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Mechanical Ventilation Guided by Uncalibrated Esophageal Pressure May Be Potentially Harmful

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Esophageal pressure can be used as a surrogate for pleural pressure for optimizing mechanical ventilation
- However, surgeries such as pelvic robotic surgery involve fluctuations in abdominal load and intrathoracic pressure that may artificially influence esophageal pressure

What This Article Tells Us That Is New

- This study enrolled patients undergoing pelvic robotic surgery and found that esophageal balloon calibration significantly improved assessment of esophageal pressure when compared with the conventional uncalibrated approach to measuring esophageal pressure

ABSTRACT

Background: Esophageal balloon calibration was proposed in acute respiratory failure patients to improve esophageal pressure assessment. In a clinical setting characterized by a high variability of abdominal load and intrathoracic pressure (*i.e.,* pelvic robotic surgery), the authors hypothesized that esophageal balloon calibration could improve esophageal pressure measurements. Accordingly, the authors assessed the impact of esophageal balloon calibration compared to conventional uncalibrated approach during pelvic robotic surgery.

Methods: In 30 adult patients, scheduled for elective pelvic robotic surgery, calibrated end-expiratory and end-inspiratory esophageal pressure, and the associated respiratory variations were obtained at baseline, after pneumoperitoneum–Trendelenburg application, and with positive end-expiratory pressure (PEEP) administration and compared to uncalibrated values measured at 4-ml filling volume, as per manufacturer recommendation. Data are expressed as median and [25th, 75th percentile].

Results: Ninety calibrations were successfully performed. Chest wall elastance worsened with pneumoperitoneum–Trendelenburg and PEEP (19.0 [15.5, 24.6] and 16.7 [11.4, 21.7] cm H_2O/l) compared to baseline (8.8 [6.3, 9.8] cm H_2O/l; $P < 0.0001$ for both comparisons). End-expiratory and end-inspiratory calibrated esophageal pressure progressively increased from baseline (3.7 [2.2, 6.0] and 7.7 [5.9, 10.2] cm H_2O) to pneumoperitoneum–Trendelenburg (6.2 [3.8, 10.2] and 16.1 [13.1, 20.6] cm H_2O; $P = 0.014$ and $P < 0.001$) and PEEP (8.8 [7.7, 15.6] and 18.9 [16.3, 22.0] cm H_2O; $P < 0.0001$ *vs.* baseline for both comparison; $P < 0.001$ and $P = 0.002$ *vs.* pneumoperitoneum–Trendelenburg) and, at each study step, they were persistently lower than uncalibrated esophageal pressure ($P < 0.0001$ for all comparisons). Overall, difference among uncalibrated and calibrated esophageal pressure was 5.1 [3.8, 8.4] cm H_2O at end-expiration and 3.8 [3.0, 6.3] cm H_2O at end-inspiration. Uncalibrated esophageal pressure swing was always lower than calibrated one ($P < 0.0001$ for all comparisons) with a difference of –1.0 [–1.8, –0.4] cm H_2O.

Conclusions: In a clinical setting with variable chest wall mechanics, uncalibrated measurements substantially overestimated absolute values and underestimated respiratory variations of esophageal pressure. Calibration could substantially improve mechanical ventilation guided by esophageal pressure.

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Esophageal pressure is conventionally used as a pleural pressure surrogate for research and clinical purposes.[1,2] However, the reliability of esophageal pressure assessment is affected by several factors: some depend on catheter balloon, others on thoracoabdominal structures and organs (*i.e.,* lung, chest wall, abdomen, esophagus).[3]

The esophageal balloon calibration has been proposed in order to overcome issues related to technical factors affecting esophageal pressure measurements.[4] Recently, a calibration technique has been applied in sedated and paralyzed patients admitted to intensive care unit with acute respiratory failure undergoing invasive controlled mechanical ventilation.[5] It consists of two steps aiming at: (1) selecting the optimal filling volume for the esophageal balloon, to optimize the transmission of respiratory tidal swings of esophageal pressure; and (2) removing the "baseline"

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artifacts that can increase the absolute baseline value of esophageal pressure above the pleural value, namely catheter balloon elastance and esophageal wall elastance. The calibration procedure increases the measurement accuracy of both chest wall driving pressure and absolute values of pleural pressure.[5–9] These measurements are essential to compute lung driving pressure and transpulmonary pressures, that physicians can use to personalize the setting of mechanical ventilation according to the patient's respiratory mechanics.[1,2,10,11] On the other hand, the two-step calibration procedure is moderately complex and time consuming, thus physicians may be reluctant to perform it systematically in their clinical practice.

