Physiological Correlation of Airway Pressure and Transpulmonary Pressure Stress Index on Respiratory Mechanics in Acute Respiratory Failure

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Abstract

Background: Stress index at post-recruitment maneuvers could be a method of positive end-expiratory pressure (PEEP) titration in acute respiratory distress syndrome (ARDS) patients. However, airway pressure (Paw) stress index may not reflect lung mechanics in the patients with high chest wall elastance. This study was to evaluate the Paw stress index on lung mechanics and the correlation between Paw stress index and transpulmonary pressure (Plt) stress index in acute respiratory failure (ARF) patients.

Methods: Twenty-four ARF patients with mechanical ventilation (MV) were consecutively recruited from July 2011 to April 2013 in Zhongda Hospital, Nanjing, China and Ospedale S. Giovanni Battista-Molinette Hospital, Turin, Italy. All patients underwent MV with volume control (tidal volume 6 ml/kg) for 20 min. PEEP was set according to the ARDSnet study protocol. The patients were divided into two groups according to the chest wall elastance/respiratory system elastance ratio. The high elastance group (H group, n = 14) had a ratio ≥30%, and the low elastance group (L group, n = 10) had a ratio <30%. Respiratory elastance, gas-exchange, Paw stress index, and Plt stress index were measured. Student’s t-test, regression analysis, and Bland–Altman analysis were used for statistical analysis.

Results: Pneumonia was the major cause of respiratory failure (71.0%). Compared with the L group, Paw was lower in the H group (5.7 ± 1.7 cmH2O vs. 9.0 ± 2.3 cmH2O, P < 0.01). Compared with the H group, lung elastance was higher (20.0 ± 7.8 cmH2O/L vs. 11.6 ± 3.6 cmH2O/L, P < 0.01), and stress was higher in the L group (7.0 ± 1.9 vs. 4.9 ± 1.9, P = 0.02). A linear relationship was observed between the Paw stress index and the Plt stress index in H group (R2 = 0.56, P < 0.01) and L group (R2 = 0.85, P < 0.01).

Conclusion: In the ARF patients with MV, Paw stress index can substitute for Plt to guide ventilator settings.

Trial Registration: ClinicalTrials.gov NCT02196870 (https://clinicaltrials.gov/ct2/show/NCT02196870).

Key words: Airway Pressure; Lung Compliance; Pulmonary; Respiratory Failure; Stress

INTRODUCTION

Mechanical ventilation (MV) is an important treatment for acute respiratory failure (ARF) in that it can improve hypoxemia, maintain lung volumes, and recruit alveoli collapse.[1] However, because of barotrauma, volutrauma, and biotrauma, MV could cause or aggravate acute lung injury not only in acute respiratory distress syndrome (ARDS) patients but also in patients with normal lung function.[2,3] The stress index, which traces the slope of the pressure-time curve during constant flow ventilation, could qualitatively detect alveolar tidal hyperinflation and tidal recruitment compared with static pressure-volume curves and computed tomography (CT) scan; therefore, titrated ventilator settings are preferred.[4,5] Grasso et al.[6] found that the stress index had the same accurate prediction of lung tidal hypertension and tidal recruitment in animals compared to CT scan. Huang et al.[7] indicated that the stress index at post-recruitment

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Received: 22-01-2016 Edited by: Ning-Ning Wang
How to cite this article: Pan C, Chen L, Zhang YH, Liu W, Urbino R, Ranieri VM, Qiu HB, Yang Y. Physiological Correlation of Airway Pressure and Transpulmonary Pressure Stress Index on Respiratory Mechanics in Acute Respiratory Failure. Chin Med J 2016;129:1652-7.
maneuvers could be an excellent method of positive end-expiratory pressure (PEEP) titration in ARDS patients. Nevertheless, the changes in respiratory system compliance do not reflect the lung compliance accurately, especially in patients with high chest wall elastance. Although transpulmonary pressure ($P_p$) could reflect the lung mechanics, the $P_p$ stress index would require an esophageal catheter and a more complex calculation whereas the airway pressure ($P_{aw}$) stress index is measured noninvasively. The present study was designed to examine the effects of high chest wall elastance on changes of lung mechanics and the correlation between $P_{aw}$ stress index and $P_L$ stress index.

