A novel method for transpulmonary pressure estimation using fluctuation of central venous pressure

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Abstract

The objective of the study is to develop a correction method for estimating the change in pleural pressure (ΔP_{pl}) and plateau transpulmonary pressure (P_L) by using the change in central venous pressure (ΔCVP). Seven children (aged < 15 years) with acute respiratory failure ($PaO_2/FiO_2 < 300$ mmHg), who were paralyzed and mechanically ventilated with a PEEP of < 10 cmH₂O and had central venous catheters and esophageal balloon catheters placed for clinical purposes, were enrolled prospectively. We compared change in esophageal pressure (ΔP_{es}), ΔCVP , and ΔP_{pl} calculated using a corrected ΔCVP (c ΔCVP -derived ΔP_{pl}). c ΔCVP -derived ΔP_{pl} was calculated as $\kappa \times \Delta CVP$, where κ was the ratio of the change in airway pressure (ΔP_{aw}) to ΔCVP during the occlusion test. c ΔCVP -derived ΔP_{pl} correlated better than ΔCVP with ΔP_{es} ($R^2=0.48$, $p=0.08$ vs. $R^2=0.14$, $p=0.4$) with lesser bias and precision in Bland–Altman analysis. The plateau P_L calculated using the c ΔCVP -derived ΔP_{pl} (17.6 ± 2.6 cmH₂O) correlated well with the ΔP_{es} -derived plateau P_L (18.1 ± 2.3 cmH₂O) ($R^2=0.90$, $p=0.001$). Our correction method can estimate ΔP_{pl} and plateau P_L from ΔCVP with a reasonable accuracy in paralyzed and mechanically ventilated pediatric patients with respiratory failure.

Keywords Central venous pressure · Esophageal pressure · Mechanical ventilation · Pleural pressure · Respiratory failure · Transpulmonary pressure

1 Introduction

Optimizing the transpulmonary pressure (P_L) has been proposed as an integral component of the lung protective strategy in the management of acute respiratory distress

syndrome (ARDS) [1]. Determination of P_L requires the measurement of the esophageal pressure (P_{es}), which is a surrogate of pleural pressure (P_{pl}), by using an esophageal balloon catheter [2]. However, the measurement of P_{es} is complicated by technical issues, including issues related to correct positioning of the esophageal catheter, acquisition of accurate measurements, and interpretation of absolute P_{es} values [3]. This explains, at least in part, why the

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measurement of Pes is not widely used in clinical settings [4, 5].

The uncertainty associated with using the absolute Pes value as a surrogate of Ppl can be partly overcome by using a method recently developed by Grasso et al. [1] in which the change in Pes (Δ Pes), instead of the absolute value, is used to derive the plateau P_L . In this so-called elastance method, plateau P_L can be calculated as follows:

$$\text{Plateau } P_L = P_{\text{plat}} \times (\Delta P - \Delta P_{\text{pl}}) / \Delta P \quad (1)$$

where P_{plat} is plateau pressure and ΔP is driving pressure (plateau pressure – peak end-expiratory pressure). Since ΔP_{pl} can be substituted by Δ Pes, Eq. (1) can also be expressed as follows:

$$\text{Plateau } P_L = P_{\text{plat}} \times (\Delta P - \Delta \text{Pes}) / \Delta P \quad (2)$$

This method does not require an absolute value of Pes, which can be influenced by several factors, including the balloon size, filling volume of the balloon, and elastance of the esophageal wall [6–8]; nonetheless, it still requires an esophageal balloon to obtain Δ Pes values.

The idea of estimating of P_L without using an esophageal balloon catheter is attractive. The validity of using the change in central venous pressure (Δ CVP) as a surrogate of ΔP_{pl} has been examined for decades [9, 10]. However, several studies have reported that Δ CVP does not always accurately reflect ΔP_{pl} [11], especially when the CVP is high [12]. Accordingly, Δ CVP has not been accepted as a surrogate of ΔP_{pl} . Furthermore, whereas the estimation of ΔP_{pl} by using Δ CVP has been attempted [9], there has not been a report of using Δ CVP to estimate the plateau P_L : another important variable used in the lung protective strategy [13].

The primary objective of this study was to develop and test the validity of a method of estimating ΔP_{pl} by using Δ CVP; this method, would obviate the need of the esophageal balloon catheter. The secondary objective was to estimate the plateau P_L using our correction method and demonstrate that the obtained plateau P_L approximates well the plateau P_L derived from Δ Pes (Δ Pes-derived plateau P_L). A part of this work was previously presented at the 47th Critical Care Congress of the Society of Critical Care Medicine [14].

