Author's response to reviews

Title: Non-invasive mechanical ventilation in patients with diffuse interstitial lung diseases.

Authors:

Stefano Aliberti (stefano.aliberti@unimib.it)
Grazia Messinesi (graziamessi@hotmail.com)
Silvia Gamberini (silvia.gamberini85@gmail.com)
Sveva Maggiolini (padme1981@hotmail.it)
Dina Visca (dinavisca@gmail.com)
Vanni Galavotti (vanni.galavotti@aopoma.it)
Fabio Giuliani (fabio.giulian@gmail.com)
Roberto Cosentini (r.cosentini@gmail.com)
Anna Maria Brambilla (brambi.brambi@gmail.com)
Francesco Blasi (francesco.blasi@unimi.it)
Raffaele Scala (raffaele_scala@hotmail.com)
Mauro Carone (Mauro.carone@fsm.it)
Francesca Luisi (francesca.luisi@virgilio.it)
Sergio Harari (sharari@hotmail.it)
Antonio Voza (antonio.voza@humanitas.it)
Antonio Esquinas (antmesquinas@gmail.com)
Alberto Pesci (alberto.pesci@unimib.it)

Version: 2
Date: 23 March 2014

Author's response to reviews:

March 22nd, 2014

Dear Editor,

The authors would like to thank both reviewers for their analysis of the manuscript. We agree with all comments and recommendations suggested by the reviewers. We have changed the manuscript to comply with reviewers’ recommendations. The following is a detailed response to each reviewer’s recommendations.

Reviewer #1

Major comment #1:

First of all apparently you didn’t calculate a sample size, that means perhaps, that for the defined main outcomes, studied population could not be sufficient to reach a statistical significance. For the same reason it’s probably difficult to consider your “data ..useful in identifying patients with DPLD who could be enrolled in large RCT to test a possible efficacy of NIV on clinical outcomes”, as you assessed in the discussion
Response to major comment #1:
We definitely agree with the reviewer. The major problem is that the evaluation of NIV in ILD patients is limited by the few patients usually treated. Because of this, it would be a great challenge to calculate an exact sample size. Furthermore, due to the “real-life” design of our study, the estimation of a sample size to power further controlled trials was not the objective of our analysis. However, we understand reviewer’s comment and, thus, we decided to delete the sentence. The following sentence has been added instead:

“From a research point of view, our data could be of help in designing further prospective observational or interventional studies to demonstrate the effectiveness of NIV in adjunct to standard medical treatment in homogeneous clinical-radiological patterns of DILD.”

Major comment #2:
Among the criteria to start NIV the P/F ratio was not always taken in account; apparently patients would have been treated even if they showed a respiratory distress, regardless the P/F. Did you compare the P/F ratio at the enrollment among the three groups (A, B and C)?

Response to major comment #2:
We understand reviewer’s comment. Respiratory distress represents an inclusion criteria for initiating NIV in our standard operating procedures. However, it should be noted that none of the patients on NIV had respiratory distress only. We compared the P/F ratio at the enrollment among the three groups. Values are shown in Figure 1. There was not a significant difference among the study groups. In view of reviewer’s comment, we decided to add this information in the footnotes of Figure 1 as follows:

“No significant difference was detected among the three study groups regarding PaO2/FiO2 ratio value on admission.”

Major comment #3:
I’m not sure whether it is appropriate to consider together pneumonia and acute heart failure. Alveolar recruitment is more difficult, sometimes impossible (a part for the perilesional areas) for collapsed areas above all when there is a focal distribution (like in pneumonia) (see Gattinoni L. NEJM 2006), then in a pulmonary oedema. Even if the results in the first hour could be the same in term of improvement of P/F, the outcomes of NIV treatment of these two etiologies of ARF are very different (see Antonelli M. ICM 2001). Actually the outcome evaluated in you study is just the clinical failure and not the P/F improvement.

