Author’s response to reviews

Title: High-frequency power of heart rate variability can predict the outcome of thoracic surgical patients with acute respiratory distress syndrome on admission to the intensive care unit: a prospective, single-centric, case-controlled study

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Author’s response to reviews:

Responses to the comments and suggestions of the reviewers

We appreciate the reviewers for their detailed and thorough review and for their helpful comments and suggestions. In the followings, we try to respond to the comments and suggestions raised by the reviewers and revised our manuscript accordingly. We believe that our manuscript has improved greatly with the inputs of the comments and suggestions of the reviewers. Many thanks.

Reviewer reports:

Fabian Dusse, M.D. (Reviewer 1): I-Chen and colleagues investigated the Impact of heart rate variability as an outcome predictor in thoracic surgery patients with ARDS. Several HRV variables are assumed to be associated with worse outcome.
Comments:

1. The methods regarding the HRV analysis is hardly understandable unless one is not familiar with Fourier analysis. Moreover the association between nVLFP and physiologic values (RAA Modulation, thermal Regulation, vagal withdrawal) is not comprehensible. I would recommend describing more extensively how the HRV analysis works and which values were calculated. The association to physiological values should be pointed out more clearly.

Response: Thank you for your comments and suggestions. The methods regarding the use of Fourier analysis in HRV analysis, the clinical significance of various frequency bands and their association to physiological values have been standardized and documented in the classical article of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology published in Circulation (1996; 93: 1043-1065), and Eur Heart J (1996; 17: 354-81), at the same time [1]. The normalized very low-frequency power (nVLFP) was not defined in that article; it was defined by our group in analogy to the normalized low-frequency power (nLFP) and normalized high-frequency power nHFP [2-6]. It may not be possible to describe extensively how the HRV analysis works and which values were calculated in this manuscript. The interested readers are advised to read the orthodox paper published in 1996. Nevertheless, we have added a paragraph to briefly describe the Fourier transform and power spectral density analysis in the Method section in the revised manuscript as follows. Hope that this small paragraph can be helpful to the readers unfamiliar with Fourier analysis and signal processing:

“Power spectral density (PSD) analysis provides the basic information about the power (variance) distributes of experimental data as a function of frequency by using parametric autoregressive modeling or non-parametric Fourier transform which are two most frequently used methods to calculate the PSD. The Fourier transform decompose the signal into its constituent frequencies; thus, the Fourier transform is the frequency domain representation of the original signal. The Fourier transform of a signal is a complex-valued function of frequency, whose absolute value represents the amount of that particular frequency present in the signal. The power of a particular frequency band is calculated by integrating the PSD within the frequency ranges of that frequency band.”


2. Many physiologic, clinical, and HRV data were taken and calculated with each other. The conclusions drawn out of the clinical data regarding ARDS outcome are not surprising and have been well described already. The large number of values does rather blurs the view on the relevant data, in particular due to the small sample size.
Response: Thank you for your comments. Since the incidence of ARDS is not very high in post-operative patients with lung or esophageal cancer, it was not easy to collect a large number of cases for statistical analysis within a study period of 2 years.

3. The discussion is, in wide parts, more a listing of studies related to outcome predictors and HRV. How to interpret the results of this study and for what they are worth in respect of the patient is not clearly pointed out. Neither similarities nor discrepancies between the different studies cited are really discussed. I would recommend focusing more on relevant data than to put every value into account.

Response: Thank you for your suggestion. The second paragraph in the Discussion was intended to point out that the HFP and TP are more sensitive than APACHE II or other conventional scores or indices used for the evaluation of severity of ARDS. The reference 21 in our previous manuscript is removed in the revised manuscript because it is not related to this topic. The lower half of the second paragraph in the Discussion is revised to read as follows:

“It was surprising to find that the conventional scores or indices for the evaluation of the severity of ARDS, such as APACHE II, ALIS, PaO2/FIO2 and AaDO2, were not significantly different between the survivors and non-survivors of ARDS. Instead, the HFP and TP were found to be capable of predicting the outcome of ARDS patients on admission to the SICU. This finding suggested that that the HFP and TP are more sensitive than the conventional scores or indices in predicting the outcome of patients with ARDS, and might be used in the monitoring of the progression of ARDS in SICU in the future.”

