Intracranial-to-Central Venous Pressure Gap Predicts the Responsiveness of ICP to PEEP in Patients with Traumatic Brain Injury

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Research article

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Abstract

Background: Mechanical ventilation (MV) with positive end-expiratory pressure (PEEP) is commonly applied in patients with severe traumatic brain injury (sTBI). However, non-indicators to predict the influence of PEEP on intracranial pressure (ICP) prevent the optimal use of PEEP. As the central venous pressure (CVP) could act as an intermediary to transduce the pressure from PEEP to ICP, we set up a new indicators PICGap (representing the gap between the baseline ICP and baseline CVP). The aim of the study was to explore the relationship between PICGap and the ICP responsiveness to PEEP. Methods: Total 112 patients with sTBI undergoing MV were finally enrolled. ICP, CVP, cerebral perfusion pressure (CPP), static compliance of respiratory system (Cst), and end-tidal carbon dioxide pressure (PetCO2) were recorded at initial level of PEEP (3 cmH2O) and adjusted levels of PEEP (15 cmH2O). PICGap was calculated by baseline ICP - baseline CVP (when PEEP=3 cmH2O). The patients enrolled were classified into either an ICP responder group or a non-responder group based on whether the increment of ICP when PEEP adjustment from 3 cmH2O to 15 cmH2O was greater than or less than 20% of baseline ICP. Parameters recorded above were compared between two groups and the prediction of ICP responsiveness to PEEP adjustment were evaluated by receiver operating characteristic (ROC). Results: Responder group had lower PICGap, lower baseline ICP, and higher baseline CVP compared with non-responder group. ROC analysis suggested that PICGap could act as a strongest predictive indicator for the ICP responsiveness to PEEP (AUC = 0.957, 95% CI: 0.918 - 0.996, p <0.001) compared with baseline ICP and baseline CVP, with a favorable sensitivity of 95.24% (95% CI: 86.91% - 98.70%) and specificity of 87.6% (95% CI: 75.76% - 94.27%) when the cut off value of 2.5mmHg was determined. Conclusion: The impact of PEEP on ICP depends on the GAP of between baseline ICP and baseline CVP, i.e. PICGap. The PICGap could be a potential predictor for ICP responsiveness to PEEP adjustment in patients with sTBI.

Background

The application of positive end-expiratory pressure (PEEP) during mechanical ventilation (MV) is essential to improve oxygenation and protect against mechanical lung injury, by increasing functional residual capacity, preventing atelectasis, reducing oxygen requirement, and raising static strain component[1-3]. MV with PEEP is often required in patients with severe traumatic brain injury (sTBI) due to neurologic, airway, pulmonary dysfunctions, etc.[4, 5].

However, concerning of the influence of PEEP on intracranial pressure (ICP) has been an obstacle of the optimal use of PEEP for a long time [6]. The influence of PEEP on ICP was first mentioned in the later 1970s [7, 8]. During last three decades, several studies explored the relationship between PEEP and ICP, but without consistent results. Shapiro et al demonstrate that application of PEEP in the 4–8 cm H_2O range caused an increase of ICP (>10 mmHg) [7]. Flexman and colleagues also found that alveolar recruitment maneuvers increased subdural pressure and reduced cerebral perfusion pressure (CPP) during neurosurgery[9]. Recent study by Boone et al found that every centimeter H_2O increase of PEEP contributed to a 0.31 mmHg increase in ICP [10], and concluded that PEEP might exert adverse effects on cerebral hemodynamics through impeding cerebral venous return and elevating ICP in patients with sTBI.

However, other studies didn't find that moderate to high level of PEEP (8-25 cmH_2O) affect ICP, CPP, and CBF of sTBI patients with normal ICP or intracranial hypertension, and even has favorable effects on improving brain tissue oxygen pressure and saturation [11-14]. The discordance of the results might relate to several factors: (1) the individual heterogeneity exists mainly involving severity and baseline ICP [15]; (2) the dose-effect relationship between PEEP and ICP hasn't been fully studied; and (3) it is unclear whether PEEP directly affects ICP or indirectly through an intermediate.

