Intubation rate, duration of noninvasive ventilation and mortality after noninvasive neurally adjusted ventilatory assist (NIV-NAVA)

Hansen, Kristina K; Jensen, Hanne I; Andersen, Torben S; Christiansen, Christian F

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MRS KRISTINA KOCK HANSEN (Orcid ID : 0000-0001-9564-958X)

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Title: Intubation rate, duration of noninvasive ventilation and mortality after noninvasive neurally adjusted ventilatory assist (NIV-NAVA)

Authors: Kristina K. Hansen¹, Hanne I. Jensen¹, Torben S. Andersen¹, Christian F. Christiansen³

Affiliations:
¹Department of Anaesthesiology and Intensive Care, Vejle Hospital, Vejle, Denmark.
²Institute of Regional Health Research, University of Southern Denmark.
³Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

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Corresponding author information:

Kristina Kock Hansen
Department of Anaesthesiology and Intensive Care, Vejle Hospital
Vejle, Denmark
Telephone: +45 61688210
E-mail: kristina.kock.hansen2@rsyd.dk

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Abstract

BACKGROUND: Asynchrony is a common problem in patients treated with noninvasive ventilation (NIV). Neurally adjusted ventilatory assist (NAVA) has shown to improve patient-ventilator interaction. However, it is unknown whether NIV-NAVA improves outcomes compared to noninvasive pressure support (NIV-PS).

METHODS: This observational cohort study included patients 18 years or older receiving noninvasive ventilation using an oro-nasal face mask for more than 2 hours in a Danish ICU. The study included a NIV-NAVA cohort (year 2013-2015) and two comparison cohorts: 1) a historical NIV-PS cohort (year 2011-2012) before the implementation of NIV-NAVA at the ICU in 2013, and 2) a concurrent NIV-PS cohort (year 2013-2015). Outcomes of NIV-NAVA (intubation rate, duration of NIV and 90-day mortality) were assessed and compared using multivariable linear and logistic regression adjusted for relevant confounders.

RESULTS: The study included 427 patients (91 in the NIV-NAVA, 134 in the historic NIV-PS and 202 in the concurrent NIV-PS cohort). Patients treated with NIV-NAVA did not have improved outcome after adjustment for measured confounders. Actually, there were statistically imprecise higher odds for intubation in NIV-NAVA patients compared with both the historical [OR 1.48, CI (0.74-2.97)] and the concurrent NIV-PS cohort [OR 1.67, CI (0.87-3.19)]. NIV-NAVA might also have a longer length of NIV [63%, CI (19-125%)] and [139%, CI (80-213%)], and might have a higher 90-day mortality [OR 1.24, CI (0.69-2.25)] and [OR 1.39, CI (0.81-2.39)]. Residual confounding cannot be excluded.

CONCLUSION: This present study found no improved clinical outcomes in patients treated with NIV-NAVA compared to NIV-PS.
Editorial Comment:

Non-invasive neurally-adjusted ventilatory assist offers an additional way to try to optimally coordinate assisted ventilatory support to spontaneously breathing patients. This both prospective and retrospective study in a single-centre ICU cohort assessed if this breathing muscle signal-adjusted assist ventilatory form was associated with better ICU patient outcomes compared to traditional assisted ventilatory support. Since there were no clear differences observed for outcomes for the groups based on the ventilatory mode, this supports the idea that for general and heterogeneous ICU patients with non-invasive spontaneous breathing support, a large clinical beneficial effect of the neurally-adjusted ventilatory mode for many patients, compared to traditional spontaneous breathing support modes, is unlikely.

Introduction

Noninvasive ventilation (NIV) is a commonly used treatment of acute respiratory failure and may prevent intubation and reintubation after extubation in the ICU. The most widely used partial ventilation mode is noninvasive pressure support (NIV-PS). The possibility of spontaneous breathing during PS is beneficial to avoid atelectasis, improve oxygenation and maintain diaphragmatic function. Despite these advantages, NIV treatment frequently fails with need for intubation and mechanical ventilation (MV). In patients with mild-to-moderate chronic obstructive pulmonary disease (COPD) and acute respiratory failure, the risk of treatment failure is 10-20%. Asynchrony between the patient’s respiratory demands and level of ventilatory assistance can be one of the reasons why the treatment fails. Vignaux et al. identified that severe asynchronies occurred in up to 43% of patients treated with NIV.