Response to major comment #3:
We definitely agree with the reviewer. A clear benefit of the application of NIV/CPAP has been demonstrated in the literature of the past two decades. On the other hand, no clear data on patients’ outcomes have been published on the application of NIV/CPAP on patients with pneumonia. We agree with the reviewer that these two diseases cannot grouped together. In light both reviewers’
comment (see below) and past literature, we decided to consider only patients with pneumonia. Group A have been redefined as only patients whose ARF was triggered by pneumonia. After re-running the statistical analysis, we found that NIV/CPAP application in DILD patients with pneumonia still improve oxygenation (P/F ratio), with no favorable impact on clinical outcomes. We decided to follow reviewer’s suggestion and now we present data with Group A including patients with pneumonia vs. Group B including patients with exacerbation. Materials and Methods, Results and Discussion have been changed accordingly.

Major comment #4:
I suspect that, due to the kind of study design, there was an significant heterogeneity in the way to administer CPAP which also can affect the outcomes. In a patient with a respiratory distress there could be a significant difference in maintenance of CPAP pressure among high-flow systems, ventilators and above all Boussignac-mask. Moreover, a part from a possible mistake in table 2 (see below in the minor comments), it seems that a lot of patients were treated by helmet CPAP by means of a ventilator, which, being aimed only at keeping airway pressure constant, lacks continuous delivery of gas to the helmet leading to a substantial CO2 rebreathing (see Taccone P. CCM2004). Moreover the CPAP values used during CPAP and PSV were apparently different (table 2): did you statistically compared them?

Response to major comment #4:
We agree with the reviewer that a heterogeneity exists in the way to administer CPAP which might affect outcomes. This is one of the main limitations of this retrospective study. However, this seems the only way so far to enroll this number of patients in a multicenter study. On the other hand, it should be noted that all of the enrolling centers have a long-term experience with NIV/CPAP in patients with acute respiratory failure. However, this limitation should be definitely reported and the following sentence has been added in the Discussion section:

“In the same way, it should be acknowledged that, although all the centers share a long-term experience with both NIV and non-invasive CPAP, heterogeneity exists in the way CPAP/NIV were administered which might have had an impact on patients’ outcomes.”

Major comment #5:
You speak about high performance ventilators for PSV, but you never include their name. Which ventilators where used in the different centers? May be a possible role of the ventilator performance in the clinical failure?

Response to major comment #5:
We understand reviewer’s concern. The following ventilators have been used among the different centers: Evita 4 (Drager), VELA (Care Fusion), Servo 300 (Maquet) and Esprit (Philips respironics). All of them are high-performance ventilators used in the centers since long time. In order to better clarify this, the following sentence has been added in the Materials and Methods section:

“NIV was administered as non-invasive pressure support ventilation (PSV) with a
high-performance ventilator, including Evita 4 (Drager), VELA (Care Fusion), Servo 300 and Servo-s (Maquet) and Esprit (Philips Respironics), or high-flow stand-alone non-invasive continuous positive airway pressure (CPAP).

Major comment #6:
Why did you consider the first ABG at 6 hrs? All patients were still ventilated at that time? Which was the median timing of clinical failure?
Response to major comment #6:
We understand reviewer’s comment. We considered the first ABG within 6 hours after initiation of treatment because, from retrospective data, almost all of the patients had at least one ABG performed at that time. At that time, all the patients were ventilated and no patients were experiencing a clinical failure. We understand that the monitoring of gas exchange was not standardized for all the patients but this was the best we did in a retrospective study, as we indicated in the limitation section of the study.

Major comment #7:
In the results you assessed that “at the univariate analysis the only factors significantly associated to clinical failure were: a history of long-term oxygen therapy, […].” However table 4 shows that the majority of patients with long term oxygen therapy (58%) didn’t fail the treatment.
Response to major comment #7:
We agree with the reviewer and we understand her/his comment. Among patients who did not fail a significantly higher proportion of patients were on LTOT in comparison to those who failed. We are sorry for this misunderstanding. In order to better clarify this, we re-phrase the sentence as follows:
“At the univariate analysis the only factors significantly associated to clinical failure were a low systolic blood pressure and a high respiratory rate before NIV treatment, see Table 4.”