Until now, there is still non-indicators to predict the influence of PEEP on ICP. Theoretically increasing intrathoracic pressure by PEEP may hinder cerebral venous return and increase ICP when MV for patients with sTBI, and the relationship between CVP and PEEP has been clarified [16, 17]. Therefore, we hypothesized, (1) CVP could act as a mediator between PEEP and ICP, (2) the effect of PEEP on ICP depends on the baseline of ICP and baseline CVP according to Starling resistor model (Figure 1). Herein, we defined a new indicator $P_{IC}Gap$, which represents the difference value between baseline ICP and baseline CVP (at initial PEEP), and explored the association between $P_{IC}Gap$ and the ICP responsiveness to PEEP adjustment.

Methods

Patient Inclusion Criteria

This prospective study was conducted between May 2016 and May 2019 in the intensive care unit (ICU) of Zhoupu Hospital, affiliated to Shanghai University of Medicine & Health Sciences. All patients diagnosed with sTBI (Glasgow Coma Scale [GCS] ≤8) and started on MV (Dräger Infinity C500, Dräger, Germany) were initially included. The patients whose hypoxemia (SpO_2<90%) still could not be corrected through increasing the FiO_2 more than 60% in combination with suction and intensive airway management were eventually enrolled in the study.

Exclusion criteria included: brain death, age below 18 or over 80 years, pregnancy, hemodynamic instability [heart rate >120 bpm or CPP (calculated by MAP-ICP) <60 mmHg], pneumothorax, pulmonary bulla, and acute myocardial infarction (elevated cardiac troponin T more than 3 times the normal upper limit accompanied by the ST-T change) etc. Approval for study conduct was granted by the clinical research ethics committee (no. ZPYYLL-2016-12), and written consent was obtained from all participants' next of kin.

Design and measurement

The treatment program was implemented referring to the Guidelines for the Management of sTBI [18]. All patients were in supine position at 30 degrees head of bed elevation and deeply sedated (0.05 mg/kg loading dose, followed by continuous intravenous infusion of midazolam 0.05–0.3 mg/kg/h and sufentanil 0.2 μg/kg/h) to maintain the Richmond Agitation-Sedation Scale (RASS) score of −5 and, thus, to remove the interference of cough and other neuronal and confounding factors on ICP. The ventilator

settings remained consistent for each enrolled patient. The tidal volume was adjusted and maintained at 8 mL/kg of predicted body weight and the plateau pressure was maintained below 30 cmH_2O. Support pressure was maintained at 12-14 cmH_2O, initial PEEP was set at 3 cmH_2O, and fraction of inspired oxygen (FiO_2) was set at 35% - 50% to maintain pulse oxygen saturation (SpO_2)>90%. The ICP was continuously monitored (Codman ICP ExpressTM, Johnson, USA) through an intraparenchimal transducers or ventricular catheter (Codman ICP Transducer, Johnson, USA) that was associated with a closed external ventricular drain if it existed during each measurement. Both central venous and arterial catheters were inserted to measure intra-arterial MAP and CVP. CPP was maintained more than 60-65mmHg. The static compliance of respiratory system (Cst) recorded from ventilator was indexed to the predicted body weight of the patients. During the study, the end-tidal carbon dioxide pressure ($PetCO_2$) (monitoring by Drager Mainstream CO_2 device, SN: ASHM-0552, Dräger, Germany) was maintained at 30-35 mmHg by adjusting tidal volume and respiratory rate, in order to avoid any effect of CO_2 on ICP [19].

The stepwise increase of PEEP was set according to the method by Lim et al [20] when the hypoxemia persisted. Briefly, 100%-FiO_2 was set up and PEEP was increased stepwise (from 3 cmH_2O to 10 cmH_2O, and to 15 cmH_2O) every 2 min, which was a recruitment maneuver known as “extended sigh”. ICP, CVP, Cst, $PetCO_2$, and CPP at the two levels of PEEP (3 cmH_2O and 15 cmH_2O) were measured respectively. After PEEP at 15 cmH_2O maintained for 2 min, baseline ventilator setting was resumed.

Based on our research hypothesis and specific relationships between CVP and PEEP[16, 17], P_{IC}Gap and other measurements (Cst, CPP, ICP, and $PetCO_2$) were compared between two groups, and the prediction of ICP responsiveness to PEEP was tested by calculating the area under curves (AUC) of the receiver operating characteristic (ROC). Because there is no specified definition of the ICP responsiveness to PEEP adjustment, we stipulated that responder and non-responder referred as to an increment greater than or less than 20% of baseline ICP respectively when PEEP set up to 15 cmH_2O.

