Author's response to reviews

Title: Performance of noninvasive ventilation in acute respiratory failure in critically ill medical-surgical patients: a prospective, observational, cohort study.

Authors:

Thiago D Corrêa (thiago.correa@einstein.br)
Paula R Sanches (paula.sanches@einstein.br)
Lúbia C de Moraes (lubia.morais@einstein.br)
Elézer Silva (silva.eliezer@einstein.br)
Farah C Scarin (farah.scarin@einstein.br)
Carmen S V Barbas (carmen.barbas@gmail.com)

Version: 3
Date: 2 October 2015

Author's response to reviews: see over
Response to the Reviewers’ comments


Dear Editor and Reviewers

Thank you for all your suggestions and constructive commentaries that helped us restructure, refine and improve our manuscript. A point-by-point response to the reviewers’ comments follows. Changes are highlighted in yellow in the revised version of the manuscript.

Reviewer 1

The authors should specify the aim of the study and what adds to studies previously published.

Response: We apologize for being unclear. We better specified the aim of the study in the revised version of the manuscript (page 5, second paragraph): “Our objective was to evaluate the rate of NIV failure in hypoxemic patients with an arterial carbon dioxide partial pressure (PaCO2) lower than 45 mmHg or equal to or higher than 45 mmHg at ICU admission. We also aimed to evaluate the predictors of NIV failure, intensive care and hospital length of stay, mortality rate at day 28 and the main complications associated with NIV.”

Our results add to the previously published studies the finding that the severity of the patient (predicted by APACHE II score) might be more important than the baseline PaCO2 levels to predicted NIV failure/success in a mixed population of acute respiratory failure patients.
The authors state NIV was delivered via BIPAP Vision (hospital NIV platform ventilator with high flow oxygen) and Syncrony (home bilevel ventilator). How did they deliver FiO2 60% as described in the text? How did they deliver expiratory VT?

Response: We acknowledge the reviewer for addressing this issue. Actually, we used the BIPAP synchrony only for palliative care patients. As these patients were not included in our study, only BIPAP vision were used in the present analysis. BIPAP vision has a FiO2 control from 21 to 100% and allows monitoring the expiratory VT, which was maintained around 6 ml/Kg of predicted body weight. We have corrected our mistake in the revised version of the manuscript (page 6, second paragraph and page 16 last paragraph).

Which guidelines the authors follows to perform EI or start NIV?

Response: We acknowledge the reviewer for addressing this important issue. The protocol of NIV application and the criteria for endotracheal intubation in our ICU follow the Brazilian Recommendations for mechanical ventilation (1). This reference was added to the revised version of the manuscript.

The criteria to start NIV is presented in page 5 (lines 19 to 23) of the revised manuscript “all consecutive patients admitted to the ICU that presented a peripheral oxygen saturation (SpO2) lower than 90% despite oxygen delivered through a Venturi Mask [fraction of inspired oxygen (FiO2) around of 50%] or by an oxygen bag (FiO2 around 100%) that received NIV, except for palliative care purposes, were included in this study [16]” and on page 6 first paragraph “Noninvasive ventilation was applied to patients admitted to the ICU that presented a SpO2 lower than 90% despite oxygen delivered through a Venturi Mask (FiO2 around of 50%) or by an oxygen bag (FiO2 around 100%) [16].”.

The criteria for endotracheal intubation is presented in page 8, second paragraph, of the revised manuscript as follows: “Criteria for endotracheal intubation included failure to maintain an arterial oxygen partial pressure (PaO2) > 60 mmHg or SpO2 > 90% with an FiO2 equal to or greater than 60%, PaCO2 higher than 60 mmHg with pH lower than 7.25, inability to protect the airways or to manage copious tracheal secretions, hemodynamic or electrocardiographic
instability, inability to tolerate the face mask, inability to correct dyspnea and progression of respiratory failure [16].

Did the authors intubate all the patients showing pH lower than 7.25 and a PaCO2 higher than 60 mmHg as stated in the text?
Response: Yes, in our ICU we intubate all patients with pH lower than 7.25 with a PaCO2 higher than 60 mmHg that have not improved during a NIV trial.

I suggest to divide the patients in two groups: pure hypoxemic (CAP-ARDS) and hypoxemic – hypercapnic and delete the other.
Response: We thank the reviewer for the interesting suggestion. As presented in Table 1, we had 28 (33%) patients with PaCO2 ≥ 45 mmHg and 57 (67%) patients with PaCO2 < 45 mmHg. We performed the additional analysis presented bellow to address the impact of baseline PaCO2 levels ≥ 45 mmHg on outcomes.