The aim of this study was to quantify the impact of a two-step calibration procedure on the esophageal pressure assessment with respect to the conventional uncalibrated approach, in different conditions of chest wall mechanics. For this purpose, we performed repeated esophageal pressure measurements in patients undergoing elective pelvic laparoscopic surgery. Indeed, due to patient's body position, induction of pneumoperitoneum and positive end-expiratory pressure application, a substantial increase from baseline values of intrathoracic pleural pressure is expected in this setting.[12–15] Optimal filling volume of the esophageal balloon depends on the surrounding intrathoracic pressure and baseline artifacts are in turn related to esophageal balloon volume.[4–9,16,17] Our hypothesis was that in a clinical setting characterized by substantial changes of the chest wall properties, the difference between uncalibrated *versus* calibrated esophageal pressure may be clinically relevant.

Materials and Methods

Patients

This is a preplanned secondary analysis of data collected in occasion of a previous randomized controlled trial comparing esophageal pressure–driven mechanical ventilation *versus* standard practice during elective pelvic robotic surgery.[18] The study was approved by the "Maggiore della Carità," ethics committee (CE 62/17) (University Hospital Novara, Italy) and registered at ClinicalTrials.gov (number NCT03153592). Written informed consent was obtained, according to local regulations, from each patient scheduled to undergo elective pelvic robotic surgery from September 2017 to January 2019 at Maggiore Hospital Novara (Italy). Inclusion criteria were: age 18 yr or older and American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status I and II. Exclusion criteria were: ASA Physical Status greater than or equal to III, pregnancy, any contraindications to naso/orogastric catheter placement.

After premedication with midazolam 0.02 mg/kg was administered, the standard vital parameters monitoring (*i.e.*, electrocardiogram, pulse oximeter, noninvasive blood pressure measurement) was applied. Anesthesia induction was warranted through propofol 2 mg/kg, remifentanil 0.15 to 0.3 $\gamma g \cdot kg^{-1} \cdot min^{-1}$, and rocuronium 0.6 mg/kg, and orotracheal intubation was assured. Patients were connected to mechanical ventilator (FLOW-I 3.0; Maquet Critical Care AB-Getinge Group, Sweden) and were all ventilated in volume control mode with an inspiratory square flow. Tidal volume ranged from 6 to 8 mg/kg of ideal body weight,[10] inspiratory oxygen fraction was chosen to maintain peripheral oxygen saturation greater than 94%, and respiratory rate was set to obtain and maintain an end-tidal carbon dioxide tension between 35 and 45 mmHg. Inspiratory time was 33%, with an inspiratory pause of 20%. No positive end-expiratory pressure (PEEP) was initially applied. Sevoflurane (1 to 2%), remifentanil 0.1 to 0.15 $\gamma g \cdot kg^{-1} \cdot min^{-1}$, and extemporary rocuronium were administered according to the anesthesia maintenance plane. The radial artery was cannulated (radial artery catheterization set; Arrow International, USA) for continuous monitoring of blood pressure.

A gastric tube equipped with both esophageal and gastric balloons (Nutrivent Sidam; Mirandola, Italy) was introduced through the nose/mouth 50 to 55 cm to reach the stomach. Before insertion, balloons were both deflated and secured with a three-way stopcock. Subsequently, esophageal and gastric balloons were connected *via* polyethylene tubes to a pressure transducer box (KleisTEK Engineering, Italy). Balloons were inflated at a volume of 4 ml and their intragastric position was confirmed by the positive pressure deflection during gentle external manual epigastric compression. Subsequently, the catheter was slowly withdrawn into the lower third of esophagus, as indicated by the appearance of cardiac artifacts on the esophageal pressure line.[1] At this point, with an esophageal balloon filling volume of 4 ml, two external manual compressions on the rib cage were applied during an expiratory hold and simultaneous positive deflections of airway and esophageal pressure were compared (validation test).[2,19–22] The test was considered passed if the ratio of esophageal to airway pressure deflections was in the 0.8 to 1.2 range. Then, the esophageal balloon was deflated and reinflated with increasing volumes from 0.5 to 8 ml, ensuring complete deflation of the balloon before each volume inflation.[5] At each volume, static expiratory and inspiratory esophageal pressure were acquired applying an expiratory and inspiratory 5-s lasting hold, respectively. Hence, to perform a two-step calibration procedure, end-expiratory esophageal pressure to balloon filling volume curves were obtained and visually analyzed. The intermediate linear section of this curve was graphically identified with its lower (minimal filling volume) and upper (maximal filling volume) limits. Optimal esophageal balloon filling volume was detected within this range of filling volumes, as the smallest one was associated with the largest respiratory tidal swing of esophageal pressure (Supplemental Digital Content 1, http://links.lww.com/ALN/C362). Subsequently, the esophageal balloon

was inflated at optimal filling volume and the validation test was repeated to definitively confirm balloon position and functioning. The esophageal reaction to balloon filling, with the generation of some pressure by the esophageal wall, was assumed to start as soon as the filling volume increased greater than the minimal filling volume.[5] Esophageal elastance was computed as the slope of the intermediate linear section of the curve.[5,23] Accordingly, pressure generated by the esophagus wall was computed as:

$$\textit{Esophageal wall pressure} = (\textit{actual filling volume} - \textit{minimal filling volume}) \times \textit{esophageal elastance}$$

Calibrated esophageal pressure was obtained filling the esophageal balloon with the optimal filling volume and subtracting the esophageal wall pressure:

$$\textit{Calibrated esophageal pressure} = \textit{raw esophageal pressure at optimal filling volume} - \textit{esophageal wall pressure at optimal filling volume}$$

Calibrated esophageal pressure obtained with the two-step calibration was used as reference, being the best possible approximation of pleural pressure. Uncalibrated esophageal pressure measurements were obtained by filling the esophageal balloon catheter to 4 ml, as per manufacturer recommendation.