The third paragraph was intended to point out that increased vagal modulation seems to be the common findings in some severe illnesses, including COPD patients with poor oxygenation state, patients with sepsis, and patients with out-of-hospital cardiac arrest.

All in all, the subject of HFR as a predictor for ARDS outcome is quite interesting and the study is well performed. But, from a clinical Point of view, the methods are hard to comprehend, the amount of presented values is confusing, thus the message of the study remains unclear.
Response: Thanks for your comments. We agree with the reviewer that the subject of HRV as a predictor for ARDS outcome is quite interesting. The methods of HRV analysis have been well documented in the literature. Most authors follow the guidelines laid down in the article published in 1996 by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [1]. We are very sorry that it may not be wise to repeat the descriptions of the methods of HRV analysis in this manuscript. Nevertheless, we have revised our manuscript in accordance with the comments and suggestions of the reviewers. Hope that our revised manuscript will be easier to read, and the message presented can be more comprehensible.

Tobias Kammerer (Reviewer 2): This prospective trial focused on a new non-invasive method to estimate survival in post-thoracic-surgery ARDS patients. Even if the statistical methods seem to be correct, there are still some serious shortcomings, especially regarding the trial design and patient recruitment.

The main critics are, in my opinion, the missing information about the patients included in the trial, insufficient information about patient recruitment and randomization, missing intraoperative data, a lack of description of the trial design, an insufficient description of the ICU data, and a short discussion.

In detail I have the following general questions and comments:

1. P1 title: Please add information about the trial design into the title (e.g. prospective, single-centric, randomized).

Response: Thank you for your comments and suggestions. The title has been changed to read: “High-frequency power of heart rate variability can predict the outcome of thoracic surgical patients with acute respiratory distress syndrome on admission to the intensive care unit: a prospective, single-centric, case-controlled study”. Randomization is not necessary because this was a case-controlled study.
2. P3 L20: Insert the number and percentage of patients in both groups.

Response: Thank you. The number of patients in the ARDS group (n=21) and control group (n = 11) was inserted in both groups, but the percentage was not inserted because the patients included in this study were consecutive patients who met the inclusion and exclusion criteria of ARDS group and control group, and none of them were dropped off during the period of study.

3. P3 L33: here and everywhere else: please avoid terms like "greater". Instead use phrases like "higher" or "increased".

Response: Thank you. All “greater” are changed to “higher” in the revised manuscript.

4. P3 L49 - 59: The Abstract Conclusion is nothing more than a restatement of the results. What is the interpretation and conclusion?

Response: Thank you. The first sentence “The non-survived ARDS patients had higher TP, LFP, HFP, and HFP/VT than the survived ARDS patients.” is changed to read: “The vagal activity of ARDS patients was enhanced as compared to that of non-ARDS patients, and the non-survived ARDS patients had higher vagal activity than those of survived ARDS patients.” in the revised manuscript so that the clinical meaning of the conclusion is more transparent.

5. P5 L42: Please delete "plays an important role in". Consider "is important for" or a similar phrase.

Response: "plays an important role in" has been changed to "is important for” in the revised manuscript.
6. P5 L58: please add a reference regarding the method of HRV measurement.

Response: A reference regarding the method of HRV measurement is added at P5 L58. Reference 18 in our previous manuscript is placed here at P5 L58 and re-numbered as reference 12.

7. P6 L4: Please add some references here.

Response: The original reference 18 is moved here and renumbered reference 12.

8. P6 L26: The last sentence sounds like a part of the discussion. Please delete.

Response: The last sentence is deleted.

9. P6 L58ff: Important information about the trial design is missing. For example, no information is given about the intraoperative procedure, neither regarding the surgery, nor the anesthesia management. How many patients received one-lung ventilation? How was the airway management (double-lumen tube, airway blocker etc.)? Was volatile or intravenous anesthesia used? What about neuraxial regional anesthesia? How was the respirator setting in the OR? Was a lung protective ventilation setting used there? Please provide more information about the management before transfer to the ICU.