2 Methods

2.1 Study design and patient selection

This prospective study was conducted in the PICU of a tertiary children's hospital. The study was approved by the institutional review board (Approval Number: 904). Patients who were younger than 15 years with acute respiratory

failure ($\text{PaO}_2/\text{F}_i\text{O}_2 < 300$ mmHg), were hemodynamically stable without ongoing fluid resuscitation and mechanically ventilated under neuromuscular blockade with a positive end-expiratory pressure (PEEP) of < 10 cmH₂O, and had central venous catheters (CVCs) and esophageal balloon catheters placed for clinical purposes, were enrolled for 4 months ending July 2016. We excluded patients in whom the correct positioning of the esophageal balloon catheter could not be confirmed.

2.2 Setting for measurement and recording

A CVC (SMAC™ Plus double 17G, Medtronic, Dublin, Ireland) was placed via the internal jugular vein, with the tip located in the superior vena cava (SVC). Airway pressure (Paw) was measured at the junction of the respirator circuit and endotracheal tube. An esophageal balloon catheter (AVEA™ Ventilator Esophageal Pressure Monitoring Tube, IMI, Saitama, Japan) was nasally inserted into the mid-lower third of the esophagus. Pes was measured in the supine position. Correct positioning of the esophageal balloon catheter was confirmed using the positive pressure occlusion test (OT) [3, 15]. The test was performed by measuring the changes in Pes and Paw (Δ Pes and Δ Paw, respectively) while the chest wall of a paralyzed patient was compressed. Specifically, the airway opening was occluded at the end-expiration and the rib cage was gently squeezed to an extent that Paw on the bedside monitor increased by approximately 10 cmH₂O. This process was repeated three times and the values were averaged for analysis (Fig. 1A). The catheter position was deemed correct when the ratio of Δ Pes to Δ Paw was between 0.8 and 1.2 [3].

CVP, Pes, and Paw were simultaneously displayed on a bedside monitor (BSM-6701, Nihon Kohden, Tokyo, Japan), which used pressure transducers of the same model (pediatric TruWave pressure monitoring transducer, Edwards, California, United States), and the data were automatically transferred to and recorded in an electric medical chart system (GAIA, Nihon Kohden, Tokyo, Japan) every 0.004 s using digital signals. Because the Paw, Pes, and CVP waveforms have cardiogenic oscillations, pressure values at the peak of the cardiogenic oscillations were used in the calculations (Fig. 1B).

2.3 Measurement and comparison of three variables that reflect ΔP_{pl}

First, we measured three variables that reflect ΔP_{pl} : Δ Pes, Δ CVP, and ΔP_{pl} calculated using the corrected Δ CVP (c Δ CVP-derived ΔP_{pl}). To calculate ΔP_{pl} by using the correction method, OT was performed to obtain a ratio of Δ Paw to Δ CVP (Fig. 1B). This ratio is expressed as “k” and it is

Fig. 1 Pressure waveforms of CVP, Pes, and Paw during the positive pressure occlusion test (**A**) and during the mechanical ventilation (**B**). **A** During chest compressions in the occlusion test, Pes and Paw waveforms fluctuate in a similar manner. The ratio of ΔPaw to ΔCVP was obtained and expressed as “κ.” Note that ΔPaw should be equal to ΔPpl during occlusion test provided the esophageal balloon catheter position is correct. **B** During mechanical ventilation, ΔPpl can be

calculated by multiplying κ with ΔCVP, assuming the ratio of ΔPpl to ΔCVP during the occlusion test and during mechanical ventilation was the same. Pressure values at the peak of the cardiogenic oscillations were used for calculation. CVP central venous pressure, Pes esophageal pressure, Paw airway pressure, ΔPes change in esophageal pressure, ΔPaw change in airway pressure, ΔCVP change in central venous pressure, ΔPpl change in pleural pressure

presumably the same as the ratio of ΔPpl to ΔCVP because ΔPaw should be equal to ΔPpl during airway occlusion. Next, the patient was placed back to the original ventilator settings. After 5 min of stabilization, ΔPes and ΔCVP were measured during mechanical ventilation. Assuming the ratio of ΔPpl to ΔCVP during the occlusion test and during mechanical ventilation is the same, cΔCVP-derived ΔPpl can be expressed as follows:

$$\text{c}\Delta\text{CVP-derived } \Delta\text{Ppl} = \kappa \times \Delta\text{CVP during the mechanical ventilation} \quad (3)$$

where κ is a ratio of ΔPaw to ΔCVP during OT.

