Peer Review File

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Reviewer A:

I read with interest the proposed article: " Regional peak flow as a novel approach to assess regional pulmonary mechanics by electrical impedance tomography: an observational validation study". The authors hypothesized that EIT-based PEEP titration is clinically beneficial during spontaneous ventilation. However, I suggest some modifications to improve the article:

Comment 1: Methods:- Line 195 "determined by a 3-sample first derivative, as described in ???". I didn´t understand this term. I suggest modifying it to the English form.

Reply: In the previous version, we accidentally left a cross-reference which somehow changed to the strange format you referred to. This cross-reference is now removed. Additionally, the technical/mathematical part of the paragraph "Automatic EIT algorithm for regional lung mechanics" is now moved to the supplemental material as advised by the other reviewer.

Comment 2: Results: Lines 242-243: "77.2% of the included 243 patients was male with a mean age of 63.9 years (± 10.5) and a BMI of 27.8 (± 4.3)." This paragraph could be improved writing.

Reply: We have rewritten this paragraph as advised. (lines 218-221) "… The average age and BMI were 63.9 years (± 10.5) and 27.8 kg/m2 (± 4.3), respectively. In total, 77.2% of the inclusions were male. In addition, 5.1% of the inclusions suffered from chronic lung disease prior to ICU admission. …"

Comment 3: Table 1 - I suggest placing Table 1 in the supplementary material or describing it in the text.

Reply: We have moved Table 1 to the supplemental material (Table S1), as advised.

Comment 4: I had difficulty understanding and visualizing the dynamic tool. The figures 2, 3 and 4 could be improved image/regional peak flow informations during PEEP titration. The best PEEP could be demonstrated to all or some patients to show the validity of the tool and attract the bedside professional.

Reply: We updated the visualization of the dynamic tool by summarizing all analysis steps in one flowchart/figure (figure 2). It illustrates the important steps of our algorithm and should give a better insight to and attract the reader/bedside professional. Plain and non-technical explanation of our methods can still be found at lines 171-183. "… In the RPF algorithm, cumulative overdistension and cumulative collapse rates are quantified, similar to Costa's algorithm (6). However, instead of calculating these rates based on regional compliances, cumulative overdistension and cumulative collapse rates are calculated based on regional peak flow (i.e., ODRPF and CLRPF). Under the assumption that regional peak airflow explains regional pulmonary compliance well, ODRPF and CLRPF may be used in SMV in the future. Analyses prior to calculating ODRPF and CLRPF, include: the determination of the aerated lung area, segmentation of each breath within all separate aerated pixels, calculation of regional peak flow within all separate aerated pixels per PEEP level, subsequent regional overdistension and collapse calculation and a factor four cubic interpolation of the regional overdistension and collapse data maps. The above-mentioned steps are illustrated in Figure 2 and full technical details of the algorithm are described in the supplemental material. Last, the cumulative overdistension and collapse rate are calculated by a weighted average approach per PEEP level identically to Costa's algorithm, which is also described in the supplemental material (6). ….."

Comment 5: In the discussion, I suggest to authors to explore more about spontaneous ventilation and use of the tool in the weaning from mechanical ventilations. The authors could explore monitoring the transition from controlled to spontaneous ventilation.

Reply: An extra paragraph called "clinical implications" is added to the discussion, in which we explore more about current EIT-driven PEEP titration application in controlled mechanical ventilation and explore the potential benefits of EIT-driven PEEP titration in later stage weaning (i.e., spontaneous mechanical ventilation). See lines 334-343. "… At present, a standardized approach for personalized PEEP in SMV is lacking. Current PEEP strategies are partially subjective and based on global lung parameters, such as the airway occlusion pressure (which is considered a surrogate for work of breathing), tidal volumes, and oxygenation status (32–35). These approaches may ultimately lead to suboptimal ventilatory strategies and potentially unnecessary lung injury. PEEP titration by EIT in ARDS in controlled mechanical ventilation has shown promising results regarding ventilator weaning success (14,15). The advantage of EIT in controlled mechanical ventilation and the results of the present study suggest that EIT-driven PEEP titration in SMV may be beneficial. However, this remains to be studied in the future. ….”

Reviewer B

The study by de Jongh et al validated the use of EIT to assess regional pulmonary mechanics and specifically regional peak flow. The authors should be commended for the hard work they did completing The authors should truly be commended for providing this interesting study. On the whole, while this is a very interesting paper in many ways, the figures and tables need a lot of work and do not capture the average reader’s understanding/attention. They should require major revisions prior to acceptance for publication. More details below, but this reviewer has a several major and minor revisions advised.

