The prognosis of severe AECOPD patients who treated with between high flow nasal cannulae and continuous airway positive pressure therapy

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Introduction

- **Severe acute exacerbation of COPD (AECOPD)**
  - A significant event that result in substantial morbidity and mortality due to a sudden worsening of COPD symptoms (shortness of breath, quantity and color of phlegm) with requiring hospitalization.
  - Antibiotic therapy and systemic corticosteroids - important treatments for patients with severe AECOPD

Backgrounds

- Respiratory failure due to severe AECOPD requiring NIV (non-invasive ventilation)
- NIV - first-line treatment for these patients with AECOPD, especially in those with moderate-to-severe decompensation (pH<7.35 and hypercapnea).
- To ensure better outcomes in terms of intubation and mortality, NIV (especially pressure support) should be initiated early, before severe acidosis occurs.

High flow nasal cannulae oxygen therapy

- **High flow nasal cannulae (HFNC) oxygen therapy**
- The delivery of heated and humidified gas via a wide bore nasal cannula (the inspiratory fraction of oxygen (FIO2) - set from 0.21 to 1.0 in a flow of up to 60 L/min)
- Studies of HFNC oxygen therapy have demonstrated an effect comparable with nasal continuous positive airway pressure (CPAP).


In a lung-injured-animal model, PaCO2 decreased as HFNC flow increased, and greater escape of gas more effectively decreased PaCO2. (effective carbon dioxide washout with HFNC)

High flow nasal cannulae oxygen therapy

• **Hypercapnic respiratory failure**

Millar et al. reported the successful use of HFNC oxygen therapy to manage the hypercapnic respiratory failure of a patient unable to tolerate conventional NIV.


• Nilius et al. investigated the effects of HFNC on COPD patients with chronic hypercapnic respiratory failure.

• After receiving 20 L/min of room air and 2 L/min of oxygen for 45 min through a nasal cannula, breathing frequency decreased and PaCO2 decreased for some.


The Purpose

• We want to evaluate the efficacy of the HFNC oxygen therapy in severe AECOPD requiring hospitalization.

• **The prospective, randomized, controlled study**

• Comparing between the HFNC oxygen therapy and NIV in severe AECOPD with moderate hypercapnic acute respiratory failure

• End points: 30-mortality, treatment failure (Intubation with mechanical ventilation rate)

• The Research was conducted under the authorization of the Yonsei University Wonju Severance Christian Hospital Institutional Review Board (IRB No. CR214005).
Study Design (Indication)

• **Indication**
  
  Severe AECOPD patients who hospitalized with moderate hypercapnic acute respiratory failure (ARF)

  A respiratory center of Yonsei University Wonju Severance hospital (an 850-bed tertiary hospital) from January 2013 to February 2015

  Age ≥ 40 year-old (yr), Former or current smoking history of ≥ 10 pack-year (py)

  COPD, according to the criteria established by the GOLD, fulfilled the requirements of FEV$_1$ < 80% and FEV$_1$/forced vital capacity (FVC) < 70% following inhalation of a bronchodilator.

• **Moderate hypercapnic ARF**
  
  defined by an arterial oxygen tension (PaO$_2$) of less than 60 mmHg (<8.0 kpa) and an arterial carbon dioxide tension (PaCO$_2$) greater than 45 mmHg (>6.0 kpa)

  characterized by pH levels between 7.25 and 7.35


The Devices

- **High-flow nasal cannula oxygen therapy** - high-flow delivery system (Optiflow; Fisher&Paykel, Auckland, New Zealand). Oxygen flows were set by the attending physician based on the patient's condition.

- **Non-invasive ventilation** - bi-level positive airway pressure in the spontaneous/timed mode (Synchrony, Respironics, INC, Murrysville, Pennsylvania, USA) supplied with an identical set of masks.

- The expiratory pressure was set at 4 cm H$_2$O pressure. The inspiratory pressure was initially set at 10 cm H$_2$O and then increased in increments of 2-4 cm H$_2$O to 20 cm H$_2$O or the maximum tolerated over 1 h.

Study Protocol (Randomization)

Severe AECOPD patients who hospitalized with moderate hypercapnic ARF, aged > 40 year-old
Prospectively enrolled (n = 80)

Excluded from this study (n = 12):
- underlying bronchial asthma (n = 4)
- lung malignancy (n = 3)
- acute myocardial infarction (n = 2)
- transfer to other hospital (n = 3)

Finally registered severe AECOPD patients (n = 68)
Demographic, clinical and laboratory findings
CAT score and mMRC dyspnea scale at stable state
Initial lung function analysis

Randomly treated with HFNC oxygen or NIV therapy
severe AECOPD with moderate hypercapnic ARF

HFNC oxygen therapy (N = 36)
NIV including CPAP or bi-level positive airway pressure (BiPAP) (N = 32)

Two kinds of end point:
- 30-day mortality
- Treatment failure (Conversion to mechanical ventilation)
Statistical analysis

- SPSS 20.0 (SPSS Inc.; Chicago, IL, USA) were used for statistical analysis. Chi-square or Fisher’s exact test was used for categorical variables and Student t or Mann-Whitney U test was used for continuous variables.

