Author's response to reviews

Title: Exhaled Breath Profiling For Diagnosing Acute Respiratory Distress Syndrome

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Author's response to reviews: see over
Reviewer 1

Major Compulsory Revisions
None

Minor Essential Revisions
1. Abstract line 12-13 – “the enose was learned...” suggest change to “trained”
   Corrected.

2. Line 14 – change “evaluation” to “evaluated”
   Corrected.

3. Line 22 – undefined abbreviation: CPE
   Corrected.

4. Abstract conclusion 1st sentence: this is phrased incorrectly – breath analysis was not used to diagnose ARDS in this study; that implies prospective use in the clinical pathway (i.e. the future aim). The authors showed only that the breath profile was somewhat different between those with and without ARDS. This phrasing is repeated in the conclusions of the manuscript body and needs to be corrected
   Thank you for your careful evaluation of our manuscript. We have revised our conclusions accordingly.
   Abstract: page 2, line 24: “An electronic nose can rapidly and non–invasively discriminate between patients with and without ARDS with modest accuracy.”
   Conclusions: page 16, line 22: “We found that an electronic nose can rapidly and non–invasively discriminate between patients with and without ARDS with modest accuracy.”

5. P10 line 19 “temportal”
   Corrected.

6. P11 Competing diagnoses para – the last two sentences are duplicating information aren’t they? Suggest one is removed
   You are completely right. We adapted the wording as follows:
   Results: page 11; line 18: “Statistical significance and discrimination increased when patients with CPE and pneumonia were compared to patients with moderate/severe ARDS (P = 0.003 and P = 0.01; table 2).”

Discretionary Revisions
1. Results and fig 2 – please explain how the 274 were “not eligible” if they didn’t fulfil the exclusion criteria.
   Patients were screened, but only found eligible if they were mechanically ventilated. We apologize for the confusion and have clarified the inclusion criteria.
   Methods: page 5; line 13: “This was a prospective single centre cohort study. All patients admitted to the ICU, with the exception of
cardiopulmonary surgery patients, were screened. The only inclusion criterion was mechanical ventilation within the first 24 hours of ICU-admission. Exclusion criteria were (1) previous ICU admission or mechanical ventilation, (2) logistic problems or (3) explicit objection to research by the family.”

2. Discussion 1st sentence. This should be toned down. I am sure ICU staff would not accept a test with the performance characteristics shown here as a potential diagnostic aid (at least when used alone) for ARDS.

We agree and tuned down that sentence as follows:

Discussion: page 12; line 2: “This study with a commercially available eNose suggests that breath analysis might be used to identify patients with ARDS if the eNose technology would mature towards this application with increased diagnostic accuracy and sensor stability.

Discussion: page 12; line 9: “These data support the suggestion that eNose assessment may qualify as a candidate test for future non-invasive diagnostic approaches of ARDS.”

3. Please comment of the high prevalence of ARDS in this cohort; approx. 1 in 3 of the ICU patients had ARDS whereas the more typically reported prevalence is 5-15%

That is correct. We added a paragraph to the discussion to clarify this discrepancy.

Discussion: page 15; line 11: “The prevalence of ARDS was high in the studied patient cohort, and higher than in most previous cohort studies. Several factors could serve as an explanation for this discrepancy. First, included patients were severely ill, as suggested by the high disease severity scores and the high mortality. Second, different from other cohorts of critically ill patients, we excluded patients after cardiopulmonary surgery. Finally, ARDS was assessed prospectively by a team of trained research fellows. Prospective assessment may identify patients that could have been missed retrospectively.”

4. The raw data had to be transformed to account for sensor drift. How could this be overcome in a “real world” cross sectional application of the enose for diagnosis?

This is a very important comment. For sure, there is a need for new sensor technologies that do not show drift over time. Probably, calibration gasses should be used for normalization.

The following paragraph was adapted to overcome this comment:

Discussion: page 16; line 11: “[...] the accuracy of sensors needs to be increased as the tested commercially available technology proved insufficient: sensor sensitivity and specificity for VOCs can be modified targeting potential biomarkers. Drift should be minimized and sensor-arrays should provide interchangeable results to allow for application in large clinical trials.”
5. I presume the models generated from the two enoses were different. Again, how would this be addressed if applied to other centres using other enoses?

Future sensor technology should allow for interchangeable results between eNoses. Please see our reaction on your previous question.

6. P11 first sentence. I’m not sure I understand this sentence correctly. Does this mean that mod/severe ARDS was correctly predicted in 45% of cases and mild ARDS in 36%? Likewise the second paragraph.

Those percentages reflect the median of the predicted probability of ARDS as a result of the logistic regression model. Thus this is not the correctly predicted percentage of ARDS but a summary of the result of logistic regression. We apologize for the confusion and have revised that sentence.

Results: page 11; line 7: “The predicted probability of group membership by the eNose (result of logistic regression) was significantly different between moderate/severe ARDS, and mild ARDS (0.45 vs. 0.36, P = 0.01).”
Reviewer 2

Major Compulsory Revisions

1. The fact that two ARDS definitions were used (references 31 and 1, respectively) should be discussed as a possible limitation of the study.

