High-Flow Nasal Cannula in Early Emergency Department Management of Acute Hypercapnic Respiratory Failure Due to Cardiogenic Pulmonary Edema

Nicolas Marjanovic, Alexandre Flacher, Loïc Drouet, Aude Le Gouhinec, Hakim Said, Jean-François Vigneau, Barbara Chollet, Sophie Lefebvre, and Mustapha Sebbane

BACKGROUND: Noninvasive ventilation (NIV) is the recommended ventilatory support for acute cardiogenic pulmonary edema (CPE) associated with acute respiratory failure or hypercapnia. High-flow nasal cannula (HFNC) has emerged as an alternative to NIV in acute hypoxemic respiratory failure. We aimed to assess the efficacy of HFNC on early changes in P_{aCO_2} and respiratory parameters in patients in the emergency department with acute hypercapnic CPE and to compare it to NIV. METHODS: We conducted a prospective observational study in consecutive emergency department patients with acute hypercapnic CPE. Subjects received either HFNC or NIV, according to the attending emergency physician's expertise in HFNC. The primary outcome was change in P_{aCO_2} after treatment for 1 h. Secondary outcomes were change in pH, breathing frequency, signs of work of breathing, and comparisons to NIV. RESULTS: Twenty-seven subjects with a discharge diagnosis of hypercapnic CPE were analyzed. Subjects had a median age of 87 y (interquartile range [IQR] 78–93); 37% were male. Twelve (44%) received HFNC, and 15 (56%) received NIV. Median of changes in P_{aCO_2} from baseline to after 1 h of treatment were 7 mm Hg (IQR 4–11, $P = .002$) for HFNC and 3 mm Hg (IQR 1–8, $P = .02$) for NIV, with no between-group difference. pH, breathing frequency and signs of work of breathing also improved after both HFNC and NIV. CONCLUSIONS: This preliminary study suggests that HFNC treatment for 1 h improves P_{aCO_2} and respiratory parameters in subjects with hypercapnic acute CPE in a manner that is comparable to NIV. Further studies are needed to assess HFNC as a possible alternative to NIV in early management of acute hypercapnic respiratory failure of cardiogenic origin. (ClinicalTrials.gov registration NCT03883555.) *Key words: respiratory insufficiency; cardiogenic pulmonary edema/heart failure; noninvasive ventilation; high-flow nasal cannula; emergency medicine.* [Respir Care 2020;65(9):1241–1249. © 2020 Daedalus Enterprises]

Introduction

Acute cardiogenic pulmonary edema (CPE) is one of the main diagnoses for patients admitted for dyspnea in emergency departments.[1] Severe CPE is associated with respiratory failure and hypercapnia in about 40% of patients.[2-4] Hypercapnia may lead to altered consciousness

The authors are affiliated with the Department of Emergency Medicine and Prehospital Care, Montpellier University Hospital, Montpellier, France.

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Fisher and Paykel provided the Optiflow Airvo2 devices. The authors have disclosed no conflicts of interest.

Correspondence: Mustapha Sebbane MD PhD, Emergency Department, Montpellier University Hospital, Hôpital Lapeyronie, 191 avenue du Doyen Gaston Giraud, 34295 Montpellier, Cedex 5, France. E-mail: m-sebbane@chu-montpellier.fr.

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and central apnea, and it may be associated with higher intubation and in-hospital mortality rates.[5-7]

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Noninvasive ventilatory support, including noninvasive ventilation (NIV) or CPAP, is recommended as a first-line treatment for acute hypoxic and hypercapnic respiratory failure associated with acute CPE, along with intravenous diuretics and a nitrate derivative.[6,8,9] NIV improves alveoli recruitment, decreases work of breathing (WOB), and improves cardiac output. Consequently, NIV allows rapid correction of respiratory and blood gas parameters in acute CPE and contributes to a reduced intubation rate and improved in-hospital mortality compared to standard oxygen therapy.[10] However, NIV may be poorly tolerated in certain patients, in whom it is associated with failure of treatment and poor outcomes.[11-13]