Next, the three variables were compared. Since ΔPes is widely accepted as a gold standard surrogate for ΔPpl [3], we assumed ΔPes was equal to ΔPpl. Then, we examined whether ΔCVP and cΔCVP-derived ΔPpl could reasonably estimate ΔPes.

2.4 Calculation and comparison of plateau P_L by using ΔPes and cΔCVP-derived ΔPpl

Each of the variables obtained in the above-described process was used to calculate the plateau P_L (ΔPes-derived plateau P_L and cΔCVP-derived plateau P_L). ΔPes-derived plateau P_L was calculated using Eq. (2). Based on Eqs. (1) and (3), cΔCVP-derived plateau P_L was calculated as follows:

$$\begin{aligned} \text{c}\Delta\text{CVP-derived plateau } P_L &= P_{\text{plat}} \times (\Delta P - \text{c}\Delta\text{CVP-derived } \Delta\text{Ppl}) / \Delta P \\ &= P_{\text{plat}} \times (\Delta P - \kappa \times \Delta\text{CVP during mechanical ventilation}) / \Delta P \end{aligned}$$

Finally, cΔCVP-derived plateau P_L was compared to ΔPes-derived plateau P_L , which was used as a gold standard surrogate for plateau P_L , to examine how closely and reliably they approximate each other.

2.5 Statistics

Continuous variables are presented as means ± standard deviations and were compared using the Student's *t* test. The Bland–Altman analysis was used to analyze agreements between ΔCVP and ΔPes, between cΔCVP-derived ΔPpl and ΔPes, and between cΔCVP-derived plateau P_L and ΔPes-derived plateau P_L . The correlation of ΔCVP and cΔCVP-derived ΔPpl with ΔPes was tested, and the correlation of cΔCVP-derived plateau P_L with ΔPes-derived plateau P_L was also tested. A *p* value of less than 0.05 was considered statistically significant for all analyses. Analyses were performed using EZR Ver. 1.36 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

3 Results

Twelve patients were enrolled in this study; five of them were excluded because correct positioning of the esophageal balloon could not be confirmed during the OT. Therefore, seven patients were included in the final analysis. The patient characteristics are shown in Table 1.

Table 1 Patient characteristics

Case	Age (months)	Weight (kg)	Diagnosis	Pplat/PEEP (cmH ₂ O)	PaO ₂ /F _i O ₂ (mmHg)	CVP (mmHg)	TV (ml/kg)
1	1	2.6	S/P cardiac surgery ^a	20/6	195	8	7.0
2	4	3.9	S/P cardiac surgery	19/5	168	5	9.6
3	31	10.8	Pneumonia	23/9	243	9	8.3
4	1	3.2	S/P cardiac surgery	26/6	96	7	10.1
5	0	2.8	S/P cardiac surgery	21/6	188	13	10.8
6	0	3.1	S/P cardiac surgery	22/6	204	10	9.7
7	12	7.7	Pneumonia	21/7	260	5	10.0
Mean ± SD	7 ± 11	4.8 ± 2.9		22 ± 2/6.4 ± 1.2	193 ± 50	8.1 ± 2.7	9.4 ± 1.2

^aPostoperative respiratory failure after correction of congenital heart disease

3.1 Measurement and comparison of three variables that reflect ΔP_{pl}

Means and standard deviations of the three variables that reflect ΔP_{pl} (ΔP_{es} , ΔCVP , and $c\Delta CVP$ -derived ΔP_{pl}) were 3.0 ± 0.8 cmH₂O, 1.8 ± 0.5 cmH₂O, and 2.7 ± 0.6 cmH₂O (Table 2). Correlations of ΔCVP and $c\Delta CVP$ -derived ΔP_{pl} with ΔP_{es} are shown in Fig. 2A; $c\Delta CVP$ -derived ΔP_{pl} correlated better with ΔP_{es} than ΔCVP did ($R^2 = 0.48$, $p = 0.083$ vs. $R^2 = 0.14$, $p = 0.407$). The Bland–Altman analysis for the agreement between $c\Delta CVP$ -derived ΔP_{pl} and ΔP_{es} showed a bias of 0.3 cmH₂O and precision of 0.6 cmH₂O, whereas the bias and precision were 1.2 cmH₂O and 0.8 cmH₂O, respectively, for the agreement between ΔCVP and ΔP_{es} . Both bias and precision were lesser when using $c\Delta CVP$ -derived ΔP_{pl} compared with when using ΔCVP (Fig. 2B, C).

3.2 Calculation and comparison of plateau P_L by using the ΔP_{es} and $c\Delta CVP$ -derived ΔP_{pl}

ΔP_{es} -derived plateau P_L and $c\Delta CVP$ -derived plateau P_L were 17.6 ± 2.6 cmH₂O and 18.1 ± 2.3 cmH₂O, respectively.

