High-Flow Nasal Cannula Versus Conventional Oxygen Therapy in Emergency Department Patients With Cardiogenic Pulmonary Edema: A Randomized Controlled Trial

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Study objective: High-flow nasal cannula is a new method for delivering high-flow supplemental oxygen for victims of respiratory failure. This randomized controlled trial compares high-flow nasal cannula with conventional oxygen therapy in emergency department (ED) patients with cardiogenic pulmonary edema.

Methods: We conducted an open-label randomized controlled trial in the ED of Siriraj Hospital, Bangkok, Thailand. Patients aged 18 years or older with cardiogenic pulmonary edema were randomly assigned to receive either conventional oxygen therapy or high-flow nasal cannula. The primary outcome was the respiratory rate 60 minutes postintervention.

Results: We enrolled 128 participants (65 in the conventional oxygen therapy and 63 in the high-flow nasal cannula groups). Baseline high-flow nasal cannula and conventional oxygen therapy mean respiratory rates were 28.7 breaths/min (SD 3.2) and 28.6 breaths/min (SD 3.5). Mean respiratory rates at 60 minutes postintervention were lower in the high-flow nasal cannula group (21.8 versus 25.1 breaths/min; difference 3.3; 95% confidence interval 1.9 to 4.6). No significant differences were found in the admission rate, ED and hospital lengths of stay, noninvasive ventilation, intubation, or mortality.

Conclusion: In patients with cardiogenic pulmonary edema in the ED, high-flow nasal cannula therapy may decrease the severity of dyspnea during the first hour of treatment. [Ann Emerg Med. 2017;70:465-472.]

Please see page 466 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Many patients present to the emergency department (ED) with cardiogenic pulmonary edema. In addition to reversing the specific underlying causes, conventional approaches to oxygen and ventilation therapy for these patients include nasal cannula oxygen, or face mask oxygen, noninvasive ventilation, and intubation.[1-6]

A novel approach to oxygen and ventilation therapy is high-flow nasal cannula oxygen, which delivers oxygenated air up to 60 L/min. High-flow nasal cannula is reported to achieve FiO_2 ranging from 21% to 100%. The flow levels are high enough to generate positive airway pressure, potentially decreasing entrapment of ambient air and providing support to reduce the work of breathing. Because high-flow oxygen can be uncomfortable, modern high-flow nasal cannula systems integrate oxygen warming and humidification to enhance patient comfort.[7-10]

Importance

There have been previous studies of high-flow nasal cannula in both adult volunteers and critically ill patients with hypoxemic respiratory failure, with results generally supporting its efficacy in reducing respiratory rate and improving oxygenation.[11-15] Most of these studies have involved cases of pneumonia in the ICU.[15-17] Few studies and no randomized controlled trials, to our knowledge, have investigated the use of high-flow nasal cannula for the treatment of cardiogenic pulmonary edema in the ED setting. Because dyspnea rescue therapy often begins in the ED, evaluation of high-flow nasal cannula application in the ED setting is important.

Editor's Capsule Summary

What is already known on this topic

High-flow nasal cannula oxygen therapy is useful in respiratory failure.

What question this study addressed

Compared with conventional oxygen therapy, does emergency department (ED) high-flow nasal cannula improve cardiogenic pulmonary edema outcomes?

What this study adds to our knowledge

In this randomized controlled trial of 128 patients in Thailand, high-flow nasal cannula improved 60-minute respiratory rate but not rates of admission, noninvasive ventilation, intubation, or mortality.

How this is relevant to clinical practice

Although not improving patient outcomes, ED high-flow nasal cannula oxygen therapy may decrease dyspnea severity in cardiogenic pulmonary edema.

Goals of This Investigation

The aim of this randomized study was to compare the effectiveness of high-flow nasal cannula with conventional oxygen therapy in ED patients with cardiogenic pulmonary edema.

MATERIALS AND METHODS

Study Design and Setting

This prospective randomized controlled study was conducted in the ED of Siriraj Hospital, a large tertiary university hospital in Bangkok, Thailand. The hospital has a total of 2,200 inpatient beds and 50 ICU beds. The ED is staffed by attending and resident-level physicians, who provide care for more than 20,000 patients per year.

This study was approved by Siriraj Institutional Review Board.

Selection of Participants

After arrival in the ED, patients potentially eligible for the study were evaluated by the attending emergency physicians. All patients received standard therapy (diuretics, nitroglycerin, nebulizer treatments, and oxygen therapy) at the discretion of the attending physician. After 10 minutes, the patients were reevaluated to assess whether they still met all inclusion criteria. The ED staff then notified the project investigators, who determined patients' eligibility, conducted patient recruitment, obtained written informed consent, completed case record forms, and ensured protocol adherence (Figure 1).

Inclusion criteria for the trial were aged 18 years or older, diagnosis of cardiogenic pulmonary edema (history of acute dyspnea, bilateral rales on physical examination, and signs of pulmonary congestion on initial chest radiograph), a pulse oximetry reading less than 95% on room air, and a respiratory rate greater than 24 breaths/min.

Exclusion criteria were need for immediate intubation or noninvasive ventilation, the presence of myocardial infarction (cardiac chest pain with ECG change or increasing cardiac enzyme levels), a Glasgow Coma Scale score less than 13, hemodynamic compromise (blood pressure <90/60 mm Hg), pregnancy, respiratory failure (respiratory rate >35 breaths/min, SpO_2 <90%, or signs of increased work of breathing, as observed by use of accessory muscles and abdominal asynchrony), end-stage renal disease (estimated glomerular filtration rate <15 mL/min per 1.73 m^2 or dialysis), contraindications to the use of equipment with positive airway pressure, and concomitant pneumonia.