Neurally adjusted ventilatory assist (NAVA) is a mode of assisted MV that delivers a pressure in proportion to the electrical activity of the diaphragm (EAdi). The EAdi signal triggers the respiratory cycles and regulates gas delivery of NAVA. A specially designed nasogastric tube with electrodes is measuring the EAdi signal.

Some studies have compared asynchrony in adults treated with NIV-PS compared with NIV-NAVA. The majority of the studies showed that NIV-NAVA improves patient-ventilator interaction significantly compared to NIV-PS. However, these studies included a very small number of patients (11-17 patients) and none included clinical outcomes. Previous research has shown that asynchrony is associated with prolonged treatment duration and mortality in mechanically ventilated patients. Therefore it would be important to examine whether decreasing asynchrony with NIV-NAVA confers into improved outcomes.
The aim of this study was to examine the clinical outcomes of patients treated with NIV-NAVA including frequency of intubation, length of ICU stay, duration of noninvasive ventilation, ICU mortality and 90-day post-discharge mortality, compared to NIV-PS.

This study hypothesized that NIV-NAVA, compared with NIV-PS, is associated with reduced intubation rate, reduced length of ICU stay and days of NIV, and reduced mortality.

Methods

Design and setting

This cohort study was based on clinical data from patients in an 8-bed ICU at Vejle Hospital, Denmark. In the historical PERIOD 1 (2011-2012) NIV-NAVA was not implemented at the ICU, whereas in PERIOD 2 (2013-2015) NIV-NAVA was an already existing treatment. After implementation of NIV-NAVA, outcomes in the NIV-NAVA group were compared with both outcomes in the historical NIV-PS group and with outcomes in the NIV-PS group in the concurrent period.

The ICU at Vejle Hospital is categorised as a mixed medical-surgical ICU receiving patients from a broad spectrum of specialities including neurology, oncology, hematology, general medicine and surgery. The patients were identified by a local clinical information system CIS (Critical Information System 4.3.0, Daintel, Denmark) at the ICU.

Study Population

Intensive care patients receiving NIV were eligible for inclusion in the study between July 1, 2011 and November 30, 2012 and between July 1, 2013 and November 30, 2015. The study is based on ordinary real time data which is prospectively collected but analyzed retrospectively.

The inclusion criteria were patients 18 years or older admitted to ICU receiving NIV >2 hours via an oronasal face mask (BiTrac SE Select, MaxShield Mask, Pulmodyne). Included patients had respiratory problems, either because of acute respiratory failure, heart failure or sepsis. Patients treated with NIV-NAVA had a nasogastric tube (NAVA catheter, 16 French, Maquet Critical Care, Solna, Sweden) and correct positioning was established according to local guidelines. Patients treated with NIV-PS had in most of the cases a regular nasogastric tube (Duodenal tube Levin/introd., CH12-16, 125cm, Unomedical).
Patients were included in the study at the time of first initiation of NIV during the ICU stay. Time on treatments with NIV-PS or NIV-NAVA included periods of NIV interruptions because of mouth hygiene, rest, meals, visits etc. These interruptions were included in the duration of NIV because it is a common part of the treatment in both modes.

Depending on what ventilation mode the patients received they were included in the given exposure cohorts. The majority of patients admitted to ICU with respiratory problems begins with NIV-PS shortly as the NIV-NAVA is getting prepared. Therefore, some patients were treated with both NIV-PS and NIV-NAVA during their ICU stay. Patients who were treated with NIV-PS ≥2/3 of the time on NIV were categorised as NIV-PS. Patients who were treated with NIV-NAVA ≥2/3 of the time on NIV were categorised as NIV-NAVA. The remaining patients were excluded from the primary analysis. This was done to study the impact of NAVA.