High-flow nasal cannula (HFNC) represents another strategy in the ventilatory management of patients with acute respiratory failure.[6,14] HFNC delivers a heated and humidified air-oxygen blend through a nasal cannula. It achieves flows up to 60 L/min and F_{IO_2} ranging from 0.21 to 1.0, both of which can be adapted to patient needs. Its effects are mediated through the delivery of PEEP and dead space washout.[15-18] HFNC is usually easier to apply and is better tolerated than NIV.[19] In adults, HFNC has been evaluated in ICU and postoperative settings in comparison to NIV and standard oxygen therapy for the treatment of hypoxemic respiratory failure.[20] Compared to conventional oxygen therapy, HFNC may decrease the need for tracheal intubation.[21] Its benefits over NIV with regard to intubation rate and mortality still require confirmation.[22-24] HFNC is emerging as an alternative strategy in the management of acute hypoxemic respiratory failure of heterogeneous etiologies. However, it has scarcely been explored in the treatment of select hypercapnic respiratory failure or in the context of early emergency department management.[25-28] In the emergency department setting, HFNC has been reported to be noninferior to NIV in preventing endotracheal intubation in unselected emergency department subjects with acute respiratory failure, as well as in the subgroup of subjects with acute decompensated heart failure.[29,30] HFNC has also been reported to lower 60-min breathing frequency compared to standard oxygen therapy in a randomized controlled trial of 128 subjects with mild acute CPE in the emergency department.[31] Recent evidence from 2 retrospective studies and secondary analysis of a randomized controlled trial suggest that HFNC may be effective in treating hypercapnia in subgroups of subjects with hypercapnic respiratory failure of all causes.[29,32,33] To our knowledge, no prospective study to date has examined the benefits of HFNC treatment in early management of acute hypercapnic respiratory failure in an emergency department.

QUICK LOOK

Current knowledge

High-flow nasal cannula (HFNC) therapy is an alternative strategy for the management of acute hypoxemic respiratory failure of heterogeneous etiologies. Recent evidence from retrospective studies and subgroup analysis of patients with hypercapnic respiratory failure of all causes suggest that HFNC may be effective in treating hypercapnia.

What this paper contributes to our knowledge

Treatment with HFNC for 1 h improved P_{aCO_2} and respiratory parameters, including pH, breathing frequency, and signs of increased work of breathing in hypercapnic patients presenting in the emergency department with respiratory failure due to acute cardiogenic pulmonary edema. HFNC might be considered as alternative support for early management of acute hypercapnic cardiogenic pulmonary edema in the emergency department setting.

We aimed to evaluate HFNC as a possible alternative to NIV in emergency department patients with acute hypercapnic CPE, assessing its efficacy with regard to early changes in P_{aCO_2}, respiratory parameters, and indirect signs of WOB and comparing it to NIV.

Methods

Study Design and Setting

We conducted a prospective, observational, and comparative study in the emergency department of Montpellier University Hospital with an annual census of 82,000 patients. This study was conducted as a preliminary study to the randomized controlled OPTICAP study (ClinicalTrials.gov: NCT02874339). Our institutional review board approved the study (IRB-MTP-12-03) with a waiver of written informed consent because the procedures were all part of routine care. It was designed and reported according to STROBE guidelines.

This study was intended as a study preliminary to a larger randomized controlled trial. Because of the novelty of the study and the lack of available data on the effect of HFNC on P_{aCO_2} at the time of study design, the sample size was calculated based on data available for NIV. We planned to include 16 subjects in each group so as to be able to show a significant 5 mm Hg decrease in P_{aCO_2}, with an alpha of 5% and a study power of 80%.

Selection of Participants

Adult patients admitted to the emergency department for acute hypercapnic respiratory failure related to acute CPE from February 2015 to September 2016 were enrolled. Inclusion criteria were: (1) signs of acute respiratory failure including breathing frequency of at least 20 breaths/min, use of accessory respiratory muscles or paradoxical abdominal movement, or associated high blood pressure; (2) clinical suspicion of acute CPE based on a history of acute CPE, bilateral crackles on chest examination, or bilateral infiltrates compatible with pulmonary edema on chest radiograph; (3) and hypercapnia defined as $P_{aCO_2} > 45$ mm Hg on arterial blood gas testing.

The main exclusion criteria were clinical suspicion of exacerbation of COPD, long-term oxygen therapy or ventilatory support for chronic lung disease, clinical suspicion of sepsis at admission including fever $> 38.5°C$, contraindication to NIV according to international guidelines[9] for NIV treatment including hemodynamic instability (mean arterial pressure < 65 mm Hg, use of vasopressors) or a Glasgow coma scale score ≤ 12 points, requirement for endotracheal intubation, and use of ventilatory support prior to inclusion, including CPAP or NIV administered before admission to the hospital.

Ventilatory Support Modalities

Subject management was performed according to our standard of care for the management of respiratory failure. At our emergency department, HFNC was used as an alternative ventilatory support to NIV in patients showing signs of respiratory failure; NIV was applied with careful monitoring to prevent escalation to invasive ventilation. Subjects received either NIV or HFNC according to the presence of an attending emergency physician with expertise in using HFNC. Standardized protocols were implemented for both NIV and HFNC treatment.