During the research, remedied accordingly in case of: (1) CPP < 60 mmHg (norepinephrine 0.3–1.0 μg/kg/min was used); (2) ICP > 25 mmHg (PEEP was restored to 0); (3) increase in pressure plateau >35cmH_2O (tidal volume was decreased and increase respiratory rate to maintain $PetCO_2$ at 30–35mmHg); (4) SpO_2 declined progressively (PEEP was restored to 0); and (5) suspicion of pneumothorax (PEEP was restored to 0, and chest radiography was undertaken). An equilibration period (≥90s) was entailed to ensure a normalized baseline $PetCO_2$ through modulation of tidal volume and respiratory rate, which described by Flexman and colleagues [21].

Statistical analysis

Categorical variables are presented as numbers and percentages and were analyzed by Fisher’s exact test. Continuous covariates, including hemodynamic variables ICP, CVP, CPP, Cst, $PetCO_2$ and CPP, were expressed as means ± standard errors. One-way analysis of variance (ANOVA) followed by the Bonferroni post hoc test was used for multiple comparisons. The predictive role of P_{IC}Gap other related parameters

recorded for ICP responsiveness to PEEP were tested by calculating the AUC of the ROC for ICP over the baseline value at the two levels of PEEP (3 and 15cmH_2O). A *p*-value less than 0.05 was considered statistically significant. All statistical analyses were performed by using SPSS 20.0 for windows (IBM Co. NY, USA).

Results

From May 2016 to May 2019, a total of 112 patients were entered into the final analysis. Baseline characteristics of the study population between responder group (n=49) and non-responder group (n=63) were shown in Table 1. Compared with non-responder group, responder group had lower P_{IC}Gap (1.63±1.33 versus 6.56±2.46 mmHg, p<0.001), lower baseline ICP (9.82 ±2.97 versus 13.10±2.74 mmHg, p<0.001), and higher baseline CVP (8.18 ±2.66 versus 6.54±2.59 mmHg, p=0.001). No severe side effects in terms of ICP, CVP, CPP, and MAP were observed when PEEP was increased to 15 cmH_2O (supplementary materials Table E).

1. The effects of PEEP adjustment on CVP and ICP between responder group and non-responder group.

Adjustment of PEEP from 3 to 15 cmH_2O increased the levels of CVP significantly in two groups (Figure 1A). There were no significantly difference in increment of CVP (ΔCVP) between responder group and non-responder group (4.39±1.30 versus 4.25±1.58, p=0.174) (Figure 1B). A significant increasing of ICP was observed in responder group when PEEP tuned up from 3cmH_2O to 15 mmHg (9.85±2.99 versus14.48±3.22 mmHg, p<0.001) and no change in non-responder group (13.10±2.74 versus 13.71±2.61 mmHg, p=0.196) (Figure 1C). 2. The predictive role of P_{IC}Gap, baseline ICP, and baseline CVP on the responsiveness of ICP to PEEP adjustment .

As showed in Table 1, P_{IC}Gap, baseline ICP, and baseline CVP were significantly different between responder group and non-responder group, and no significant difference was found in the other variables. The predictive ability of P_{IC}Gap, baseline ICP, and baseline CVP were test through ROC. As showed in Figure 3, P_{IC}Gap had the strongest predictive ability for the responsiveness of ICP to PEEP increase (AUC= 0.957, 95% CI: 0.918 - 0.996, p < 0.001) among the three parameters. At the cut off value of 2.5mmHg, P_{IC}Gap had favorable sensitivity of 95.24% (95% CI: 86.91% - 98.70%) and specificity of 87.6% (95% CI: 75.76% - 94.27%) in predicting ICP responsiveness to PEEP. However, baseline ICP had evidently weaker predictive ability than P_{IC}Gap (AUC=0.782, 95% CI: 0.693 - 0.781, p < 0.001) and baseline CVP had the weakest ability to predict the responsiveness among the three parameters (AUC = 0.660, 95% CI: 0.560 - 0.760, p = 0.004).