Patients were also excluded if 1) NIV was a result of an extubation failure, 2) NIV was provided as a pressure controlled mode (PC), 3) patients did not have registered clinical data because of severe chronic respiratory failure (e.g. amyotrophic lateral sclerosis).

Some patients were admitted to ICU and meeting the inclusion criteria more than once in the same period. Only the patient’s first treatment of NIV at the ICU was included to ensure independency between data.

All patients were ventilated with a SERVO-i(Maquet, Solna, Sweden). After implementing NIV-NAVA at the ICU, all ventilators were equipped with the available version (8.00.01) of the NAVA software. The noninvasive version of the ventilator software was used to both NIV-PS and NIV-NAVA.

Outcomes
The study included five outcome measures: 1) intubation during ICU stay, 2) ICU length of stay, 3) duration of NIV, 4) ICU mortality, and 5) 90-day post-discharge mortality (from the day discharged from ICU and until 90 days thereafter). The 90-day post-discharge mortality included any death, irrespective of place of death.

Covariates
The following covariates, which have all been linked with the current outcomes, could be potential confounders and were included: sex, age, body mass index (BMI), first pH after ICU admission, Simplified Acute Physiology Score (SAPS) II, Acute Physiology and Chronic Health Evaluation (APACHE) II score, first Sequential Organ Failure Assessment (SOFA) score, unit setting (medical or surgical), and
reason for ICU admission (acute respiratory failure, acute heart failure or sepsis). All covariates, except for the severity of illness scores, were measured at baseline when patients were admitted to the ICU, just before start of treatment.

The severity of illness scores were, except for five patients, only measured on patients with ICU length of stay >24 hours, because the scores include measurements within the first 24 hours.

Statistical Analysis

No sample-size calculation was conducted because we had a predefined period.

Data tabulated included all the covariates mentioned above. For descriptive analyses, continuous data was reported as median (interquartile range) and categorical data as number of events and proportions (%).

The association between NIV group and outcomes was examined using multivariable regression (days of ICU stay and days of NIV) and multivariable logistic regression (intubation during ICU, ICU mortality and 90-day mortality) adjusted for the covariates sex, age, BMI, pH and unit setting. The covariates were categorised into following categories based on international standards and clinical relevance: BMI (<18.5, 18.5-<25, 25-30 and >30 kg/m\(^2\)), pH (<7.15, 7.15-7.24, 7.25-7.34, 7.35-7.45 and >7.45) and SAPS II score (<25, 25-49, and ≥50). Log-transformation of the continuous outcomes was made to get normal distribution of the data.

As expected, the severity of illness scores were not available on the majority of patients with days of ICU ≤24 hours (94%). To evaluate the impact of severity of illness, the analysis was done including adjustment for SAPS II score in patients with ICU length of stay >24 hours. The APACHE II score and the first SOFA score were not included in the analysis because of collinearity with the SAPS II score.

For every association, both the unadjusted and the adjusted estimates were presented together with the estimate from the severity of illness-adjusted association in patients admitted at ICU >24 hours. All comparisons were two-sided with a 5% significance level considered as being statistically significant.

Estimates were presented with 95% confidence interval. Statistical analyses were conducted using Stata version 14.2.

Ethics
According to Danish law, this observational study did not need (and therefore could not get) approval from the Regional Committee on Health Research Ethics for Southern Denmark. A waiver from patient consent to use medical record data was obtained from the Danish Patient Safety Authority (3-3013-1345/1) and the study was registered with the Danish Data Protection Agency Southern Denmark Region (15/5384). The study was performed according to the Declaration of Helsinki.

Results

A total of 721 intensive care patients receiving NIV were eligible for inclusion in the study between July 1, 2011 and November 30, 2012 and between July 1, 2013 and November 30, 2015. The patient enrolment is outlined in a flowchart (Figure 1). After exclusion of 294 patients, the study included 427 patients. Hereof 134 patients were enrolled in the study as a historical NIV-PS group (PERIOD 1). After implementation of NIV-NAVA (PERIOD 2), 91 patients were enrolled as a NIV-NAVA group and 202 patients were enrolled as a concurrent NIV-PS group.

