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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Version: 2 Date: 06 Feb 2018

Author’s response to reviews:

Fabian Dusse, M.D. (Reviewer 1): The authors are right that the methods regarding the Fourier analysis in HRV analysis has been described in the cited articles (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology). But, anyway, for clinicians not familiar with the method, and I expect the majority of anesthesiologists and intensivists are not, a brief explanation would be helpful to follow this interesting topic. Therefore I appreciate the addition of the paragraph to describe the method.

Comments:

P3 L23f: The term "had lung or esophageal cancer surgery" is redundant in this sentence. I recommend restructuring the sentence, e.g. like as follows "Patients who had lung or esophageal cancer surgery were included either in the ARDS group if they developed ARDS after surgery or in the control group if they did not.

Response: Thank you very much for your suggestion. The sentence in question is now revised to read: “Patients who had lung or esophageal cancer surgery were included either in the ARDS
group (n=21) if they developed ARDS after surgery or in the control group (n=11) if they did not.”

P4 L23: I recommend to change the term "a poor prognostic sign" into, e.g., "an indicator for poor prognosis", to make it less capable for misunderstanding.

Response: Thank you. The term “a poor prognostic sign" is changed to “an indicator for poor prognosis” in the revised manuscript.

P4 L23: I recommend replacing the term "patients including thoracic surgical patients" into "patients following thoracic surgery"

Response: Thank you. The term “patients including thoracic surgical patients" is changed to “patients following thoracic surgery” in the revised manuscript.

P9 L39: Here and in the entire manuscript: "nonsurvivors" and "non-survivors" are used inconsistently. I recommend using "non-survivors".

Response: Thank you. All "nonsurvivors" are changed to "non-survivors" in the revised manuscript.

P15 L26: The revised paragraph in the manuscript differs from the one mentioned in the responses to the reviewers comments. Please define which version is the right one.

Response: We are very sorry for the inconsistence. The correct version is in the following: “In this study it was found that the APACHE II, ALIS, PaO2/FIO2 and AaDO2 were not significantly different between the survived and non-survived ARDS patients; instead, the HFP and TP were found to be the independent predictors of mortality in ARDS patients on admission to the SICU (p < 0.05). This result suggested that the non-invasive HRV indices such as HFP and
TP were more sensitive than the conventional scores or indices such as APACHE II, ALIS, PaO2/FIO2 and AaDO2 in predicting the outcome of surgical patients with ARDS.”

6. P16 L7: Please replaces "parameters" in "variables"
Response: Thank you. The "parameters" in that sentence is replaced by "variables" in the revised manuscript.

7. P17 L23: Typing error "underlying"
Response: Thank you for the correction. The typing error “underlisng” is now corrected to read “underlying”.

8. P19 L30: I recommend deleting the rest of the sentence ("because...") , which sounds more like an excuse for not recording additional values. The explanation does not provide relevant information.
Response: Thank you for your comments. The whole paragraph about the second limitation is removed because a lot of perioperative data of the patients are included in the revised manuscript.

9. P20 L11: (see comment 3.) I recommend changing the sentence like as, e.g., "Increased vagal modulation might be an indicator for poor prognosis in critically ill patients" to make it less capable for misunderstanding.
Response: Thank you very much for your suggestion. The sentence is now changed to read: “Increased vagal modulation might be an indicator for poor prognosis in critically ill patients following thoracic surgical patients.”
Tobias Kammerer (Reviewer 2): I appreciate the substantial amount of work that the authors have done in providing a significant revision. The manuscript is improved. Unfortunately, some issues remain, and some new one has been introduced. Attention to these will improve the manuscript further.

The main critics are still the missing information about the patients included in the trial and missing perioperative data.

Response: A lot of perioperative data of the patients are included in the revised manuscript.

In detail I have the following general questions and comments:

There is still a lack of information about the intraoperative procedure and the anesthesia management. Although this was a case-control study, you should be able to provide these data retrospectively. As a minimum you should give the following information: How many patients received thoracic surgery in your hospital during the trial duration and how many (n/%) developed ARDS?

Response: During the 2 years study period of this study, 817 patients received lung or esophageal surgery, and 22 patients developed ARDS. The incidence rate of ARDS after thoracic surgery for lung or esophageal surgery was 2.69%. Among those ARDS patients, 7 patients were not included in the study because of arrhythmia.

How was the ASA classification and comorbidities? ("Thoracic Revised cardiac Risk index" Salati et al. Curr Surg Res (2016); 4:37)?