Correlations of $c\Delta CVP$ -derived plateau P_L with ΔP_{es} -derived plateau P_L are shown in Fig. 3A. The $c\Delta CVP$ -derived plateau P_L correlated well with ΔP_{es} -derived plateau P_L ($R^2 = 0.90$, $p = 0.001$). The Bland–Altman analysis for the agreement between $c\Delta CVP$ -derived plateau P_L and ΔP_{es} -derived plateau P_L showed a bias of -0.4 cmH₂O and precision of 0.8 cmH₂O (Fig. 3B).

4 Discussion

We have developed a novel correction method to estimate ΔP_{pl} by using ΔCVP in paralyzed and mechanically ventilated pediatric patients with acute respiratory failure. The correction method was able to estimate ΔP_{es} more accurately than the method using ΔCVP . Furthermore, the $c\Delta CVP$ -derived plateau P_L (plateau P_L derived from ΔCVP by using our correction method) had high correlation with ΔP_{es} -derived plateau P_L .

Monitoring and limiting the tidal change in P_L (ΔP_L) and plateau P_L has been recommended to minimize the stress applied to the lungs in patients with ARDS [13]. However,

Table 2 Variables measured to obtain the change in pleural pressure and plateau transpulmonary pressure

Case	$\Delta P_{es}/\Delta P_{aw}$ during OT	$\Delta P_{aw}/\Delta CVP$ during OT (κ)	ΔP_{es} (cmH ₂ O)	ΔCVP (cmH ₂ O)	$c\Delta CVP$ -derived ΔP_{pl} (cmH ₂ O)	ΔP_{es} -derived plateau P_L (cmH ₂ O)	$c\Delta CVP$ -derived plateau P_L (cmH ₂ O)
1	0.84	1.23	2.9	2.5	3.1	15.8	15.5
2	0.91	1.55	2.5	1.1	1.7	15.6	16.8
3	0.80	1.35	3.0	1.9	2.6	18.1	18.7
4	1.05	1.63	3.0	1.5	2.5	22.2	22.8
5	0.95	1.92	2.8	1.5	2.8	17.0	17.0
6	0.84	1.33	2.3	2.2	2.9	18.8	18.1
7	0.89	1.62	4.8	2.3	3.7	13.8	15.5
Mean ± SD	0.90 ± 0.08	1.52 ± 0.22	3.0 ± 0.8	1.8 ± 0.5	2.7 ± 0.6	17.3 ± 2.5	17.8 ± 2.3

ΔP_{es} change in esophageal pressure, ΔP_{aw} change in airway pressure, OT occlusion test, ΔCVP change in central venous pressure, ΔP_{pl} change in pleural pressure, $c\Delta CVP$ -derived ΔP_{pl} ΔP_{pl} calculated using a corrected ΔCVP , ΔP_{es} -derived plateau P_L plateau P_L derived from ΔP_{es} , $c\Delta CVP$ -derived plateau P_L plateau P_L derived from corrected ΔCVP

Fig. 2 Correlations of Δ CVP and $c\Delta$ CVP-derived Δ Ppl with Δ Pes (A) and the Bland–Altman analysis for the agreement between Δ CVP and Δ Pes (B) and between $c\Delta$ CVP-derived Δ Ppl and Δ Pes (C). A A solid line represents a simple linear regression line of Δ CVP. A broken line represents a simple linear regression line of $c\Delta$ CVP-derived

Δ Ppl. B, C Solid lines, bias (B 1.2 cmH₂O, C 0.3 cmH₂O); broken lines, ± 1.96 SD of the bias (B 2.7, -0.3 cmH₂O; C 1.5, -0.8 cmH₂O). Δ CVP change in central venous pressure, Δ Ppl change in pleural pressure, $c\Delta$ CVP-derived Δ Ppl Δ Ppl calculated using a corrected Δ CVP, Δ Pes change in esophageal pressure

Pes monitoring is still seldom used in the implementation of such a strategy in clinical settings, partly due to the difficulty of properly positioning the esophageal balloon, of finding the best filling volume of the balloon, and of interpreting the obtained values [3]. The elastance method that uses the change in Pes during mechanical ventilation, instead of the absolute values, to calculate chest wall elastance can overcome the challenge of obtaining accurate absolute Pes values [1]. Furthermore, a calibration procedure to make the measurement of absolute values of Pes more reliable by finding the best filling volume may help in the implementation of Pes measurement in clinical settings [7]. However, these methods still require an esophageal balloon and some degree of expertise. Accordingly, esophageal balloons were used in only 0.8% of the patients with ARDS in a recent survey [16].