   We respectfully disagree that this is a limitation of the study. The definition of ARDS did indeed change during the data collection but we handled this carefully. All patients were prospectively scored by the 1994 definition and re-assessed following the Berlin definition, which was used as the reference standard in the manuscript. We clarified the methods section with regard to this point and discussed this in the manuscript.

   Methods: page 6; line 15: “A team of trained clinical research fellows prospectively scored the presence of ARDS [31], which was later re-evaluated according to the new Berlin definition that included the separation in mild, moderate and severe ARDS [1]. Importantly, the assessors were always blind for the eNose signal. All observers were trained on several occasions before the start of the study. All assessors had attended meetings in which clinical case vignettes were discussed and had at least 6 months of work experience [32]."

   Discussion: page 14; line 9: “Although the use of two ARDS definitions may seem a possible limitation we feel that we handled this carefully as all analyses were performed with the Berlin definition, which is more clearly defined with regards to disease severity and radiological criteria.”

2. Were bilateral pneumonia and CPE the only alternative diagnoses in the population studied? Were all patients with other causes of bilateral infiltrates (e.g. alveolar hemorrhage or interstitial lung disease) excluded from the analysis?

   Thank you for this excellent question. CPE and pneumonia were the only competing diagnoses we separated in the analysis. All other patients, including those with interstitial lung disease were included in the control group if they did not fulfill the ARDS criteria. We clarified this in the manuscript.

   Methods: page 8; line 13: “ARDS patients were classified as cases and used to train and validate a diagnostic algorithm. Control patients did not fulfill the criteria for ARDS, but could have infiltrates on chest radiography or oxygenation problems, and had no or a low likelihood of having pneumonia or CPE (e.g. a patients with interstitial lung disease could be in the control group). The trained algorithm was used to predict the probability of group membership in the patients with competing diagnoses (pneumonia and CPE).”

3. Did the control group consist of intubated patients with normal chest X-rays or was a CT scan used for the exclusion of lung infiltrates?

   We apologize for the confusion and acknowledge that this may have been unclear. The control group did not fulfill all criteria for
ARDS but could have infiltrates on the CXR or CT-scan. CT-scans were not performed routinely. We clarified the groups that were studies in our reaction to your previous question.

4. Did the authors take into account in the analysis the differences in minute ventilation (and perhaps not volume as it is expressed in l/min) in their exhaled air analysis?

We tried to evaluate possible confounders of the exhaled air analysis in the sensitivity analysis. Table 3 shows that minute volume ventilation does not influence the log odds-ratio of the eNose signal for ARDS.

Diagnosis: Page 15; line 1: “Second, we cannot exclude that patient–related factors such as ventilation strategies, therapy, comorbidities and exposure to metabolic active compounds are (partly) responsible for the altered exhaled breath signal. However, sensitivity analyses showed that ventilator settings such as minute volume ventilation and comorbidity are probably not responsible for the found signal.”

5. Some of the pneumonia patients present a PaO2/FiO2 ratio <300 (as revealed by the corresponding IQR 241-447). How was ARDS excluded in those patients?

Patients can have a low PaO2/FiO2 but still not fulfill the ARDS definition.

6. The authors need to admit that the discrimination between ARDS and the two competing diagnoses (CPE and pneumonia) presented marginal or no statistical significance, with the exception of moderate/severe ARDS. Even in that case the AUCs of 0.76 represent a moderate diagnostic performance. This needs to be discussed extensively, since this represents the actual challenge in clinical practice. Interestingly, those cases were characterized by a high specificity in contrast to the ARDS vs. control comparisons that were characterized by a high sensitivity with low specificity. The authors also need to comment on this.

Thank you for your careful consideration of this problem. We agree with you that the discrimination between ARDS and the competing diagnoses is small and have added a paragraph to the discussion.

Diagnosis: page 13; line 15: “Patients with ARDS were discriminated from patients pneumonia and CPE with modest accuracy. However, differentiation between these disease states is regarded as one of the major clinical challenges in this patient population and in this scenario the eNose does not seem to provide answers. Diagnostic accuracy did increase when only patients with moderate/severe ARDS were regarded as cases, but was still moderate. Interestingly, the discrimination between moderate/severe ARDS and controls was profoundly sensitive whilst comparison to pneumonia was mostly specific. Thus ARDS can be excluded with confidence when compared to control subjects while it can’t be when compared to pneumonia.
patients. Possibly, some patients in the pneumonia group actually had ARDS but chest x-ray was too insensitive to detect the bilateral infiltrates. Alternatively, some patients with ARDS also had pneumonia and the differences in exhaled VOCs was just too small to separate these phenotypes adequately.”

Minor Essential Revisions
1. Please define CPE in the Abstract
   Defined.
2. The Ethics Committee approval should follow the design of the study
   Corrected.