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High-flow nasal cannula oxygen therapy for refractory hypoxemia in hospitalized older patients with end-stage respiratory failure

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Abstract

Limited data exist regarding the effectiveness of high-flow nasal cannula (HFNC) oxygen therapy in older patients with terminal acute respiratory failure (ARF). We examined the impact of HFNC on arterial oxygenation after failure of conventional oxygen therapy (COT) and non-invasive ventilation (NIV) or continuous positive airway pressure (CPAP) in a retrospective physiologic study of 37 consecutive patients admitted to a geriatric ward with end-stage ARF who received HFNC for refractory hypoxemia after failure of NIV/CPAP (n=18) or COT (n=19). Oxygenation parameters obtained during initial respiratory support were compared with those measured after the transition to HFNC. We observed that 22 patients died, 2 were transferred to the intensive care unit, and 13 were discharged alive. A “do not intubate” status was identified in 17 of the 22 deceased patients. Following HFNC application, improvements were observed in partial pressure of oxygen (PaO₂, p<0.0001), oxygen saturation (SO₂, p<0.0001), PaO₂/fraction of inspired oxygen (FiO₂) ratio (p=0.004), and peripheral SO₂ (p<0.0001). Oxygenation improvements were greater after transition from NIV/CPAP despite lower FiO₂ set with HFNC and in patients discharged alive despite unchanged FiO₂. HFNC successfully corrected refractory hypoxemia following NIV/CPAP or COT failure in patients with terminal ARF hospitalized in a geriatric acute-care ward.

Key words: acute respiratory failure, acute care, refractory hypoxemia, high-flow nasal cannula oxygen therapy, palliative care.

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Introduction

Acute respiratory failure (ARF) is a leading cause of emergency hospitalization among older individuals and often accompanies end-stage acute geriatric syndromes.^{1,2}

High-flow nasal cannula (HFNC) oxygen therapy, a type of non-invasive respiratory strategy, delivers a very high flow of heated and humidified gas mixture (up to 60 L/min) with a fraction of inspired oxygen (FiO₂) up to 100%, providing a continuous positive pressure in the airways and a wash-out of expired gas.³⁻⁵ Clinical guidelines suggest HFNC – rather than non-invasive ventilation (NIV) or continuous positive airway pressure (CPAP) – as first-line supportive therapy in patients with hypoxemic ARF requiring more than 6 L/min of conventional oxygen therapy (COT) to reach a peripheral oxygen saturation (SpO₂) above 92%.^{3,4} In addition, HFNC is better tolerated than NIV/CPAP and offers several advantages, including ease of use and the possibility to speak, eat, and drink without disrupting ventilation.³⁻⁵

The role of HFNC for patients with terminal and severe ARF remains largely underexplored, particularly in those without cancer.⁶ Although refractory hypoxemia is the strongest predictor of intubation and transfer to the intensive care units (ICUs),⁷ invasive

mechanical ventilation (IMV) may not improve the outcome of terminally ill hypoxemic patients.⁵ In some cases, counteracting refractory hypoxemia therefore means avoiding unjustified intubations.^{5,7} The ability of HFNC to correct hypoxemia more than COT and NIV/CPAP in severe, end-stage ARF has never been studied.⁶ This is pivotal in developing evidence-based protocols and optimizing the non-invasive management of end-stage ARF in geriatric patients.

Methods

We conducted a retrospective review of all 37 consecutive patients who started HFNC for ARF during their stay in the Unit of Geriatrics at Azienda Ospedaliera di Cosenza from January 1 to December 31, 2017. At that time, in the absence of clear indications by evidence-based guidelines, we always initiated respiratory support with COT or NIV/CPAP and then switched to HFNC only in cases of hypoxemic failure and when immediate intubation was not feasible. Patients were initially treated with (i) NIV, as bi-level pressure support through a face mask with inspiratory pressure between 14 and 20 cmH₂O and expiratory pressure of 4-6 cmH₂O; (ii) CPAP through a Boussignac mask with oxygen flow of at least 15 L/min; and (iii) COT, through nasal prongs or Venturi mask. FiO₂ during

NIV/CPAP or COT was calculated as follows: $21 (\text{FiO}_2 \text{ of room air}) + (3 \times \text{L/min of O}_2 \text{ flow})$.⁸ The clinical decision of resorting to HFNC was mainly dictated by the incapacity to obtain a $\text{SpO}_2 \geq 92\%$ after at least one hour of treatment with COT or NIV/CPAP.