We enrolled patients from September 2015 to March 2016.

Interventions

After written informed consent was obtained from the patient, legal representative, or surrogate decisionmaker, subjects were randomized to either conventional oxygen therapy or high-flow nasal cannula (Figure 2). The randomization was performed in a 1:1 ratio permuted block of 4 with sealed opaque envelopes.

In the conventional oxygen therapy group, oxygen was delivered by a nasal cannula or nonrebreather mask.

In the high-flow nasal cannula group, high flow of air with supplemental oxygen was delivered by an Optiflow cannula interface using an AIRVO 2 blower humidifier (Fisher & Paykel Healthcare, Auckland, New Zealand). The initial flow rate was set at 35 L/min and could be increased to 60 L/min. The FiO_2 was adjusted to maintain oxygen saturation as indicated by a pulse oximetry reading of greater than or equal to 95% and was maintained at that level for 60 minutes in both groups. After the end of the 60-minute protocol, the chosen modality was continued at the discretion of the treating physician.

In addition to the study intervention, all subjects received standard dyspnea interventions, including medication such as diuretics and nitroglycerin, urine output assessment, and vital signs monitoring every 15 minutes.

Early termination criteria included failure to tolerate high-flow nasal cannula, respiratory failure (respiratory

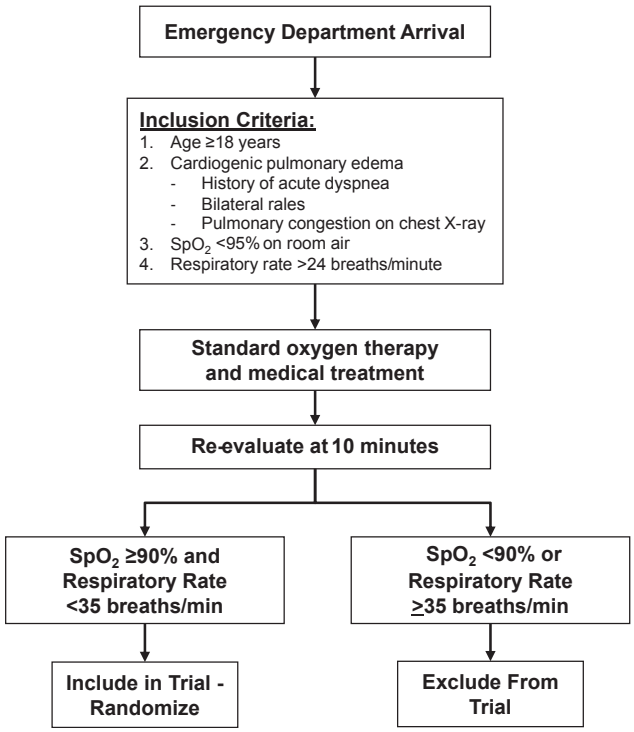

Figure 1. Patient screening and enrollment.

rate >35 breaths/min, SpO_2 <90%, ratio of PaO_2/FiO_2 <200 mm Hg, or signs of increased work of breathing), pulse rate greater than 120 beats/min or greater than 30% increase above baseline, and noninvasive mean arterial pressure greater than 30% above baseline before intervention.

If one or more of the termination criteria were met, the oxygen therapy was escalated toward noninvasive ventilation or converted straight to mechanical ventilation.

Methods of Measurement and Outcome Measures

The primary outcome was the respiratory rate 60 minutes after initiation of the randomized treatment (conventional oxygen therapy or oxygenation by high-flow nasal cannula). Respiratory rate was measured directly by the primary investigators, who auscultated and counted breath sounds for 1 full minute with a stethoscope.

Secondary outcomes included SpO_2, pulse rate (measured by auscultation of heart sounds for 1 minute), blood pressure, severity of dyspnea (evaluated with a visual analog scale[18] ranging from 1 to 10), rate of adverse events (thoracic and cervical discomfort, feeling hot, aspiration, and nasal ulceration), requirement for escalation to intubation or noninvasive ventilation within 24 hours after ED arrival, ED and hospital length of stay, mortality within 7 days, and pulmonary edema grade as determined by chest radiograph findings[19-21] (Appendix E1, available online at http://www.annemergmed.com).