HFNC was administered via large- or medium-bore binasal prongs, using an Airvo2 system (Fisher and Paykel Healthcare, Courtabeuf, France). Flow was initially set at 60 L/min, temperature was set at 37°C, and F_{IO_2} was adjusted to maintain a target S_{pO_2} of at least 92%. Flow, F_{IO_2}, and temperature could be adjusted to patient tolerance, as recommended.

NIV was administered through a face mask or oronasal mask (Respironics, Philips Healthcare, France), in a pressure controlled continuous spontaneous ventilation mode using a dedicated device (Monnal T60 and T75, Airliquide Medical Systems, Antony, France). Initial settings were: PEEP 5–10 cm H_2O, pressure support 6–10 cm H_2O above PEEP, and F_{IO_2} adjusted to a target S_{pO_2} of at least 92%.

Both ventilatory treatments were applied in 1-h sessions and resumed as needed, according to international guidelines for NIV treatment.[9] Subjects were closely monitored, with repeat clinical evaluation every 15 min and serial blood gas testing every hour. Standard oxygen therapy was administered as required to maintain a target S_{pO_2} of at least 92% between sessions or at termination. Oxygen was delivered by nasal cannula or nonrebreather mask. Ventilatory support sessions were ended if signs of acute respiratory failure had resolved or when endotracheal intubation criteria had been met.

Prespecified criteria for endotracheal intubation were used to avoid the risk of delayed intubation: hemodynamic instability, deterioration of neurologic status, or signs of persisting or worsening respiratory failure as defined by at least 2 of the following criteria: breathing frequency > 40 breaths/min, lack of improvement in signs of high respiratory muscle work load, and $S_{pO_2} < 90\%$ despite high F_{IO_2} (ie, $F_{IO_2} > 0.80$).[14] All subjects received concomitant standard medical therapy for CPE, including intravenous diuretics and nitrate derivative.

Outcome Measurements

This was a preliminary study aimed at exploring the value of HFNC in the setting of hypercapnia. We chose P_{aCO_2}, which is an objective measurement, as the primary outcome. We evaluated its change at an early time point, ie, at 1 h after initiation of ventilatory support. Secondary outcomes were change in breathing frequency, signs of increased WOB, results of blood gas analysis, and comparisons between HFNC and NIV. All outcome criteria were measured via serial evaluation performed at baseline and at 5–10 min after the end of each 1-h ventilatory session, with the subject receiving standard oxygen therapy as required to maintain a target S_{pO_2} of at least 92%, according to our standard of care and international guidelines.[9]

Arterial blood gas testing was carried out according to clinical routine testing. Blood (1 mL) was sampled by radial artery puncture and collected in heparinized syringes. Blood gas analyses were performed at the central biochemistry laboratory using the Omni-S COBAS B221 system (Roche Diagnostics, France). Normal ranges were as follow: pH = 7.35–7.45; P_{aCO_2} = 35–45 mm Hg; P_{aO_2} = 78–98 mm Hg; HCO_3^- = 22–26 mmol/L; base excess = −2 to +2 mmol/L. Hypercapnia was defined as $P_{aCO_2} > 45$ mm Hg. Acidosis was defined as pH ≤ 7.34.

Clinical parameters including breathing frequency, signs of increased WOB, and vital signs were assessed serially by the treating emergency physician. Breathing frequency was measured over 1 min. Signs of increased WOB were evaluated based on the use of accessory respiratory muscles (intercostal and subcostal muscles) and paradoxical abdominal breathing. Each of the 3 signs was graded from 1 (absent) to 5 (very high). Scores were subsequently added

on a 15-point scale assessing the overall severity of signs of increased WOB.

We also collected chest radiographs and laboratory data including NT-proBNP, hs-cTNT, C-reactive protein, and blood cell counts according to our standard of care to adjudicate discharge diagnosis. Discharge diagnosis was adjudicated retrospectively upon review of subject medical records, secondary to all additional examinations, including hospitalization data, by 2 independent emergency physicians. Diagnosis of acute CPE was established according to the ESC Guidelines for diagnosis and treatment of acute heart failure.[8]

Statistical Analysis

Data were collected prospectively by the attending emergency physicians or research assistants using a standardized form. Data were recorded and stored in an Excel database before transfer to SPSS 23.0 software (IBM, Armonk, New York) for analysis.