HFNC therapy was started with a FiO_2 of $\geq 50\%$ and a flow of ≥ 40 L/min. Both parameters were titrated to obtain a $\text{SpO}_2 > 92\%$. HFNC therapy was then continued for 24 hours a day.

In a physiologic study, the values of selected respiratory variables measured during the initial type of respiratory support were compared with the corresponding values obtained in each patient after the switch to HFNC, with patients serving as their own controls. Values from the last arterial blood gas (ABG) analysis prior to HFNC initiation were compared with those of the first ABG performed within one day after HFNC initiation. Percentage variation of the partial pressure of oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio before and after HFNC initiation was calculated as follows: $[\text{PaO}_2/\text{FiO}_2 \text{ during HFNC} - \text{PaO}_2/\text{FiO}_2 \text{ before HFNC}] \div \text{PaO}_2/\text{FiO}_2 \text{ before HFNC} \times 100$. Basal SpO_2 and the corresponding $\text{SpO}_2/\text{FiO}_2$ were measured a few minutes before the switch to HFNC and compared with values detected not later than 30 minutes after HFNC application.

Normally distributed data were analyzed by a t-test for paired and unpaired data, while not normally distributed data were analyzed by the Wilcoxon or the Mann-Whitney U test. The chi-squared test was used for categorical data. According to a global effect size of 25% with a type I error of 0.05, the sample size had a power of 87% (GPower 3.1.7).

Patients or their close relatives provided written consent to use anonymously extracted data for research purposes. The study was approved by the Institutional Review Board.

Results

The cohort was divided into two groups: patients discharged alive (positive clinical outcome, $n=13$) and 24 patients (negative clinical outcome) who died in the ward ($n=22$) or were transferred to the ICU ($n=2$). Among the 22 deceased patients, one succumbed immediately after intubation, and another refused intubation. Additional 17 patients (of the 22 deceased patients) were classified as “do not intubate” by ward physicians (7 patients) or consulting intensivists (10 patients), based on comorbidities, age, current clinical conditions, and previous functional and cognitive status. As reported in Table 1, the mean age was 82 ± 7.6 years, active cancer was present in 35% of patients, and dementia in 60%. No significant difference was observed in clinical characteristics, baseline diseases, and acute causes of ARF between the two groups. Acute heart failure (43.2%) was the main cause of ARF, followed by pneumonia (37.8%), sepsis (32.4%), chronic obstructive pulmonary disease (COPD) exacerbation, and simple aspiration (both 21.6%).

A total of 18 patients were supported with NIV or CPAP before starting HFNC, while the remaining 19 patients were pre-treated with COT (Table 2). Pre-HFNC ABG analysis was performed in all 37 patients and showed that 12 out of the 37 patients had significant hypercapnia, *i.e.*, arterial partial pressure of carbon dioxide (PaCO_2) ≥ 60 mmHg. ABG analysis control during HFNC was available in 31 (19 with negative clinical outcome and 12 with positive clinical outcome) out of the 37 patients and was always performed within 24 hours from HFNC application (Table 2).

HFNC therapy was started after recognized failure of the initial respiratory support to ameliorate arterial oxygenation. In the negative clinical outcome patients, HFNC treatment was conducted until in-hospital death (22 patients) or transfer to the ICU (2 patients). In the positive clinical outcome group, HFNC was de-escalated to COT following respiratory improvement in 11 patients, who were discharged with long-term COT thereafter; the remaining 2 patients of

the positive clinical outcome group were treated with HFNC up to the end of their hospital stay and were discharged with a prescription of HFNC (about 35 L/min of flow and 45% of FiO_2) for the post-discharge setting.

PaO_2 (from 53.7 ± 14.3 to 76 ± 17.4 mmHg, $p < 0.0001$), ABG analysis oxygen-hemoglobin saturation (SO_2 : from 86 ± 5.9 to 94 ± 6.4 , $p < 0.0001$), $\text{PaO}_2/\text{FiO}_2$ (from 98.3 ± 30.2 to 123 ± 43.2 , $p = 0.004$), and SpO_2 (from 87.9 ± 5.4 to 95.5 ± 2.9 , $p < 0.0001$) increased in the total group after HFNC initiation.