On the other hand, it is not uncommon for the mechanically ventilated patient with respiratory failure to have a CVC inserted via internal jugular vein. Changes in the Ppl that are associated with respiration are reflected in the changes in CVP obtained from SVC [12]. Studies have been conducted to investigate whether Δ CVP can be used to estimate Δ Ppl without using an esophageal balloon catheter.

Although several studies have shown there is some correlation of Δ CVP with Δ Pes [9, 10, 17], conflicting data showing there is poor correlation have also been reported [11, 12]. Consequently, the use of Δ CVP as a surrogate of Δ Ppl, while appealing, is not widely accepted. Thus, we developed a simple correction method that would make it possible to derive Δ Ppl from Δ CVP without an esophageal balloon catheter. Our study demonstrated that our correction method improved the accuracy of Δ Ppl estimation by using Δ CVP in paralyzed, mechanically ventilated pediatric patients. Furthermore, our correction method could be used to estimate the plateau P_L with a clinically acceptable accuracy without using an esophageal balloon.

There were several limitations in our study. First, our study was conducted in a small population. In our experience, it is not uncommon for pediatric patients to fail OT even if the position of the balloon appears appropriate on X-ray. We aimed to include 10 patients for the final analysis based on the population size ($n=9-10$) of the previous studies [9, 10]. We enrolled 12 patients with the assumption that about 15% of the patients would not pass the occlusion test. In the current study, however, 5 (42%) of 12 cases were

Fig. 3 Correlation between cΔCVP-derived plateau P_L and ΔPes-derived plateau P_L (A). The Bland–Altman analysis for the agreement between cΔCVP-derived plateau P_L and ΔPes-derived plateau P_L (B). A broken line represents a simple linear regression line. B A solid line, bias (−0.4 cmH₂O); broken line, ± 1.96 SD of the bias (1.2, −2.1 cmH₂O). cΔCVP-derived plateau P_L plateau P_L derived from the corrected value of change in CVP, ΔPes-derived plateau P_L plateau P_L derived from the change in Pes

excluded because they did not pass OT despite the seemingly correct position of the balloon on the X-ray. This speaks to the necessity of a method to estimate transpulmonary pressure without an esophageal balloon. Second, the patients included in the study were all young. In adults, who have a higher ratio of chest wall elastance to lung elastance, the influence of ΔPpl estimation error on the value of estimated plateau P_L would increase based on Eq. (1). Thus, the estimation of cΔCVP-derived plateau P_L using our correction method may be more prone to errors in adults. Third, in this study, cases of severe ARDS with a high chest wall elastance who would benefit most from transpulmonary pressure measurement were not included. This is partly because we excluded patients requiring PEEP ≥ 10 cmH₂O for whom opening the respiratory circuit to perform OT would be clearly harmful. It remains to be tested whether our method can be applied to such cases with a high chest wall elastance or severe ARDS. Fourth, most of our patients underwent cardiac surgery prior to developing respiratory failure. While the sternum was closed in all patients, it is yet unknown as to how this may have affected their chest wall

properties. Another limitation arises from the assumption that the ratio of ΔPaw to ΔCVP during OT is the same as the ratio of ΔPpl to ΔCVP during mechanical ventilation. We have not confirmed whether this assumption is true in various clinical conditions, such as those associated with extremely high or low CVP levels. Whereas the deviation of ΔCVP from ΔPpl has been reported at different levels of CVP [9, 12], we reasoned that it was unlikely that the absolute CVP values would affect our correction method, which uses the ratio of ΔPaw to ΔCVP. Furthermore, we performed OT immediately before measuring ΔCVP during mechanical ventilation to minimize the possible effects due to the change in intravascular volume status. Nonetheless, further research is required to test whether intravascular volume status affects the accuracy of our method. Finally, it remains unclear whether our method can be applied to spontaneously breathing patients with mechanical ventilatory support because this study was conducted only in paralyzed patients. This could be a potential area of interest in future studies.

In conclusion, we have shown that our correction method can estimate ΔPpl from ΔCVP with a reasonable accuracy in paralyzed and mechanically ventilated pediatric patients with acute respiratory failure. The method can help in the assessment of ΔP_L and plateau P_L without using an esophageal balloon catheter. Validity of our correction method needs to be confirmed in various patient populations.

Author contributions MK designed the study, contributed to data collection, interpretation of data and wrote the initial draft of the manuscript. MT designed the study and contributed to analysis. YI contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other authors have contributed to data collection and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Conflict of interest The authors disclose no conflict of interest.

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