Response: Since our study was not focusing on the ARDS caused by surgery or anesthesia, those information regarding the intraoperative procedure, type of surgery, anesthesia drugs used, type of ventilation, airway management, fluid management, respirator setting and arterial blood gases in the OR, management before transfer to the ICU, etc., were not collected. The patients included
in the ARDS group in this study were those who have received thoracic surgery, developed ARDS later on, and were transferred to the SICU.

10. P7 L7-11: Was the trial registered in an online trial register? If yes, please add the trial registration number. Furthermore, to the best of my knowledge, a written informed consent from the family members is not the correct procedure for a prospective trial. Even if only data are collected, the consent of the patients should be done in advance. Especially, as it was a matter of elective interventions. This point seems to me particularly critical in view of a possible publication.

Response: Since this was a clinical observational study, rather than a clinical trial of new drug, new method, or new device, only permissions by the ethical committees of two medical centers involved were applied before the study. No registration in an online trial register was done.

In the control group, the informed consent was signed by both patient and his/her family. In the ARDS group, many informed consent was signed by the family under the agreement of the dyspneic patient who nodded his/her head to express his/her agreement. In only a few cases when the patient was too sick to express his/her thought, the informed consent was signed by the family.

11. P7 L23ff: Please give much more data about the included patients (kind of surgery, duration of surgery, duration of ventilation, ASA classification, comorbidities, co-medication, intraoperative PaO2/FiO2, intraoperative fluid balances, transfusion rate etc.). You can include these data into table 1 (demographics).

Response: Since this study was not designed to explore the relation between ARDS and surgery-related factors, and since the patients in the ARDS group was included only when they developed ARDS after the surgery, those information related to surgery including the kind of surgery, duration of surgery, duration of ventilation, ASA classification, comorbidities, co-medication, intraoperative PaO2/FiO2, intraoperative fluid balances, transfusion rate, etc., were
not collected during the surgery. Nevertheless, the medication in the SICU that might influence the HRV are added to Table 1 and 2 in the revised manuscript.

12. P7 L26: when exactly was the diagnosis of ARDS done after arrival on the ICU? Which monitoring was used for diagnosis (chest x-ray, CT scan)? How many patients had infiltrates and where were they localized? And if the diagnosis "ARDS" was done only after admission to the intensive care unit, how is it possible that the ventilation was already adapted (for example: PEEP=5mbar in the non-ARDS group)?

Response: The diagnosis of ARDS was made based on the abnormal infiltration in the chest x-ray, rapid deterioration of labored breathing and hypoxemia within 5 days, in accordance with the ARDS guideline. CT scan was not used in the diagnosis of ARDS. In the non-ARDS group, a PEEP of 5 cmH2O was often used by the attending physician to help expand the lungs, especially when lobectomy has been performed on those patients with lung cancer.

13. P7 L30: Please add here all exclusion and inclusion criteria.

Response: The “Study Participants” subsection is rewritten as follows to include all all exclusion and inclusion criteria:

“This study was conducted in the SICU of a tertiary medical center. All patients were older than 18 years old. Two groups of patients were included in this study. Patients who had been received thoracic surgery because of lung or esophageal cancer, developed ARDS, and were transferred to the SICU for intensive care, were included as the ARDS group. Patients who received thoracic surgery because of lung or esophageal cancer and were transferred to the SICU for post-operative care, were included as the control group. The ARDS was diagnosed according to the Berlin Definition [2]. A draft definition consists of 3 mutually exclusive categories of ARDS based on the degree of hypoxemia: mild (200 mm Hg < PaO2/FIO2 ≤ 300 mm Hg), moderate (100 mm Hg < PaO2/FIO2 ≤ 200 mm Hg), and severe (PaO2/FIO2 ≤ 100 mm Hg) with 4 ancillary variables for severe ARDS: radiographic severity, respiratory system compliance (≤ 40 mL/cm H2O), positive end-expiratory pressure (≥ 10 cm H2O), and corrected expired volume
per minute (≥ 10 L/min). Patients with severe coronary artery disease, persistent arrhythmia, cardiac pacing, diabetes mellitus, cerebral vascular accident (CVA), or major diseases of kidney or autoimmune system were excluded from the study. Patients with persistent arrhythmias or cardiac pacing were excluded from the study because of their heart rhythms were not appropriate for HRV analysis.”