Major:

Comment 1: Could the authors please make an effort to reduce the number of abbreviations in this article? Especially the nonstandard ones like CL for “collapse” or OD for “overdistention.” The authors reference Frerichs et al’s “Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the TRanslational EIT developmeNt stuDy group.” And we recommend revisiting and following the recommendations of this group when presenting data. Terms such as delta-z are also confusing as they are often used for global tidal impedance difference and usually provided in AUs.

Reply: We substituted OD and CL abbreviations for “cumulative overdistension” and “cumulative collapse”. Whenever we talk about “tidal impedance differences” we now use “ΔZ” in general. In figure 2, we use “regional ΔZ” for referring to “regional tidal impedance differences” and “global ΔZ” for referring to “global tidal impedance differences”. In Frerichs et al. pixel (i.e., regional) tidal impedance differences were written as “ΔZj” in mathematical format where “j” represents the pixel number and therefore we use this format in supplemental material where we describe the technical/mathematical algorithm details. In Frerichs et al. we could not find specific terms for a specific calculated variable for one specific PEEP level. In the supplemental material of the present manuscript we use the term “n” for this specific matter. For example: ODj,n is equal to the regional overdistension rate for pixel “j” at the nth PEEP level in the decremental PEEP trial.

Comment 2: Line 82 – The terms “ODRPF-ODP500” and “CLRPF-CLP500” to describe the primary outcomes are confusing. Please define what they are and put those equations in parentheses underneath or next to them when used. They should not be used as definitions in the abstract, figures, etc. but be used as descriptions to remind readers what we are measuring. In addition, the numbers provided to not have definitions unless this reviewer missed them. Significant values should have p-values defined in the abstract and results.

Reply: We changed the above-mentioned terms to “… an association between ODRPF and ODP500 …” and likewise for CLRPF and CLP500 (see line 78-82). P-values are added to the mixed-model and intraclass correlation outcomes (see lines 79-83). “… Seventy-eight patients were included. Linear mixed models revealed an association between ODRPF and ODP500 of 1.03 (0.98-1.08, $p<0.05$) and between CLRPF and CLP500 of 0.91 (0.80-1.02, $p<0.05$). ICC values ranged from 0.68 – 0.84 ($p<0.05$) for ODRPF and ODP500 and from 0.69 – 0.84 ($p<0.05$) for CLRPF and CLP500 (PEEP 10 to PEEP 24). The mean bias between ODRPF and ODP500 in these PEEP levels ranged from 0.79% to 4.01% and from -1.60% to 0.02% between CLRPF and CLP500. …”

Comment 3: Line 148 – please provide rationale for not including multiple measurements for validation. Surely that would provide more robust and applicable data for the readers and future users of EIT to follow.

Reply: We agree that a larger data-set (by allowing multiple measurements per subject) increases robustness of the analyses. We chose to do single measurements for the present study, because it allowed easier execution of the intraclass correlation coefficient analyses, as we performed separate ICC analyses per PEEP level (line 155-158). In our case, it would require a more extensive/challenging ICC calculation if we had allowed multiple measurements. “… Although the MaastrICCht cohort included serial EIT measurements per patient, only the first EIT measurement of an included patient is used for validation analyses in the present investigation for simple and easy to interpret agreement analyses. …”

Comment 4: Figure 1 –Please define "Significant Cdyn Loss". Recommend strongly to not have the term "Eyeballing", it is too colloquial, should not be in figure 1. Did you use a certain percentage, like 10 or 20% drop? Or did you look at a specific drop in Vt? This should be defined in the methods. Since the authors aim to provide a standardized protocol that others can follow, they should show us what they did.