Quantitative data were analyzed as median (interquartile range [IQR]) and were compared at baseline between groups using a Mann-Whitney *U* test. Qualitative data were analyzed as numbers and proportion and were compared between groups using a chi-square test or a Fisher exact test. The primary outcome was reported as the median of differences (IQR) in P_{aCO_2} between baseline values and values after 1 h of treatment. Changes in secondary outcomes between baseline values and values after 1 h of treatment were reported as median of differences (IQR). Before- and after-treatment comparisons were tested using the Wilcoxon signed-rank test. Between-group differences for frequency data were reported as odds ratios and 95% CIs; CIs were calculated using the modified Wald method. Results were considered statistically significantly different if $P \leq .05$ or if the 95% CI did not include 1 for the odds ratio.

Results

We enrolled a total of 45 subjects who presented with hypercapnic respiratory failure suspected to be due to acute CPE over the study period (Fig. 1). We excluded 5 patients who presented with prespecified exclusion criteria, including underlying exacerbation of COPD or sepsis.

We secondarily excluded 8 subjects with a final diagnosis other than CPE at emergency department or hospital discharge, leaving 27 subjects in the study analysis. Subjects were elderly with a median age of 87 y (IQR 78–93). They presented with severe acute respiratory failure, as shown by a breathing frequency of 32 breaths/min (IQR 26–39) and indirect signs of increased WOB recorded in 22 (81%) subjects, and moderate respiratory acidosis (Table 1). Main precipitating factors for CPE were atrial fibrillation (15%), hypertensive crisis (26%), and respiratory tract infection

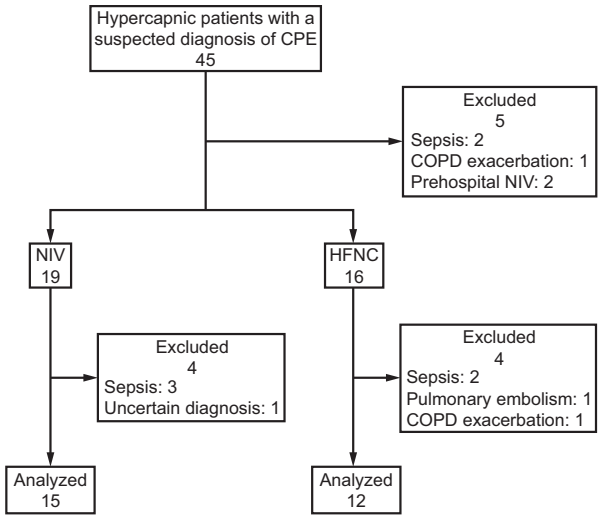

Fig. 1. Flow chart of subjects through the study. CPE = cardiogenic pulmonary edema; NIV = noninvasive ventilation; HFNC = high-flow nasal cannula.

(22%). Fifteen (56%) subjects received NIV, and 12 (44%) received HFNC as ventilatory support. Baseline characteristics were similar in both treatment groups (Table 1).

HFNC was administered for a median duration of 67 (IQR 60–90) min, with a median flow range of 50 (IQR 40–60) L/min and a median F_{IO_2} of 0.50 (IQR 0.40–0.57). NIV was administered for a median duration of 70 (IQR 60–90) min. NIV was provided in the pressure controlled continuous spontaneous ventilation mode, with median F_{IO_2} of 0.60 (IQR 0.34–0.62). HFNC was not terminated prematurely before the end of the 1-h ventilatory session in any subject, whether because of worsening of respiratory failure or failure to tolerate the treatment. Two (7%) subjects were transferred to ICU after emergency department management; both had been treated with NIV. No subjects required escalation to invasive ventilation, whether in the emergency department or the ICU.

Compared to baseline, P_{aCO_2} significantly improved 1 h after initiation of treatment in both treatment groups (Table 2, Fig. 2). The median change in P_{aCO_2} (mm Hg) between baseline and after 1 h of treatment was 7 (IQR 4–11, $P = .002$) for HFNC and 3 (IQR 1–8, $P = .02$) for NIV.

pH improved 1 h after initiation of treatment in both treatment groups (Table 2, Fig. 3). The median change in pH was 0.08 (IQR 0.04–0.24, $P = .005$) for HFNC and 0.04 (IQR 0.01–0.12, $P = .005$) for NIV. Breathing frequency and signs of increased WOB also significantly improved 1 h after initiation of treatment in both treatment groups (Table 2, Fig. 3).

