Author’s response to reviews

Title: Use of esophageal balloon pressure-volume curve analysis to determine esophageal wall elastance and calibrate raw esophageal pressure: a bench experiment and clinical study

Authors:

Xiu-Mei Sun (sunxm1993@163.com)
Guang-Qiang Chen (cgqcgq@126.com)
Hua-Wei Huang (vivian198543@163.com)
Xuan He (hexuan1204@icloud.com)
Yan-Lin Yang (jasons808@hotmail.com)
Zhong-Hua Shi (katelynszh@163.com)
Ming Xu (sunnykiwi2008@163.com)
Jian-Xin Zhou (zhoujx.cn@icloud.com)

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Author’s response to reviews:

Dear editor:

We responded the comments of reviewers point by point and uploaded the revision of manuscript with track changes. If a clean version of the revised manuscript is needed, please inform me.

Thank you!

Editor Comments:

You should better express, in the background section, what is already known and what is the unanswered question your study aims to address.

Although this may be clear to researchers in the field, it may appear elusive to general readers.

Responses: We mentioned in the Background section that “our work was relevant for the absolute measurement of esophageal pressure”. We also re-arranged the primary and secondary aims of the study (page 5-6, line 104-119).
Tommaso Mauri (Reviewer 1): Interesting study on oesophageal elastance and its impact on oesophageal pressure measurement.

Introduction is clear, just more precisely mention that the topic is relevant for absolute measures of transpulmonary pressure but also relative measures based on lung/respiratory system elastance exist.

Responses: We added “Although release-derived and elastance-derived strategies have been proposed to compute relative transpulmonary pressure, eliminating the influence of balloon surrounding structures on the absolute measurement of Pes may also be required.” in the Background section (page 5, line 94-97).

Methods section is very long, consider reducing it by 30-50% and move some of the content to an online supplement.

Responses: We tried our best to condense the methods section from 1485 to 1263, and moved some figures and table 1 to Additional file.

The rationale for performing the patients study is not clear.

Responses: To indicate the rationale for performing the clinical study, we added secondary aims to test our introduced simple method for the esophageal elastance estimation and the esophageal pressure calibration in the clinical study (In the Background section, page 5-6, line 103-119).

Table 1 is very little useful to the results, consider moving it in the online supplement.

Responses: Revised.

Why Vbest was so different between in vitro and in vivo?

Responses: We added: “… it could be noticed that in vivo VBEST was markedly larger than in vitro value, which might suggest the contact reaction of the balloon to the esophageal wall. However, this phenomenon requires further investigation” (page 17-18, line 374-377).

Too many figures, please choose 2-3 most interesting and move others online.

Responses: We only remained 3 figures (for bench experiment setup, balloon P-V curve analysis and agreement analysis for the estimated and measured elastance). Others were moved to Additional files.

The proposed test for calibration is with 2 points (0.6 and 1.4) or 3 (0.6 1.0 1.4)?

Responses: Revisions were made to clearly describe the method. For estimation of esophageal wall elastance, only balloon volumes of 0.6 and 1.4 ml were used (Methods section, page 11, line 245-249). “For the small-volume balloon used in the present study, all clinical best volume were also located between 0.6 and 1.4 ml, and no significant difference was found in either the
ΔPes/ΔPaw ratio during the occlusion test or calibrated Pes among balloon volumes within this range. Therefore, we further suggest a simple procedure for balloon volume test and Pes calibration for the Cooper balloon catheter. The balloon can only be inflated to three volumes of 0.6, 1.0 and 1.4 ml, and the volume with largest tidal swing in balloon pressure could be selected as the best volume. Esophageal wall elastance can be simply estimated only using pressures at balloon volumes of 0.6 and 1.4 ml, and the raw Pes at the best volume is calibrated” (Discussion section, page 18, line 385-392).

Davide Chiumello (Reviewer 2):

SUGGESTION: MAJOR REVISION

In the present study, Dr. Sun and coll. sought to investigate the feasibility and performance of a previously published and established calibrating procedure for esophageal pressure in a balloon with a smaller volume than previously investigated.

A bench and experimental study was designed to test the hypothesis: gas-tight glass chamber with different inner volumes and different inner pressurization were used to simulate different balloon-surrounding conditions. After progressive, intermittent inflation of the balloon, balloon and chamber pressure-volume curves were plotted; balloon transmural pressure was calculated to assess the working filling volume, and chamber elastance was estimated from the slope of the intermediate, linear section of the balloon PV curve. The clinical study was conducted on consecutive postoperative patients with delayed emergence from general anesthesia. Again, progressive, intermittent inflation of the balloon was performed, and balloon PV curves were constructed. The intermediate, linear section of the PV curve was analyzed to identify the balloon working volume, the ideal filling volume and to estimate esophageal wall elastance. The findings of the study are that the analysis of the slope of the linear, intermediate section of the balloon PV curve agreed with bench, simulated values of balloon-surrounding elastance, that the calibration procedure worked accurately even in a balloon with a volume smaller than previously investigated. Moreover, a simplified method for the estimation of esophageal elastance was proposed and validated.