Reply: We updated the protocol figure (figure 1). Now, we visualized the global tidal impedance difference during an incremental/decremental PEEP trial which included the definitions of the end of the incremental PEEP trial (i.e., upper limit) and the end of the decremental PEEP trial (i.e., lower limit). In the majority of inclusions, we were able to reach PEEP 24. However, some patients who were admitted for a longer period of time, could not reach PEEP 24 because of worsened pulmonary compliance. In these patients we had special attention for a specific EIT tool which visualizes the regional compliance loss/gain due to increased PEEP and from the moment we saw a loss of regional compliance in the complete ventilated area we stopped the incremental trial. Unfortunately, this tool within the Pulmovista does not facilitate a specific summarizing value/number for regional compliance loss, rather than a "compliance loss" image. Nevertheless, if the patient's peripheral oxygen saturation dropped below 88%, we stopped the incremental PEEP trial as well. Therefore, stopping the incremental PEEP trial remained subjective to some extent in some patients. We stopped the decremental PEEP trial when either the patient's peripheral oxygen saturation dropped below 88% or when the patient's respiratory system dynamic compliance decreased. We chose this end-point because during a decremental PEEP trial the respiratory system dynamic compliance improves from higher PEEP levels to lower PEEP levels to the point where alveolar collapse occurs due to too low PEEP. We considered further PEEP reduction clinically unnecessary. The protocol is explained in lines 142-155: "… The protocol used during an EIT measurement is described earlier in the supplemental material of Tas et al. and is summarized in Figure 1 (17). It comprises a stepwise incremental PEEP trial from baseline PEEP and a subsequent stepwise decremental PEEP trial from the upper limit in 2 cmH2O steps taking approximately 30 to 60 seconds, preferably starting at a PEEP of 24 cmH2O. Other mechanical ventilation settings such as the driving pressure, inspiratory and expiratory time, inspiratory rise time, respiratory rate and the fraction of inspired oxygen remained constant during the EIT measurement. Due to each inclusion's individual clinical status, the number of steps within the PEEP trial may have varied. The upper limit of the incremental PEEP trial was reached at the PEEP level where either solely regional compliance loss (i.e., alveolar overdistension) and no further recruitment was measured, as assessed by EIT or when the peripheral oxygen saturation declined below 88%. The lower limit for the decremental trial was reached at the PEEP level where significant regional compliance loss (i.e., alveolar collapse) is measured, as assessed by EIT or when the respiratory system dynamic compliance declines or when the peripheral oxygen saturation declined below 88%. …"

Comment 5: Figures 1 should really have more information in this reviewer's opinion. This reviewer suggests changing the format to vertical boxes and then adding pictures or monitoring parameters if possible, such as combining it some images such as those listed in figure 2. Figure 2 as written is difficult to follow. It is very difficult to tell where the aerated regions are changing, etc. If it is possible to add color, that would be very helpful. Otherwise adding approximate percentages would make it possible to follow. Perhaps rearrange figure 1 into vertical columns, use an arrow to combine the subsequent steps in figure 2 in the 2nd vertical column, then another arrow to the third column could be analysis details very descriptively written currently in the Methods and in Figures 3/4.

Reply: As mentioned in major feedback point 4, we updated figure 1 by implementing an illustration of the PEEP trial which visualizes the incremental and decremental PEEP trial instead of a flowchart with plain text. Also, the end points of the incremental and decremental PEEP trial are explained more extensively, as mentioned earlier in feedback point 4. We did not choose to combine figure 1 with figure 2, 3 and 4 since we would like to keep the EIT measurement protocol separate from the newly developed algorithm. The algorithm we propose in the present manuscript does not require the use of the one specific PEEP trial end points we defined in the present study. The future users of this algorithm can choose to set absolute or relative end-points based on the clinician's wishes, as long as all mechanical ventilator settings except for PEEP remain constant across the PEEP trial. Instead of figure 2, 3 and 4 and the corresponding mathematical/technical description in the paragraph "Automatic EIT algorithm for regional lung mechanics" (from line 160 in the previous version), we constructed a flowchart figure with 9 subplots which in which we aim to visualize the steps taken in the algorithm and we hope it leads to a better understanding of the algorithm for the average reader. In lines 170-183 the important algorithm steps are pointed out without difficult mathematical/technical explanation. The full technical/mathematical details are placed in the supplemental material.

Comment 6: The methods section entitled "Automatic EIT algorithm for regional lung mechanics" is extremely technical and difficult to follow, especially due to the prevalence of abbreviations. The majority of it would be better suited for the supplement for non-technical readers, and would be better illustrated in more clearly and creatively drawn figures.