HFNC improved breathing frequency with a median change of 5 breaths/min (IQR 2–12, $P = .028$). HFNC also reduced the severity of increased WOB with a median change of 3 (IQR 1–6, $P = .005$) on the 15-point scale, and

Table 1. Subject Characteristics at Baseline

	Overall	HFNC	NIV	*P*
Age, y	87 (78–93)	91 (77–94)	82 (79–92)	.40
Men	10 (37)	7 (58)	3 (20)	.057
Women	17 (63)	5 (42)	12 (80)	
History				
Chronic lung disease	7 (26)	4 (33)	3 (20)	.66
Cardiogenic heart failure	8 (30)	3 (25)	5 (33)	.17
Hypertension	15 (56)	5 (51)	10 (67)	.26
Diabetes	5 (18)	2 (17)	3 (20)	>.99
Clinical parameters				
Temperature, °C	37.1 (36.5–37.5)	37.5 (36.5–37.7)	37.1 (36.4–37.3)	.23
f, breaths/min	32 (26–39)	34 (27–41)	29 (26–36)	.28
S_{pO_2}, %*	95 (91–98)	93 (90–98)	96 (94–98)	.31
Oxygen flow at baseline, L/min	4 (1–9)	3 (1–8)	5 (2–14)	.21
Heart rate, beats/min	86 (75–118)	97 (80–128)	79 (68–98)	.058
SBP, mm Hg	148 (117–177)	156 (124–172)	146 (111–184)	>.99
DBP, mm Hg	72 (62–89)	80 (63–85)	71 (61–92)	.94
Signs of increased WOB	22 (81)	11 (92)	11 (73)	.22
Increased WOB score†	6 (4–10)	7 (4–9)	6 (3–11)	.72
Biological parameters				
P_{aCO_2}, mm Hg	55 (49–64)	50 (49–61)	60 (48–71)	.45
P_{aO_2}, mm Hg	102 (70–136)	99 (61–155)	102 (72–125)	.88
pH	7.29 (7.22–7.35	7.30 (7.20–7.36)	7.29 (7.21–7.35)	.98
HCO_3^-, mEq	27 (25–29)	27 (25–30)	27 (24–29)	.49
NT-proBNP, ng/L	4,547 (1,821–8,929)	3,520 (1,579–11,585)	5,069 (1,970–8,369)	.76
hs-cTNT, ng/L	41.6 (25.4–72.5)	38.9 (29.5–74.4)	44.9 (17.6–74.9)	.67
Creatinine, μmol/L	98 (68–117)	91 (69.8–114.8)	110 (63–126)	.58
White blood cell count, 10^9/L	9.1 (6.4–14)	9.7 (6.9–13.4)	8.2 (6–17.9)	.46
Other therapeutics				
Furosemide	27 (100)	12 (100)	15 (100)	>.99
Nitrate derivative	16 (59)	8 (67)	8 (53)	>.99
Antibiotics	3 (11)	2 (17)	1 (7)	>.99
β_2 agonist	6 (22)	3 (25)	3 (20)	>.99

Data are presented as median (interquartile range) or *n* (%). *P* values refer to comparison between groups. Overall: *n* = 27 subjects; HFNC: *n* = 12 subjects; NIV: *n* = 15 subjects.
* S_{pO_2} could be recorded with or without standard oxygen therapy.
† Work of breathing is scored on a 15-point scale.
HFNC = high-flow nasal cannula
NIV = noninvasive ventilation
f = breathing frequency
SBP = systolic blood pressure
DBP = diastolic blood pressure
WOB = work of breathing
NT-proBNP = N-terminal pro b-type natriuretic peptide
hs-cTNT = hypersensitive cardiac troponin-T

the number of subjects with signs of increased WOB by 73% ($P = .008$).

NIV improved breathing frequency with a median change of 8 breaths/min (IQR 2–12, $P = .036$), and signs of increased WOB with a median change of 2 (IQR 0–4, $P = .005$) on the 15-point scale. The number of subjects with signs of increased WOB was reduced by 54% ($P = .031$).

There was no between-group difference in changes in P_{aCO_2} at 1 h after initiation of treatment (Table 2). There was no between-group difference in percent of subjects with normalized P_{aCO_2} or in other blood gas or clinical parameters recorded at 1 h, except for breathing frequency($P = .02$).