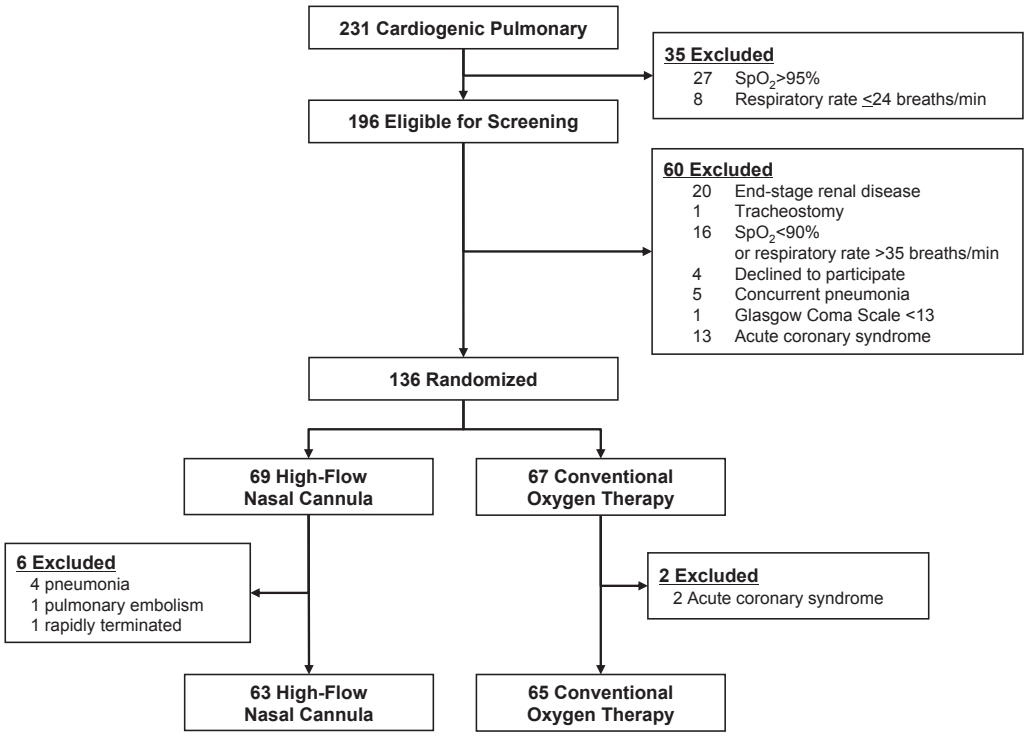

Figure 2. Enrollment and randomization of study participants.

Primary Data Analysis

All statistical tests were performed with PASW (version 18.0; SPSS, Inc., Chicago, IL), R (version 3.2.1; R Foundation for Statistical Computing, Vienna, Austria), and nQuery Advisor (version 6.0; Statsols, Cork, Ireland). The study statistician analyzed the data, blinded to the patients' allocated group throughout the assessment. All analyses were performed on a modified intention-to-treat basis. Patients who received a final diagnosis other than cardiogenic pulmonary edema and those whose participation was rapidly terminated before the study outcomes could be measured at the 15-minute mark were withdrawn from the analysis.

To compare quantitative variables with non-normal distribution between 2 groups, Mann-Whitney's *U* test was used. Results are reported as median difference and 95% confidence interval (CI) (based on bootstrap resampling method in R). In regard to comparison of qualitative variables between 2 groups, χ^2 or Fisher's exact test was used and results are reported as relative risk and 95% CI.

We estimated that respiratory rate 60 minutes after initiation of conventional oxygen therapy and high-flow nasal cannula would be 29 and 25 breaths/min, respectively. Using an SD of 8, 2-sided type I error of 0.05, and 80% power, we estimated requiring a total of 64 patients per group.

RESULTS

Characteristics of Study Subjects

During the study period, 231 patients presented to the ED with suspected cardiogenic pulmonary edema; 196 were eligible for inclusion, and 136 underwent randomization. Reasons for nonenrollment included end-stage renal disease, respiratory failure, patient refusal, concurrent pneumonia, myocardial infarction, depressed consciousness, and inability to apply high-flow nasal cannula (tracheostomy).

In accordance with the a priori–modified intention-to-treat plan, 7 patients (2 in the conventional oxygen therapy group and 5 in the high-flow nasal cannula group) were excluded from the primary analysis because the final diagnosis at hospital discharge was a condition other than cardiogenic pulmonary edema. One patient was terminated early from the study protocol because of the need for intubation within 10 minutes after high-flow nasal cannula use. A total of 128 patients (65 in the conventional oxygen therapy group and 63 in the high-flow nasal cannula group) completed the study protocol and were included in the modified intention-to-treat population (Figure 2). There was no exclusion because of missing data.

Mean participant age was 70 years (SD 15). More female patients (64.8%) than male ones were recruited in both groups. Patient characteristics were similar between the 2 groups. The time from ED arrival to randomization was comparable in both groups. Initial vital signs on ED arrival and at the start of intervention were also similar. There were no major differences in cotreatments and initial oxygen requirement (Table 1).

In the conventional oxygen therapy group, 51 patients (78.5%) received oxygen by a standard nasal cannula and 14 (21.5%) received it by nonrebreather mask. The median oxygen flow rate was 3 L/min (interquartile range 3 to 5). The initial settings in the high-flow nasal cannula group were a median flow rate of 35 L/min (interquartile range 25 to 40) and FiO_2 of 0.50 (SD 0.13). Patients in the high-flow nasal cannula group remained connected to the device for a median of 175 minutes (minimum to maximum 10 to 560 minutes). One participant requested to remove the high-flow nasal cannula after 10 minutes of intervention because of severe discomfort.

Sixty-minute conventional oxygen therapy and high-flow nasal cannula respiratory rates were 25.1 breaths/min (SD 3.6) and 21.8 breaths/min (SD 4.1) (mean difference 3.3 breaths/min; 95% CI 1.9 to 4.6). The 30-minute respiratory rate was also lower in the high-flow nasal cannula group (mean difference 3.1 breaths/min; 95% CI 1.8 to 4.4), as was the 15-minute respiratory rate (mean difference 1.8 breaths/min; 95% CI 0.5 to 3) (Figures 3 and 4). The changes in the conventional oxygen therapy and high-flow nasal cannula respiratory rates during the first 15-minute interval were 1.3 breaths/min (SD 2.4) and 3.1 breaths/min (SD 3) (mean difference –1.8 breaths/min; 95% CI –2.7 to –0.9). The change from the second 15-minute interval (minutes 15 to 30) was also more prominent in the high-flow nasal cannula group (mean difference –1.3 breaths/min; 95% CI –2.1 to –0.4). However, the change during the latter 30 minutes (minutes 30 to 60) was not significantly different between the 2 groups (mean difference –0.2; 95% CI –1.1 to 0.7) (Table 2). Oxygen saturation at 60 minutes was 98.7% (SD 1.5) in the conventional oxygen therapy and 99.2% (SD 1.2) in the high-flow nasal cannula group (mean difference –0.5%; 95% CI –1 to –0.02). Other physiologic parameters, including the Dyspnea Scale score, were not significantly different between the 2 groups (Table 2).