Discussion

In the present study, based on our hypothesis that CVP was an intermediary which deliveries pressure from PEEP exerted to ICP, we found that ICP was increased after PEEP only when baseline ICP was close

to CVP, i.e. P_{IC}Gap was narrower in responder group than non-responder group (1.63±1.33 versus 6.55±2.46 mmHg) which mean the same increment of CVP (4.39±1.30 versus 4.25±1.58) could disappear the P_{IC}Gap for responder group, but not for non-responder group (Figure 1). We also evaluated the possibility whether the P_{IC}Gap, baseline ICP, and baseline CVP could predict the ICP responsiveness to PEEP in patients with sTBI. The results suggested that P_{IC}Gap should be the strongest predictive indicator among the three parameters. The P_{IC}Gap less than 2.5 mmHg could predict the ICP responsiveness to PEEP tuned up to 15 cmH_2O. To our best knowledge, this is the first study to demonstrate that PEEP-induced changes of ICP depended on P_{IC}Gap rather than PEEP itself.

Although the cerebral hemodynamic is not governed entirely by the extradural venous pressure due to normal ICP (8-13 mmHg) was higher than the venous pressure outside the dura (0-5 mmHg), the changes of extradural venous pressure transfer to the brain circulation might rely on the certain situation [22]. The degree of subdural venous collapse was related to the difference between ICP and extradural venous pressure, and this passive collapse acts as a variable venous outflow resistance. Alteration of extradural venous pressure causes up- or downregulation of venous outflow resistance through the self-regulation of the degree of passive collapse according to the Starling resistor model [23].

CVP could act as a surrogate marker of extradural venous pressure, because the pressure falls in jugular venous was negligible when at supine position. The preliminary experiment also showed that the values of CVP were the same as that of jugular bulb pressure. According to the Starling resistor model [23], once the value of CVP after PEEP exceeded baseline ICP, venous outflow resistance would be down-regulated to the lower limit. In such a situation, the brain circulation would be impeded and ICP rise accordingly.

Relationship between PEEP and CVP has been validated by previous studies. Stepwise PEEP elevation induces an increase of CVP [17]. An increase of 12 cmH_2O of PEEP caused a more than 4 mmHg rise of CVP in current study, which was consistent with previous findings [17]. Thus, it was reasonable to infer that PEEP led to the elevation of CVP directly, and whether CVP after PEEP could increase ICP depended on the extent of CVP narrowing the P_{IC}Gap.

The lower value of P_{IC}Gap means that the CVP after PEEP is easier to exceed baseline ICP, then the Starling resistor would lose effectiveness as a result of the elimination of venous outflow resistance. As indicated in Table 1, patients with responsiveness to PEEP adjustment had the relatively lower P_{IC}Gap compared with the non-responder group. Thus, based on the hypothesis that CVP is an intermediary which connects PEEP to ICP, we found that PICGap, as a new indicator, could provide a rational explanation on the underlying mechanism, which also accounted for the individual heterogeneity proposed by Yang and colleagues [15].

Brain compliance is unfavorable in patients with sTBI because of the cerebral edema caused by injury. In this case, cerebral venous return impeded by elevated CVP after PEEP would contribute to the ICP increasing after P_{IC}Gap got narrowed till to zero. A study by Robba and colleagues investigated the effects of pneumoperitoneum and Trendelenburg position on ICP in non-brain injured patients (lower ICP)

and demonstrated that pneumoperitoneum and the Trendelenburg position increased ICP [24]. There was no significant change in arterial blood pressure and CPP in the study. Although the CVP was not monitored in their studies, increased ICP might be due to obstruction of cerebral venous return theoretically [25].

Several studies used baseline ICP to predict the responsiveness of ICP to PEEP, and found that patients with lower baseline ICP had positive response to various PEEP [26, 27]. There results were consistent with our findings. Those with higher mean baseline ICP experienced no significant changes of ICP during the alteration of PEEP. However, these studies have not clarified that the certain ICP value could predict the responsiveness of ICP to PEEP. Our results also showed that baseline ICP could not be a favorable predictive indicator compared with P_{IC}Gap.

It should be mentioned that the responsiveness of ICP to PEEP may be influenced by compliance of respiratory system [28, 29]. Patients with low-compliance lungs showed that cerebral hemodynamics and ICP were not influenced by the application of PEEP, because less compliance may not transmit the increased pressure to the entire intrathoracic space effectively. In current study, all of the enrolled patients had normal compliance (Table 1).