- Cox proportional hazard model was used to estimate hazard ratio (HR) for 30-day mortality and intubation rate between two groups. Cumulative survival and intubation rate was evaluated using a Kaplan-Meier approach and the log-rank test.

- Continuous variables were expressed in the form of mean value ± standard deviation and $P$-value less than 0.05 was considered to be statistically significant.
## Results

Table 1. The characteristics of HFNC and NIV patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HFNC</th>
<th>NIV</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>36</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>72.1 ± 9.0</td>
<td>72.9 ± 10.2</td>
<td>0.701</td>
</tr>
<tr>
<td>Gender, n (% male)</td>
<td>23 (63.9)</td>
<td>22 (68.8)</td>
<td>0.659</td>
</tr>
<tr>
<td>CAT score, mean ± SD</td>
<td>24.6 ± 7.7</td>
<td>26.0 ± 5.1</td>
<td>0.46</td>
</tr>
<tr>
<td>*mMRC dyspnea scale, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 1</td>
<td>8 (22.2)</td>
<td>5 (15.6)</td>
<td></td>
</tr>
<tr>
<td>2 – 4</td>
<td>28 (77.8)</td>
<td>27 (84.4)</td>
<td>0.435</td>
</tr>
<tr>
<td>Smoking amount, pack-year, mean ± SD</td>
<td>41.1 ± 25.5</td>
<td>42.3 ± 22.7</td>
<td>0.822</td>
</tr>
<tr>
<td>BMI, kg/m², mean ± SD</td>
<td>20.8 ± 2.8</td>
<td>20.7 ± 3.1</td>
<td>0.915</td>
</tr>
<tr>
<td>Underlying comorbid conditions, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (77.8)</td>
<td>25 (78.1)</td>
<td>0.925</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (44.4)</td>
<td>24 (75.0)</td>
<td>0.049</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>12 (33.3)</td>
<td>15 (46.9)</td>
<td>0.337</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1 (2.8)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>old pulmonary tuberculosis</td>
<td>6 (16.7)</td>
<td>8 (25.0)</td>
<td>0.149</td>
</tr>
<tr>
<td>Pre-exacerbation use of medication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>28 (77.8)</td>
<td>20 (62.5)</td>
<td>0.278</td>
</tr>
<tr>
<td>Long-acting muscarinic antagonists</td>
<td>20 (55.6)</td>
<td>20 (62.5)</td>
<td>0.606</td>
</tr>
<tr>
<td>Long-acting beta_2 agonists</td>
<td>28 (77.8)</td>
<td>24 (75.0)</td>
<td>0.751</td>
</tr>
<tr>
<td>†Systemic corticosteroids</td>
<td>8 (16.7)</td>
<td>2 (6.8)</td>
<td>0.213</td>
</tr>
<tr>
<td>‡Former antibiotics</td>
<td>10 (27.8)</td>
<td>2 (6.8)</td>
<td>0.061</td>
</tr>
<tr>
<td>End points, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>30-day mortality</td>
<td>8 (22.2)</td>
<td>9 (28.1)</td>
<td>0.509</td>
</tr>
<tr>
<td>Treatment failure (Intubation)</td>
<td>12 (33.3)</td>
<td>16 (50.0)</td>
<td>0.082</td>
</tr>
</tbody>
</table>

BMI = body mass index; CAT = Chronic obstructive pulmonary disease assessment test; mMRC = modified Medical Research Council; n = number; SD: standard deviation; y = years

*mMRC dyspnea scale consists in five statements that describe almost the entire range of dyspnea from none (grade 0) to almost complete incapacity (grade 4).

†Systemic corticosteroids uses were included when the patients have been prescribed within 3 months.

‡Former antibiotics uses were included when the patients have been prescribed within 3 months.

Treatment failure was defined that the patients underwent intubation with mechanical ventilation due to continuous hypoxia and hypercapnea despite of HFNC or NIV therapy.
### Results