Response: Six patients out of 11 patients in the control group were classified as ASA I, and 5 patients as ASA II. For the 21 patients in the ARDS group, 1 patient was classified as ASA I, 5 patients as ASA II, 4 patients as ASA III. Six patients in the ARDS group had no ASA classification because they were not operated during this admission, but had thoracic surgery within 1 year, and were admitted due to ARDS caused by rapidly progressing pneumonia.

Regarding comorbidities, 3 patients in the control group and 4 patients in the ARDS group had hypertension (p = 0.667). In the ARDS group, 2 patients in the non-survivors’ subgroup and 2 patients in the survivors’ subgroup had hypertension (p = 0.228). 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.

(3) What was the primary diagnosis in these patients?
Response: In the control group, 6 patients had lung cancer and 5 patients had esophageal cancer. In the ARDS group, 9 patients had lung cancer, 5 patients had esophageal cancer, 1 patient had esophageal rupture, and 6 patients had pneumonia induced ARDS after the thoracic surgery.

(4) What kind of surgery was used (VATS vs open surgery)?
Response: In the control group, 10 patients received VATS for lobectomy or esophageal resection, and 1 patient received laminectomy because of lung cancer metastasis. In the ARDS group, 12 patients received VATS for lobectomy or esophageal resection, 3 patients received open lung surgery, and 6 patients received thoracic surgery within the past 1 year and were admitted to the SICU because of ARDS caused by pneumonia.

(5) How long was the duration of surgery and one-lung ventilation?
Response: In the control group the duration of surgery was 255 (245-450) minutes (median and interquartile range). In the ARDS group, the duration of surgery was 250 (165-375) minutes. In the operation room, after endotracheal intubation and positioning of the patient, the bronchus blocker was used to start one-lung ventilation. If there was no problem in oxygenation, the surgery was started. After the completion of surgery and before the closing of operation wound, one-lung ventilation was stopped and the patient was put back to two-lung ventilation. The endotracheal tube with bronchus blocker was then changed to oral endotracheal tube, and the operation wound was closed if there was no problem in oxygenation. There were no records on the times when one-lung ventilation was started and stopped. Therefore, no data on the duration of one-lung ventilation can be found in the anesthesia record in our hospital.

(6) What about transfusion rate?
Response: In the control group, 5 out of 11 patients received blood transfusion. The transfusion rate in the control group was 45.5%. In the ARDS group, the transfusion rate was 40% because 6 out of 15 patients who received thoracic surgery during this admission had blood transfusion.

(7) How was the airway management (double-lumen tube, bronchus blocker)?
Response: In the control group 2 patients received bronchus blocker, and 9 patients received double-lumen intubation. In the ARDS group, 15 patients received thoracic surgery during this admission; among them 5 patients received bronchus blocker, and 10 patients received double-lumen intubation.
(8) Was volatile or intravenous anesthesia used?

Response: All 26 patients receiving thoracic surgery in this study were operated under volatile anesthesia.

(9) How was the respirator setting in the OR?

Response: We are sorry that we cannot find the record of respirator setting in the anesthesia record of the patients in the OR.

2. The same applies to intensive care data: As a minimum you should provide for ARDS patients: length of ventilator support, ICU stay, hospital stay, ventilator free days, fluid balances and transfusion rates, vasopressors and catecholamines, re-thoracotomy rate, rate of postoperative pulmonary complications (re-intubation rate etc.), antibiotics, SAPS and TISS score, incidence and kind of major cardiovascular events, cause of deaths.

Response: The length of ICU stay was 25 (20 - 43) days (median and interquartile range) in the ARDS group, and was 21 (11 - 44) days in the control group. In the 15 patients with ARDS who had received thoracic surgery during this admission, the re-intubation rate was 46%, the mean ventilator free hour was 54 hours, and the re-thoracotomy rate was zero. After surgery, Unasyn was given to all patients for post-operative care. In the ARDS group, 6 patients used Norepinephrine and 2 patients used Dopamine for blood pressure maintenance. Five patients in the ARDS group died of severe sepsis. The SOFA score of the patients in the ARDS group was 8 (7-10) (median and interquartile range). The fluid balances, transfusion rate, vasopressors and catecholamine use, and other relevant perioperative data are shown in Table 1 in the revised manuscript.

Please add the exact time period of patient recruitment.

Response: When the patient was admitted to the SICU, we explained the current status of the patient, the reason of admission to SICU, the treatment that would be given to the patient, etc., to the patient and his/her family at the bedside. When the patient’s condition met the inclusion criteria of the study, we explained the purpose of the study, the way of data collection, and the possible risk of the study to the patient and his/her family. If the patient agreed to participate in the study, the informed consent was signed by both patient and his/her family, and the patient was included in the study. When Midazolam and Fentanyl were applied to the ARDS patient because of dyspnea and anxiety, the patient could not sign the informed consent by himself/herself but still could express his/her willingness or unwillingness to participate in this
study by nodding or shaking head because the RASS of the patient was around -1 and -2. In that case, the next of kin of the patient signed the informed consent on behalf of the patient if the patient nodded his/her head. If the patient did not express his/her willingness to participate in the study, the patient was not included in the study. The written informed consent could be withdrawn by the patient and the family at any moment during the study.