Reply: We agree on this feedback point. As mentioned in feedback point 5, we moved the mathematical/technical details to the supplemental material. In lines 170 to 183 the important algorithm steps are pointed out without difficult mathematical/technical explanation. "… In the RPF algorithm, cumulative overdistension and cumulative collapse rates are quantified, similar to Costa's algorithm (6). However, instead of calculating these rates based on regional compliances, cumulative overdistension and cumulative collapse rates are calculated based on regional peak flow (i.e., ODRPF and CLRPF). Under the assumption that regional peak airflow explains regional pulmonary compliance well, ODRPF and CLRPF may be used in SMV in the future. Analyses prior to calculating ODRPF and CLRPF, include: the determination of the aerated lung area, segmentation of each breath within all separate aerated pixels, calculation of regional peak flow within all separate aerated pixels per PEEP level, subsequent regional overdistension and collapse calculation and a factor four cubic interpolation of the regional overdistension and collapse data maps. The above-mentioned steps are illustrated in Figure 2 and full technical details of the algorithm are described in the supplemental material. Last, the cumulative overdistension and collapse rate are calculated by a weighted average approach per PEEP level identically to Costa's algorithm, which is also described in the supplemental material (6). …"

Comment 7: Line 239 & Results section. The paper requires a consort diagram.

Reply: We constructed a consort diagram (see figure 3 and line 214-218). "Of all mechanically ventilated patients (n = 98) admitted to the ICU during the given study period, 93 patients were mechanically ventilated primarily for COVID-19. Due to either the absence of ventilator data from the first EIT measurement or the absence of an EIT measurement or missing EIT data due to not recording, no RPF analysis was performed in 15 out of 93 patients, resulting in a total of 78 included patients for analysis (Figure 3)."

Comment 8: Figure 5 as written is difficult to understand. The authors should provide a descriptive title, not "Peep 14" and write out what the axes are measuring, not just an equation. That way readers will understand what the authors are trying to convey.

Reply: We deleted figure 5 from our manuscript, as we already present this figure in the supplemental material. Separately, this figure does not add new information to our results.

Comment 9: Table 3 – please provide p-values rather than just indicating with a * that they are significant.

Reply: We added a "p-value" column in the mixed model and agreement (ICC) tables (table 2 and table 3).

Comment 10: Lines 281, 285 and others **-** The discussion section in several areas can sound critical in areas, especially when using terms such as "misleading" or "lacking strong definitions". Recommend commenting on specific needs but making sure to be respectful of the hard work other authors also do.

Reply: We did not intend to criticize our fellow researchers in the EIT field. We changed our terminology in order to sound more moderate, but we made sure we still commented on specific needs. See lines 252-253, 256-257 and 263. "" … However, these studies rather focused on ventilation distributional parameters than on regional lung mechanics. Another study by Mauri et al. designed an algorithm describing regional overdistension for the dependent and non-dependent lung regions (25). They used the global tidal volume from the ventilator to calculate dorsal and ventral compliance under the assumption that the measured aerated area by EIT represents the complete lung, which may lead to an affected calculation of true regional compliances. Also, all the above-mentioned studies did not consider the collapse phenomenon, a fundamental concept in ARDS lungs and in SMV patients when end-expiratory transpulmonary pressures are negative (26). Becher et al. proposed an EIT-based algorithm to determine regional compliance in PSV (27). They used a low-flow ventilation approach during PSV to design a quasi-static pressure-volume (PV) loop and subsequently calculated the slope of the PV-loop (i.e., compliance). In some cases, this may be an unwise approach, as a patient may not tolerate such a low-flow procedure, especially during a PEEP trial. …"

Minor:

Comment 11: Line 114 – The way this is phrased makes it sound like an advertisement: "The most widely used EIT tool for titrating PEEP in CMV is designed by Costa et al. and is able to quantify regional and cumulative overdistension…" This reviewer suggests rephrasing "EIT technology has the ability quantify…"

Reply: We implemented the suggestion of the reviewer (line 108-110) " … Electrical impedance tomography (EIT) is a non-invasive and radiation free technique which has the ability to quantify regional pulmonary mechanics in controlled mechanical ventilation (CMV) modes. EIT technology has been studied extensively for titrating PEEP in CMV (6–13) …"

Comment 12: Line 119 – please rephrase, for example: "The drawback of available algorithms for EIT-based PEEP titration include that they are limited to CMV…" Similar suggestions for lines 119 and 123. State what you're doing and use references, but major author references should be done in the discussion.