The study deals with an interesting topic and was performed with rigorous methodology. Esophageal pressure measurement is being increasingly performed to estimate the contribution of the chest wall in respiratory system physiology and to evaluate inspiratory effort. Esophageal pressure is considered to estimate pleural pressure. However, the filling volume of the esophageal balloon may significantly influence the measurement due to the elastance of the esophageal wall itself.

Responses: Thank you for your interest in our study.

I have some criticism:

-the aim of the study was not clearly stated, nor it is completely understandable from the text: apparently, the main aim was to examine the relationship between the estimation of esophageal
elastance from the analysis of the linear intermediate section of the PV curve, with the direct measurement of balloon-surrounding pressure. However, from the first part of the discussion, it seems that also calibration of the value of esophageal pressure by the esophageal wall pressure was an outcome, as well as the comparison of a simplified method for the estimation of esophageal elastance with the conventional one. If this is the case, it should be more clearly stated in the introduction.

Responses: We added the secondary aims in the Background section: “Based on previously introduced methods [refs of Milic-Emili 1964 (PMID: 14155283) and Mojoli 2016 (PMID: 27063290)], we developed a simplified procedure for the Ees estimation and Pes calibration. The secondary aims included the assessment of the agreement between the standard and simple methods, and the comparison of calibrated Pes values among different filling volumes” (page 6, line 112-118).

-How was the number of patients included in the clinical study determined? A main outcome should be clearly stated and a sample size calculation performed on that outcome. The same consideration applies for the experimental study

Responses: We added sample size description in the Statistical analysis section, and calculated 95% confidence interval of the agreement of limit in Bland-Altman analysis (page 12-13, line 264-268).

-In the methods section some parts are difficult to understand for a reader who is not completely familiar with the literature cited. Please, better explain the simplified method of estimation of esophageal elastance (lines 215-218), and clearly state that the comparison of the two methods is an outcome of the study.

Responses: We added the secondary aims (the comparison of the estimation esophageal elastance between the conventional method and our introduced method, and of calibrated Pes values among different filling volumes) in the Background section (page 5-6, line 103-118). In the Method section, we explained the simplified method as: “In each of the patient’s balloon volume test, intermediate linear section on the end-expiratory balloon P-V curve (i.e. range of clinical Vmin to Vmax) enclosed filling volume of 0.6 to 1.4 ml. Therefore, we simplified the estimation of Ees only using parameters at these two filling volumes, as the difference of end-expiratory balloon pressure between 0.6 ml and 1.4 ml divided by 0.8 ml (1.4 - 0.6 ml) ” (page 12, line 245-249)

Similarly, the correction of esophageal pressure by esophageal wall pressure seems to be different from the method previously reported by Mojoli et al (Crit care 2016; 20:98), as Pew should be the product of Ees and the balloon volume from the actual filling volume to Vmin. Please also explain how the calibrated value of esophageal pressure was calculated and that the comparison among corrected values for the different filling volumes was an outcome of the study

Responses: An additional outcome measure was added in the Background section (as the previous response). We used the method introduced by Milic-Emili et al. 1964 (PMID: 14155283) to calculate esophageal wall recoil pressure and calibrate raw esophageal pressure. A
A description of the calibration method was added: “The raw esophageal pressure values were calibrated by extrapolating to the zero balloon volume, which could also be expressed as: calibrated esophageal pressure = raw esophageal pressure - esophageal wall recoil pressure” (page 11-12, line 239-244).

As the authors disclosed in the limitation section, the patient population enrolled is composed mainly by patients without acute respiratory failure, and with presumably healthy lungs, enrolled when delayed recovery from anesthesia was expected. Please, add to table 3 the inspiratory and expiratory esophageal pressure, as well as the partitioned respiratory system, chest wall and lung elastance of the patient population. As expected, patients had a nearly-normal oxygenation; however, they were ventilated with quite elevated airway pressure (median PEEP of 9, median plateau pressure of 20): please comment

Responses: Because we did not collect esophageal pressure at the patients enrollments, we just added elastance of respiratory system (median 22.2, interquartile range 17.5–25.2 cmH2O/L) in revised Table 2. During the balloon volume test, we did not change clinical settings of tidal volume, PEEP and FiO2. After reviewing our patients population, we found that half of the patients were after intracranial operations. Intracranial operations usually have long duration and postoperative atelectasis is prevalent. We think that physicians may wanted to use a relatively high PEEP for prevention and treatment of lung collapse.

-Please, comment the fact that Mojoli et al found that the best filling volume for the Nutrivent esophageal balloon catheter displayed significant variability among patients and in the different conditions studied, while in the present study Vbest was very similar among patients.

Responses: Revised. We think this discrepancy might be explained by the low variation in balloon with small geometric volume (added in Discussion section: page 17, line 362-366).

-In Table 4 the method for the correction of esophageal pressure seems to differ from that proposed by other authors. Please, better report the correction method used. Also, the table would be more informative if it was constructed using individual patient volumes (e.g. each patient Vmin, Vbest, Vmax) as well as fixed volumes (0.6, 0.8, 1 ml, etc) as it is now.

