoris, and/or CHF)	24 (82.8)	6 (60)	18 (94.7)	0.04
o chronic renal failure	7 (24.1)	2 (20)	5 (26.3)	>0.99
o psychiatric disorders	7 (24.1)	3 (30)	4 (21)	0.66
Clinical, laboratory and blood gas data on IRCU admission				
Time since symptom onset, days	3 (3–34)	3 (3–5)	3 (3–34)	0.28
GCS	15 (3–15)	14.5 (4–15)	15 (3–15)	0.74
Heart rate, beats/min	83 (56–122)	82 (56–110)	83 (61–122)	0.32
Respiratory rate, breaths/min	21 (12–38)	18 (12–29)	23.5 (12–38)	0.06
Pts with temperature ≥38°C, *n* (%)	4 (13.8)	1 (10%)	3 (15.8)	>0.99
White blood cell count, $\times 10^9/L$	7.82 (2.62–19.34)	6.8 (2.62–19.34)	7.95 (4.45–18.8)	0.59
D-dimer, µg/L	289.5 (106–1831)	262 (106–579)	294.5 (106–1831)	0.16
Serum C-reactive protein, mg/dL	75 (4.9–180.6)	47.5 (5.57–180.6)	82 (4.9–148.9)	0.68
PaO_2 (O_2 suppl), mmHg	70 (30–165.6)	73.3 (53–143.3)	70 (30–165.6)	0.62
$PaCO_2$, mmHg	58 (45.4–85.6)	61.4 (45.7–71.6)	56 (45.4–85.6)	0.51
Arterial pH	7.33 (7.1–7.64)	7.32 (7.20–7.52)	7.36 (7.1–7.64)	0.46
SaO_2, %	94.85 (82–99)	94.5 (92–99)	95.35 (82–98.9)	0.79
PaO_2/FiO_2, mmHg	135.56 (45.45–510.77)	153.9 (78.25–354.17)	123 (45.45–510.77)	0.89
ROX index	9.38 (3.30–21.90)	8.53 (6.39–21.90)	10.11 (3.30–19.07)	0.75
Clinical outcomes				
Intubation, *n* (%)	3 (10.3)	0 (0)	3 (15.8)	0.53
Patients died during hospitalization, *n* (%)	10 (34.5)	0 (0)	10 (52.6)	0.005
Length of IRCU stay, days	8 (2–25)	7.5 (2–19)	8 (1–25)	0.94
$PaCO_2$ at discharge from IRCU	46.9 (32–69.3)	45.8 (36–57)	41.7 (32–69.3)	0.96

Note: *p* values refer to differences between HFNO and NIV groups.

Abbreviations: CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; GCS, Glasgow Coma Scale; HFNO, high flow nasal oxygen; IRCU, Intermediate Respiratory Care Unit; MI, myocardial infarction; NIV, non-invasive ventilation; OSA, obstructive sleep apnea; PaO_2/FiO_2, arterial oxygen tension to inspired oxygen fraction ratio; SaO_2, arterial oxygen saturation.

related to HFNO utilization including barotrauma, epistaxis, and nose irritation were recorded.

The study's primary endpoint, which was defined to assess the efficacy of HFNO as a second-line therapy, was the intubation rate during the IRCU stay. The study's secondary endpoints were: (a) the in-hospital mortality rate; (b) the length of the hospital stay; and (c) the $PaCO_2$ level at discharge from the IRCU. The survival from the time of admission to the IRCU was likewise compared. The independent unpaired Student's *t* test was used to compare normally distributed continuous variables; nonparametric data were compared using the Mann–Whitney *U*-test. Categorical variables were compared using the Chi-squared test or Fisher's Exact Test, as indicated. Survival from the time of admission to IRCU was calculated using the Kaplan–Meier method; the log rank test was used to compare the survival curves of the two groups.