All patients tolerated high-flow nasal cannula, and there were no serious or life-threatening complications in patients undergoing oxygen therapy with high-flow nasal cannula (Table E1, available online at http://www.annemergmed.com). There were no differences in the admission rate or

Table 1. Patient characteristics.*

Variables	Total (n=128)	COT (n=65)	HFNC (n=63)	Difference (95% CI)
Age, y, mean (SD)	70 (15)	71.2 (14.2)	70.4 (15.9)	0.7 (−4.5 to 6)
Female sex, No. (%)	83 (64.8)	36 (55.4)	47 (74.6)	−19 (−47.1 to 8.7)
Underlying disease				
Diabetes mellitus, No. (%)	58 (45.3)	29 (44.6)	29 (46.0)	−1.4 (−24.7 to 21.9)
Hypertension, No. (%)	92 (71.9)	41 (63.1)	51 (81.0)	−17.9 (−47.3 to 11.5)
Dyslipidemia, No. (%)	44 (34.4)	15 (23.1)	29 (46.0)	−23 (−43.3 to −2.6)
Chronic obstructive pulmonary disease, No. (%)	10 (7.8)	3 (4.6)	7 (11.1)	−6.5 (−16.2 to 3.2)
Chronic kidney disease, No. (%)	34 (26.6)	17 (26.2)	17 (27.0)	−0.8 (−18.7 to 17)
Ischemic heart disease, No. (%)	51 (39.8)	25 (38.5)	26 (41.3)	−2.8 (−24.7 to 19.1)
Valvular heart disease, No. (%)	23 (18.0)	14 (21.5)	9 (14.3)	7.3 (−7.4 to 21.9)
Atrial fibrillation, No. (%)	19 (14.8)	12 (18.5)	7 (11.1)	7.4 (−6 to 20.7)
Estimated glomerular filtration rate, mL/min per 1.73 m^2, mean (SD)	55 (28.5)	55 (24.7)	54.9 (32.3)	0.3 (−10 to 10)
Initial ED presentation				
Respiratory rate, breaths/min, mean (SD)	31 (3.8)	31.2 (3.9)	30.8 (3.7)	0.4 (−0.9 to 1.8)
Mean arterial pressure, mm Hg, mean (SD)	103.9 (20.2)	103.2 (20)	104.7 (20.4)	−1.6 (−8.7 to 5.5)
Pulse rate, beats/min, mean (SD)	87.6 (21.9)	89.1 (24.2)	86.1 (19.3)	3 (−4.7 to 10.7)
Oxygen saturation, %, mean (SD)	88.7 (8)	88.2 (9.8)	89.3 (5.5)	−1 (−3.8 to 1.8)
Dyspnea score (0–10), mean (SD)	8.4 (1.8)	8.7 (1.6)	8.1 (1.9)	0.6 (−0.4 to 1.2)
Vital signs at randomization				
Respiratory rate, breaths/min, mean (SD)	28.6 (3.4)	28.6 (3.5)	28.7 (3.2)	−0.04 (−1.2 to 1.1)
Mean arterial pressure, mm Hg, mean (SD)	100.2 (18.4)	99.5 (18.4)	101 (18.4)	−1.5 (−7.9 to 4.9)
Pulse rate, beats/min, mean (SD)	86 (21)	87.5 (23.3)	84.5 (18.3)	3 (−4.4 to 10.3)
Oxygen saturation, %, mean (SD)	98.2 (1.9)	98.2 (1.8)	98.3 (1.9)	−0.1 (−0.8 to 0.5)
Dyspnea score (0–10), mean (SD)	6.9 (2.2)	6.9 (2.2)	6.9 (2.3)	0.1 (−0.7 to 0.9)
Time to randomization, min, mean (SD)	47.4 (28.2)	44.6 (28.4)	50.3 (28)	−5.7 (−15.5 to 4.2)
Concurrent treatments				
Furosemide, No. (%)	128 (100.0)	65 (100.0)	63 (100.0)	1 (1 to 1)
Furosemide dose, mg, median (minimum, maximum)	40 (20, 250)	40 (20, 250)	40 (40, 250)	0 (0 to 0)
Time to first dose, min, median (minimum, maximum)	19 (3, 100)	19 (3, 95)	19 (5, 100)	0 (−21.8 to 8)
Intravenous nitroglycerin, No. (%)	13 (10.2)	6 (9.2)	7 (11.1)	−1.8 (−12.9 to 9.2)
Bronchodilator, No. (%)	22 (17.2)	12 (18.5)	10 (15.9)	2.6 (−11.7 to 16.9)
Initial oxygen therapy				
Nasal cannula, No. (%)	92 (71.9)	51 (78.5)	41 (65.1)	13.4 (−16 to 42.8)
Bag-valve-mask ventilation, No. (%)	36 (28.1)	14 (21.5)	22 (34.9)	−13.4 (−31.8 to 5.0)
Oxygen flow rate, L/min, median (IQR)	3 (3 to 8)	3 (3 to 5)	5 (3 to 10)	−2 (−2 to 1)
Urine output at 60 min, mL, mean (SD)	686.4 (404.8)	674.2 (383.6)	699.1 (428.4)	−24.9 (−167 to 117.2)
ED disposition				
Discharged, No. (%)	37 (28.9)	19 (29.2)	18 (28.6)	0.6 (−18 to 19.3)
Admitted to hospital, No. (%)	45 (35.2)	25 (38.5)	20 (31.7)	6.7 (−13.8 to 27.3)
Observation room, No. (%)	51 (39.8)	25 (38.5)	26 (41.3)	−2.8 (−24.7 to 19.1)
Transferred to other hospital, No. (%)	5 (3.9)	2 (3.1)	3 (4.8)	−1.7 (−8.5 to 5.2)