Discussion

To our knowledge, this is the first prospective study specifically designed to assess the efficacy of HFNC treatment in the early management of patients with respiratory failure due to hypercapnic acute CPE. This study also compares HFNC to NIV in the treatment of hypercapnia in a population of subjects presenting with acute respiratory failure of homogenous etiology in the setting of early emergency department management. There are limited data to date comparing the efficacy of HFNC to that of NIV in hypercapnic respiratory failure. Our results indicate that 1 h of

Table 2. Changes in Blood Gas Analysis and Other Parameters After Treatment

	HFNC			NIV			P*
	Baseline	After 1 h HFNC	P	Baseline	After 1 h NIV	P	
Blood gas analysis							
P_{aCO_2}, mm Hg	50 (49–61)	45 (42–49)	.002	60 (48–71)	52 (44–61)	.02	.08
ΔP_{aCO_2}, mm Hg	NA	7 (4–11)	NA	NA	3 (1–8)	NA	.09
P_{aCO_2} normalization	NA	7 (8)	NA	NA	6 (5)	NA	.43
pH	7.30 (7.20–7.36)	7.38 (7.36–7.42)	.005	7.29 (7.21–7.35)	7.34 (7.30–7.40)	.005	.11
P_{aO_2}, mm Hg	99 (61–155)	89 (75–99)	.42	102 (72–125)	83 (72–126)	.86	.7
Respiratory parameters							
f, breaths/min	34 (27–41)	26 (25–29)	.03	29 (26–36)	21 (18–26)	.036	.03
S_{pO_2}, %	93 (90–98)	95 (94–98)	.44	96 (94–98)	96 (95–97)	.16	.56
Increased WOB	11 (92)	3 (25)	.008	11 (73)	5 (33)	.031	.69
WOB score†	7 (4–9)	3 (3–4)	.005	6 (3–11)	3 (3–4)	.005	.65
Vital signs							
Heart rate, beats/min	97 (80–128)	81 (73–128)	.24	79 (68–98)	76 (63–93)	.036	.14
SBP, mm Hg	156 (124–172)	143 (117–162)	.07	146 (111–184)	128 (109–142)	.02	.11
DBP, mm Hg	80 (63–85)	70 (57–80)	.31	71 (61–92)	66 (58–71)	.13	.42

Data are presented as median (interquartile range) or *n* (%). Changes in P_{aCO_2} are reported as median of differences (interquartile range). *P* values refer to comparison between groups.
* *P* values refer to comparisons between HFNC and NIV at 1 h. $P \leq .05$ is considered statistically significant.
† Work of breathing is scored on a 15-point scale.
HFNC = high-flow nasal cannula
NIV = noninvasive ventilation
NA = not applicable
f = breathing frequency
WOB = work of breathing
SBP = systolic blood pressure
DBP = diastolic blood pressure

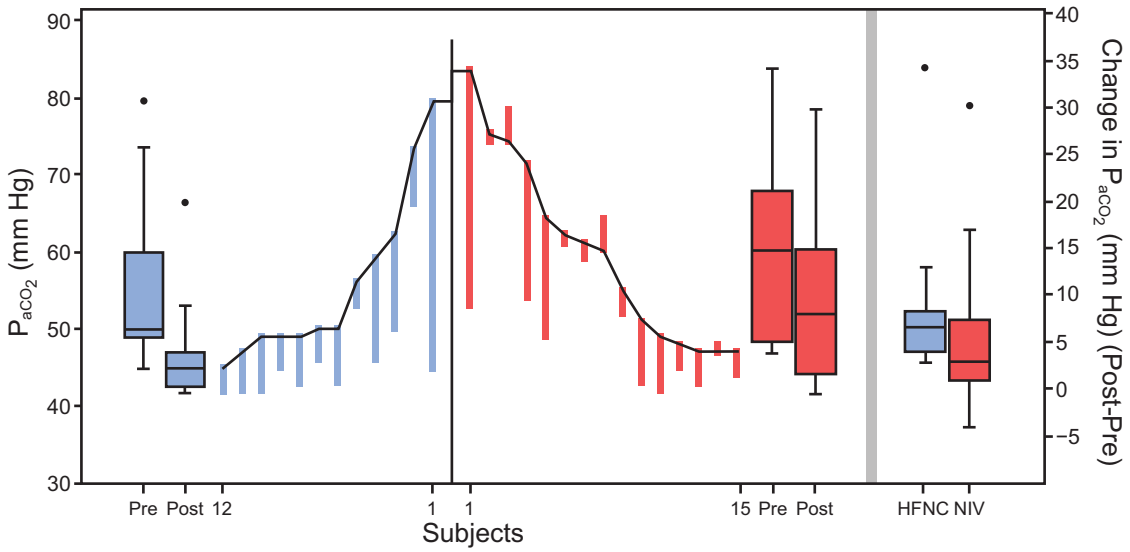

Fig. 2. P_{aCO_2} in hypercapnic subjects with cardiogenic edema receiving high-flow nasal cannula or noninvasive ventilation. Hybrid parallel line plot showing P_{aCO_2} values from baseline (pre) to after a 1-h ventilatory session (post) with HFNC (blue) or NIV (red). The lines depict change in P_{aCO_2} for each subjects, the box plot depicts median P_{aCO_2} and quartiles. Median changes in P_{aCO_2} are shown in the farther right pane. The black circle indicates outliers. HFNC = high-flow nasal cannula, NIV = noninvasive ventilation.