The pressure generated by the overstretched esophageal balloon wall was assumed to start as soon as the balloon filling volume increased to greater than the maximal filling volume.[5,16] For filling volumes greater than the maximal filling volume, the pressure in the esophageal balloon is the pleural pressure plus the pressure generated by the esophageal wall and by the balloon wall; thus, the balloon wall pressure was computed by subtracting the calibrated esophageal pressure (as a surrogate for pleural pressure) and esophageal wall pressure from the esophageal pressure measurement:

$$\textit{Balloon wall pressure} = \textit{esophageal pressure} - \textit{esophageal wall pressure} - \textit{calibrated esophageal pressure}$$

Study Protocol

These calibration procedures were applied at the following time-points: (1) at baseline, with zero end-expiratory pressure conditions; (2) after pneumoperitoneum and Trendelenburg position application without PEEP; and (3) after 20 min from PEEP application in presence of pneumoperitoneum and Trendelenburg. The validation tests with 4 ml and optimal balloon filling volume were performed only at baseline.

Measurements

Flow and airway pressure were obtained through a heated pneumotachograph (Fleisch no. 2; Fleisch, Switzerland) installed between the endotracheal tube and respiratory circuit. Esophageal and gastric pressure were acquired through the aforementioned catheter. Then, flow and airway pressure, together with esophageal and gastric signals, were recorded, digitalized, and collected *via* a specific acquisition system on a personal computer (ICU Lab; KleisTEK Engineering, Italy) from baseline to PEEP application, and the calibration data were computed through a dedicated sheet (Excel; Microsoft, USA).[5]

Demographic characteristics such as gender, age, ASA score, body mass index, and predicted body weight were acquired.

Statistical Analysis

No power calculation was carried out before the study and the sample size was based on the available data from patients enrolled in the trial. The continuous variables, having the data a nonnormal distribution as assessed by D'Agostino and Pearson test, were reported as median value and [25th, 75th percentile]; the minimum–maximum interval was also described. The measures performed in the three study settings were compared by nonparametric ANOVA for repeated measures (Friedman test); *post hoc* multiple comparisons were performed by Dunn test. Comparisons between calibrated and uncalibrated parameters were performed by Wilcoxon matched-pairs rank test. A Bland–Altman analysis was employed to describe the end-inspiratory and end-expiratory agreement between uncalibrated and calibrated esophageal pressure and, when their absolute differences were greater than 2 and 5 cm H_2O, they were considered clinically relevant and potentially harmful, respectively. Moreover, an absolute difference between uncalibrated and calibrated esophageal pressure swings greater than 2 cm H_2O and/or greater than 25% and greater than 5 cm H_2O and/or greater than 50% was considered clinically relevant and potentially harmful, respectively.[5] Categorical variables, whether dichotomous or nominal, were described by number and percentage and were evaluated with chi-squared or Fisher exact test. A two-tailed test has been considered for the hypothesis testing procedure and statistically significant values were considered to reach P values less than 0.05. Statistical analyses were conducted using Prism 6.0 software (Graph-pad, USA).

Results

From September 2017 to January 2019 (as shown in Supplemental Digital Content 2, http://links.lww.com/ALN/C363), 31 of 49 eligible patients were enrolled, with one patient excluded because of waveform signal alteration; thus, 90 esophageal balloon calibrations were finally performed and analyzed in 30 patients. Demographic characteristics are presented in table 1.

PEEP was 0.0 [0, 0] cm H_2O at baseline, 0.0 [0, 0] cm H_2O at pneumoperitoneum–Trendelenburg, and 6.0

Table 1. Demographic Characteristics

Patients	(n = 30)
Male sex, n (%)	15 (50)
Female sex, n (%)	15 (50)
Age, yr	63.0 [52.0, 70.5]
ASA classification I, n (%)	6 (20)
ASA classification II, n (%)	24 (80)
Body mass index, kg/m^2	24.5 [21.5,26.9]
Predicted body weight, kg	64.5 [54.6,70.0]

Data are presented in number and percentage (in brackets) or median and [25th, 75th percentile]. ASA, American Society of Anesthesiologists Physical Status.