The patients’ demographic and clinical characteristics in PERIOD 1 and PERIOD 2, together with the NIV-NAVA group and the concurrent NIV-PS group, are presented in Table 1. Patients in the historical PERIOD 1 were similar to patients in PERIOD 2, except for a few variables. At ICU admission, patients in PERIOD 2 had a lower pH and a higher PaCO$_2$ compared to patients in PERIOD 1. Furthermore, PERIOD 2 included more medical patients and more patients with BMI 18.5-<25 than PERIOD 1. In all groups, 10-11% of the included NIV patients had acute hypoxemic respiratory failure(PaCO$_2$ < 6.5 kPa and PaO$_2$ < 8.0 kPa).

Patients in the NIV-NAVA group were similar to those in the historical group and concurrent NIV-PS group in terms of age, acute respiratory failure and severity of illness scores. The NIV-NAVA group had a higher proportion of non-surgical patients compared with the two NIV-PS groups. Patients in the NIV-NAVA group had a lower pH, a higher PaCO$_2$ and a lower PaO$_2$/FiO$_2$ ratio compared with the patients in the two NIV-PS groups.

The demographic and clinical characteristics in patients with a length of ICU stay >24 hours in each NIV-group are presented in Table 2. The tendency was similar to Table 1 with a lower pH and higher PaCO$_2$ in the NIV-NAVA group, compared to the historical and concurrent NIV-PS group. Each of the three severity of illness scores were similar between the groups.In patients admitted for more than 24 hours in the ICU, only 0-4% had acute hypoxemic respiratory failure.
The associations between the NIV groups and the outcomes are presented in Table 3 and Table 4. Despite adjustment for measured confounders, NIV-NAVA was not associated with improved outcome. Although adjusted estimates were statistically imprecise and residual confounding by indication cannot be excluded, NIV-NAVA patients were intubated more frequently during ICU compared with the historical and concurrent NIV-PS group [23% vs 21% and 18%]. This association persisted after adjustment (Table 3 and 4). Furthermore, a stronger association was found in patients with length of ICU stay >24 hours after adjustment for SAPS II score, especially in the comparison between NIV-NAVA and the concurrent NIV-PS group.

Both length of ICU stay and length of NIV were higher in the NIV-NAVA group compared with the two NIV-PS groups. The days of ICU stay were longer in the NIV-NAVA group compared with the historical NIV-PS group and the concurrent NIV-PS group (Table 3 and 4). In addition, the regression analysis showed virtually the same associations both before and after adjustment. The adjusted estimates became weaker in patients admitted to ICU>24 hours.

Patients in NIV-NAVA group had a higher ICU mortality and 90-day mortality compared with the historical and concurrent NIV-PS group, respectively (Table 3 and 4). In addition, the adjusted logistic regression showed the same association in the comparison with the historical NIV-PS group and with the concurrent NIV-PS group. After including the SAPS II score in the adjustment in patients >24 hours the odds ratios attenuated. The results are presented in Table 3 and Table 4.

We registered the administrations of sedation to the patients in all groups. We registered remifentanil, midazolam and morphine. Only 36 patients of a total of 427 were treated with remifentanil or midazolam. Approximately 60% of the patients in each group were treated with morphine.

Outcomes versus adjustment variables are presented in Supplementary Table 1.
Discussion

In this cohort study based on data from patients treated with NIV-NAVA, compared to patients in a historical and concurrent NIV-PS group, we could not confirm the hypothesis that NIV-NAVA ventilation mode improves clinical outcomes compared to NIV-PS. We found that patients treated with NIV-NAVA were intubated more frequently, had a longer ICU stay and length of NIV and had a higher ICU and 90-day post-discharge mortality after adjustment for measured confounders but the estimates were statistically imprecise.

To our knowledge, no studies, on invasive or noninvasive ventilation, have primarily examined the clinical outcomes of NAVA compared with PS. However, secondary outcomes from a randomized trial by Demoule et al. on invasive mechanical ventilation showed no significant differences between NAVA and PS for ICU mortality. A recently finalized, randomized clinical trial aimed to examine if NAVA will improve clinical outcomes of mechanical ventilation, but the results has not yet been published. Although the results from studies on the impact of NAVA in intubated and mechanically ventilated patients cannot be applied to NIV, it could help guide future trials on NIV-NAVA versus NIV-PS.