Major comment #8:
Lastly, I don’t agree with your conclusion that the clinical implication of your results are that NIV could be considered a valuable option in patients with ARF triggered by pneumonia and acute heart failure. In fact you found only a better increase in the P/F than in the other groups, but the outcome was the same. This doesn’t mean that the improvement in gas exchange would be useful “to gain time meanwhile medical therapy may remove the trigger”. These patients received a medical therapy, however their outcome was not better than in the other groups.
Response to major comment #8:
We definitely agree with the reviewer. Her/his comment is right. We cannot say this. What we can say is that NIV can improve oxygenation, although there is no benefit on outcomes. In order to make this clear, we remove our sentence and
we re-phrase it as follows:

“Our findings have important implications from both a clinical and a research point of view. In clinical practice, NIV could be considered an option in patients with DILD whit an ARF triggered by acute heart failure or pneumonia to improve oxygenation. How this physiological benefit could be translated in a better clinical outcome need to be demonstrated in a controlled perspective randomized trial”

Minor comment #1:
Table 1 and 4 are too long. I don’t think it is useful to report all that data in the general population
Response to minor comment #1:
We agree with the reviewer. According to her/his comment, we decided to delete several variables from both Table 1 and Table 2. A new Table 1 and Table 2 are reported.

Minor comment #2:
Table 1: why did you consider a “previous episode of pneumonia” a co-morbidity?
Response to minor comment #2:
We agree with the reviewer and we decided to delete this variable from both Table 1 and Table 2.

Minor comment #3:
Table 2: numbers reported as (% )in the table need to be revised: for CPAP generator, relative percentage were calculated on the total study population (=65 pts) while for PSV interface relative percentage was calculated on the PSV treatment (=21). Please use the same criteria. Moreover, for CPAP interface percentage reported are not corrected at all, either by calculating them on the total study population or by calculating them on the CPAP treatment only.
Response to minor comment #3:
We agree with the reviewer and we are sorry for this mistake. We have checked all the percentages in Table 2 and have corrected them.

Minor comment #4:
Table 3: in the title “clinical [..]according to the two groups”, you meant three, I think
Response to minor comment #4:
We agree with the reviewer comment and we have corrected our mistake.

Reviewer #2

Major comment #1:
The manuscript would benefit from a revision by an expert in the English medical language
Response to major comment #1:
We agree with the reviewer. The manuscript was reviewed by an English expert.

Major comment #2:
The term diffuse parenchymal lung disease is misleading since other diseases such as emphysema are also parenchymal diseases. I suggest the authors to use along the manuscript the term “diffuse interstitial lung disease (DILD)”, which fits better with the type of patients included in the study.

Response to major comment #2:
We agree with the reviewer. Following her/his comment we decided to change the term diffuse parenchymal lung disease (DPLD) with interstitial lung disease (ILD) along all the manuscript.

Major comment #3:
Inclusion of both pneumonia and acute heart failure. I agree with the authors in that causes of ARF potentially reversible would benefit better from NIV than other causes. However, there is extensive information in the literature illustrating that patients with acute heart failure respond to NIV much better than patients with pneumonia. Therefore, analysing together both groups of patients may lead to significant bias. Since there are only 5 patients with acute heart failure, I suggest the authors to compare patients with pneumonia with those with acute exacerbation of fibrosis. With only 5 patients with acute heart failure, a simple informative description of their outcomes would be enough.