[5.0, 11.0] cm H_2O during the last study phase ($P < 0.0001$ *vs.* baseline and *vs.* pneumoperitoneum–Trendelenburg) while tidal volume was slightly larger with PEEP application (7.8 [7.5, 8.0] ml/kg; $P = 0.036$ *vs.* baseline; $P = 0.036$ *vs.* pneumoperitoneum–Trendelenburg) compared to the other two phases (7.6 [7.2, 7.8] ml/kg at baseline; 7.6 [7.4, 7 .8] ml/kg at pneumoperitoneum–Trendelenburg).

At baseline, the validation test was passed in 13 of 30 cases (43.3%), when a balloon volume of 4 ml was injected, and in all the cases after the optimization of the balloon filling ($P < 0.0001$).

Results of the 90 calibration procedures are shown in table 2. Overall, minimal and optimal esophageal balloon filling volume were 1.0 [0.5, 1.0] ml and 1.5 [1.0, 2.5] ml (range, 0.5 to 5.0), respectively; optimal filling volume was equal to minimal filling volume in 27 of 90 cases (30%) and it was lower than the recommended 4 ml in 85 of 90 cases (94.4%). Optimal filling volume slightly increased with pneumoperitoneum–Trendelenburg (2.0 [1.0, 2.5] ml; $P = 0.043$ *vs.* baseline) and PEEP administration (2.0 [1.5, 2.5] ml; $P = 0.005$ *vs.* baseline) compared to baseline (1.0 [0.5, 2.0] ml). Overall, maximal filling volume was 4.0 [3.0, 5.0] ml and it was less than 4 ml in 38 of 90 calibrations (42.2%). When the 4-ml filling volume was greater than the maximal filling volume, the esophageal balloon wall pressure was 1.6 [0.9, 4.1] cm H_2O, with a maximum value of 18.2 cm H_2O. Esophageal elastance was 1.3 [1.0, 2.3] cm H_2O/ml and generated an esophageal wall pressure of 0.9 [0.0, 2.0] cm H_2O (range, 0.0 to 6.2) with optimal filling volume, and 4.1 [3.1, 6.9] cm H_2O (range, 0.7 to 16.9) with 4 ml ($P < 0.0001$).

Calibrated and uncalibrated values of esophageal pressure at the three study steps are also shown in table 2, figure 1, and in Supplemental Digital Content 3 (http://links.lww.com/ALN/C364). End-expiratory calibrated esophageal pressure progressively increased from baseline (3.7 [2.2, 6.0] cm H_2O) to pneumoperitoneum–Trendelenburg (6.2 [3.8, 10.2] cm H_2O; $P = 0.014$) and PEEP application (8.8 [7.7, 15.6] cm H_2O; $P < 0.0001$ *vs.* baseline; $P < 0.001$ *vs.* pneumoperitoneum–Trendelenburg), and it was lower than end-expiratory uncalibrated esophageal pressure at each study phase ($P < 0.0001$ for all comparisons).

Table 2. Esophageal Balloon Calibration

Parameters	Study Steps: Baseline	Pneumoperitoneum–Trendelenburg	Pneumoperitoneum–Trendelenburg PEEP	*P* Value
Minimal filling volume (ml)	0.5 [0.5, 1.0]	1.0 [0.5, 1.0]	1.0 [0.5, 1.1]	0.288
Maximal filling volume (ml)	4.0 [3.0, 5.0]	4.0 [3.0, 4.0]	3.5 [3.0, 5.0]	0.169
Optimal filling volume (ml)	1.0 [0.5, 2.0]	2.0 [1.0, 2.5]†	2.0 [1.5, 2.5]‡	0.001
Esophageal elastance (cm H_2O/ml)	1.2 [1.1, 2.2]	1.7 [1.2, 2.6]	1.1 [0.9, 2.0]	0.045
Balloon recoil at 4 ml (cm H_2O)	0.5 [0.0, 1.2]	0.5 [0.1, 3.7]	0.8 [0.1, 1.4]	0.079
Esophageal wall pressure at optimal filling volume (cm H_2O)	0.5 [0.0, 1.4]*	1.4 [0.4, 2.4]*	0.9 [0.3, 1.7]*	0.036
Esophageal wall pressure at 4 ml (cm H_2O)	4.0 [3.5, 7.6]	5.2 [3.1, 7.8]	3.4 [2.8, 5.2]	0.177
End-expiratory calibrated esophageal pressure (cm H_2O)	3.7 [2.2, 6.0]*	6.2 [3.8, 10.2]*§	8.8 [7.7, 15.6]*‖#	< 0.0001
End-expiratory uncalibrated esophageal pressure (cm H_2O)	9.6 [5.9, 13.4]	13.2 [8.6, 22.2]**	14.6 [12.1, 24.5]‖††	< 0.0001
End-inspiratory calibrated esophageal pressure (cm H_2O)	7.7 [5.9, 10.2]*	16.1 [13.1, 20.6]***	18.9 [16.3, 22.0]*‖‡‡	< 0.0001
End-inspiratory uncalibrated esophageal pressure (cm H_2O)	12.1 [9.7, 17.6]	20.8 [17.6, 27.4]‖	23.1 [20.5, 27.6]‖	< 0.0001
Calibrated esophageal pressure tidal swing (cm H_2O)	4.1 [2.9, 4.9]*	8.6 [7.2, 11.3]*‖	7.8 [5.9, 9.9]*‖	< 0.0001
Uncalibrated esophageal pressure tidal swing (cm H_2O)	3.2 [1.9, 4.3]	6.4 [4.8, 9.1]‖	6.3 [4.3, 8.4]‖	< 0.0001
Chest wall elastance (cm H_2O/l)	8.8 [6.3, 9.8]	19.0 [15.5, 24.6]‖	16.7 [11.4, 21.7]‖§§	< 0.0001