Tables 3 and 4 present the same pre-post comparisons after stratification, respectively, for clinical outcomes (negative and positive), or for the type of initial respiratory support before the application of HFNC (NIV/CPAP and COT).

Discussion and Conclusions

In 2017, our protocol for ARF required starting respiratory support with COT or NIV/CPAP, resorting to HFNC only in cases of inadequate oxygenation and when intubation was not immediately feasible. The primary reason for escalating from NIV/CPAP or COT to HFNC was thus refractory hypoxemia, evidenced by a baseline $\text{PaO}_2/\text{FiO}_2$ ratio of approximately 100. This clinical scenario also enabled us to evaluate the impact of the unusual “escalation” from NIV/CPAP to HFNC in patients with end-stage ARF, a transition that was never previously investigated.^{3-6,9,10} In line with studies of HFNC-treated adult patients in non-intensive hospital wards,⁹ the mortality rate in our patients was 59%, indicating an end-of-life setting.

Despite such a poor prognosis, in this selected population, we observed a significant increase in arterial oxygenation following the application of HFNC, not only in patients initially treated with COT but particularly in those who escalated from NIV/CPAP, *i.e.*, the most severe cases. In these patients, the improved oxygenation occurred despite a lower FiO_2 set with HFNC compared to the previous NIV/CPAP setting. Consequently, the percentage increase in the $\text{PaO}_2/\text{FiO}_2$ ratio after initiating HFNC was significantly higher in patients who transitioned from NIV/CPAP than in those who transitioned from COT. Similarly, patients who were discharged alive showed a better oxygenation response to HFNC compared to those with negative clinical outcomes (deceased or transferred to ICU), obtained without increasing FiO_2 . This, again, resulted in a significantly greater percentage increase in the $\text{PaO}_2/\text{FiO}_2$ ratio for survivors, reflecting their greater clinical resilience.

These findings suggest that HFNC may be more effective than COT and NIV/CPAP in improving oxygenation in patients with terminal and very severe ARF. In COVID-19 patients, the superiority of HFNC compared to other supportive treatments was more significant in subgroups characterized by greater respiratory severity.⁴ In non-COVID-19 patients with $\text{PaO}_2/\text{FiO}_2$ below 150, HFNC prevented intubation better than NIV, likely due to improved oxygenation.^{11,12} Of note, in our study, HFNC also reduced PaCO_2 and significantly increased pH in the escalation from COT, reflecting the wash-out effect of CO_2 exerted by HFNC.³

Overall, our findings suggest that in the hospital management of end-of-life refractory hypoxemia, HFNC should precede NIV/CPAP and can also be proposed when moderate hypercapnia complicates hypoxemia. Along with the subsequent clinical experience, mainly implemented during the COVID-19 pandemic, the present observations changed our routine therapeutic practice, which currently includes HFNC as the preferential treatment of type 1 ARF when hypoxia is not adequately compensated by COT, in accordance with updated guidelines.^{3,4} In the absence of relevant hypercapnia and respiratory acidosis, HFNC can be preferred over NIV or CPAP as first-line treatment, particularly in geriatric end-stage patients for

Table 1. Descriptive and clinical variables.