Responses: The calibration method was revised as mentioned above. Because a Table containing individual patient’s data is too large to put into the main manuscript, we added an Additional file 6 (Table S2) to illustrate the balloon volume data and esophageal wall elastance in individual patient. Detailed results in measured esophageal pressures and positive pressure occlusion test at each filling volume are also shown in Additional file 5.

-Please, clarify the position of patients during the study.

Responses: Revised as “During the study, the patients were remained in supine position with the head of the bed elevated to 30°” (page 10-11, line 220-221)

-Line 83: please modify "inclined" with "linear"
Responses: Revised.

Savino Spadaro, M.D., Assistant professor (Reviewer 3): The authors in this study evaluate the relationship of the slope of the intermediate linear section on the balloon P-V curve with the balloon-surrounding elastance (in vitro) and Ees (in vivo) using a balloon with a small volume. The authors reproduced the experiment conducted by Mojoli and coworkers (Critical Care 2016) in vitro and verify the results in a clinical context. In my opinion, the aim of this study is not original and the readers could be not interested in these technical aspects. In several parts of the work, the authors reproduce methods known in literature. (See reference 10 and 13) Furthermore, the paper suffers from several methodological limitation.

Major comments

The authors investigated the calibration of a single balloon with a small volume; so reported in the introduction that there are no data about the calibration with large geometric volume. Please explain the rationale of this choice. Is it clinical relevant? What is the differences that could be influence the measurements?

Responses: In clinical study conducted by Mojoli et al. only one type of balloon with a relatively large geometric volume has been investigated for balloon volume test and esophageal pressure calibration (page 5, line 100-102). The Cooper catheter (with a small-volume balloon) is another esophageal balloon used in clinical researches (such as in our reference #7, Chen et al, PMID 28372575). Because balloon filling volume may influence the accurate measurement of esophageal pressure, we performed the present study to assess the established method for balloon volume test, esophageal wall elastance estimation and esophageal pressure calibration in a small-volume-balloon catheter.

Please give information about the pre-calibration using water column. Page 6 line 115. The description is not accurate.

Responses: We added the method for pressure transducer calibration as: “Pressure transducers were pre-calibrated using two points calibration function in the ICU-Lab, with one reference as atmospheric pressure and another one as 10 cm water column in a U shape tube.” in the Additional file 1_Detailed methods (bottom in page 1).

Please explain in which way do you check the systematic leaks (page 7 line 140)

Responses: We revised as: “During the experiment, connections in the chamber system were sealed with silicone sealant. After a positive pressure of 30 cmH2O was added in the chamber, systematic leaks were excluded if decreasing in the chamber pressure was less than 1 cmH2O during the first 1-min equilibrating period.” in the Additional file 1_Detailed methods (top in page 3).

In the clinical study were enrolled postoperative patients with delayed emergency from general anesthesia. Please explain this inclusion criteria. What is the reason of admission in ICU? What
is the comorbidities of these patients? This setting of patients is not accurate to interpret adequately the results of the use of esophageal pressure. I would underline that it is not indication for use of PES in this context. The data reported in table 3 are not accurate to describe the patients population.

Responses: The patients enrolled in the present study were those with delayed extubation and need for mechanical ventilation during postoperative period. Because a lot of neurosurgical patients were admitted in our unit, we usually performed Pes monitoring in mechanically ventilated neurosurgical patients to guide ventilator settings and weaning (we added in revised Methods section, page 10, line 200-201). We excluded those patients with contraindications for esophageal balloon catheter insertion and evidence of active air leak from the lung.

In the section methods, page 9 lines 183-186 "continuous infusion of midazolam, fentanyl and bolus of vecuronium were administered…" do you evaluate the RASS score? There is not reported if the patients were assessed using neuro-muscular monitoring during the experiment.

Responses: Because the reason for the use of sedatives and vecuronium (as needed) was to eliminate the spontaneous breathing during balloon volume test, we did not assess the sedation level and paralysis during the study, but just observed the inspiratory efforts. We added “The absence of spontaneous inspiratory effort was confirmed by the absence of a negative airway pressure swing during a 3-second end-expiratory occlusion” in the revised manuscript (page 10, line 210-212).

The patients were studied only in controlled mechanical ventilation. The evaluation of calibration procedure in active patients is another relevant aspect to verify in this field. This could be another relevant limitation that limited the interest for this paper.

Responses: We added this limitation in the Discussion section (page 19, line 407-408).

In discussion, the authors proposed that it is possible to test other balloons using three volumes … (page 17 line 344). Taking into account the methodology of this study and the results, it is very strong to support this statement.

Responses: We suggested that further investigations are needed for the use of simple procedure in other balloon catheters, especially for large volume balloons (page 19, line 418-419)

Minor comments:

The title of manuscript did not reflect the contents. I suggest to modify the title accordingly.

Responses: The title has been revised as “Use of esophageal balloon pressure-volume curve analysis to determine esophageal wall elastance and calibrated raw esophageal pressure: a bench experiment and clinical study”.
Page 12 lines 242: "in accordance with our anticipation" --- please change with " in according with previous .."

Responses: Has been revised.