Several limitations of this study should be mentioned that the sample size is relatively small for a clinical study, and the impact of PEEP on the CBF has not been evaluated. However, we kept $PetCO_2$ maintaining at the normal level, and elevation of ICP was in a permissible range, thus we speculated that the CBF would be stable. Furthermore, although the P_{IC}Gap is a dynamic marker, the P_{IC}Gap couldn't change dramatically in the early stage of TBI for certain patient after neurosurgery, which ensured the predictive value individually.

Conclusions

The impact of PEEP on ICP depends on the GAP between baseline ICP and CVP. The P_{IC}Gap could be a potential predictor for ICP responsiveness to PEEP adjustment in patients with sTBI.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the clinical research ethics committee of Shanghai University of Medicine & Health Sciences Affiliated Zhoupu Hospital (ZPYYLL-2016-12). Written consent was obtained from all participants' next of kin because enrolled patients in the study were in a coma state.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Competing interests

The authors declare they have no potential conflicts of interest relevant to this research work. **Funding**

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Authors' contributions

H P L, Y N L, Z H C, and Q Y L planned and performed experiments, supervised the study, analyzed the data and drafted the manuscript. L Zand W Q participated in performing the experiment. All authors read and approved the final version of the manuscript.

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Tables

Table 1. Patients characteristics at PEEP of 3 cmH_2O between responder group and non-responder group.

	Responder group (n = 49)	Non-Responder group (n = 63)	*p*
Male, n (%)	31 (41.89)	43 (58.11)	0.688
Age, years, mean (SD)	46.96 (11.88)	49.02 (10.49)	0.334
Causes of brain injury, n (%)			
Cerebral contusion	28 (57.1)	38 (60.3)	0.735
Parenchymal hematoma	14 (28.6)	17 (27.0)	0.852
Subdural hematoma	7 (14.3)	8 (12.7)	0.807
GCS, mean (SD)	5.43 (1.61)	5.16 (1.35)	0.336
Hemodynamics variables			
CVP, mmHg, mean (SD)	8.18 (2.66)	6.54 (2.59)	0.001
MAP, mmHg, mean (SD)	78.00 (5.55)	79.60 (4.57)	0.097
ICP, mmHg, mean (SD)	9.82 (2.97)	13.10 (2.74)	< 0.001
CPP, mmHg, mean (SD)	66.67 (4.58)	66.51 (4.03)	0.840
HR, bpm, mean (SD)	74.97 (13.36)	78.88 (14.47)	0.104
P_{IC}Gap, mmHg	1.63 (1.33)	6.55 (2.46)	< 0.001
$PetCO_2$, mmHg	33.00 (3.13)	33.05 (3.06)	0.931
CrsI, ml/kg/cmH_2O	1.30 (0.06)	1.31 (0.06)	0.865

GCS, Glasgow Coma Score; CVP, central venous pressure; MAP, mean arterial pressure; HR, heart rate; ICP, intracranial pressure; CPP, cerebral perfusion pressure; $PetCO_2$, end-tidal carbon dioxide pressure; CstI, the static compliance of respiratory system (Cst) indexed to the predicted body weight of the patients.

Table E. Patients characteristics at PEEP of 15 cmH_2O between responder group and non-responder group.

	Responder group (n = 49)	Non-Responder group (n = 63)	*p*
Hemodynamics variables			
CVP, mmHg, mean (SD)	13.35 (3.01)	10.76 (3.70)	< 0.001
MAP, mmHg, mean (SD)	80.18 (5.28)	78.29 (6.43)	0.097
HR, bpm, mean (SD)	79.34 (15.61)	82.29 (16.54)	0.084
ICP, mmHg, mean (SD)	14.45 (3.20)	13.71 (2.61)	0.183
CPP, mmHg, mean (SD)	65.73 (4.58)	64.57 (5.82)	0.253
$PetCO_2$, mmHg	33.73 (3.11)	33.43 (3.07)	0.604
CrsI, ml/kg/cmH_2O	1.30 (0.05)	1.29 (0.05)	0.243

CVP, central venous pressure; MAP, mean arterial pressure; HR, heart rate; ICP, intracranial pressure; CPP, cerebral perfusion pressure; $PetCO_2$, end-tidal carbon dioxide pressure; CstI, the static compliance of respiratory system (Cst) indexed to the predicted body weight of the patients.