Reply: We implemented the suggestion of the reviewer (line 115, 119-121) "… The drawback of currently available algorithms is that their use is limited to CMV because it requires an equally distributed airway pressure phase which occurs during the plateau pressure phase after end-inspiration. In SMV, stable plateau phases are not always present, which would result in inaccurate quantification of regional pulmonary mechanics calculations (16). Therefore, a new EIT algorithm could be helpful for titrating PEEP in SMV if it can assess regional pulmonary mechanics (i.e., cumulative overdistension and cumulative collapse rates) without extra bedside actions. …"

Comment 13: Line 139 – define CORADS score

Reply: We defined the CORADS score and added the corresponding reference (line 136-142). " … From March 2020 to May 2020, adults (18+ years) with a CORADS score (a categorical assessment for pulmonary involvement of COVID-19 at unenhanced chest computed tomography) of 4 and 5 or PCR proven COVID-19 infection, who were mechanically ventilated using pressure-controlled ventilation and who were subjected to an EIT measurement at the intensive care unit of the Maastricht University Medical Center+ were included in this study (18). …"

Comment 14: Line 140 – the authors define CMV in more globally applicable terms "pressure-controlled ventilation." In audiences in areas like North America, CMV is not usually used, they will use PRVC, etc. This should be included in the abbreviation area and defined earlier in the paper to help capture a global audience.

Reply: We unintendingly defined pressure-controlled ventilation as CMV. In the present study we only included pressure-controlled ventilation patients, since this mechanical ventilation mode is standard practice in our ICU in (COVID-19) ARDS patients.

Comment 15: Line 146 – this reviewer believes that the protocol used should be included in this publication and not referenced in a separate paper.

Reply: We included the full protocol in our methods section (lines 143-159), as well as updated figure 1 (the visualization of the EIT measurement protocol, as mentioned in the major revisions point 5). " … The protocol used during an EIT measurement is described earlier in the supplemental material of Tas et al. and is summarized in Figure 1 (17). It comprises a stepwise incremental PEEP trial from baseline PEEP and a subsequent stepwise decremental PEEP trial from the upper limit in 2 cmH2O steps taking approximately 30 to 60 seconds, preferably starting at a PEEP of 24 cmH2O. Other mechanical ventilation settings such as the driving pressure, inspiratory and expiratory time, inspiratory rise time, respiratory rate and the fraction of inspired oxygen remained constant during the EIT measurement. Due to each inclusion's individual clinical status, the number of steps within the PEEP trial may have varied. The upper limit of the incremental PEEP trial was reached at the PEEP level where either solely regional compliance loss (i.e., alveolar overdistension) and no further recruitment was measured, as assessed by EIT or when the peripheral oxygen saturation declined below 88%. The lower limit for the decremental trial was reached at the PEEP level where significant regional compliance loss (i.e., alveolar collapse) is measured, as assessed by EIT or when the respiratory system dynamic compliance declines or when the peripheral oxygen saturation declined below 88%. ..."

Comment 16: Line 195 – the authors switch languages and alphabets here for a second which is very confusing. Please utilize reference numbers where appropriate.

Reply: In the previous version, we accidentally left a cross-reference for a mathematical equation which somehow changed to the strange format you refer to. This cross-reference is now removed.

Comment 17: Line 477 - Figure 1 – This reviewer recommends changing Cdyn to the more CRSdyn.

Reply: We implemented this feedback, as advised. (Figure 1)

Comment 18: Table 2 – Overall this table requires a caption with the abbreviations to be defined. The second column should have a title to it. The numbers in parentheses should be defined. Age should be "years"; Gender should be listed as "male" not "men"; is "inspiratory pressure" the same as "pressure control" or "delta P"? May be useful to define multiple ways for easier understanding

Reply: We added the abbreviations in the caption and changed the units of age and gender, as advised. The definition of inspiratory pressure is the sum of PEEP and the driving pressure. In pressure-controlled ventilation PEEP and the inspiratory pressure are set by the clinician to create a driving pressure, which is now explained in the caption.

Additional change to the manuscript: In addition to the above-mentioned feedback, we added an extra data analysis step to our algorithm. New insight made us believe that the Pulmovista 500 EIT device incorporates an interpolation technique before calculating cumulative overdistension and collapse rates. This means that in the previous version of our manuscript, we compared our cumulative overdistension and collapse rates (based on 32x32 pixels) to cumulative overdistension and collapse rates from the Draeger's Pulmovista 500 based on presumably a larger, yet unknown spatial resolution. Therefore, we performed an interpolation technique (factor four cubic approach increasing the spatial resolution by a factor 4, which increased the spatial resolution from a 32x32 to a 497x497 pixels grid) on the regional overdistension/collapse maps. This barely led to any changes in the mixed-model outcomes, but resulted in increased ICC scores for the majority of PEEP levels in both overdistension and collapse rates, indicating an improvement of agreement between our regional peak flow algorithm and the compliance-based algorithm proposed by Costa et al. and used in the Pulmovista 500.