**Methods**

**Patients**

This study was a prospective physiological study. The protocol was approved by the Research Ethics Board of Zhongda Hospital (Southeast University, Jiangsu, China) and Ospedale S. Giovanni Battista-Molinette Hospital (Turin, Italy). Patients were consecutively recruited from July 2011 to April 2013 in Zhongda Hospital and Ospedale S. Giovanni Battista-Molinette Hospital, Turin. Written informed consent was obtained from substitute decision makers. The study was registered in http://www.ClinicalTrials.gov (No. NCT02196870).

Inclusion criteria were as follows: (1) minimum age of 18 years and <85 years of age, (2) duration of controlled MV for at least 36 h, (3) $PaO_2/FiO_2 < 300$ mmHg (1 mmHg = 0.133 kPa), and (4) implementation of an esophageal catheter. Exclusion criteria were as follows: refusal of consent, hemodynamic instability (i.e., need for vasopressor, epinephrine at any dosage, or norepinephrine >5 μg/min, or dopamine or dobutamine >5 μg·kg⁻¹·min⁻¹ to maintain systolic arterial blood pressure >90 mmHg), acute brain injury, upper gastrointestinal bleeding, pneumothorax, pneumomediastinum, chest tube with persistent air leak, severe vomiting, and contraindication to insertion of a gastric tube.

**Experimental protocol**

All patients meeting inclusion criteria were measured in a 30°–45° semirecumbent position under volume control MV. Patients were divided into two groups according to the ratio of chest wall elastance/respiratory system elastance. The high elastance group had a ratio ≥30%, and the low elastance group had a ratio <30%.[8]

**Patients’ preparation**

Patients were administered a continuous infusion of morphine, fentanyl or remifentanil and propofol or midazolam for analgesia and sedation, and Richmond Agitation and Sedation Scales (RASSs) were 0–1. The patients were intubated and mechanically ventilated (Servo 1550, Novametrix Company, USA) in the supine position, and ventilator settings were chosen by the physicians. An invasive artery line and an intravenous line were placed to monitor the arterial blood pressure and central venous pressure. An esophageal catheter was placed in an adequate position to measure esophageal pressure ($P_{es}$).[9]

**Study protocol**

At the initiation of the study, the patients were deeply sedated (RASS scales were −4 to −5) without spontaneous breathing and ventilated in the control mode with a tidal volume (VT) of 6 ml/kg, respiratory rate of 15 breaths/min, inspiratory/expiratory ratio of 1:2, and a fraction of inspired oxygen and PEEP that were set according to the ARDSnet protocol.[10] A set of parameters was obtained 20 min later. If patients experienced hypotension during sedation or high VT ventilation, fluid resuscitation was administered, and vasopressors was administered if necessary. If hypotension persisted after treatment, measurements had to be stopped, and the patient was withdrawn from the study.

**Measurements**

**Respiratory elastance measurements**

Flow was measured with a heated pneumotachograph (Ventrac 1550, Novametrix Company, USA) connected to a differential pressure transducer inserted between the Y-piece of the ventilator circuit and the endotracheal tube. The pneumotachograph was linear over the experimental range of flow. $P_{aw}$ was measured proximal to the endotracheal tube with a pressure transducer. Changes in intrathoracic pressure were evaluated by assessment of $P_{aw}$. The correct position of the esophageal balloon was verified by the occlusion test as previously described.[10] $P_p$ was calculated by $P_{aw}$ minus $P_{es}$. The pressure required to distend the respiratory system, named plateau pressure ($P_{plat_{RS}}$), and the pressure required to distend the lung, named end inspiratory $P_L$ ($P_{plat_{L}}$). Total PEEP (PEEP = applied PEEP + intrinsic PEEP) of the respiratory system (PEEP$_{tot_{RS}}$) and of the chest wall (PEEP$_{tot_{CW}}$) were measured as the $P_{plat_{RS}}$ in $P_{aw}$ and $P_{es}$ during an end-expiratory occlusion, referenced to their values at the elastic equilibrium point of the respiratory system. All the variables described above were displayed and collected on a personal computer.