3 | RESULTS

The 29 patients who were admitted to the IRCU during the study period with a diagnosis of hARF who required NIV were considered eligible to participate in the retrospective study. In most cases, the patients showed mild to moderate hypercapnia [58 (45.4–85.6) mmHg]. Ten out of the 29 (34.5%) showed NIV intolerance and were switched to HFNO. The remaining 19 patients tolerated NIV. The patients' baseline characteristics and clinical/laboratory data at IRCU admission were similar in the two groups (Table 1). Signs of NIV intolerance presented a median of 8.5 (2–33) hours after NIV was initiated. NIV intolerance was caused by: anxiety and/or agitation (7 cases), claustrophobia (2 cases), and sense of suffocation (1 case). HFNO was easy to set up and well-tolerated by all the patients; no complications related to its use were recorded. The patients showed mild to moderate hypercapnia at the time they were switched [$PaCO_2$: 53.9 (48–61.8) mmHg]. As can be seen in Table 1, the intubation rate was not significantly different in the HFNO and NIV groups [0/10 (0%) vs. 3/19 (15.8%); $p = 0.53$]. The in-hospital mortality rate was significantly lower in the HFNO group in comparison to the NIV group [0/10 (0%) vs. 10/19 (52.6%); $p = 0.005$]. The log-rank test showed that the patients in the HFNO group survived for a significantly longer time period with respect to those in the NIV group [538.3 ± 65.4 vs. 229.7 ± 65.4 days; ($p = 0.009$)] (Figure 1).

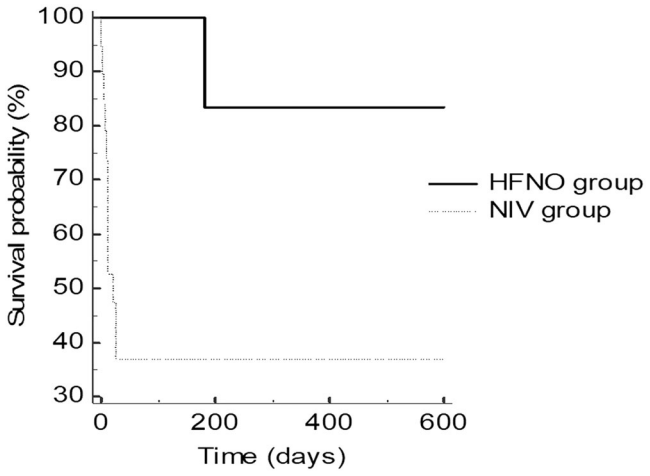

FIGURE 1 Kaplan–Maier estimates of survival function after Intermediate Respiratory Care Unit admission, stratified according to the group of origin. HFNO, high flow nasal oxygen; NIV, noninvasive ventilation.

4 | DISCUSSION

The study's main finding was that hARF consequent to COVID-19 can be addressed with HFNO in the patients who were intolerant to NIV and that a switch to HFNO is possible, frequent and not necessarily associated to a worse prognosis. Since the level of CO_2 retention was mild to moderate in most of our patients, it is unclear if HFNO can be effective in subjects with severe acute hypercapnia. Several hypotheses can be advanced to explain HFNO's positive efficacy in these patients. First, it may decrease respiratory rate, improve breathing pattern, and subsequently reduce inspiratory effort and the work of breathing, thereby alleviating respiratory distress.[9] Second, delivering high-flow gas HFNO treatment may produce positive end-expiratory pressure, increase end-expiratory lung volumes and improve lung compliance and blood gas exchange.[10] Third, HFNO may clear the upper airways of expired air, which reduces anatomic dead space by decreasing rebreathing, making ventilation more efficient and leading to effective $PaCO_2$ reduction.[11]

According to studies on its use, the NIV failure rate ranges between 15% and 25% in adult patients with hARF[12]: In comparison, the approximate 35% rate of NIV intolerance found in the study patients seems surprisingly high. These authors can only hypothesize that the patients studied were particularly frightened by the COVID-19 experience which caused them to be extremely agitated and fearful of death, factors that may have contributed to their intolerance to NIV treatment.[12]

The study's limitations include the small number of patients studied and its retrospective nature, which may have caused a significant bias. As the study was conducted in a single center, the generalizability of its results is, of course, questionable. Despite these limitations, the study's data suggest that HFNO can be considered a safe, well tolerated, effective second-line treatment in patients with mild to moderate hARF secondary to COVID-19 intolerant to NIV. Bearing in mind that several distinct etiologies may share a common pathophysiological pathway, the Authors can hypothesize that HFNO could represent a good second choice respiratory support in patients intolerant to NIV with hARF secondary to other causes.