COT, Conventional oxygen therapy; *HFNC*, high-flow nasal cannula; *IQR*, interquartile range.
*Data are presented as mean (SD), No. (%), median (IQR), or median (minimum, maximum). Difference is reported as mean, rate, or median difference (95% CI).

length of ED or hospital stay between the 2 cohorts. The noninvasive ventilation, intubation, and mortality rates also showed no significant differences between the 2 groups (Table 2). One patient in the high-flow nasal cannula group died on revisiting the hospital 5 days after intervention, one required intubation within 24 hours, and one needed to stop receiving the treatment after 10 minutes because intubation was required, which might have been caused by extreme respiratory distress from exacerbation of concurrent chronic obstructive pulmonary disease. The latter patient was excluded from the trial and the analysis; therefore, the intubation rate of this patient was disregarded.

Chest radiograph pulmonary edema grades before and after the intervention were not significantly different, with 0.8% and 11.7% missing data in the conventional oxygen therapy and high-flow nasal cannula group, respectively. The change in the pulmonary edema grade after improvement of the patients' clinical signs and symptoms was also comparable (Table E2, available online at http://www.annemergmed.com).

The primary analysis was performed on a modified intention-to-treat basis, including only subjects with post hoc–verified cardiogenic pulmonary edema. We repeated the analysis with the full intention-to-treat population; this analysis (N=67 in the conventional oxygen therapy and 69 in

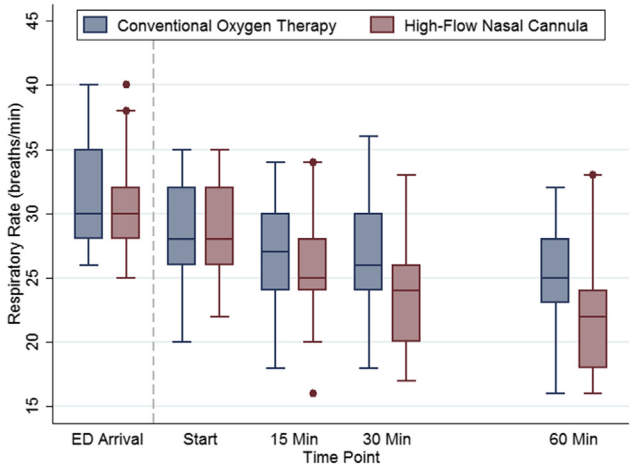

Figure 3. Respiratory rate at each point.

the high-flow nasal cannula group) showed results similar to those of the modified intention-to-treat analysis (Table E3, available online at http://www.annemergmed.com).

LIMITATIONS

There are several limitations to the study. First, this trial was conducted in a single center in Thailand, limiting the external validity to other centers with different settings. Second, it included only patients with mild to moderate symptoms; thus, the results are not fully generalizable because patients with severe respiratory distress who were at risk for noninvasive ventilation, intubation, a prolonged length of stay, and death were already excluded, making the differences in these aspects unable to be statistically determined. This limitation might also have been due to the number of patients, which was not large enough to deliver such results. Third, the duration of the intervention was only 60 minutes, which may have been insufficient for evaluating the long-term efficacy of high-flow nasal cannula. Fourth, there were some missing data in regard to the grading of pulmonary edema from the chest radiograph findings, primarily because of missed follow-up radiograph examinations. However, this is justifiable, considering that the improvement in the patients' clinical signs and symptoms was acceptable.

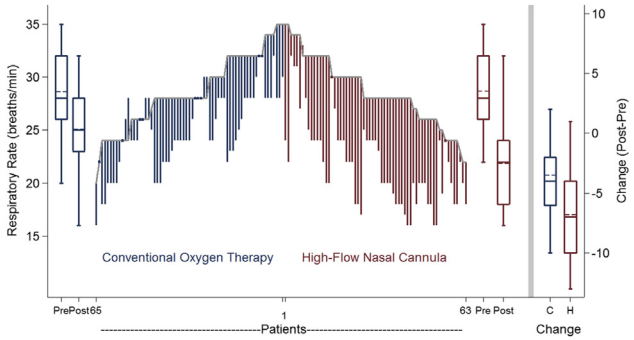

Figure 4. Changes in respiratory rates. Waterfall plot depicts subject respiratory rate at the start (0 minutes) and end (60 minutes) of the protocol.

DISCUSSION

In this randomized trial of ED patients with cardiogenic pulmonary edema, we observed that 60-minute respiratory rate was significantly lower with high-flow nasal cannula than conventional oxygen therapy. Similarly, the lower respiratory rates at 15 and 30 minutes were lower with high-flow nasal cannula. We found that high-flow nasal cannula could deliver effective oxygenation and comfort with minimal complications or life-threatening adverse events.