NIV failure occurred in 25.0% (7/28) of patients with PaCO2 ≥ 45 mmHg and in 33.3% (19/57) of patients with PaCO2 < 45 mmHg (Odds ratio for PaCO2 ≥ 45 mmHg: 0.67, 95%CI 0.24 to 1.844; p=0.435). The median (IQR) length of ICU stay [2 (1-8) vs. 4 (2-10), respectively for PaCO2 ≥ 45 mmHg and < 45 mmHg; p=0.101] and hospital stay [19 (9-30) vs. 21 (12-37), respectively for PaCO2 ≥ 45 mmHg and < 45 mmHg; p=0.165] were not affected by baseline PaCO2 levels.

In-hospital mortality [3/28 patients (10.7%) vs. 14/57 patients (24.6%), respectively for PaCO2 ≥ 45 mmHg and < 45 mmHg; p=0.160] and 28-day mortality [3/28 patients (10.7%) vs. 6/57 patients (10.5%), respectively for PaCO2 ≥ 45 mmHg and < 45 mmHg, p=1.000] did not differ between patients with baseline PaCO2 ≥ 45 mmHg or < 45 mmHg.

Since the PaCO2 levels, regardless the etiology of acute respiratory failure, have not affected our study outcomes, we speculated that split the patients in two groups as suggested by the reviewer and exclude few patients from the analysis would not affect the main study findings while preserving the number of studied patients. Nevertheless, if the reviewer insists, we are prepared to make the necessary exclusions.
These analyses were added to the abstract (Page 2), to the methods section (Page 9, line 11), to the results section (pages 10 to 12), discussion section (page 12, first paragraph) and to the conclusion (page 17) of the revised manuscript.

Reviewer 2

Blood gas analysis reported as baseline obtained after patient stabilization, and no data are provided about blood gases before starting NIV.

Response: We acknowledge the reviewer for addressing this important issue. In our unit, if a patient exhibits a SpO₂ below 90% at the ICU admission, a ventury mask (FiO₂ around 50%) is immediately applied to the patient. Patients admitted to the ICU from the emergency room is transported using oxygen bag (FiO₂ around 100%). If a patient is already using an oxygen mask or oxygen bag and did not achieve a SpO₂ >90%, a BIPAP vision is installed and the FiO₂ adjusted to achieve a SpO₂ >90%. Then, after the patient’s stabilization on NIV, the baseline arterial blood gas is collected to guide further adjustments on ventilation. Therefore, blood gas analysis before NIV initiation were not routinely performed.

Some concerns may derive from criteria of interruption of the NIV trial, because the decision was made by the attending physician and no data are reported about case of interruption, and physiological conditions of the patient at the interruption time.

Response: Thank you for your observation. We made this point more clear in the revised version of the manuscript (Page 8, second paragraph): “Criteria for endotracheal intubation included failure to maintain an arterial oxygen partial pressure (PaO₂) > 60 mmHg or SpO₂ > 90% with an FiO₂ equal to or greater than 60%, PaCO₂ higher than 60 mmHg with pH lower than 7.25, inability to protect the airways or to manage copious tracheal secretions, hemodynamic or electrocardiographic instability, inability to tolerate the face mask, inability to correct dyspnea and progression of respiratory failure [16].”
We added a new subheading in the results section (RESPONSE TO NIV AND COMPLICATIONS; page 10) and presented more clearly the data concerning NIV interruption (Pages 10-11): “NIV failure occurred in 25.0% (7/28) of patients with PaCO2 ≥ 45 mmHg and in 33.3% (19/57) of patients with PaCO2 < 45 mmHg (OR 0.67, 95%CI 0.24 to 1.84; p=0.435) (Table 1). In 61.5% (16/26) of patients, NIV failure occurred during the first 24 hours of noninvasive mechanical ventilation. The main reasons for endotracheal intubation included progression of hypoxemia in 65.4% (17/26), neurological deterioration in 19.2% (5/26), gastric distension 7.7% (2/26), hemodynamic instability 3.8% (1/26) and patients’ dangerous agitation 3.8% (1/26) (Table 2).”