| | Overall population (n=37) | Negative clinical outcome group (n=24) | Positive clinical outcome group (n=13) | p |
|--|------------------------------|---|---|-------|
| Age, years | 82.0±7.6 | 81.1±8.3 | 83.9±6.1 | 0.300 |
| Sex (males/females) | 22/15 | 15/9 | 7/6 | 0.608 |
| Current smoking | 8 (21.6) | 6 (25.0) | 2 (15.4) | 0.497 |
| Dementia | 22 (59.5) | 14 (58.3) | 8 (61.5) | 0.849 |
| Bedsore | 9 (24.3) | 7 (29.2) | 2 (15.4) | 0.350 |
| Hypertension | 22 (59.5) | 15 (62.5) | 7 (53.8) | 0.608 |
| Type 2 diabetes mellitus | 12 (32.4) | 9 (37.5) | 3 (23.0) | 0.370 |
| Chronic heart failure | 14 (37.8) | 7 (29.2) | 7 (53.8) | 0.139 |
| Chronic kidney disease | 11 (29.7) | 5 (20.8) | 6 (46.2) | 0.107 |
| Chronic coronary disease | 5 (13.5) | 3 (12.5) | 2 (15.4) | 0.806 |
| Atrial fibrillation | 9 (24.3) | 6 (25.0) | 3 (23.0) | 0.896 |
| COPD | 16 (43.2) | 9 (37.5) | 7 (53.8) | 0.337 |
| Current malignancies | 13 (35.1) | 10 (41.7) | 3 (23.0) | 0.258 |
| Pre-admission disability | 22 (59.5) | 15 (62.5) | 7 (53.8) | 0.608 |
| Home oxygen therapy | 3 (8.1) | 1 (4.1) | 2 (15.3) | 0.232 |
| Causes of acute respiratory failure | | | | |
| Acute Heart Failure | 16 (43.2) | 8 (33.3) | 8 (61.5) | 0.098 |
| Aspiration | 8 (21.6) | 7 (29.2) | 1 (7.6) | 0.129 |
| Pneumonia | 11 (29.7) | 7 (29.2) | 4 (30.8) | 0.918 |
| Aspiration pneumonia | 3 (8.1) | 2 (8.3) | 1 (7.6) | 0.945 |
| Interstitial lung disease | 1 (2.7) | 1 (4.1) | 0 (0) | 0.999 |
| Sepsis | 12 (32.4) | 10 (41.7) | 2 (15.3) | 0.103 |
| COPD exacerbation | 8 (21.6) | 4 (16.7) | 4 (30.8) | 0.319 |
| ARDS | 3 (8.1) | 3 (12.5) | 0 (0) | 0.538 |
| Bronchiectasis exacerbation | 1 (2.7) | 0 (0) | 1 (7.6) | 0.351 |
| Acute stroke | 7 (18.9) | 6 (25.0) | 1 (7.6) | 0.199 |

n, number; COPD, chronic obstructive pulmonary disease; ARDS, adult respiratory distress syndrome. Values are expressed as number (percentage) or mean ± standard deviation. Pre-admission disability is defined as dependency in 3 or more Activities of Daily Living (ADL) 15 days before hospital admission.

Table 2. Clinical severity and hospital management.

| | Overall population (n=37) | Negative clinical outcome group (n=24) | Positive clinical outcome group (n=13) | p |
|---|------------------------------|---|---|---------|
| Altered mental status | 23 (62.2) | 17 (70.8) | 6 (46.2) | 0.139 |
| Admission SBP, mmHg | 121.4±25.4 | 124.4±30.1 | 116.0±13.9 | 0.351 |
| Admission DBP, mmHg | 73.2±11.4 | 74.2±13.1 | 71.6±8.0 | 0.517 |
| Admission body temperature, °C | 36.4±0.8 | 36.5±0.8 | 36.3±0.8 | 0.529 |
| Inotropic therapy | 10 (27.0) | 7 (29.2) | 3 (23.0) | 0.690 |
| NIV or CPAP before HFNC | 18 (48.6) | 13 (54.2) | 5 (38.5) | 0.361 |
| COT before HFNC | 19 (51.4) | 11 (45.8) | 8 (61.5) | 0.361 |
| ABG analysis pre-HFNC, days from admission | 5 (2-8) | 3 (1-8) | 6 (5-7) | 0.418 |
| ABG analysis during HFNC, days from HFNC initiation | 0 (0-1) | 0 (0-1) | 1 (0-1) | 0.177 |
| HFNC initiation, days from admission | 6 (2-9) | 3.5 (1-9) | 7 (6-9) | 0.179 |
| HFNC initial flow, L/min | 55.1±7.6 | 58.3±3.8 | 49.2±9.3 | <0.0001 |
| HFNC alternated with NIV | 2 (5.4) | 2 (8.3) | 0 (0) | 0.531 |
| Length of HFNC therapy, days | 4 (2-7) | 2 (1-5.25) | 6 (5-10) | 0.011 |
| Length of hospital stay, days | 13 (7-18) | 9.5 (4-15) | 21 (13-25) | 0.002 |

n, number; mmHg, millimeters of mercury; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIV, non-invasive ventilation; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; ABG, arterial blood gases. Values are expressed as number (percentage), mean ± standard deviation, or median (interquartile range).