4. P12, L36: was fentanyl only given to ARDS patients? If yes: what was used as a pain killer in the non-ARDS group? What about regional anesthesia?

Response: 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.

5. Generally, please add relevant information you gave me in your comments (for example the target MBP of > 60 mmHg) into the text.

Response: Vasopressors or catecholamines (0.05 ~ 0.11 μg·hr⁻¹·min⁻¹) were used in 8 patients in the ARDS group to keep mean blood pressure > 60 mmHg to maintain proper cerebral perfusion pressure.

6. If you provide perioperative data, you should do a multivariate analysis with further variables. For example smoker status, thoracic revised cardiac risk index, ASA classification, preoperative inflammatory lab parameters etc.

Response: Thanks for your suggestion. We include the smoker status, use of sedatives and vasopressors, HR, TP, LFP, HFP/VT, RASS, SOFA, type of surgery, surgical time, blood transfusion rate, intraoperative ETT, intraoperative I/O, re-intubation, ASA classification, WBC, and CRP in Table 1 and Table 2 in the revised manuscript. We try to follow reviewer’s suggestion to include these variable for adjustment in the multivariate analysis, and fail to get a result from regression model due to small sample size and model overfitting.
7. Your comment No.33: please add this explanation into the main text.

Response: The explanation for increased vagal modulation in ARDS patients has been revised and added to the Discussion of the revised manuscript as follows: “It has been shown 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 [37]. Thus, the increased vagal modulation in ARDS patients might be the pathophysiological response of the patients to counteract the cytokines synthesis, attenuate the amount of cytokines in the serum, and prevent the cytokines-induced systemic inflammation in ARDS.”

8. P4, L20: This conclusion cannot be done due to the fact, that you did not calculate further variables with multivariate regression. HFP is a predictor, but maybe not the best of all.

Response: Thanks for the comments and suggestions. We apologize for not clearly interpreting the selection criteria of the variables in the multivariate analysis in our previous manuscript. In this study, the 10 events per variable (EPV-10) rule [28, 29] was used in logistic regression model to avoid the overfitting problem, which is a generally accepted criterion in multivariable analysis. With a sample size of 32 patients (11 patients in the control group and 21 patients in the ARDS group), the inclusion of only three variables in the multivariate analysis to ensure adequate statistical power is reasonable.

The ASA classification, intraoperative anesthesia, fluid balance, drugs, etc., were not significantly different between the survivors and non-survivors of ARDS; only the RASS of the non-survivors was significantly lower than that of the survivors (Table 2). In univariate analysis, the TP, HFP and RASS were found to be the significant predictors of mortality for ARDS patients in the SICU (p < 0.05) (Table 4). Since the TP and HFP were highly correlated with each other while the RASS did not correlate with either TP or HFP (Table 3), two separate models in multivariate analysis including HFP and TP adjusted for RASS, age and gender were used. After adjustment for RASS, age and gender, the HFP (p = 0.025) and TP (p = 0.024) were found to be the significant independent predictors of mortality in ARDS patients in the SICU (Table 4). As depicted in Figure 1, the AUCs and 95% confidence intervals (CI) of TP and HFP in predicting mortality in ARDS patients on admission to the SICU were 0.850 (95% CI = 0.685-1.000; p = 0.021) and 0.888 (95% CI = 0.741-1.000; p = 0.010), respectively. Among all variables assessed in this study, HFP was the best predictor in predicting mortality in ARDS patients on admission to the SICU. Thus, our previous conclusion that increased vagal modulation might be a poor prognostic sign in critically ill patients including thoracic surgical patients is still valid.
Reference:


9. P15, L39: To support this hypothesis you should add a multivariate analysis with these parameters too.

Response: We try to follow the reviewer’s suggestion to include those variables for adjustment in the multivariate analysis, but we fail to get a result from the regression model due to small sample size and model overfitting. More details have been explained in our response to Question 8.

10. P18, L4ff: This is one reason, why you should give these information in the tables! Additionally you can find some minor corrections in the revised pdf-file attached.

Response: The ASA classification, intraoperative anesthesia, fluid balance, and drugs were not significantly different between the survivors and non-survivors of ARDS (revised Table 2). Thank you very much for your corrections.