14. P7 L49: when exactly upon admission were the different scores determined?

Response: Thank you. The ALIS, AaDO2, APACHE II, demographic data, vital signs, medication, ventilator parameters including respiratory rate (RR), PInsp, TInsp, VT, PEEP, minute ventilation (MV), FIO2, Cdyn, and arterial blood gases data were recorded within 4 hours of their admission to the SICU.

15. P7 L52: Why were the patients without ARDS not extubated immediately after surgery? What were the decision criteria for postoperative mandatory ventilation?

Response: The non-ARDS patients in the control group were placed under mandatory ventilation support in the SICU after surgery for 2 to 3 hours until they awaked from anesthesia. Before that, the patients were not extubated because they had not awaked from anesthesia yet. The HRV analysis and the collection of other relevant clinical data were done during this short period from their admission to SICU to extubation.

16. P8 L26 ff: I’m not sure whether the reader is familiar with the method of HRV analysis. Please provide more details about this procedure (which device was used etc.).

Response: The method of HRV analysis has been standardized in the paper published in Circulation in 1996 by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Heart Rate Variability: Standards of
Measurement, Physiological Interpretation, and Clinical Use. Circulation 1996; 93: 1043-1065). The MP35 multichannel recorder (BIOPAC Systems, Goleta, CA, USA) was used to record the ECG signals for 12 minutes.

17. P10 L17: Please add additional data about the patients: how many patients were screened during which time period, how many declined consent, how many were randomized for the trial etc.). Please add also the percentage of patients in each group. Furthermore, the proportion of ARDS patients is surprisingly high (>65%). Therefore, more data about the overall population of screened patients would give important information.

Response: Twenty-one ARDS patients matching the inclusion criteria without the conditions of the exclusion criteria were included in this two years’ study. None of them declined consent. This was a case-controlled study, no randomization was needed because there were no needs to stratify the ARDS patients into two groups. The collections of ARDS and non-ARDS patients were not performed during the same period of time. The ARDS patients were collected first, and the non-ARDS patients were collected later. Therefore, the percentage of patients was 100% in each group, and it was not meaningful to calculate the proportion of ARDS patients in this study.

18. P10 L20: Here and everywhere else: please change µg/hr to µg·hr⁻¹.

Response: The “µg/hr” is changed to “µg·hr⁻¹”, “mg/hr” is changed to “mg·hr⁻¹”, and “µg/hr/min” is changed to “µg·hr⁻¹·min⁻¹”.

19. P10 L23: the phrase "produce a state of calm" is not precise enough. Please give data like RASS score or similar sedation scores. Additionally, it is uncommon, that no analgesia was given. Which kind of post-surgical pain management was performed and how long was it done. Was spontaneous breathing allowed during mechanical ventilation? What was the ventilator mode (PCV, BiPAP etc.)?
Response: Thank you. The data of RASS are added. The Fentanyl was given to the patients in the post-operative period for post-surgical pain killing. The Fentanyl was given to the non-ARDS patients for 24-48 hours, while it was given to the ARDS patients for more than 48 hours. The collection of ECG data for HRV analysis and other data was performed within 4 hours of their admission to the SICU. Spontaneous breathing was allowed during mechanical ventilation because pressure control ventilation (PCV) was used to minimize the risk of barotrauma.

20. P10 L26: it seems unlikely, that vasopressors were used only in the ARDS group. Please give information about vasopressor, catecholamine, co-medications and analgo-sedativa in table 1.

Response: Thank you. Vasopressors were used only in the ARDS patients if their blood pressures were unstable. Vasopressors were not used in the non-ARDS patients because their blood pressures were relatively stable. The use of Midazolam and Norepinephrine in both groups of patients are added in Tables 1 and 2 in the revised manuscript.

21. P10 L30: what is the definition of "adequate blood pressure"? Did you define hemodynamic target values in dependence of comorbidities?

Response: The MBP was maintained at > 60 mmHg.

22. P10 L30: when exactly and how often were ECG recordings taken within 4 hours?

Response: The ECG was recorded only once within 4 hours of admission to the SICU. Since ECMO and other treatment modalities were often needed in the ARDS patients, the ECG recording and HRV analysis should be performed before the institution of ECMO and other treatment modalities lest the results of HRV analysis should be influenced by those treatment efforts.
23. P10 L36: here and everywhere else in the results section: please add exact p values to show significances.