whom the goal is not prolonged survival, but the improvement of arterial oxygenation without compromising quality of life.^{3-6,9,10}

Indeed, the decision to intubate frail geriatric patients may be controversial and often taken in response to hypoxemia refractory to noninvasive treatments.^{5,7} Therefore, the HFNC-related oxygenation improvement is an important clinical goal and may reduce unjustified intubation solely dictated by untreatable hypoxemia even with NIV/CPAP.^{5,7} These results add to the limited data on the role of HFNC in the palliative treatment of terminal hospitalized older ARF

patients, particularly regarding the comparison with NIV/CPAP that was never previously investigated.^{6,9,10.}

The choice of the type of supportive care in hospitalized geriatric patients has ethical and practical implications. HFNC provides more comfortable respiratory support compared to NIV/CPAP and assures greater treatment duration and continuity while preserving comfort in terminal patients.^{3-6,9,10} The HFNC-related improved oxygenation reduces the indications for intubation, representing a crucial advantage. Intubation and IMV cause

Table 3. Comparisons of respiratory values before and after high-flow nasal cannula application in groups stratified according to the clinical outcome.

| | Negative clinical outcome | | | Positive clinical outcome | | |
|---|---------------------------|-------------|---------|---------------------------|-------------|---------|
| | Before HFNC | During HFNC | p | Before HFNC | During HFNC | p |
| Arterial blood gases | | | | | | |
| | n=19 | | | n=12 | | |
| pH | 7.39±0.08 | 7.41±0.12 | 0.544 | 7.44±0.07 | 7.44±0.07 | 0.749 |
| PaCO ₂ | 47.9±15.7 | 47.5±15.4 | 0.888 | 46.4±8.6 | 46.3±7.0 | 0.979 |
| PaO ₂ | 56.7±16.9 | 74.2±18.0 | <0.0001 | 48.9±6.7 | 78.9±16.8 | <0.0001 |
| SO ₂ | 86.0±6.2 | 92.7±7.9 | 0.005 | 85.9±5.5 | 96.3±1.6 | <0.0001 |
| PaO ₂ /FiO ₂ | 99.6±30.3 | 111.2±45.9 | 0.225 | 96.3±31.3 | 141.6±31.9 | 0.003 |
| % variation of PaO ₂ /FiO ₂ | 12.9 (-23.4/45.1) | | | 48.1 (23.3/91.1) | | |
| Pulse oximetry | | | | | | |
| | n=24 | | | n=13 | | |
| SpO ₂ | 87.4±6.4 | 94.9±3.4 | <0.0001 | 88.9±2.9 | 96.6±1.5 | <0.0001 |
| FiO ₂ | 62.8±16.9 | 70.2±15.2 | 0.081 | 55.1±13.6 | 57.5±10.5 | 0.628 |
| SpO ₂ /FiO ₂ | 1.49±0.4 | 1.42±0.3 | 0.506 | 1.7±0.5 | 1.7±0.3 | 0.924 |

HFNC, high-flow nasal cannula; n, number; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen; SO₂, oxygen-hemoglobin saturation; FiO₂, fraction of inspired oxygen; SpO₂, peripheral oxygen saturation measured by pulse oximetry; *p is for the comparison of the percentage (%) variation of PaO₂/FiO₂ between groups. The oxygenation effect of HFNC was greater in patients with a positive clinical outcome, despite lower initial oxygenation levels. In these cases, arterial oxygenation improved without an increase in FiO₂ after the switch to HFNC, resulting in a significantly greater percentage increase in PaO₂/FiO₂ for the positive clinical outcome group compared to the negative outcome group. Values are expressed as mean ± standard deviation or median (interquartile range).