Some methodological issues need to be considered when interpreting our findings. This study is strengthened by a complete follow-up, which minimizes the risk of selection and information bias. Registration of mode of NIV, intubation, death and potential confounders (sex, age, BMI, pH and unit setting) was automatically registered in CIS limiting information bias. In addition, information bias was reduced by having one person (the first author) to review all the charts.

However, the study had some limitations. Excluding patients based on information after study inclusion (treated with NIV-NAVA or NIV-PS ≤ 2 hours or < 2/3 of the total time on NIV or being treated with NIV-PS or NIV-NAVA more than once in the “period”) may have resulted in selection bias and thus distorted measures of association.
Patients were not randomized to their respective treatment. As a result, patients treated with NIV-NAVA or NIV-PS may have been unbalanced for unmeasured factors including patient type, lifestyle factors, physicians’ preferences, skills of the physicians and nurses on call, and level of therapy or frailty. Although the study adjusted for important potential confounders, others were lacking, e.g. comorbidity, which may have an impact on choice of NIV and also increases the risk of outcomes of interest.

The NIV-NAVA group consisted of patients with the most severe disease. It is likely that the newer and more expensive NIV-NAVA was used mostly in patients with the most severe disease. Thereby, there is a risk of confounding by indication. This bias would be more pronounced when comparing NIV-NAVA patients with NIV-PS patients in the concurrent time period, whereas the comparison between the historical NIV-PS and concurrent NIV-NAVA is somewhat different and should not introduce as much bias. Thus, the historical NIV-PS is a mixture of patients with different severities of diseases contrary the NIV-NAVA group. Our finding of higher ORs of the outcomes when comparing NIV-NAVA to the NIV-PS in the concurrent time period than when comparing to the historical NIV-PS group confirm this hypothesis.

We aimed to reduce confounding by severity of illness when adjusting for SAPS II score. However, the SAPS II score used in the study were measured during the first 24 hours of the ICU stay, i.e. potentially after study inclusion. As a result, we cannot rule out that NIV treatment modality might have affected the severity of illness scores and thereby influenced the adjustment for confounding. Using individual parameters of the severity of illness scores might have improved the adjusted analyses but these data were not available.

Treatment with morphine to approximately 60% of the patients in each group may have influenced the treatment with NIV and thereby the outcome. Unfortunately, data on whether morphine was administered before NIV treatment (potential confounder) or during NIV treatment (potential intermediate step) is not available. We did not include the morphine data in the analysis because the indication for treatment was not documented and could have been influenced by the NIV treatment itself. Additionally, because patients treated with morphine were evenly distributed between the three groups, it was not expected to influence the comparison between the groups.

Patients treated with NIV-NAVA or NIV-PS may have been unbalanced for measured and unmeasured factors. We adjusted for measured potential confounders, but we cannot exclude that unmeasured factors or residual confounding could have influenced our findings. Nevertheless, this is the first study that examines the clinical outcomes in patients treated with NIV-NAVA compared to NIV-PS providing the first evidence that NIV-PS may not be superior to NIV-NAVA.
Conclusion

This present study found no improved clinical outcomes in patients treated with NIV-NAVA compared to NIV-PS. Further clinical studies, preferably clinical trials, are required to assess the potential clinical benefit of NIV-NAVA compared to NIV-PS.
References


32. Davies JD, Gentile MA. What does it take to have a successful noninvasive ventilation program? *Respir Care.* 2009;54(1):53-61.
Figure 1 Flow diagram of the enrollment of the patients

**PERIOD 1**

HISTORICAL NIV-PS

- 236 patients treated with NIV-PS were identified from the critical information system (CIS)

- 236 patients were eligible for inclusion

**PERIOD 2**

NIV-NAVA

- 225 patients treated with NIV-NAVA were identified from the critical information system (CIS)

- 186 patients were eligible for inclusion

NIV-PS

- 260 patients treated with NIV-PS were identified from the critical information system (CIS)