Response: The p values are added in the Results section.

24. P10 L46: the phrase "as expected" should only be written in the discussion section, but not in the results section. Please delete.

Response: The “as expected” is deleted.

25. P10 L49-55: This sentence is an interpretation of the results and should therefore be moved to the discussion. Furthermore, isn’t it possible, that other variables could have been predictive too? Have you also done a multivariable analysis for parameters like duration of ventilation, fluid balances, postoperative pulmonary complications, re-intubation etc.?

Response: The sentence “The ARDS patients seemed to have higher vagal modulation and smaller sympathetic modulation than the non-ARDS patients.” has been moved to the Discussion section with some modification. Since the data including the duration of ventilation, fluid balances, postoperative pulmonary complications, re-intubation, etc., were not collected beforehand, these variables were not included in the multivariable analysis in this study.

26. P10 L58 to P11 L7: Please provide a more detailed description of the results. Also, please avoid terms like "greater". Add mean and p values whenever you show your results.

Response: All the “greater” are replaced by “higher”. The mean and p values are added for the presentation of the results.
27. P11 L1: Please give the information, that Murray’s ALI score was used and add a reference.

Response: Murray’s reference is added to the “Physiological Measurements” subsection where it first appears. The reference 12 is placed in the 2nd line of the 2nd paragraph in P 8.


Response: The “appeared to be” was replaced by “were”.

29. P11 L39: Please delete "marginally" and give the exact p value.

Response: The “marginally” is deleted, and the exact p values are given to the parameters TP (p = 0.047) and HFP (p = 0.02).

30. P12 L1: Please add p values here.

Response: The p values for TP (p = 0.673), LFP (p = 0.577), and HFP (p = 0.843) were added there in the revised manuscript.

31. P12 L10: The entire discussion is too short and requires a substantial revision. For example, less pathophysiologic description of increased vagal modulation and their possible influence on ARDS is given. This is especially important as most readers will not be familiar with this topic. A limitations section is completely missing.
Response: The Discussion has been revised extensively. Increased vagal modulation was found in post-operative lung or esophageal cancer patients with ARDS in this study. The pathophysiology of increased vagal modulation and their possible influence on cancer patients with ARDS is not clear yet. However, the study of Borovikova et al (Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature, 2000. 405(6785): p. 458-62) gave us some idea about the possible pathophysiological mechanism of increased vagal tone in patients with ARDS. Borovikova et al found that direct electrical stimulation of the peripheral vagus nerve in vivo during lethal endotoxaemia in rats could inhibit tumor necrosis factor (TNF) synthesis in liver, attenuated peak serum TNF amounts, and prevented the development of shock. Thus, a physiologic response to counterbalance the cytokines-induced systemic inflammation in ARDS might account for the increased vagal tone in ARDS patients. Further studies are warranted to investigate the underlying mechanism of increased vagal modulation in critically ill patients including ARDS.

Limitations of the study has been added.

32. P12 L17: Please avoid words like "we" or "our" and use a different term.

Response: The "we" and "our" are replaced by “this study” or “the present study” in the revised manuscript.

33. P13 L14: please give some possible pathophysiologic declaration to underline your assumption.

Response: The possible pathophysiological mechanism of increased vagal modulation in post-operative lung or esophageal cancer patients has been given in the revised manuscript.
34. P13 L17-36: Here, only the results of previous trials are listed. Please add also, as a short resume, the possible explanation and interpretation of the results, given by the different authors in the original publication and compare them with your results.

Response: A new sentence “These results suggested that HRV measures can be used in the monitoring and prognosis of critically ill patients and that increased cardiac vagal and decreased cardiac sympathetic activities might be indicative of poor prognosis.” is added after the list of the results of previous study in the revised manuscript. The possible explanation and interpretation of those results are given as a separate paragraph beneath that paragraph.

35. P13 L45-52: This conclusion seems premature. The descriptive character of the study does not allow such a statement. For this purpose, prospective intervention studies are required. Please formulate this sentence more cautiously. Additionally, why should this be interestingly only in cancer surgery? Here again, more data about the diagnoses and surgical procedure of the included patients would be meaningful.