Criteria for transfer to spontaneous breathing are not defined, as well, the total NIV time has not been reported. These informations would be interesting because 1) might be related to the underlying disease and to the prognosis, 2) could show the mean attitude of the physicians, 3) may help to define early or late NIV failure. Response: We acknowledge the reviewer for addressing this important issue. Criteria for transfer to spontaneous breathing and the time under NIV were added to the revised version of manuscript (Page 7, second paragraph): “NIV success patients were maintained coupled to a BIPAP vision continuously during a 24-hour period. Afterwards, NIV parameters were re-adjusted based on SpO2, arterial blood gas analysis (specially PaCO2 levels), ventilator parameters (expiratory tidal volume, respiratory rate and mask leakage) and patient’s comfort. When FiO2 was lower than 50%, respiratory rate lower than 30 breaths per minute, expiratory tidal volume higher than 5 mL/kg of predicted body weight with a pressure support lower than 10 cm H2O and PEEP lower than 8 cm H2O, NIV was discontinued and oxygen ventury mask of 50% initiated. If an oxygen ventury mask of 50% was well tolerated during a one-hour period, the ventury mask of 50% was alternated with NIV (1 hour in ventury mask of 50% and 3 hours in NIV) until the patient could stay spontaneously breathing. The maximal time allowed on full NIV support was 24 hours. After 24 hours on NIV, patients that could not stay for at least one hour on oxygen ventury mask was defined dependent on NIV and was intubated and mechanically ventilated.”
As discussed by the authors, solid organ transplantation was showed to be one of comorbidities relevant in the NIV failure group, and may probably be involved in the apparently paradoxical result (reported in p. 11, raw 10) of the association between younger patient’s age and NIV failure. The NIV failure rate in immunocompromised patients has been reported to be higher than general ARF population treated in ICU, and is reported to be higher than 50% (2). We suggest to evaluate if consider separately this subgroup of patients.

Response: Thank you for your comment and observation. We agree with the reviewer that it would be interesting to perform a separate analysis including only the immunocompromised patients. Nevertheless, our study was designed to address the impact of NIV failure on outcomes in a mixed population of patients with acute respiratory failure. The proposed analysis by the reviewer would produce a group with a very small sample size (we had only nine patients with acute respiratory failure and solid organ transplantation, Table 1), increasing the rate of type 1 and type 2 errors and misleading interpretations. Therefore we would like to keep the solid organ transplant patients in this analysis and better discuss this specific group of patients in the discussion section. Finally, we added your recommended references in the revised version of the manuscript.

Now the discussion sections reads as follows (Page 15, first paragraph):

“We found a higher prevalence of transplanted patients in the NIV failure group than in the NIV success group. A significant reduction in intubation rate and ICU length of stay using NIV for respiratory failure in recipients of solid organ transplantation have been reported [27–29]. Contrary to these findings, we observed a higher incidence of NIV failure in transplanted patients [7/9 (77.7%)]. In our study, transplanted patients were comparatively younger than non-transplanted patients (45 ± 15 vs. 77 ± 13 years, respectively, p<0.001). The younger age and higher failure rate in the transplanted patients may have contributed to the finding that comparatively younger age (67 ± 21 vs. 77 ± 14) was an independent predictor of NIV failure in our study.”
Please discuss better the statement in p. 11, raw 2-3; mortality did not differ according to Fisher’s test (table 3), but survival probability was higher in NIV success group according to Log-rank (Figure 2).

Response: The mortality at day 28 did not differ between NIV failure and success groups [5/26 (19.2%) vs. 4/59 (6.8%), respectively for NIV failure and NIV success groups; p=0.124 with Fisher`s exact test] (Table 3). The same finding was observed when a survival analysis was performed (p= 0.073 with Log-rank test). The two tests (Fisher’s exact test and Log-rank test) yielded different p values (both >0.05) because the survival analysis takes into account the time to event (NIV failure) and censoring, while the Fisher`s exact test does not.

Please explain the choice of limiting variables analyzed to those presented in more than five patients in each group and provide the list of variables excluded and their prevalence (p. 9, raw 8-9).

Response: We acknowledge the reviewer for addressing this important issue. We first carried out a univariate logistic regression analysis aiming to identify which predictors (explanatory or independent variables) were associated with NIV failure/success (dependent variable). Only those variables presented in more than five patients in each group were included in this analysis. The cut off value of five patients was chosen arbitrarily.

The appropriate sample size for a given analysis depends on the acceptable levels of type I and type II errors, the expected magnitude of the relationships between the independent and dependent variables and the frequency of the dependent variable. The more explanatory variables, the larger the sample size required for a logistic regression. Since more independent variables require more cases, and a minimum of 10 cases per independent variable has been recommended (2). Our study involved 85 patients. Therefore, including only those variables presented in more than five patients in each group allows us to limit the number of predictors included in the multivariable analysis.