Our observations are consistent with those of many previous studies of high-flow nasal cannula.[12-17,22-24] A small crossover study by Roca et al[8] found an improvement in oxygenation and a decrease in respiratory rate after application of high-flow nasal cannula in respiratory failure patients. An observational study by Sztrymf et al[14] also stated that high-flow nasal cannula compared with conventional oxygen therapy could improve respiratory parameters and oxygenation in patients with acute respiratory failure. Another crossover study comparing high-flow nasal cannula with conventional oxygen therapy and noninvasive ventilation[15] concluded that the high-flow nasal cannula delivered oxygen in participants with mild to moderate hypoxemic respiratory failure effectively and that it could bridge the gap between conventional oxygen therapy, noninvasive ventilation, and invasive mechanical intervention. However, these previous nonrandomized trials were conducted in ICUs, and most of the patients had a primary diagnosis of pneumonia. To our knowledge, this is the first randomized evaluation of high-flow nasal cannula in ED patients with cardiogenic pulmonary edema.

Even though the differences were small, the reductions in the respiratory rate after 15 and 30 minutes were significantly in favor of high-flow nasal cannula. Although the respiratory rate was also reduced at 60 minutes, it was not statistically significant. This finding is consistent with the results of a previous study of patients with acute hypoxemia in the same ED[16]; a significant decrease in the respiratory rate and degree of dyspnea occurred only at 5, 10, 15, and 30 minutes, not at 60 or 120 minutes. This may indicate that the use of high-flow nasal cannula in the ED is largely beneficial only within the first 30 minutes. After this interval, other cotreatments might attain

Table 2. Primary and secondary outcomes.*

Variable	Total (n=128)	COT (n=65)	HFNC (n=63)	Difference (95% CI)
Primary outcome				
Respiratory rate at 60 min, breaths/min, mean (SD)	23.5 (4.2)	25.1 (3.6)	21.8 (4.1)	3.3 (1.9 to 4.6)
Secondary outcomes				
Respiratory rate at 15 min, breaths/min, mean (SD)	26.5 (3.7)	27.3 (3.6)	25.6 (3.5)	1.8 (0.5 to 3)
Respiratory rate at 30 min, breaths/min, mean (SD)	25 (4)	26.5 (3.9)	23.5 (3.6)	3.1 (1.8 to 4.4)
Change in respiratory rate from 0–15 min, breaths/min, mean (SD)	2.2 (2.8)	1.3 (2.4)	3.1 (3)	−1.8 (−2.7 to −0.9)
Change in respiratory rate from 15–30 min, breaths/min, mean (SD)	1.4 (2.5)	0.8 (2.5)	2.1 (2.4)	−1.3 (−2.1 to −0.4)
Change in respiratory rate from 30–60 min, breaths/min, mean (SD)	1.5 (2.6)	1.5 (2.6)	1.6 (2.7)	−0.2 (−1.1 to 0.7)
Mean arterial pressure at 15 min, mm Hg, mean (SD)	95.5 (16.7)	96.1 (15.8)	94.9 (17.6)	1.2 (−4.7 to 7)
Mean arterial pressure at 30 min, mm Hg, mean (SD)	93.9 (15.8)	93.8 (14.6)	94 (17.1)	−0.2 (−5.8 to 5.3)
Mean arterial pressure at 60 min, mm Hg, mean (SD)	93 (15.4)	91.3 (13.7)	94.9 (16.9)	−3.6 (−8.9 to 1.8)
Pulse rate at 15 min, beats/min, mean (SD)	83.8 (20.7)	84.7 (22.3)	82.9 (19)	1.7 (−5.5 to 9)
Pulse rate at 30 min, beats/min, mean (SD)	83.3 (19.4)	83.9 (21.4)	82.8 (17.2)	1.1 (−5.7 to 7.9)
Pulse rate at 60 min, beats/min, mean (SD)	81 (19.4)	81.7 (21.3)	80.4 (17.4)	1.3 (−5.5 to 8.1)
Oxygen saturation at 15 min, %, mean (SD)	98.5 (1.8)	98.3 (1.7)	98.8 (1.8)	−0.5 (−1.1 to 0.8)
Oxygen saturation at 30 min, %, mean (SD)	98.7 (1.6)	98.5 (1.8)	98.9 (1.4)	−0.4 (−1 to 0.2)
Oxygen saturation at 60 min, %, mean (SD)	99 (1.4)	98.7 (1.5)	99.2 (1.2)	−0.5 (−1 to −0.02)
Dyspnea score at 15 min (0–10), mean (SD)	5.5 (2)	5.6 (2.1)	5.4 (2)	0.3 (−0.5 to 1)
Dyspnea score at 30 min (0–10), mean (SD)	4.6 (2.1)	4.8 (2.2)	4.4 (1.9)	0.4 (−0.3 to 1.1)
Dyspnea score at 60 min (0–10), mean (SD)	3.4 (2.1)	3.6 (2.2)	3.1 (2)	0.5 (−0.3 to 1.2)
Comfort score (0–10), mean (SD)	7.2 (2.2)	6.4 (1.9)	8.1 (2)	−1.8 (−2.4 to −1.1)
ED length of stay, h, median (minimum, maximum)	6.4 (1.6, 43.8)	6 (1.6, 20.5)	6.9 (2, 43.8)	−0.9 (−2.1 to 0.2)
Admission rate, No. (%)	45 (35.2)	25 (38.5)	20 (31.7)	6.7 (−13.8 to 27.3)
Hospital length of stay, days, median (minimum, maximum)	1.1 (0.1, 27.6)	1.2 (0.1, 17.4)	1.1 (0.1, 27.6)	0.1 (−0.9 to 2.3)
Noninvasive ventilation within 24 h, No. (%)	4 (3.1)	3 (4.6)	1 (1.6)	3 (−3.1 to 9.2)
Intubation within 24 h, No. (%)	1 (0.8)	0 (0)	1 (1.6)	−1.6 (−4.7 to 1.5)
Mortality in 7 days, No. (%)	1 (0.8)	0 (0)	1 (1.6)	−1.6 (−4.7 to 1.5)