Data are presented as median and [25th, 75th percentile]. *P* values refer to Friedman test. *Indicates *P* value from Wilcoxon rank test, whereas †, ‡, §, ‖, #, **,††,‡‡, and §§ refer to *P* value from *post hoc* multiple comparison Dunn test.

*$P < 0.0001$, calibrated *versus* uncalibrated variables. †$P = 0.043$ *versus* baseline. ‡$P = 0.005$ *versus* baseline. §$P = 0.014$ *versus* baseline. ‖$P < 0.0001$ *versus* baseline. #$P < 0.001$ *versus* pneumoperitoneum–Trendelenburg. **$P < 0.001$ *versus* baseline. ††$P = 0.020$ *versus* pneumoperitoneum–Trendelenburg. ‡‡$P = 0.002$ *versus* pneumoperitoneum–Trendelenburg. §§$P = 0.043$ *versus* pneumoperitoneum–Trendelenburg.

PEEP, positive end-expiratory pressure.

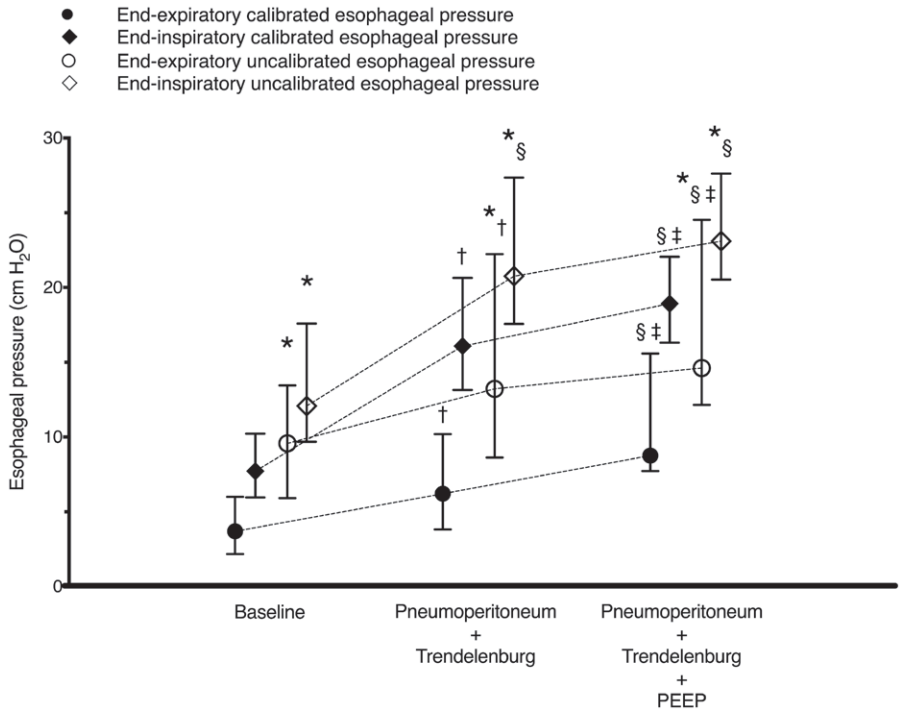

Fig. 1. Calibrated and uncalibrated esophageal pressure. Data are presented as median (*circles* and *parallelograms*) and [25th, 75th percentile] (*whiskers*). Calibrated (*solid circles*) and uncalibrated (*hollow circles*) esophageal pressure at end-expiration; calibrated (*solid parallelograms*) and uncalibrated (*hollow parallelograms*) esophageal pressure at end-inspiration. *Indicates *P* value from Wilcoxon rank test, whereas †, §, and ‡ refer to *P* values from *post hoc* multiple comparison Dunn test. †*Versus* baseline: for expiratory uncalibrated esophageal pressure $P < 0.001$, for inspiratory calibrated esophageal pressure $P < 0.001$, and for expiratory calibrated esophageal pressure $P = 0.014$. §*Versus* baseline: $P < 0.0001$. ‡*Versus* pneumoperitoneum–Trendelenburg: for expiratory uncalibrated esophageal pressure $P = 0.020$; for inspiratory calibrated esophageal pressure $P = 0.002$; and for expiratory calibrated esophageal pressure $P < 0.001$. PEEP, positive end-expiratory pressure.