Below we provide a list of all variables included and excluded (variables with a p value >0.25 on univariate logistic regression analysis) from multivariate logistic regression analysis. Their respective prevalence were presented on Tables 1 and 2 of the submitted manuscript.
<table>
<thead>
<tr>
<th>Risk factors (predictors)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95%CI</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>0.97</td>
<td>0.94-0.99</td>
</tr>
<tr>
<td>Male gender*</td>
<td>2.24</td>
<td>0.86-5.83</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)*</td>
<td>0.98</td>
<td>0.95-1.00</td>
</tr>
<tr>
<td>Heart rate (bpm)*</td>
<td>1.02</td>
<td>1.00-1.05</td>
</tr>
<tr>
<td>APACHE II score*</td>
<td>1.10</td>
<td>1.00-1.21</td>
</tr>
<tr>
<td>Arterial pH*</td>
<td>0.95</td>
<td>0.89-1.01</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)*</td>
<td>0.87</td>
<td>0.78-0.97</td>
</tr>
<tr>
<td>PaCO2 ≥ 45 mmHg</td>
<td>0.67</td>
<td>0.24-1.84</td>
</tr>
<tr>
<td>PaO2/FiO2</td>
<td>1.00</td>
<td>0.99-1.00</td>
</tr>
<tr>
<td>Arterial lactate (mg/dl)*</td>
<td>1.05</td>
<td>0.99-1.10</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>0.35</td>
<td>0.04-3.10</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.90</td>
<td>0.16-4.97</td>
</tr>
<tr>
<td>Transplantation*</td>
<td>6.79</td>
<td>1.22-37.70</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>0.43</td>
<td>0.05-3.89</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.79</td>
<td>0.23-2.77</td>
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<tr>
<td>Cardiovascular disease</td>
<td>0.73</td>
<td>0.18-2.93</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.55</td>
<td>0.57-4.21</td>
</tr>
<tr>
<td>Community acquired pneumonia</td>
<td>1.22</td>
<td>0.47-3.17</td>
</tr>
<tr>
<td>Cardiogenic pulmonary edema</td>
<td>0.53</td>
<td>0.16-1.80</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome*</td>
<td>2.57</td>
<td>0.68-9.80</td>
</tr>
<tr>
<td>Acute COPD</td>
<td>0.97</td>
<td>0.23-0.66</td>
</tr>
</tbody>
</table>

* = predictors included in the multivariate analysis.

**Reviewer 3**

Manuscript aim is unclear

*Response: We apologize for being unclear. We better specified the aim of the study in the revised version of the manuscript:*
Page 5, second paragraph: “Our objective was to evaluate the rate of NIV failure in hypoxemic patients with an arterial carbon dioxide partial pressure (PaCO2) lower than 45 mmHg or equal to or higher than 45 mmHg at ICU admission. We also aimed to evaluate the predictors of NIV failure, intensive care and hospital length of stay, mortality rate at day 28 and the main complications associated with NIV.”

Page 8, last paragraph: “Our primary outcome was the incidence of NIV failure, defined by the need of endotracheal intubation and mechanical ventilation in hypoxemic patients with PaCO2 < 45 mmHg and ≥ 45 mmHg at ICU admission. Secondary outcomes were the main indications for acute application of NIV, the predictors of NIV failure, ICU and hospital lengths of stay, in-hospital and mortality at day 28 and the main complications associated with noninvasive ventilation.”

What is the mean of clinical – surgical ICU patients.
Response: Our 41-bed ICU is a general (mixed) ICU where medical (sepsis, myocardial infarction, pneumonia, ARDS, COPD exacerbation, etc) and surgical (post-operative patients, i.e., elective, emergency and urgency surgeries) patients were admitted. The term clinical-surgical ICU was removed from the manuscript and replaced by mixed ICU in the revised manuscript version (page 1 line 1; page 2, line 10 and page 5, line 14).

Are inotropic agent or vasopressor agent usage excluded?
Response: It is recommended that NIV should not be used in patients with hemodynamic or electrocardiographic instability (3). Therefore, in our ICU unstable patients requiring vasopressors are not submitted to NIV. Such patients wherever necessary, are intubate and mechanically ventilated.

Have do authors SOFA scores?
Response: Unfortunately, we did not collected the SOFA score of the studied patients. Only APACHE II score were collected.
What are surgical definitions of patients?

Response: Surgical patients are those admitted to the ICU during the post-operative period (cardiac, abdominal, brain surgeries or solid organs transplantation).

Authors should write NIV indications and arterial blood gases of patients?

Response: We apologize for being unclear. The NIV was indicated to all consecutive acute respiratory failure patients admitted to the ICU that presented a peripheral oxygen saturation (SpO\textsubscript{2}) lower than 90% despite oxygen delivered through a Venturi Mask [fraction of inspired oxygen (FiO\textsubscript{2}) around of 50%] or by an oxygen bag (FiO\textsubscript{2} around 100%). This issue was acknowledged in the revised version of the manuscript (Page 6, first paragraph) as follows: “Noninvasive ventilation was applied to patients admitted to the ICU that presented a SpO\textsubscript{2} lower than 90% despite oxygen delivered through a Venturi Mask (FiO\textsubscript{2} around of 50%) or by an oxygen bag (FiO\textsubscript{2} around 100%) [16].”

The main causes of acute respiratory failure requiring NIV are presented in table 2, page 25 of the revised manuscript. The results of baseline arterial blood gases analysis are presented on table 1 of the revised manuscript (Page 24).

How do authors explain NIV failed of younger patients?

Response: We acknowledge the reviewer for addressing this important issue. Reviewer 2 also made similar comment. Please, see the response above.

References