Response to major comment #3:
We definitely agree with the reviewer. A clear benefit of the application of NIV/CPAP has been demonstrated in the literature of the past two decades. On the other hand, no clear data on patients’ outcomes have been published on the application of NIV/CPAP on patients with pneumonia. We agree with the reviewer that these two diseases cannot grouped together. In light of reviewer’s comment and past literature, we decided to consider only patients with pneumonia. Group A have been redefined as only patients whose ARF was triggered by pneumonia. After re-running the statistical analysis, we found that NIV/CPAP application in ILD patients with pneumonia still improve oxygenation (P/F ratio), with no favorable impact on clinical outcomes. We decided to follow reviewer’s suggestion and now we present data with Group A including patients with pneumonia vs. Group B including patients with exacerbation. Materials and Methods, Results and Discussion have been changed accordingly.

Major comment #4:
Pooling together patients treated with CPAP and NIV. In spite of a case report from the authors (reference 16), CPAP and NIV should not be equivalent in patients with DILD and therefore analysing together both treatments may lead to significant bias. Additionally, CPAP was preferentially delivered with Helmet, while NIV with face mask. The authors are not clear when they define what criteria was used to choose between both treatments (in page, lines 2 to 4 they should explain more clearly what treatment corresponds these criteria). This
possible bias deserves a comment in the discussion, probably in the limitations section. In addition to compare the current Groups A and B, a comparison of the characteristics and outcomes between patients treated with CPAP or NIV would improve the manuscript.

Response to major comment #4:

We understand reviewer’s comment. First of all, we reviewed all the data and we updated the criteria to start either CPAP or PSV. In view of this, we decided to modify the sentences in the Materials and Methods section as follows:

“Criteria for application of CPAP in the study centers included the presence of both severe acute respiratory failure (PaO2/FiO2 ratio less than 200) and respiratory rate exceeding 30 breaths/minute or use of accessory respiratory muscles or paradoxical abdominal motion, in the absence of respiratory acidosis (pH < 7.35, PaCO2 # 45 mmHg). Criteria for application of PSV in the study centers included the presence of respiratory acidosis (pH < 7.35, PaCO2 # 45 mmHg) and a respiratory rate exceeding 30 breaths/minute or use of accessory respiratory muscles or paradoxical abdominal motion.”

We also agree with the reviewer that CPAP and NIV are not equivalent in patients with DILD and therefore analyzing together both treatments may lead to significant bias. Because of the small sample size we are not able to compare patients with CPAP vs. PSV according to ARF and ILD. However, this is a crucial point and, thus, we decided to report this in the limitation section of the discussion, as follows:

“although this was a multicenter study, the limited number of patients did not allow us to highlight possible differences between PSV and CPAP”

Major comment #5:

In general, do not repeat most of the numeric values that are already shown in tables; just state the message or the information, since number can be read in the tables.

Response to major comment #5:

We agree with the reviewer. In view of her/his comment we delete data on the Results section that were reported also in tables (i.e. Table 2)

Major comment #6:

Discussion, last paragraph of page 14 and first paragraph of page 15. The authors suggest that NIV is a valuable option in patients with ARF triggered by acute heart failure or pneumonia; however, the can’t state this since actually their clinical outcomes were completely similar to those from acute exacerbation of fibrosis. In the same paragraph, the statement on the special indication of NIV in lung transplant based on the experience with patients with cystic fibrosis is somewhat speculative since there is no data to sustain this statement.

Response to major comment #6:

We definitely agree with the reviewer. Her/his comment is right. We cannot say
this. What we can say is that NIV can improve oxygenation, although there is no
benefit on outcomes. In order to make this clear, we remove our sentence and
we re-phrase it as follows:

“Our findings have important implications from both a clinical and a research
point of view. In clinical practice, NIV could be considered an option in patients
with ILD whit an ARF triggered by acute heart failure or pneumonia to improve
oxygenation. How this physiological benefit could be translated in a better clinical
outcome need to be demonstrated in a controlled perspective randomized trial.”

We also changed the sentence on lung transplantation as follows:

“A special indication of NIV in ILD might be in those patients who have an
indication for lung transplant, although no data have been published on this
topic.”