HFNC treatment effectively improves P_{aCO_2} and pH, as well as respiratory parameters such as breathing frequency and signs of increased WOB in this specific patient population. Furthermore, our results suggest that HFNC may be as effective as NIV in improving P_{aCO_2} after a 1-h ventilatory session in this specific patient population.

Besides studies exploring the use of HFNC to treat COPD exacerbation, data in the literature regarding acute

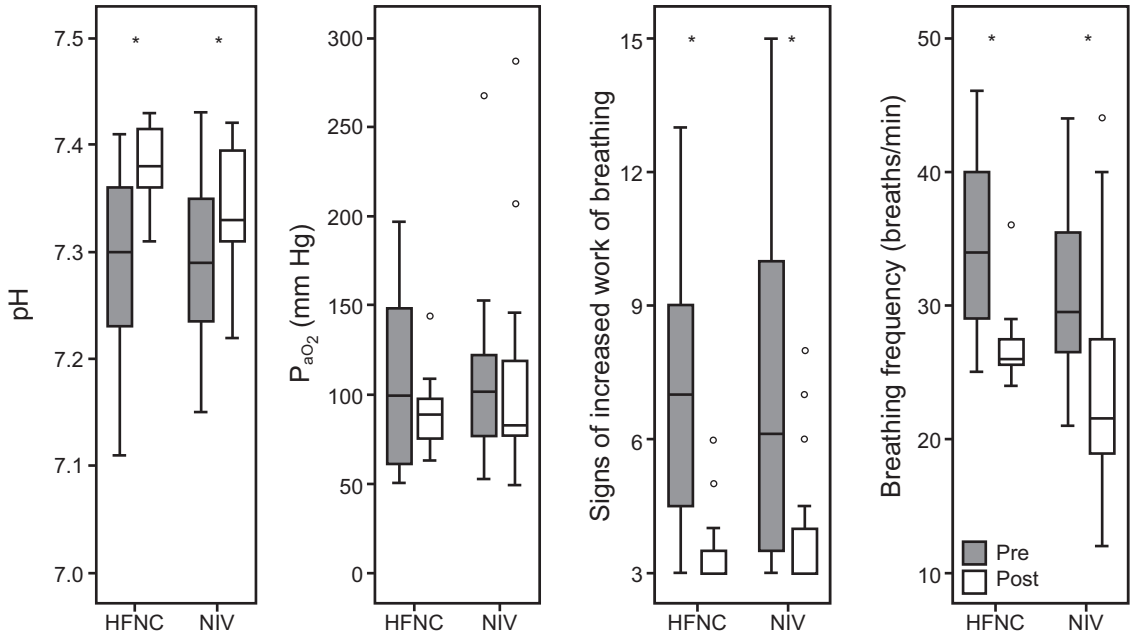

Fig. 3. Change in blood gas parameters, signs of increased work of breathing, and breathing frequency. Box plots present data recorded at baseline (pre) and after a 1-h ventilatory session with HFNC or NIV (post). Boxes show median and first and third quartiles, whiskers represent 1.5 times the interquartile range from the median. pH and P_{aCO_2} are results from arterial blood gas analysis performed at a central laboratory. Signs of increased work of breathing are measured on a 15-point scale evaluating the use of accessory respiratory muscles (intercostal and subcostal muscles) and paradoxical abdominal breathing (5 points each). The open circles indicate outliers; * indicates significant difference from baseline to after a 1-h ventilatory treatment ($P \leq .05$). HFNC = high-flow nasal cannula; NIV = noninvasive ventilation.

hypercapnic respiratory failure are from subjects with unselected respiratory failure. Our results confirm the effect of HFNC on hypercapnia reported previously in a subset of emergency department subjects with hypercapnic respiratory failure of all causes in 2 retrospective studies.[32,33] Our results are also in line with the decrease in P_{aCO_2} reported by Doshi et al[29] in a randomized controlled trial of subjects in the emergency department with unselected acute respiratory failure. Doshi et al[29] reported a reduction in P_{aCO_2} of > 5 mm Hg at 1 h after both HFNC and NIV, and a further decrease at 4 h in their subgroup analysis of 121 hypercapnic subjects.[30]

Hypercapnia is a common complication in patients with acute CPE. The causes are multiple and still poorly understood. An undocumented underlying chronic lung disease that increases dead space could favor hypercapnia.[3,4] In addition, rib cage stiffness and respiratory muscle fatigue caused by increased airway pressure and obstruction due to edema may lead to alveolar hypoventilation and hypercapnia. In our study population, which excluded chronic lung diseases and sepsis, age, and high body mass index may be associated factors.