- 299 patients were eligible for inclusion

**PERIOD 2**

- 51 patients treated with NIV-PS from NIV-NAVA group

- 12 patients treated with NIV-NAVA from NIV-PS group

- 95 patients were excluded:
  - 25 were treated with NIV-PS ≤ 2 hours
  - 29 patients were treated with NIV-NAVA < 2/3 of the time on NIV
  - 35 patients were intubated and were treated with NIV-NAVA afterwards
  - 6 were treated with NIV-NAVA more than once in the period

- 97 patients were excluded:
  - 43 patients were treated with NIV-PS ≤ 2 hours
  - 13 patients were treated with NIV-PS < 2/3 of the time on NIV
  - 14 patients were intubated and were treated with NIV-PS afterwards
  - 4 patients didn’t have registered clinical data because of severe chronic respiratory failure
  - 1 patient was treated with his/her own Bipap-machine
  - 22 were treated with NIV-PS more than once in the period

102 patients were excluded:

- 48 were treated with NIV-PS ≤ 2 hours
- 25 were treated with NIV-PS < 2/3 of the time on NIV
- 15 were intubated and were treated with NIV-PS afterwards
- 1 didn’t have registered clinical data because of severe chronic respiratory failure
- 1 were < 18 years
- 1 had another reason for ICU admission than the inclusion criteria
- 11 were treated with NIV-PS more than once in the period
Data: Baseline NIV-PS is registered in PERIOD 1, 01.07.2011-30.11.2012. NIV-NAVA and NIV-PS are registered in PERIOD 2, 01.07.2013-30.11.2015.

1 Misclassification of initially registered NIV type identified by medical record review.

2 Misclassification of initially registered NIV type identified by medical record review.

3 Inclusion criteria: NIV > 2 hours, NIV-NAVA or NIV-PS ≥ 2/3 of the time on NIV, ≥18 years, reason for ICU admission: acute respiratory problems.

Abbreviations: Bipap = Bi-level Positive Airway Pressure; CIS = Critical Information System; ICU = intensive care unit; NIV-NAVA = noninvasive ventilation – neutrally adjusted ventilator assist; NIV-PS = noninvasive ventilation – pressure support.
Table 1  Main clinical characteristics of the patients at the inclusion in the study.

<table>
<thead>
<tr>
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<th>PERIOD 1</th>
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<th>PERIOD 2</th>
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<table>
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<th>NIV-PS (n=202)</th>
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<td>Period 2 (n=237)</td>
<td>Period 3 (n=81)</td>
<td>Period 4 (n=156)</td>
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<tr>
<td>pH</td>
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<td>PaO₂/FiO₂ (mmHg)</td>
<td>164.29 (128.38-231.96)²</td>
<td>166.65 (125.31-228.2)²</td>
<td>160.92 (126.88-210.19)³</td>
<td>169.66 (122.51-233.68)³</td>
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<td>9.49 (8.17-11.7)²</td>
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<td>41 (33-48)</td>
<td>42 (29-50)</td>
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<tr>
<td>APACHE II score</td>
<td>24 (20-28)</td>
<td>25 (21-28)³</td>
<td>24 (21-29)</td>
<td>25 (20-28)³</td>
</tr>
<tr>
<td>First SOFA score</td>
<td>5 (3-7)³</td>
<td>5 (4-7)³</td>
<td>5 (4-7)³</td>
<td>5 (3-6)³</td>
</tr>
</tbody>
</table>

Continuous data is presented as median (interquartile range/25-75th percentiles) and categorical data is presented as number of events (%).

† Acute Hypoxemic Respiratory Failure defined as PaCO₂ < 6.5 kPa and PaO₂ < 8.0 kPa.

Data: Historical NIV-PS is registered in PERIOD 1, 01.07.2011-30.11.2012. NIV-NAVA and NIV-PS are registered in PERIOD 2, 01.07.2013-30.11.2015.