Response: The conclusion has been revised to read: “The vagal modulation of the thoracic surgical patients with ARDS was enhanced as compared with that of non-ARDS patients, and the non-survived ARDS patients had higher vagal activity than the survived ARDS patients. The vagal modulation-related variables such as HFP and TP might be used as predictors to identify ARDS patients with high risk of mortality on admission to the SICU, especially the HFP. Increased vagal modulation might be a poor prognostic sign in critically ill patients including thoracic surgical patients, and anticholinergic and sympathomimetic agents might be tried to correct the autonomic dysfunction of ARDS patients.”

In this prospective study, we focused on patients after lung or esophageal cancer surgery. Similar studies can also be performed on ARDS patients due to various kinds of etiology in the future to verify our findings.

36. P14 L7-20: Again, your conclusion is nothing more than a restatement of the results. What is the interpretation and conclusion?
Response: The results of the present study were: (1) The HFP was significantly lower while the nHFP/VT was significantly higher in the ARDS group as compared with the non-ARDS group; (2) The non-survived ARDS patients had higher TP, LFP, HFP, and HFP/VT than those of the survived ARDS patients; (3) Firth logistic regression analysis identified HFP and TP as the independent predictors of mortality in ARDS patients on admission to the SICU; and (4) The HFP was found to be the best predictor of mortality in ARDS patients.

Our interpretations were: (1) The vagal modulation of the thoracic surgical patients with ARDS was enhanced as compared with that of non-ARDS patients; (2) The non-survived ARDS patients had higher vagal activity than the survived ARDS patients; (3) The vagal modulation-related variables such as HFP and TP might be used as predictors to identify ARDS patients with high risk of mortality on admission to the SICU, especially the HFP; (4) Increased vagal modulation might be a poor prognostic sign in critically ill patients including thoracic surgical patients, and anticholinergic and sympathomimetic agents might be tried to correct the autonomic dysfunction of ARDS patients.

The conclusions are related to, but not the same as, the results.

37. Figure 1: Please avoid interpretative statements in the figure legends. Delete the last sentence here.

Response: The last sentence in the figure legend of Figure 1 is deleted.

38. Table 1 and other tables: give data as no. (%).

Response: Twenty-one consecutive ARDS patients were included in the study group in this two years’ study. None of the ARDS patients were dropped off from the study because this was a simple observational case-controlled study.
39. Table 1: please add additional demographic data (see above). As a minimum the reader should know: underlying disease, comorbidities, ASA classification, co-medication, perioperative antibiotics, preoperative lung function (FEV1, blood gas analyzes etc.), duration of surgery and anesthesia, kind of surgery (open vs. thoracoscopy, wedge resection, pneumonectomy etc.), duration of one-lung ventilation, lung separation technique, intraoperative blood loss, urinary output and fluid balances, neuraxial or other regional anesthesia). Add also statistical analysis to compare these variables.

Response: Those surgery-related factors mentioned by the reviewer were not recorded and included in the analysis, because this study was intended to investigate whether and what HRV measures can be used to identify the ARDS patients with poor outcome, rather than to find out what surgery-related factors were associated with the occurrence and outcome of ARDS. Therefore, those surgery-related factors cannot be provided in the revised manuscript. If we have another chance to perform a similar study in the future, those surgery-related factors shall be included in the study.

40. Table 2: Please give more data about the ARDS patients. As a minimum you should provide: length of ventilator support, hospital stay, ventilator free days, fluid balances, vasopressors and catecholamines, re-thoracotomy rate, rate of adverse events (reintubation rate, resuscitation etc.), antibiotics, sedation, co-medication, SAPS and TISS score, RASS score, incidence of postoperative delirium and neurocognitive disorder. Add also statistical analysis to compare these variables.

Response: Those therapeutic factors mentioned by the reviewer were not recorded and included in the analysis during the study period because this study was intended to investigate whether and what HRV measures can be used to identify the ARDS patients with poor outcome, rather than to find out what therapeutic factors were associated with the occurrence and outcome of ARDS. Therefore, those therapeutic factors cannot be provided in the revised manuscript. If we have another chance to perform a similar study in the future, those therapeutic factors shall be included in the study.