Static elastance of the respiratory system (Est$_{RS}$) was calculated with the following formula: $(P_{plat_{RS}} - PEEP_{tot_{RS}})/VT$. Static elastance of the chest wall (Est$_{CW}$) was calculated as $(P_{plat_{CW}} - PEEP_{tot_{CW}})/VT$. Static elastance of the lung (Est$_{L}$) was calculated as Est$_{RS} - $Est$_{CW}$.[11]

**Stress index measurements**

$P_{aw}$ stress index and $P_L$ stress index were measured as follows: flow, $P_{aw}$ and $P_s$ signals were collected for a duration of 3 min every 5 min. The beginning and the end of each recorded breath by means of a threshold value (0.1 L/s) on the flow signal were identified. Individual flow and $P_{aw}$ and $P_s$ signals were hence averaged and smoothed by a filter that averaged the signal over a 120-millisecond time window. The beginning and the end of such a constant portion were marked by cursors onto the flow trace. To eliminate on and off flow transient, the constant flow portion was further narrowed by adding 50-millisecond offsets after the beginning (time 0) and before the end (time 1) of
the constant flow portion. The portions of mean $P_{aw}$-time and $P_{l}$-time curves encompassed in the time interval (time $0$ – time $1$) were fitted to the following equation using the Levenberg–Marquardt algorithm. The $R^2$ value of the fitting was computed and displayed. The fitting algorithm provided the coefficients $a$, $b$, and $c$ that best described the $P_{aw}$-time and $P_{l}$-time curve in such a time interval. The coefficient $a$ represents the slope of the $P_{aw}$-time and $P_{l}$-time relationship in the time $0$ – time $1$ interval, and the coefficient $c$ is the value of $P_{aw}$ and $P_{l}$ at time $0$. The coefficient $b$ (stress index) is a dimensionless number that describes the shape of the $P_{aw}$-time and $P_{l}$-time curves. The values of coefficient $b < 1$ indicate that compliance increases with time, whereas compliance decreases with time for the values of the coefficient $b > 1$. Finally, $b = 1$ indicates a constant compliance during tidal inflation. Calculations were aborted if one of the following conditions occurred: (1) the constant portion in the flow signal could not be found because of noise, artifacts, or air leakage; (2) the duration of the time $0$ – time $1$ interval was shorter than one-third of the inspiratory time; (3) the $R^2$ values of the fitting were 0.95; and/or (4) the values of coefficient $b$ calculated on the first and second half of the time $0$ – time $1$ interval were either both lower than, higher than, or equal to $0.9$–$1.1$.\[13\]

**Stress measurements**

Stress was calculated according to the formula: Stress = $(P_{plat} - P_{PEEP}) \times Est/L_{Res}$.\[14\]

**Gas-exchanges**

Arterial blood gasses, included pH, PCO$_2$, PO$_2$, PO$_2$/FiO$_2$, were measured.

**Statistical analysis**

According to former study, Albaiceta et al.\[15\] recruited ten ARDS patients to assess the differences in lung mechanics between ARDS from pulmonary (ARDSp) and extrapulmonary (ARDSe) origin, the results found there is differences between ARDSp and ARDSe lung mechanics are present in the $P_{aw}$-volume curve, but also in the $P_{l}$-volume curve, therefore, in our physiological study, the sample size was 10 in each group. Sample size calculation showed that seven patients per group would provide 80% power at a two-sided $\alpha$ level of 0.05 to detect a 0.15 difference in $P_{aw}$ stress index and $P_{l}$ stress index.

Data are presented as the mean ± standard deviation (SD). Comparisons between the two groups were performed followed by a Student’s t-test for the samples. A $P < 0.05$ indicated significant differences. Regression analysis was performed with the least-squares method. The consistency of the $P_{aw}$ stress index and $P_{l}$ stress index was evaluated by Bland–Altman analysis. Statistical analysis was performed using the software SPSS 20.0 (IBM, USA).

**RESULTS**

There were 24 patients enrolled in the study, and all patients completed the study protocol. The Acute Physiology, Age, and Chronic Health Evaluation II (APACHE II) score was 16.7 ± 4.4, and pneumonia (71%) was the major condition that induced respiratory failure in the patients. PO$_2$/FiO$_2$ was 215.5 ± 49.5 mmHg. The $P_{aw}$ stress index was 0.96 ± 0.11, and the $P_{l}$ stress index was 0.98 ± 0.15 [Table 1].