*Data are presented as mean (SD), No. (%), or median (minimum, maximum). Difference is reported as mean, rate, or median difference (95% CI).

their highest efficacy and interfere with the study results. A longer intervention period with a larger number of patients and the inclusion of other objective parameters are needed to clarify this issue.

Aside from its efficacy, a commonly raised question is whether patients can tolerate high-flow nasal cannula. In this trial, we found that all subjects tolerated high-flow nasal cannula very well, which was in accordance with many previous studies.[11-17,22-24] In fact, almost all participants opted to continue using high-flow nasal cannula after completion of the data collection period, with a maximum duration of 9 hours.

To our knowledge, this study is the first randomized controlled trial to compare conventional oxygen therapy with high-flow nasal cannula in patients with cardiogenic pulmonary edema in the ED. Our results could be applied to ED care for cardiogenic pulmonary edema patients. Not only could high-flow nasal cannula improve patients' ventilation and oxygenation initially but also it might provide beneficial effect in their final outcome. Nevertheless, there are numerous areas in which future research can provide better proof of high-flow nasal cannula's benefits and generalize its validity. Other dynamic and objective parameters, such as blood gas analysis and lung ultrasonographic findings, and a decrease in the need for further resources such as ICU could be included as outcome measures. In addition, an emphasis on patients with more severe hypoxemia and a longer duration of high-flow nasal cannula use may help to better evaluate its efficacy and identify changes in the noninvasive ventilation, intubation, and mortality rates.

In conclusion, treatment with high-flow nasal cannula helps to improve oxygenation and respiratory rate in ED patients with cardiogenic pulmonary edema.

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Author contributions: OM and TN conceived the study, designed the trial, and supervised the conduct of the trial and data collection. OM, AM, US, NP, WC, TC, CP, and TN recruited the

patients and managed the data, including quality control. PT interpreted the radiologic outcomes. OM analyzed the data. OM drafted the article, and all authors contributed substantially to its revision. OM takes responsibility for the paper as a whole.

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APPENDIX E1

Termination criteria

Patient cannot tolerate HFNC

Respiratory rate $\geq$35 breaths/min during intervention

Oxygen saturation <90% during intervention

Pulse rate >120 beats/min or >30% increase above baseline during intervention

Noninvasive mean arterial pressure >30% above baseline during intervention

Signs of increased work of breathing (use of accessory muscles and abdominal asynchrony during intervention)

Ratio of PaO_2/FiO_2 <200 mm Hg during intervention

Physician's discretion

Pulmonary edema grading

Grade 0: Normal chest radiograph result

Grade 1: Evidence of upper lobe diversion on chest radiograph

Grade 2: Interstitial edema on chest radiograph

Grade 3: Alveolar edema on chest radiograph

Table E1. HFNC settings and complications.

	Values
HFNC setting	
Initial flow rate, median (IQR), L/min	35 (25–40)
FiO_2, mean (SD)	0.5 (0.1)
Duration of use, median (IQR), min	175 (10–560)
Duration of use, median (IQR), h	2.9 (0.2–9.3)
HFNC complications, mean (SD)	
None	57 (89.0)
Discomfort	2 (3.1)
Feeling hot	4 (6.3)

IQR, Interquartile range.

Table E2. Outcomes of pulmonary edema grading from chest radiograph.*

	Total (n=127)	COT (n=65)	HFNC (n=62)	Relative Risk (95% CI)
Pulmonary edema grade from chest radiograph before intervention (P_0)				
Grade 0	2 (1.6)	2 (3.1)	0	5 (0.2–102.1)
Grade 1	27 (21.3)	16 (24.6)	11 (17.7)	1.4 (0.7–2.8)
Grade 2	59 (46.5)	26 (40.0)	33 (53.2)	0.8 (0.5–1.1)
Grade 3	39 (30.7)	21 (32.3)	18 (29.0)	1.2 (0.7–1.9)
	(n=113)	(n=57)	(n=56)	
Pulmonary edema grade from chest radiograph after intervention (P_1)				
Grade 0	9 (8.0)	5 (8.8)	4 (7.1)	1.2 (0.3–4.3)
Grade 1	38 (33.6)	18 (31.6)	20 (35.7)	0.9 (0.5–1.5)
Grade 2	50 (44.2)	28 (49.1)	22 (39.3)	1.3 (0.8–1.9)
Grade 3	16 (14.2)	6 (10.5)	10 (17.9)	0.6 (0.2–1.5)
Change in pulmonary edema grade after intervention (P_0–P_1)				
−2	2 (1.8)	1 (1.8)	1 (1.8)	1 (0.1–15)
−1	6 (5.3)	3 (5.3)	3 (5.4)	1 (0.2–4.7)
0	53 (46.9)	27 (47.4)	26 (46.4)	1 (0.7–1.5)
1	44 (38.9)	23 (40.4)	21 (37.5)	1.1 (0.7–1.7)
2	6 (5.3)	1 (1.8)	5 (8.9)	0.2 (0.02–1.6)
3	2 (1.8)	2 (3.5)	0	4.9 (0.2–100.1)

*Data are presented as No. (%).