End-inspiratory calibrated esophageal pressure raised moving from baseline (7.7 [5.9, 10.2] cm H_2O) toward pneumoperitoneum–Trendelenburg (16.1 [13.1, 20.6] cm H_2O; $P < 0.001$ *vs.* baseline) and PEEP trial (18.9 [16.3, 22.0] cm H_2O; $P < 0.0001$ *vs.* baseline; $P = 0.002$ *vs.* pneumoperitoneum–Trendelenburg), being persistently lower than uncalibrated esophageal pressure over all study phases ($P < 0.0001$, for all comparisons).

Tidal swing of calibrated esophageal pressure was higher with pneumoperitoneum–Trendelenburg (8.6 [7.2 to 11.3] cm H_2O; $P < 0.0001$ *vs.* baseline) and PEEP application (7.8 [5.9, 9.9] cm H_2O; $P < 0.0001$ *vs.* baseline) compared to baseline (4.1 [2.9, 4.9] cm H_2O) and it was larger than the corresponding uncalibrated one at each study step ($P < 0.0001$ for all comparisons).

Chest wall elastance increased with pneumoperitoneum–Trendelenburg (19.0 [15.5, 24.6] cm H_2O/l; $P < 0.0001$ *vs.* baseline) and PEEP administration (16.7 [11.4, 21.7] cm H_2O/l; $P < 0.0001$ *vs.* baseline; $P = 0.043$ *vs.* pneumoperitoneum–Trendelenburg) with respect to baseline (8.8 [6.3, 9.8] cm H_2O/l).

Figure 2 depicts the Bland–Altman analysis of agreement between uncalibrated and calibrated esophageal pressure at both end-expiration and end-inspiration in the 90 conditions. At end-expiration, the difference between uncalibrated and calibrated esophageal pressure was 5.1 [3.8, 8.4] cm H_2O (range, 0.8 to 35.1 cm H_2O), and was clinically relevant in 87 of 90 cases (96.7%) and potentially harmful in 47 of 90 (52.2%). The end-inspiratory difference between uncalibrated and calibrated esophageal pressure was 3.8 [3.0, 6.3] cm H_2O (range 0.5 to 25.2 cm H_2O), and was clinically relevant in 83 of 90 cases (92.2%) and potentially harmful in 28 of 90 (31.1%). Both biases were positively correlated with the value of esophageal pressure, as suggested by slope analysis (slope, 0.3; 95% CI, 0.2 to 0.5 at end-expiration; $P < 0.001$; slope, 0.2; 95% CI, 0.0 to 0.3; $P = 0.012$ at end-inspiration).

Figure 2 also shows the Bland–Altman analysis of agreement between uncalibrated and calibrated esophageal pressure tidal swing. The uncalibrated and calibrated esophageal pressure tidal swing difference was −1.0 [−1.8, −0.4] cm H_2O (range, −9.9 to 0.2 cm H2O), and was clinically relevant