KEYWORDS
acute respiratory failure, COVID-19, high flow nasal oxygen, noninvasive ventilation

AUTHOR CONTRIBUTIONS

Federico Lionello: Conceptualization; formal analysis; writing—original draft. **Gabriella Guarnieri**: Formal analysis; methodology. **Giovanna Arcaro**: Data curation; investigation. **Andrea Vianello**: Conceptualization; writing—review & editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The clinical and respiratory function data that support the findings of this study are available at https://intranet.sanita.padova.it at the request of the interested party.

TRANSPARENCY STATEMENT

The lead author Andrea Vianello affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Federico Lionello
Gabriella Guarnieri
Giovanna Arcaro
Andrea Vianello

Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy

Correspondence
Andrea Vianello, Fisiopatologia Respiratoria, Ospedale-Università di Padova, Via Giustiniani, 2, 35128 PADOVA, Italy.
Email: andrea.vianello@aopd.veneto.it

ORCID

Andrea Vianello http://orcid.org/0000-0002-8790-6029

REFERENCES

1. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J*. 2017;50:1602426. doi:10.1183/13993003.02426-2016
2. Carron M, Freo U, Bahammam AS, et al. Complications of non-invasive ventilation techniques: a comprehensive qualitative review of randomized trials. *Br J Anaesth*. 2013;110:896-914. doi:10.1093/bja/aet070
3. Liu J, Duan J, Bai L, Zhou L. Noninvasive ventilation intolerance: characteristics, predictors, and outcomes. *Respir Care*. 2016;61:277-284. doi:10.4187/respcare.04220
4. Nishimura M. High-flow nasal cannula oxygen therapy in adults. *J Intensive Care*. 2015;3:15. doi:10.1186/s40560-015-0084-5
5. Huang Y, Lei W, Zhang W, Huang J. High-flow nasal cannula in hypercapnic respiratory failure: a systematic review and meta-analysis. *Can Respir J*. 2020;2020:7406457. doi:10.1155/2020/7406457
6. Cortegiani A, Longhini F, Madotto F, et al. High flow nasal therapy versus noninvasive ventilation as initial ventilatory strategy in COPD exacerbation: a multicenter non-inferiority randomized trial. *Crit Care*. 2020;24(1):692. doi:10.1186/s13054-020-03409-0
7. Ovtcharenko N, Ho E, Alhazzani W, et al. High-flow nasal cannula versus non-invasive ventilation for acute hypercapnic respiratory failure in adults: a systematic review and meta-analysis of randomized trials. *Crit Care*. 2022;26:348. doi:10.1186/s13054-022-04218-3
8. Xu C, Yang F, Wang Q, Gao W. Comparison of high flow nasal therapy with non-invasive ventilation and conventional oxygen therapy for acute hypercapnic respiratory failure: a meta-analysis of randomized controlled trials. *Int J Chronic Obstruct Pulm Dis*. 2023;18:955-973. doi:10.2147/COPD.S410958
9. Adams CF, Geoghegan PH, Spence CJ, Jermy MC. Modelling nasal high flow therapy effects on upper airway resistance and resistive work of breathing. *Respir Physiol Neurobiol*. 2018;254:23-29. doi:10.1016/j.resp.2018.03.014
10. Mauri T, Turrini C, Eronia N, et al. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med*. 2017;195:1207-1215. doi:10.1164/rccm.201605-0916OC
11. Möller W, Feng S, Domanski U, et al. Nasal high flow reduces dead space. *J Appl Physiol*. 2017;122:191-197. doi:10.1152/japplphysiol.00584.2016
12. Ngandu H, Gale N, Hopkinson JB. Experiences of noninvasive ventilation in adults with hypercapnic respiratory failure: a review of evidence. *Eur Respir Rev*. 2016;25(142):451-471. doi:10.1183/16000617.0002-2016

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