Table E3. Sensitivity analysis of primary and secondary outcomes of all included patients (intention-to-treat analysis).*

Variable	Total (n=128)	COT (n=65)	HFNC (n=63)	Difference (95% CI)
Primary outcome				
Respiratory rate at 60 min, breaths/min, mean (SD)	25.3 (3.7)	21.8 (4.1)	3.4 (2.1 to 4.8)	3.3 (1.9 to 4.6)
Secondary outcomes				
Respiratory rate at 15 min, breaths/min, mean (SD)	27.4 (3.7)	25.5 (3.4)	1.9 (0.7 to 3.1)	1.8 (0.5 to 3)
Respiratory rate at 30 min, breaths/min, mean (SD)	26.7 (3.9)	23.4 (3.6)	3.3 (2 to 4.6)	3.1 (1.8 to 4.4)
Change in respiratory rate from 0–15 min, breaths/min, mean (SD)	1.3 (2.4)	3 (2.9)	−1.7 (−2.6 to −0.8)	−1.8 (−2.7 to −0.9)
Change in respiratory rate from 15–30 min, breaths/min, mean (SD)	0.7 (2.5)	2.1 (2.3)	−1.4 (−2.2 to −0.6)	−1.3 (−2.1 to −0.4)
Change in respiratory rate from 30–60 min, breaths/min, mean (SD)	1.4 (2.5)	1.6 (2.6)	−0.1 (−1.1 to 0.7)	−0.2 (−1.1 to 0.7)
Mean arterial pressure at 15 min, mm Hg, mean (SD)	96 (16.1)	94.7 (17.5)	1.3 (−4.4 to 7)	1.2 (−4.7 to 7)
Mean arterial pressure at 30 min, mm Hg, mean (SD)	93.8 (14.6)	93.3 (17.2)	0.5 (−4.9 to 5.9)	−0.2 (−5.8 to 5.3)
Mean arterial pressure at 60 min, mm Hg, mean (SD)	91.3 (13.7)	94.9 (16.9)	−3 (−8.1 to 2.2)	−3.6 (−8.9 to 1.8)
Pulse rate at 15 min, beats/min, mean (SD)	85 (22.3)	83.9 (19.3)	1.1 (−6 to 8.1)	1.7 (−5.5 to 9)
Pulse rate at 30 min, beats/min, mean (SD)	84.7 (21.7)	83.6 (17.5)	1.1 (−5.6 to 7.8)	1.1 (−5.7 to 7.9)
Pulse rate at 60 min, beats/min, mean (SD)	82.4 (21.4)	81.4 (17.7)	1 (−5.6 to 7.7)	1.3 (−5.5 to 8.1)
Oxygen saturation at 15 min, %, mean (SD)	98.3 (1.7)	98.7 (2.2)	−0.4 (−1.1 to 0.2)	−0.5 (−1.1 to 0.8)
Oxygen saturation at 30 min, %, mean (SD)	98.5 (1.8)	98.9 (1.4)	−0.4 (−1 to 0.2)	−0.4 (−1 to 0.2)
Oxygen saturation at 60 min, %, mean (SD)	98.8 (1.5)	99.2 (1.2)	−0.5 (−1 to −0.01)	−0.5 (−1 to −0.02)
Dyspnea score at 15 min (0–10), mean (SD)	5.6 (2.1)	5.4 (2)	0.1 (−0.6 to 0.8)	0.3 (−0.5 to 1)
Dyspnea score at 30 min (0–10), mean (SD)	4.8 (2.2)	4.5 (1.9)	0.3 (−0.4 to 1)	0.4 (−0.3 to 1.1)
Dyspnea score at 60 min (0–10), mean (SD)	3.6 (2.2)	3.1 (2.1)	0.3 (−0.4 to 1.1)	0.5 (−0.3 to 1.2)
Comfort score (0–10), mean (SD)	6.3 (1.9)	8 (2.2)	−1.7 (−2.4 to −1)	−1.8 (−2.4 to −1.1)
ED length of stay, h, median (minimum to maximum)	6 (1.6, 20.5)	6.9 (2, 43.8)	−0.9 (−2.1 to 0.2)	−0.9 (−2.1 to 0.2)
Admission rate, No. (%)	25 (37.3)	23 (33.3)	3.9 (−15.9 to 23.9)	6.7 (−13.8 to 27.3)
Hospital length of stay, days, median (minimum to maximum)	1.2 (0.1, 17.4)	1.1 (0.1, 27.6)	0.1 (−0.9 to 2.3)	0.1 (−0.9 to 2.3)
Noninvasive ventilation within 24 h, No. (%)	3 (4.5)	1 (1.4)	3 (−3 to 8.7)	3 (−3.1 to 9.2)
Intubation within 24 h, No. (%)	0 (0)	2 (2.9)	−2.8 (−6.9 to 1.1)	−1.6 (−4.7 to 1.5)
Mortality in 7 days, No. (%)	0 (0)	1 (1.4)	−1.4 (−4.3 to 1.4)	−1.6 (−4.7 to 1.5)

*Data are presented as mean (SD), No. (%), or median (minimum to maximum). Difference is reported as mean, rate, or median difference (95% CI).