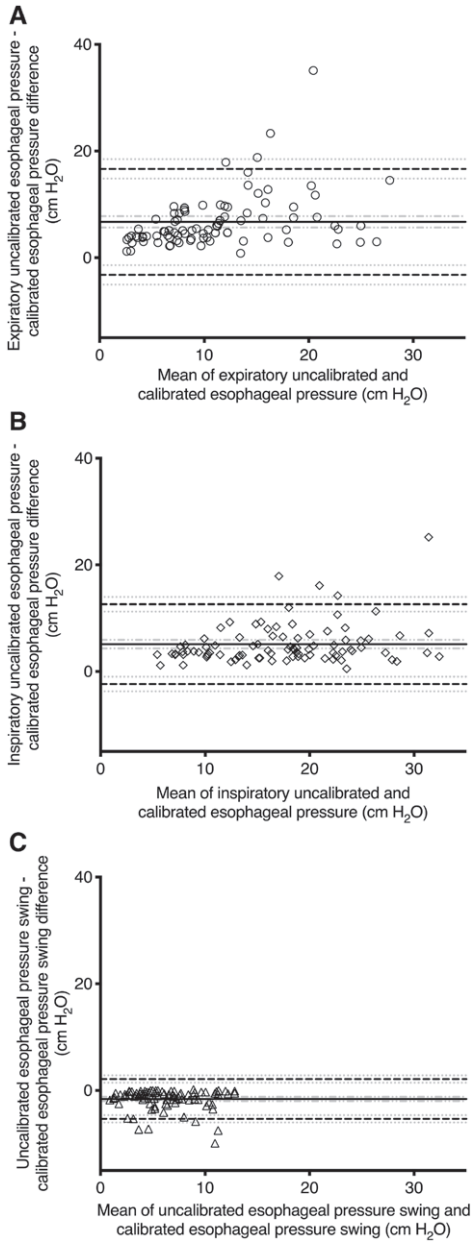

Fig. 2. Bland–Altman analysis of esophageal pressure. Bland–Altman analyses of agreements between uncalibrated and calibrated esophageal pressure showing bias (*continuous line*) with the related 95% CI (*dashed/dotted lines*), lower limit of agreement (*dashed line*), upper limit of agreement (*dashed line*), and the associated 95% CI. (*A*) *Hollow circles*, agreement between uncalibrated and calibrated esophageal pressure at end-expiration, 6.7 (5.7 to 7.8) cm H_2O, −3.2 (−5.0 to −1.4) cm H_2O, 16.7 (14.8 to 18.5) cm H_2O. (*B*) *Hollow parallelograms*, agreement between uncalibrated and calibrated esophageal pressure at end-inspiration, 5.1 (4.3 to 5.9) cm H_2O, −2.4 (−3.7 to −1.0) cm H_2O, 12.6 (11.2 to 14.0) cm H_2O. (*C*) *Hollow triangles*, agreement between uncalibrated and calibrated esophageal pressure swing, −1.6 (−2.0 to −1.2) cm H_2O, −5.3 (−6.0 to −4.6) cm H_2O, 2.1 (1.5 to 2.8) cm H_2O.

in 36 of 90 cases (40.0%) and potentially harmful in 13 of 90 (14.4%). For the esophageal pressure swing, the bias did not change with the value of esophageal pressure as shown by slope analysis (slope, −0.0; 95% CI, −0.2 to 0.1; $P = 0.460$).

In 27 (30%) cases, time length of the calibration procedure was measured, and it was 11.5 [11.0, 13.0] min (range, 10.0 to 15.0 min).

Discussion

In the current study, the esophageal balloon calibration was systematically applied in a clinical setting characterized by variable abdominal load and chest wall elastance (*i.e.,* elective pelvic robotic surgery). The main findings can be summarized as follows: (1) the esophageal balloon calibration was successfully and repeatedly performed in a setting characterized by a high variability of intrathoracic pressure; (2) by optimizing the balloon filling volume at each measurement, as opposed to the use of standard 4-ml recommended volume, validation occlusion test was always passed; and (3) uncalibrated measurements substantially overestimated absolute values and underestimated respiratory variations of esophageal pressure as assessed by the calibrated technique.

The esophageal balloon calibration has been carried out in bench[16,24] and clinical settings, such as acute respiratory failure or postoperative patients admitted to the intensive care unit.[5,6,17,25] Its clinical impact is uncertain and it is not clear whether the time eventually spent by healthcare professionals to perform the procedure at bedside is justified. Thus, we compared calibrated and uncalibrated esophageal pressure measurements in a clinical setting (*e.g.,* pelvic robotic surgery) where chest wall mechanics change over time because of pneumoperitoneum, head-down position, and PEEP application.[12–15] In our patients, we observed substantial variations of the abdominal load (as suggested by baseline end-expiratory esophageal pressure changes) and chest wall elastance (as suggested by esophageal pressure tidal swing changes). It is recommended that esophageal balloon calibration be performed each time a substantial change of intrathoracic pressure is suspected. In fact, esophageal balloon optimal filling volume depends on the surrounding intrathoracic pressure, and baseline artifacts are in turn related to esophageal balloon volume.[4–9,16,17] Thus, we hypothesized that in a clinical setting characterized by substantial changes of chest wall properties, the difference between uncalibrated and calibrated esophageal pressure measurement could be clinically relevant. In all of our patients, esophageal balloon calibration was successfully performed at each study step, thus confirming its feasibility in the current setting. On the other hand, the two-step calibration procedure is moderately complex and time consuming (10 to 15 min in our investigation), thus physicians may be reluctant to perform it systematically in their everyday clinical practice, therefore, the integration of a simplified or automatic procedure in mechanical ventilators and/or in monitoring systems is desirable.[1,8,25]

The first step of the calibration procedure is the balloon filling volume optimization aiming to: (1) maximize the transmission of respiratory changes of pleural pressure; and (2) avoid balloon overstretching and the associated balloon elastic recoil. To validate the esophageal pressure measurement, a test is usually performed to check whether the transmission of changes of pleural pressure is almost complete. It was recently demonstrated that in intubated, paralyzed, acute respiratory failure patients undergoing controlled mechanical ventilation, the validation test is passed in a higher number of cases by applying an optimized filling volume compared to a standard volume.[5] Therefore, in case of an unsuccessful validation test, the balloon volume should be checked and optimized before any attempt to improve the balloon position. In the current study, the optimization of filling volume allowed the validation test to be passed in all cases, which is in agreement with results from the original description of the procedure. On the contrary, when the 4-ml volume was employed, the test was passed in less than 50% of the attempts, suggesting that, to save time, the balloon filling optimization should be performed even before the validation test. Moreover, the optimal filling volume progressively increased in our patients when pneumoperitoneum, Trendelenburg, and PEEP were subsequently applied. This is consistent with previous observations[5] and underlines the need to recheck the balloon filling whenever an intrathoracic pressure change is likely.