The ability of HFNC to reduce P_{aCO_2} in hypercapnic CPE may be mediated by complex mechanisms. Two main mechanisms have been identified in experimental and pilot studies. First, HFNC is able to provide continuous washout of dead space in the upper airways, preventing the rebreathing of CO_2.[15,16] HFNC thereby enables a functional reduction in dead space and reduces minute ventilation by slowing down the breathing frequency and reducing WOB, as shown in subjects with COPD.[34] HFNC also provides a slight level of PEEP (ie, 2–5 cm H_2O), which improves alveolar recruitment and tidal volume, contributing to alveoli clearance and to P_{aCO_2} reduction. The PEEP-like effect is dependent on air flow, as well as on a closed mouth.[35] It may be reduced to 0–2 cm H_2O in open-mouth patients, as observed in subjects after cardiac surgery.[18,20] The PEEP-like effect may be lowered in patients with acute hypercapnic CPE, who are often unable to maintain a closed mouth during HFNC treatment due to severe respiratory failure. However, a flow-mediated effect that optimizes alveolar ventilation and gas exchange could also play a role in the rapid decrease in P_{aCO_2} observed in our study, where a high flow was administered to subjects (ie, 50 L/min).

In addition to the improvement in P_{aCO_2} and pH, our results suggest that HFNC may be effective in decreasing the breathing frequency and signs of increased WOB. The improved breathing frequency and reduced signs of increased WOB obtained after 1 h of treatment in our study probably result from all of these mechanisms combined. HFNC has been shown to confer effects similar to those of NIV on diaphragmatic WOB as estimated with diaphragm

ultrasound. Additional benefits of HFNC over NIV have been reported in adult subjects with cystic fibrosis who had been stabilized after over median 3 days under NIV. Both breathing frequency and minute ventilation were reduced.[36] No effects were observed on transcutaneous CO_2 in this physiologic study, which included 15 subjects ventilated with HFNC and NIV for 30 min in a cross-over random order, which was probably due to the short duration of HFNC treatment.[37] NIV seemed to have a greater effect on breathing frequency than HFNC in our subjects. We assumed that NIV combined the effect of pressure support and high PEEP to improve breathing frequency more quickly than HFNC, for which PEEP is limited, especially when suboptimal nasal flow was administered (ie, < 60 L/min) or when the mouth of the patient was open.[17-18]

Several limitations have to be acknowledged. The main limitation is the small sample recruited from a single emergency department. The lack of a randomized study design and of blinding are 2 other major limitations. The choice of ventilatory support was based on the presence of an attending emergency physician trained in the use HFNC. We cannot exclude the possibility that emergency department physicians' expertise may have biased our results. We cannot exclude selection bias, with NIV administered to more severe patients. Indeed, there seems to be a trend toward a higher baseline P_{aCO_2} level in the NIV group. The study sample and resulting power (68%) were lower than planned. However, the effects of HFNC on P_{aCO_2} were higher than expected a priori, resulting in a significant difference in the primary outcome. This study was intended as pilot study. Preliminary data were used to design a well-powered, randomized controlled noninferiority trial comparing the efficacy of HFNC and NIV in subjects with hypercapnic respiratory failure due to CPE treated in the emergency department (OPTICAP). Although a drop of 5–10 mm Hg in P_{aCO_2} following 1 h of HFNC treatment may not be relevant clinically, especially in patients with severe hypercapnia, it should be regarded as a sign of early response to HFNC. Absence of improvement in P_{aCO_2}, with no associated improvement in pH or signs of WOB, at 1 h should prompt the emergency physician to reconsider the treatment pathway or to consider escalating treatment to NIV or invasive mechanical ventilation.

Conclusions

Our results, although preliminary, support the use of HFNC as alternative support for the early emergency department management of hypercapnia in patients with hypercapnic respiratory failure related to acute CPE. HFNC could be considered as an alternative to NIV in patients in the emergency department who are intolerant to NIV or for whom NIV is contraindicated. Further randomized controlled studies are needed to explore the efficacy of HFNC compared to that of NIV in terms of longer duration and subject-centered outcomes in acute hypercapnic CPE.

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