Figures

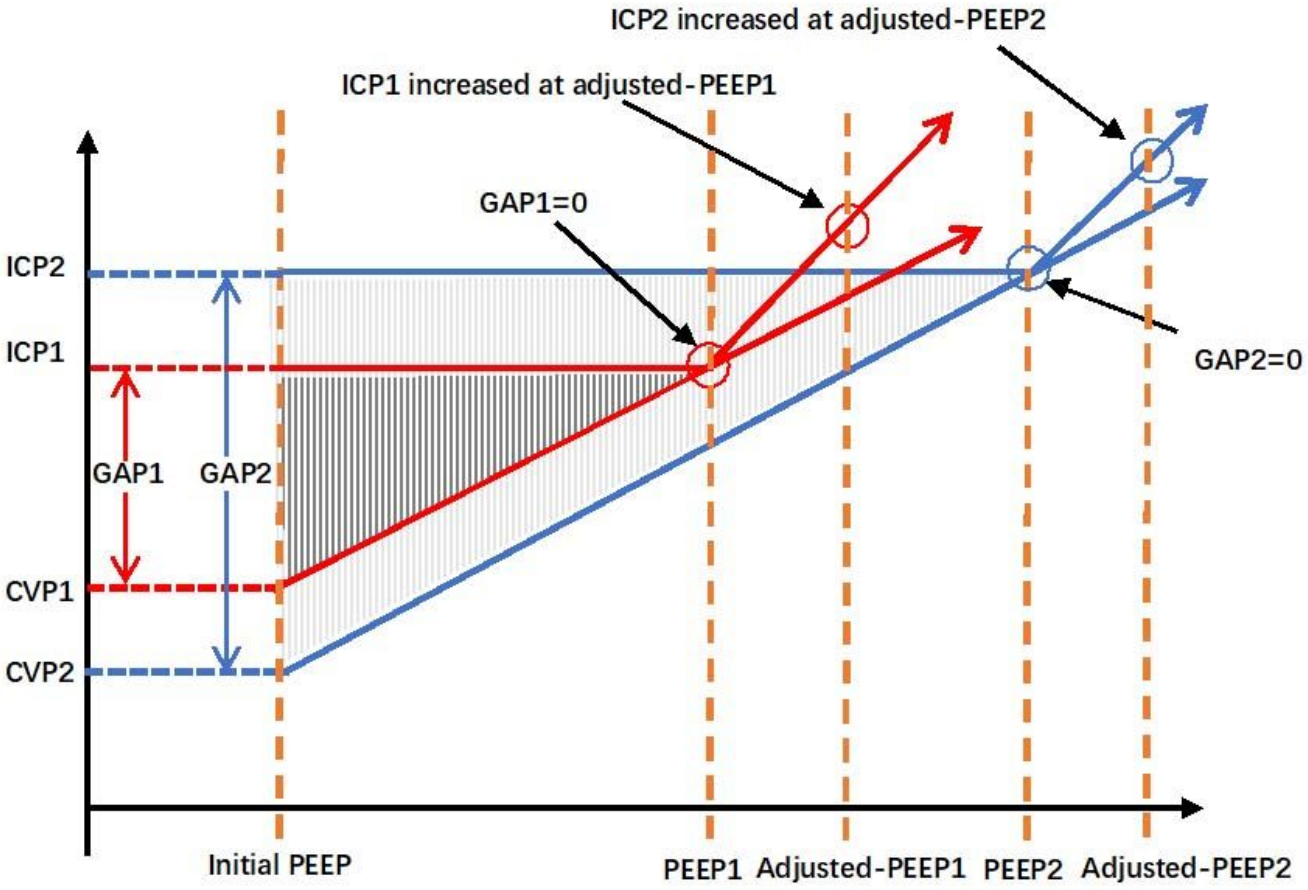

Figure 1

Schematic diagram for research hypothesis. CVP1 and CVP2 increased from baseline value when PEEP was elevated from initial PEEP, however, ICP1 and ICP2 remained unchanged in the beginning. Thus, GAP1 and GAP2 got narrowed gradually till disappeared when PEEP reached up to PEEP1 and PEEP2 (see dark grey shade and light grey shade). PEEP1 and PEEP2 were critical pressure (this moment, GAP1=0 and GAP2=0) for patient A and patient B respectively, and thereafter, CVP1 at adjusted-PEEP1 would exceed the value of baseline ICP which would contribute to elevation of ICP1, and likewise for CVP2 at adjusted-PEEP2. Value of CVP and ICP at initial PEEP were termed baseline ICP and baseline CVP respectively (the same below). ICP1 and CVP1 represented intracranial pressure and central venous pressure at