**Effects of chest wall elastance on respiratory elastance and oxygenation**

The patients were divided into two groups according to the former study\[16\] a high chest wall elastance group (H group) whose chest wall/respiratory system elastance was higher than 30% and a low chest wall elastance group (L group) whose chest wall/respiratory system elastance was lower than 30%. Compared with the L group, the PEEP setting was low in the H group (5.7 ± 1.7 cmH$_2$O vs. 9.0 ± 2.3 cmH$_2$O, $P < 0.01$). However, no significant difference was observed in oxygenation (219.5 ± 66.0 mmHg vs. 212.6 ± 36.0 mmHg, $P = 0.74$) and respiratory system elastance (24.9 ± 8.6 cmH$_2$O/L vs. 21.0 ± 6.0 cmH$_2$O/L, $P = 0.21$) between L and H groups [Table 2]. Compared with the H group, lung elastance was higher (20.0 ± 7.8 cmH$_2$O/L vs. 11.6 ± 3.6 cmH$_2$O/L, $P < 0.01$), and stress was higher (7.0 ± 1.9 cmH$_2$O vs. 4.9 ± 1.9 cmH$_2$O, $P = 0.02$) in the L group. The results showed that lung injury was more severe in the L group than in the H group [Table 2].

**Correlation of stress index in airway pressure and transpulmonary pressure in the H group**

No difference was observed between the stress index in $P_{aw}$ and $P_{l}$ (0.94 ± 0.11 vs. 0.99 ± 0.11, $P = 0.24$). A highly significant correlation was found between $P_{aw}$ stress index and $P_{l}$ stress index.

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**Table 1: Clinical baseline characteristics of the acute respiratory failure patients ($n = 24$)**

| Parameters                        | Value   |
|-----------------------------------|---------|
| Age (years), mean ± SD            | 73.83 ± 11.17 |
| Sex (male/female)                 | 12/12   |
| Surgical patients, n (%)          | 5 (21)  |
| Medical patients, n (%)           | 19 (80) |
| Cause of ARF, n (%)               |         |
| Pneumonia                         | 17 (71) |
| Intestinal obstruction            | 3 (13)  |
| Hepatapostema                     | 1 (4)   |
| Pancreatitis                      | 1 (4)   |
| Transfusion-related acute lung injury | 1 (4)  |
| Inspiration                       | 1 (4)   |
| APACHE II, mean ± SD              | 16.7 ± 4.4 |
| PEEP (cmH$_2$O), mean ± SD        | 7.0 ± 2.5 |
| PO$_2$/FiO$_2$ (mmHg), mean ± SD  | 215.5 ± 49.5 |
| Est$_{aw}$(cmH$_2$O/L), mean ± SD | 22.6 ± 7.3 |
| Est$_{aw}$(cmH$_2$O/L), mean ± SD | 15.1 ± 7.0 |
| Est$_{aw}$(cmH$_2$O/L), mean ± SD | 7.5 ± 3.7 |
| P$_{aw}$ stress index, mean ± SD  | 0.96 ± 0.11 |
| P$_{l}$ stress index, mean ± SD   | 0.98 ± 0.15 |

APACHE II: Acute Physiology, Age, and Chronic Health Evaluation II; Est$_{aw}$: Respiratory system elastance; Est$_{aw}$: Lung elastance; Est$_{cw}$: Chest wall elastance; P$_{aw}$ stress index: Airway pressure stress index; P$_{l}$ stress index: Transpulmonary pressure stress index; PEEP: Positive end-expiratory pressure; ARF: Acute respiratory failure; SD: Standard deviation.
In the H group. In the linear regression analysis, the correlation coefficient $R^2$ of the stress index in $P_{aw}$ and $P_L$ is 0.56 ($P < 0.01$) [Figure 1]. According to the Bland–Altman analysis, all data were distributed on a mean ± 2SD scale (Bias: −0.04 ± 0.11, 95% limits of agreement: −0.25–0.17) [Figure 2]. The results suggested that for the patients with high chest wall elastance did not act on the $P_{aw}$ stress index, and the $P_{aw}$ stress index and $P_L$ stress index were consistent in evaluating lung mechanics.

Correlation of stress index in airway pressure and transpulmonary pressure in the L group

No difference between the $P_{aw}$ stress index and the $P_L$ stress index was observed in the L group (0.98 ± 0.16 vs. 1.02 ± 0.20, $P = 0.49$). A correlation was found between $P_{aw}$ and $P_L$, and the correlation coefficient $R^2$ of the stress index in $P_{aw}$ and $P_L$ was 0.85 ($P < 0.01$) [Figure 3]. According to the Bland–Altman analysis, all were distributed on a mean ± 2SD scale (Bias: −0.03 ± 0.11, 95% limits of agreement: −0.25–0.18) [Figure 4]. The results showed that for the patients with chest wall elastance/respiratory system elastance lower than 30%, the $P_{aw}$ stress index was similar to the $P_L$ stress index in evaluating lung mechanics.