Table 4. Comparisons of respiratory values before and after high-flow nasal cannula (HFNC) application in groups stratified according to the respiratory support before the switch to HFNC.

| | NIV or CPAP before HFNC | | | COT before HFNC | | |
|---|-------------------------|-------------|---------|-------------------|-------------|---------|
| | Before HFNC | During HFNC | p | Before HFNC | During HFNC | p |
| Arterial blood gases | | | | | | |
| | n=17 | | | n=14 | | |
| pH | 7.38±0.09 | 7.38±0.12 | 0.872 | 7.44±0.06 | 7.46±0.05 | 0.042 |
| PaCO ₂ | 49.3±16.3 | 50.5±14.3 | 0.654 | 44.8±8.1 | 42.9±9.2 | 0.346 |
| PaO ₂ | 56.1±18.3 | 79.6±18.4 | <0.0001 | 50.8±6.5 | 71.7±15.7 | <0.0001 |
| SO ₂ | 85.3±7.2 | 93.2±8.4 | 0.007 | 86.9±3.8 | 95.1±2.5 | <0.0001 |
| PaO ₂ /FiO ₂ | 92.0±32.0 | 133.2±44.3 | 0.001 | 105.9±26.9 | 110.6±39.9 | 0.665 |
| % variation of PaO ₂ /FiO ₂ | 53.8 (5.2/86.2) | | | 11.6 (-26.2/27.4) | | |
| Pulse oximetry | | | | | | |
| | n=18 | | | n=19 | | |
| SpO ₂ | 88.6±5.1 | 95.4±3.9 | <0.0001 | 87.3±5.7 | 95.6±1.8 | <0.0001 |
| FiO ₂ | 71.6±12.6 | 66.1±16.1 | 0.158 | 49.3±10.5 | 65.4±14.2 | <0.0001 |
| SpO ₂ /FiO ₂ | 1.3±0.2 | 1.5±0.4 | 0.008 | 1.9±0.5 | 1.5±0.3 | 0.011 |

NIV, non-invasive ventilation; CPAP, continuous positive airways pressure; HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; n, number; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen; SO₂, oxygen-hemoglobin saturation; FiO₂, fraction of inspired oxygen; SpO₂, peripheral oxygen saturation measured by pulse oximetry; *p is for the comparison of the percentage (%) variation of PaO₂/FiO₂ between groups. HFNC markedly improved arterial oxygenation especially in patients pre-treated with NIV/CPAP. For these patients, HFNC significantly enhanced oxygenation even with a slightly decreased FiO₂ set with HFNC, leading to a significantly greater percentage increase in PaO₂/FiO₂ compared to the COT group. Notably, switching from COT to HFNC also resulted in a significant increase in pH, due to reduced pCO₂ levels. Values are expressed as mean ± standard deviation or median (interquartile range).

ventilator-associated pneumonia, delirium, and longer hospital stays, but in end-stage patients these complications are rarely balanced by a survival gain.^{1,2,5}

It should be mentioned, however, that local factors may have contributed to the failure of NIV/CPAP in correcting hypoxemia, including patient-ventilator asynchronies, low expiratory pressure, discomfort, and air leaks.¹³ These issues are somewhat inevitable when treating older ARF patients with NIV/CPAP in non-intensive hospital wards, where most of such patients are currently managed.^{1,2,13,14} In this context, HFNC emerges as a valuable alternative, especially in geriatric patients who are less tolerant of NIV/CPAP.^{13,14}

This study also provides an interesting insight into the issue of ARF in older patients. Consistent with previous larger studies^{1,2,14,15}, we found that heart failure, sepsis, and pneumonia were more frequent etiologies of ARF than acute exacerbation of COPD. ARF may be an epiphenomenon of terminal illnesses - including degenerative cerebral diseases - and many patients had more than one underlying causes.^{1,2,14,15}

A limitation of the study is the relatively small number of patients. However, since patients served as their own controls, the sample size was sufficient to demonstrate the statistical significance of the oxygenation improvements after HFNC. The measurement of respiratory parameters shortly after HFNC initiation indicates that these improvements can factually be attributed to HFNC. While the retrospective nature is another limitation, it allowed for a “real-world” observation of patients typically excluded from randomized trials.

In conclusion, HFNC provided significant improvements in arterial oxygenation when used as an escalation treatment for refractory hypoxemia after COT or NIV/CPAP failure in patients with severe, terminal ARF hospitalized in an acute-care geriatric ward.

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Informed consent: obtained.

Patient consent for publication: at admission, patients (or their close relatives for patients with cognitive impairment or altered mental status) provided written consent, included as part of the medical record, for use of anonymously extracted data from the medical record for publication of retrospective observational research.

Availability of data and materials: raw data are available from the first/corresponding author upon reasonable request.

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