different levels of PEEP for patient A. ICP2 and CVP2 referred to intracranial pressure and central venous pressure at for patient B. GAP1 and GAP2 were calculated by ICP1-CVP1 and ICP2-CVP2. PEEP mean positive end-expiratory pressure.

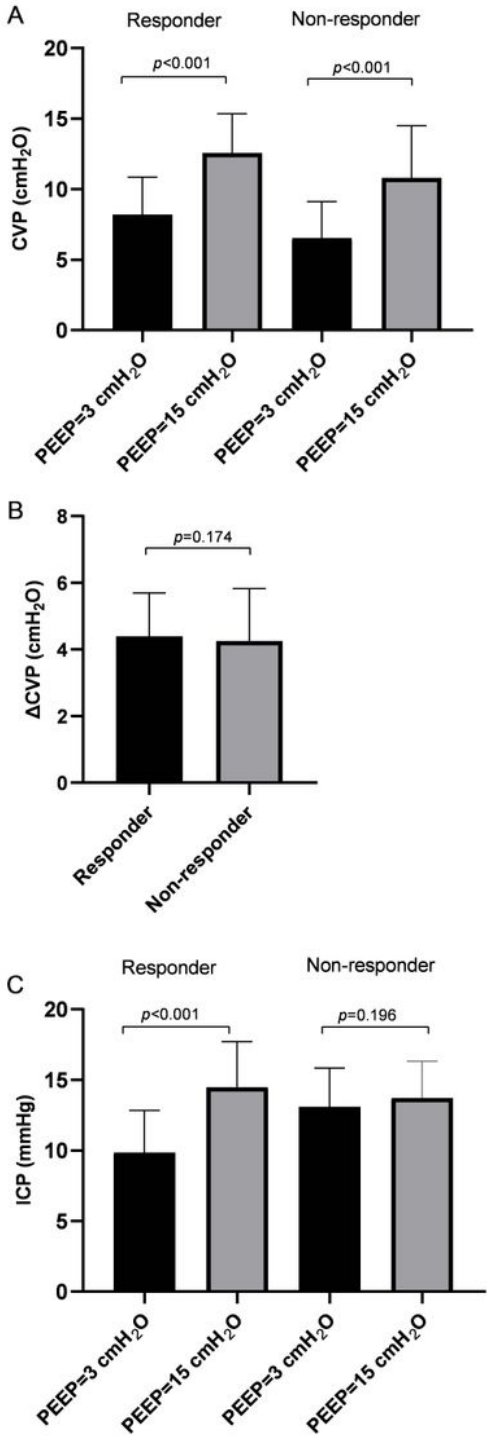

Figure 2

Effects of PEEP adjustment on CVP and ICP between responder group and non-responder group. Adjustment of PEEP from 3 to 15 cmH2O increased the levels of CVP significantly in two groups (Figure 1A). There were no significantly difference in increment of CVP (ΔCVP) between responder group and non-responder group (Figure 1B). A significant increasing of ICP was observed in responder group when

PEEP tuned up from 3cmH2O to 15 mmHg and no change in non-responder group (Figure 1C) PEEP, positive end-expiratory pressure; ICP, intracranial pressure; CVP, central venous pressure.