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; BMI = body mass index; ICU = intensive care unit; NIV-NAVA = noninvasive ventilation – neurally adjusted ventilatory assist; NIV-PS = noninvasive ventilation – pressure support; PaCO₂ = partial pressure of carbon dioxide in arterial blood; PaO₂ = partial pressure of oxygen in arterial blood; PaO₂/FiO₂ = ratio between partial pressure of
oxygen in arterial blood and fraction of inspired oxygen; SAPS= Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Main clinical characteristics of the patients at the inclusion in the study with length of ICU stay &gt; 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PERIOD 1</td>
</tr>
<tr>
<td>Variables</td>
<td>Historical NIV-PS</td>
</tr>
<tr>
<td></td>
<td>(n=106)</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60 (57)</td>
</tr>
<tr>
<td>Female</td>
<td>46 (43)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>71.5 (66-78)</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>9 (9)</td>
</tr>
<tr>
<td>18.5-&lt;25</td>
<td>49 (46)</td>
</tr>
<tr>
<td>25-30</td>
<td>31 (29)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>17 (16)</td>
</tr>
<tr>
<td><strong>Unit setting</strong></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>84 (79)</td>
</tr>
<tr>
<td>Surgical</td>
<td>22 (21)</td>
</tr>
<tr>
<td><strong>Reason for ICU admission</strong></td>
<td></td>
</tr>
<tr>
<td>Acuterespiratory failure</td>
<td>89 (84)</td>
</tr>
<tr>
<td>Acuteheartfailure</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>12 (11)</td>
</tr>
<tr>
<td><strong>Blood gases at ICU admission</strong></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.35 (7.24-7.42)</td>
</tr>
<tr>
<td>Parameter</td>
<td>Period 1</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>PaO₂/FiO₂, mmHg</strong></td>
<td>166.5 (133.75-232.5)(^a)</td>
</tr>
<tr>
<td><strong>PaCO₂, kPa</strong></td>
<td>6.71 (4.81-9.2)(^e)</td>
</tr>
<tr>
<td><strong>PaO₂, kPa</strong></td>
<td>9.92 (8.51-11.6)</td>
</tr>
<tr>
<td>Acute Hypoxemic Respiratory Failure(^†)</td>
<td>4 (4)</td>
</tr>
<tr>
<td><strong>Severity of illness scores</strong></td>
<td></td>
</tr>
<tr>
<td>SAPS II score</td>
<td>41 (31-50)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>24 (20-28)</td>
</tr>
<tr>
<td>First SOFA score</td>
<td>5 (3-7)</td>
</tr>
</tbody>
</table>

\(^a\) n=103, \(^b\) n=223, \(^c\) n=78, \(^d\) n=145, \(^e\) n=105, \(^f\) n=232, \(^g\) n=79

Continuous data is presented as median (interquartile range/25-75th percentiles) and categorical data is presented as number of events (%).

\(^†\) Acute Hypoxemic Respiratory Failure defined as PaCO₂ < 6.5 kPa and PaO₂ < 8.0 kPa.

Data: Historical NIV-PS is registered in PERIOD 1, 01.07.2011-30.11.2012. NIV-NAV and NIV-PS are registered in PERIOD 2, 01.07.2013-30.11.2015.

Please see Table 1 legend for expansion of abbreviations.
<table>
<thead>
<tr>
<th>NIV-NAVA</th>
<th>Historical</th>
<th>ICU stay &gt; 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>91</td>
<td>134</td>
</tr>
<tr>
<td>Intubation during ICU</td>
<td>21 (23)</td>
<td>28 (21)</td>
</tr>
</tbody>
</table>
ICU mortality 24 (26) 32 (23) 1.19 0.64-2.20 1.31 0.67-2.54
90-day mortality 47 (52) 62 (46) 1.24 0.73-2.11 1.24 0.69-2.25