Table 2. Comparison of clinical, laboratory and functional parameters

<table>
<thead>
<tr>
<th>Variables, mean ± SD</th>
<th>HFNC (n=36)</th>
<th>NIV (n=32)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical (on admission)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mean BP, mm Hg</td>
<td>94.0 ± 20.2</td>
<td>97.8 ± 22.6</td>
<td>0.400</td>
</tr>
<tr>
<td>PR, beats/min</td>
<td>105.0 ± 17.5</td>
<td>107.6 ± 21.4</td>
<td>0.530</td>
</tr>
<tr>
<td>RR, /min</td>
<td>24.4 ± 4.0</td>
<td>25.1 ± 5.8</td>
<td>0.493</td>
</tr>
<tr>
<td><strong>Laboratory (on admission)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.31 ± 0.29</td>
<td>7.31 ± 0.28</td>
<td>0.951</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>80.8 ± 8.6</td>
<td>79.8 ± 9.6</td>
<td>0.591</td>
</tr>
<tr>
<td>PaO$_2$, mm Hg</td>
<td>50.8 ± 10.0</td>
<td>49.1 ± 8.9</td>
<td>0.398</td>
</tr>
<tr>
<td>PaCO$_2$, mmHg</td>
<td>55.0 ± 11.3</td>
<td>54.4 ± 8.3</td>
<td>0.778</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>12.9 ± 2.4</td>
<td>13.1 ± 2.3</td>
<td>0.813</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.5 ± 0.3</td>
<td>3.3 ± 0.5</td>
<td>0.135</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>8.0 ± 7.8</td>
<td>9.4 ± 11.6</td>
<td>0.608</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>12.5 ± 19.4</td>
<td>28.2 ± 14.9</td>
<td>0.214</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.86 ± 0.73</td>
<td>0.86 ± 0.46</td>
<td>0.975</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>259.7 ± 390.0</td>
<td>330.2 ± 475.4</td>
<td>0.437</td>
</tr>
<tr>
<td><strong>Functional (before admission)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>post-bronchodilator</td>
<td></td>
<td></td>
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<tr>
<td>FEV$_1$, L</td>
<td>1.06 ± 0.54</td>
<td>0.93 ± 0.41</td>
<td>0.255</td>
</tr>
<tr>
<td>FEV$_1$, % pred</td>
<td>51.2 ± 43.1</td>
<td>43.1 ± 16.5</td>
<td>0.092</td>
</tr>
<tr>
<td>FVC, % pred</td>
<td>72.9 ± 22.5</td>
<td>62.6 ± 17.0</td>
<td>0.058</td>
</tr>
<tr>
<td>FEV$_1$/FVC, %</td>
<td>48.2 ± 13.8</td>
<td>48.3 ± 14.9</td>
<td>0.976</td>
</tr>
</tbody>
</table>

BNP = B-type natriuretic peptide; BP = blood pressure; BUN = blood urea nitrogen; CRP = C-reactive protein; FEF$_{25-75\%}$ = forced expiratory flow $25-75\%$; FEV$_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity; Hb = hemoglobin; HCO$_3^-$ = serum bicarbonate ion; n = number; PaCO$_2$ = arterial carbon dioxide partial pressure; PaO$_2$ = arterial oxygen partial pressure; PCT = procalcitonin; PR = pulse rate; Pred = predictive value; RR = respiratory rate; SD = standard deviation
Results

Figure. Survival rate, Intubation rate due to treatment failure

Figure 1. Cumulative survival rate between HFNC and NIV oxygen therapy

- $P$-value = 0.558, HR: 0.783
  (95%CI: 0.346 - 1.775)

Figure 2. Cumulative intubation rate between HFNC and NIV oxygen therapy

- $P$-value = 0.139, HR: 0.618
  (95%CI: 0.327 – 1.169)
Results

Figure. pH, PaO$_2$, and PaCO$_2$ change after 6 hours

Figure 1. pH after 6 hours between HFNC and NIV oxygen therapy

Figure 2. PaO$_2$ after 6 hours between HFNC and NIV oxygen therapy

\( P\)-value = 0.171

\( P\)-value = 0.153
Results
Figure. pH, PaO$_2$, and PaCO$_2$ change after 6 hours

$P$-value = 0.023

Figure 1. PaCO$_2$ after 6 hours between HFNC and NIV oxygen therapy
Conclusion

- pH and PaO$_2$ was improved in HFNC oxygen therapy group beside to NIV group.

- Hypercapnea was more improved in HFNC oxygen therapy group than NIV group in severe AECOPD with respiratory failure.

- No statistically significant difference of 30-day mortality and intubation with mechanical ventilation rate (due to treatment failure) - between HFNC and NIV oxygen therapy in severe AECOPD with moderate hypercapnic acute respiratory failure

- HFNC oxygen therapy may be alternative to NIV therapy in severe AECOPD with moderate hypercapnic acute respiratory failure.

- Multicenter and prospective study will be further required.
Limitation

• Single center study

• Post-bronchodilator FEV1 (%, predictive) between two groups – not significantly different ($P$-value=0.092), but lower in NIV group than HFNC group

• In this study, moderate hypercapnic respiratory failure - determined by only initial arterial blood gas analysis on emergency room visit regardless of conventional oxygen therapy

• No appropriate procedure of HFNC oxygen therapy in severe AECOPD - Oxygen flows were set by only the attending physician based on the patient's condition.