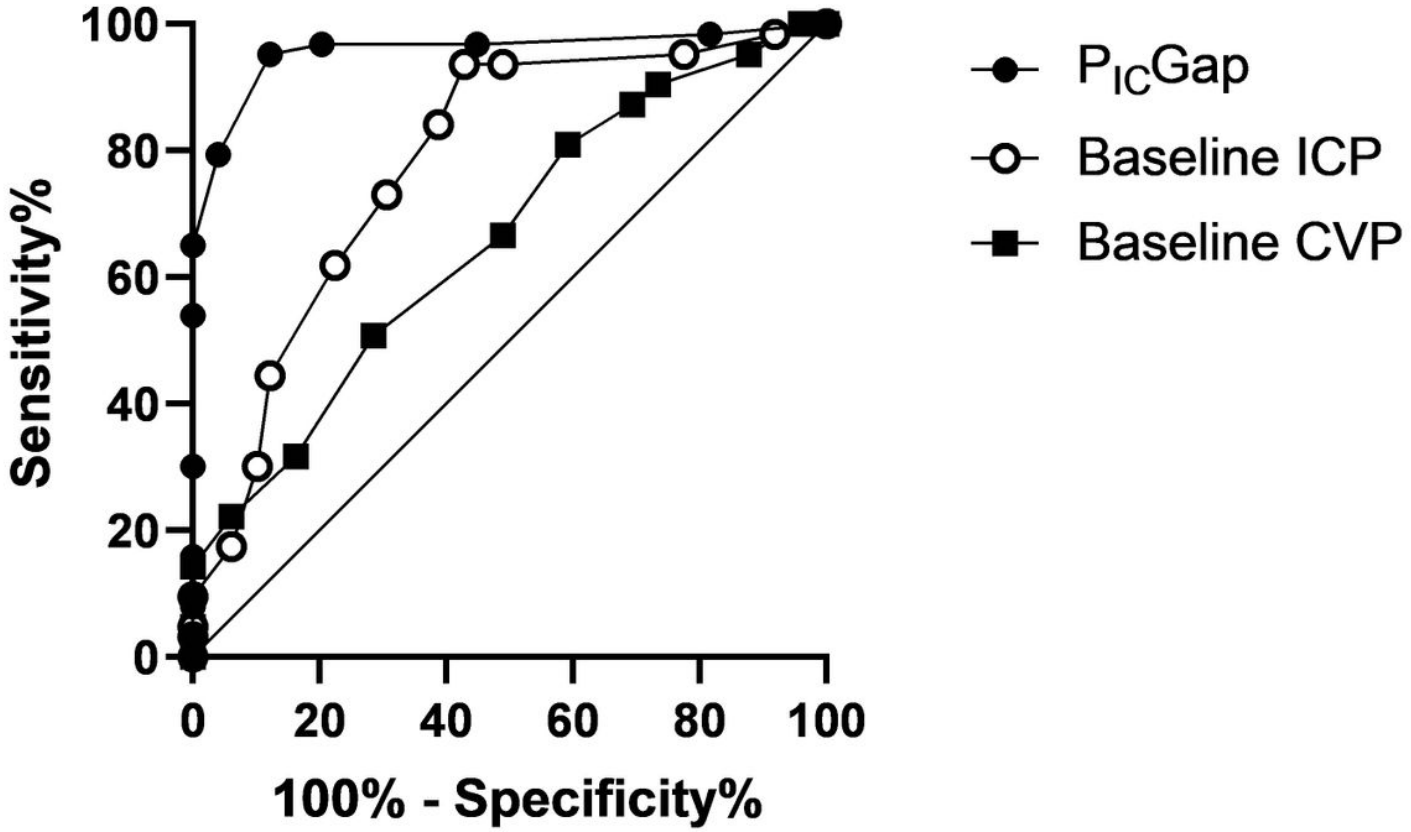

Figure 3

The predictive role of PICGap, baseline ICP, and baseline CVP for ICP responsiveness to PEEP: AUC of ROC for predicting ICP responsiveness to PEEP adjustment. PICGap had a strongest ability to predict the responsiveness of ICP to PEEP increase (AUC = 0.957, 95% CI: 0.918 - 0.996, p <0.001) among the three parameters. However, baseline ICP had evidently weaker predictive ability than PICGap (AUC=0.782 for baseline ICP, 95% CI: 0.693 - 0.781, p <0.001) and baseline CVP had the weakest ability to predict the responsiveness (AUC = 0.660 for CVP, 95% CI: 0.560 - 0.760, p =0.004). PICGap, the difference value between baseline ICP and CVP; ICP, intracranial pressure; AUC, area under curve; ROC, receiver operating characteristic.