<table>
<thead>
<tr>
<th>NIV-NAVA</th>
<th>Historical</th>
<th>Crude</th>
<th>95% CI</th>
<th>Adjusted</th>
<th>95% CI</th>
<th>Adjusted**</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIV-PS</td>
<td>Coeff.</td>
<td></td>
<td>Coeff.</td>
<td></td>
<td>Coeff.</td>
<td></td>
</tr>
<tr>
<td>Days of ICU stay</td>
<td>2.92 (1.67-6.44)</td>
<td>2.33 (1.14-5.97)</td>
<td>1.31</td>
<td>1.00-1.73</td>
<td>1.46</td>
<td>1.11-1.93</td>
<td>1.22</td>
</tr>
<tr>
<td>Days of NIV</td>
<td>1.29 (0.75-2.46)</td>
<td>0.81 (0.29-2.46)</td>
<td>1.52</td>
<td>1.12-2.10</td>
<td>1.63</td>
<td>1.19-2.25</td>
<td>1.36</td>
</tr>
</tbody>
</table>

Absolute categorical data is presented as number of events (%) and absolute continuous data is presented as median (interquartile range/25-75th percentiles). Relative continuous data are transferred from logarithm to the original scale (days).

*Adjusted for sex, age, BMI, pH and unit setting

** Patients with ICU stay > 24 hours. Adjusted for sex, age, BMI, pH, unit setting and SAPS II score

Data: Historical NIV-PS is registered in PERIOD 1, 01.07.2011-30.11.2012. NIV-NAVA are registered in PERIOD 2, 01.07.2013-30.11.2015.

Abbreviations: ICU = intensive care unit; NIV-NAVA = noninvasive ventilation – neurally adjusted ventilatory assist; NIV-PS = noninvasive ventilation pressure support.
Table 4 Associations between NIV-NAVA and NIV-PS (PERIOD 2) - Absolute and relative outcomes

<table>
<thead>
<tr>
<th></th>
<th>NIV-NAVA</th>
<th>NIV-PS</th>
<th>Crude 95% CI</th>
<th>Adjusted* 95% CI</th>
<th>Adjusted** 95% CI</th>
<th>Adjusted*** 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>91</td>
<td>202</td>
<td>293</td>
<td>293</td>
<td>233</td>
<td></td>
</tr>
<tr>
<td>Intubation during ICU</td>
<td>21 (23)</td>
<td>36 (18)</td>
<td>1.38 (0.75-2.54)</td>
<td>1.67 (0.87-3.19)</td>
<td>2.02 (0.97-4.19)</td>
<td></td>
</tr>
<tr>
<td>ICU mortality</td>
<td>24 (26)</td>
<td>38 (19)</td>
<td>1.55 (0.86-2.77)</td>
<td>1.40 (0.75-2.63)</td>
<td>1.22 (0.58-2.58)</td>
<td></td>
</tr>
<tr>
<td>90-day mortality</td>
<td>47 (52)</td>
<td>87 (43)</td>
<td>1.41 (0.86-2.32)</td>
<td>1.39 (0.81-2.39)</td>
<td>1.22 (0.64-2.34)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>NIV-NAVA</th>
<th>NIV-PS</th>
<th>Crude Coeff.</th>
<th>Adjusted* Coeff.</th>
<th>Adjusted** Coeff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of ICU stay</td>
<td>2.92 (1.67-6.44)</td>
<td>1.96 (1.02-4.7)</td>
<td>1.43 (1.11-1.84)</td>
<td>1.73 (1.35-2.20)</td>
<td>1.42 (1.14-1.79)</td>
</tr>
<tr>
<td>Days of NIV</td>
<td>1.29 (0.75-2.46)</td>
<td>0.50 (0.25-1.17)</td>
<td>2.23 (1.69-2.92)</td>
<td>2.39 (1.80-3.13)</td>
<td>2.27 (1.65-3.10)</td>
</tr>
</tbody>
</table>

Absolute categorical data is presented as number of events (%) and absolute continuous data is presented as median (interquartile range/25-75th percentiles). Relative continuous data are transferred from logarithm to the original scale (days).

*Adjusted for sex, age, BMI, pH and unit setting

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** Patients with ICU stay > 24 hours. Adjusted for sex, age, BMI, pH, unit setting and SAPS II score

Data: NIV-NAVA and concurrent NIV-PS are registered in PERIOD 2, 01.07.2013-30.11.2015.

Please see Table 3 legend for expansion of abbreviations.