Minor comment #1:
Abstract, page 3, fourth line of results. “A significant …” or perhaps “No
significant …”.
Response to minor comment #1:
We agree with the reviewer. We have changed the sentence as follows:

“No significant difference in PaO2/FiO2 ratio, PaCO2 and pH values during NIV
treatment was detected in patients with a radiological pattern of usual interstitial
pneumonia (UIP) and non-specific interstitial pneumonia (NSIP).”

Minor comment #2:
Information on patients with do-not-intubated decisions. The authors describe
that the minority of majority with treatment failure were not intubated or did not
undergo ECMO. Therefore, a clear description of patients with decisions to limit
therapeutic effort or do-not-intubate is needed, both in the methods and the
results.
Response to minor comment #2:
This is a crucial point and we thank the reviewer for her/his comment. The DNI
order is a important step in the management of NIV patients. The point is that this
is a retrospective trial and we do not have precise data do-not-intubate orders.
We were not able to derive from the chart a clear indication for ETI or DNI order
for all the patients. Because of this, we decided to acknowledge this as an
important limitation of the study in the Discussion section:

“Our study has several limitations. First, data were retrospectively collected and
this could have led to potential bias in the evaluation and characterization of the
etiology of ARF among centers as well as the collection of information on
do-not-intubate orders.”

Minor comment #3:
Results, page 10, last line of paragraph 1). The sentence “A first diagnosis of
DPLD was made in two patients” should be better explained.
Response to minor comment #3:
We understand reviewer comment. Based on her/his suggestion we decided to modify the sentence as follows:
“A first diagnosis of ILD was made in two patients without a previous history of respiratory diseases.”

Minor comment #4:
Results, page 10, second paragraph). In the description of group C, only 7 cases as stated, while this group consisted of 10 patients.
Response to minor comment #4:
We agree with the reviewer. No enough clinical data were available for the review committee to characterize the etiology of ARF in 3 patients. Thus, Group C counts for 7 patients. We have corrected this along all the manuscript and Tables.

Minor comment #5:
Discussion, page 13, paragraph 2, line 3. At the light of the present results the authors can not state that NIV represents a valuable option since they did not demonstrate this treatment to be better than standard medical care and indeed there is no evidence on this. A better statement here would be that NIV is often used in this indication.
Response to minor comment #5:
We agree with the reviewer. Following her/his comment we decided to modify the sentence as follows:
“Although a lack of data exists on this topic, NIV is often used in ILD patients during an acute deterioration in daily clinical practice.”

Minor comment #6:
Discussion. In the same paragraph, line 9. The authors did not observe different NIV response according to the cause of ARF. They found immediate improvement of oxygenation in patients from Group A, but actually both groups had similar clinical response in terms of clinical failure rate. This statement should be tempered.
Response to minor comment #6:
We agree with the reviewer. According to her/his comment we decided to modify the sentence as follows:
“Our study did not identify differences in terms of NIV response in terms of oxygenation based on the type of ILD, but the cause of ARF”

Minor comment #7:
Table 3. There are no significant differences between the 3 groups regarding the outcomes; therefore the right column on comparisons between groups A and B is no necessary.
Response to minor comment #7:
We agree with the reviewer. Based on her/his comment we decided to delete the right column of Table 3

Minor comment #8:
Figure 1. The clarity of this figure can be substantially improved. First, the scales in the Y axes can be amplified so that differences between groups and time points can be better observed; I may suggest either using breaks in these axes and/or using SEM bars instead of SD, since SEM bars are shorter. Second, values at each time point can be put in the same vertical line and connect both time points with lines so that changes between before and 6-h after NIV can be more clear. Third, the entire population values can be deleted since this figure is intended to compare the 3 groups.

Response to minor comment #8:
We thank the reviewer for her/his comment. We have followed her/his suggestion, the entire population values have been deleted and figure 1 has been changed accordingly.