The second step of the calibration procedure is the esophageal elastance assessment to quantify, and eventually remove from esophageal pressure measurement, the pressure generated by the esophageal wall as a reaction to the increased cross-sectional area of the balloon. This artifact affects the absolute value of esophageal pressure that becomes substantially higher than the corresponding pleural one. When direct uncalibrated measurements of esophageal pressure are performed, disproportionally high values are usually recorded.[26] This is not an exclusive problem of large balloons; the same or even larger effect can be observed with small balloons for adult and pediatric use as well.[6,7] In human cadavers and pigs, when the baseline artifact related to esophageal elastance was taken into account while filling the esophageal catheter, then esophageal pressure reflected the absolute value of the intrathoracic pressure at mid-level of the chest.[9]

A second mechanism by which the measured esophageal pressure can further increase above the pleural value is the already mentioned balloon overstretching. The calibration procedure, avoidance of balloon overstretching, and removal of the effect of esophageal elastance make esophageal pressure absolute values closer to the pleural ones.[5,8,9]

Absolute esophageal pressure is used to compute transpulmonary pressure and personalize mechanical ventilation setting,[10,27,28] to limit known mechanisms of ventilator-induced lung injury such as cyclic opening and closing of distal airways and alveoli (atelectrauma) and tidal lung overdistention (barovolotrauma). In fact, it was suggested that atelectrauma can be avoided by setting PEEP to maintain slightly positive end-expiratory transpulmonary pressure, whereas limiting end-inspiratory transpulmonary pressure can prevent lung overdistention.

Does the improvement of the absolute esophageal pressure measurement justify the effort of performing the calibration procedure? The results of our study suggest that this is probably the case.

In our setting, direct uncalibrated esophageal pressure measurements substantially overestimated the calibrated values at both end-expiration and end-inspiration at each study step. The gap was clinically relevant in almost all cases and potentially harmful in 30 to 50% of cases. Such an overestimation of the absolute pleural pressure may lead to setting unnecessarily high PEEP and inspiratory lung stress exceeding the safe threshold, when an esophageal pressure–guided mechanical ventilation strategy is adopted.

This discrepancy between calibrated and uncalibrated measurements may also explain the limited clinical impact of a noncalibrated esophageal pressure–guided ventilation when compared to standard practice.[27,29]

To note, in our study, the use of the recommended 4-ml filling volume was associated with a larger overestimation of absolute esophageal pressure than in the original study, when the same procedure was performed with the same catheter but in a different setting.[5] Three main factors can explain this difference. First, the optimal filling volume was in average 2 ml in our patients, whereas it was 3.5 ml in the original study (*i.e.,* closer to the 4-ml volume). Second, the esophageal elastance was higher in our study: on average, 1.7 *versus* 1.1 cm H_2O/ml. These differences are probably related to the different setting: head-down position of patients undergoing elective surgery with pneumoperitoneum *versus* head-up position of acute respiratory failure patients. Accordingly, the increase of esophageal wall pressure associated with the use of 4 ml instead of the optimal volume was much higher in our investigation than in the previous one (on average, 4 cm H_2O *vs.* 1 cm H_2O). Third, the 4-ml recommended volume was higher than the maximal balloon filling volume in more than 40% of measurements in our patients, whereas this was almost never the case in the previous study. At volumes larger than the maximal filling volume, the balloon is overstretched and generates some elastic recoil pressure; the esophageal balloon wall pressure in our study was, on average, 3 cm H_2O, with values as high as 18 cm H_2O.

Limitations

Our study has several limitations. First, the number of patients included was relatively small, although large enough to conduct a feasibility study.[30] However, the total number of esophageal calibration procedures was similar or greater than that reported in previous studies.[5,19,23] Second, our investigation was conducted in a mixed population,

composed of normal and overweight subjects; differences in response to esophageal balloon filling[31] have been reported, related both to patient gender and body mass index.[32] Third, only one specific type of esophageal catheter was used in the study; however, the calibration procedure can be successfully performed with all the esophageal catheters available for clinical use, provided that the filling volumes range is adapted to the balloon size.[16,20,24] Fourth, the study was conducted in patients undergoing pelvic robotic surgery; findings cannot be directly applied to acute respiratory failure patients. Fifth, the validation test, *via* manual chest compressions during an end-expiratory occlusion maneuver, was performed only at baseline to avoid interferences with surgical procedures[33]; however, special care was taken to avoid any displacement of the catheter during the study and balloon filling was optimized at each study step per protocol. Last, the thresholds used to define the difference between uncalibrated and calibrated esophageal pressure as clinically relevant or potentially harmful were arbitrarily chosen.

In conclusion, in a clinical setting characterized by a variable abdominal load and chest wall elastance, esophageal manometry integrated with the balloon calibration is feasible and should allow more accurate estimate of absolute values and respiratory changes of pleural pressure. Conversely, the traditional uncalibrated approach is poorly reliable in this setting, because of artifacts related to esophageal wall and balloon itself, with possible adverse implications if a mechanical ventilation strategy guided by esophageal pressure is adopted.

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Competing Interests

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