**Discussion**

High chest wall elastance plays a role in lung mechanics and it could influence stress index sometimes; however, high chest wall elastance did not work on $P_{aw}$ stress index in respiratory failure patients in this study. The main finding of the present study was that the $P_{aw}$ stress index can substitute for $P_L$ in MV for patients with ARF.

The respiratory system consists of the lungs and the chest wall. $P_{aw}$ acts on the respiratory system and can be divided into $P_L$ and transchest wall pressure. Therefore, at the

| Parameters                        | H group ($n = 14$) | L group ($n = 10$) | $t$  | $P$  |
|-----------------------------------|-------------------|-------------------|-----|-----|
| Age (years)                       | 75.9 ± 9.7        | 71.0 ± 13.0       | 1.1 | 0.30|
| APACHE II                         | 14.1 ± 3.9        | 16.7 ± 2.4        | −1.9 | 0.07|
| $\text{PaO}_2/\text{FiO}_2$ (mmHg)| 212.6 ± 36.0      | 219.5 ± 66.0      | −0.3 | 0.74|
| PEEP (cmH$_2$O)                   | 5.7 ± 1.7         | 9.0 ± 2.3         | −4.1 | 0.00|
| $E_{stw}$ (cmH$_2$O/L)            | 21.0 ± 6.0        | 24.9 ± 8.6        | −1.3 | 0.21|
| $E_{stw}$ (cmH$_2$O/L)            | 11.6 ± 3.6        | 20.0 ± 7.8        | −3.6 | 0.00|
| $E_{stw}$/Est$_{cw}$              | 9.4 ± 3.5         | 4.9 ± 1.9         | 3.7  | 0.00|
| Stress                            | 4.9 ± 1.9         | 7.0 ± 1.9         | −2.7 | 0.02|
| $P_{aw}$ stress index             | 0.94 ± 0.11       | 0.99 ± 0.11       | −1.1 | 0.24|
| $P_L$ stress index                | 0.98 ± 0.16       | 1.02 ± 0.20       | −5.4 | 0.59|

H group: High chest wall elastance group; L group: Low chest wall elastance group; APACHE II: Acute Physiology and Chronic Health Evaluation II; Est$_{rs}$: Respiratory system elastance; Est$_{cw}$: Lung elastance; Est$_{aw}$: Chest wall elastance; $P_{aw}$ stress index: Airway pressure stress index; $P_L$ stress index: Transpulmonary pressure stress index; SD: Standard deviation.

Figure 1: Correlation between $P_{aw}$ stress index and $P_L$ stress index in H group ($n = 14$). Regression equation of the line: $Y = 1.054x - 0.01249$, $R^2 = 0.56$, $P < 0.01$. $P_{aw}$: Airway pressure; $P_L$: Transpulmonary pressure; H group, high chest wall elastance group.

Figure 2: Bland–Altman analysis of $P_{aw}$ stress index and $P_L$ stress index in H group ($n = 14$). Bias: −0.04 ± 0.11, 95% limits of agreement: −0.25–0.17. $P_{aw}$: Airway pressure; $P_L$: Transpulmonary pressure; SI: Stress index; H group: High chest wall elastance group.

Figure 3: Correlation between $P_{aw}$ stress index and $P_L$ stress index in L group ($n = 10$). Regression equation of the line: $Y = 1.749x - 0.7106$, $R^2 = 0.85$, $P < 0.01$. $P_{aw}$: Airway pressure; $P_L$: Transpulmonary pressure; L group: Low chest wall elastance group.
The P_{aw} stress index could be used to reflect lung mechanics in the patients with pulmonary ARF. Owens monitored 22 pneumonia-induced ARF patients and found that the P-V curve of the respiratory system could reflect the changes in lung elastance.\(^{19}\) Pereira found that changes in chest wall elastance only influenced the lower inflection point of the respiratory system P-V curve, and the effects of the chest wall on respiratory mechanics could be compensated by PEEP.\(^{20}\) Therefore, Grasso et al. and Terragni et al.\(^{14,21}\) showed that the P_{aw} stress index and the P_{L} stress index have a good correlation in ARDS patients. The results were similar in our study. Twenty-four ARF patients were involved in this study, and the P_{aw} stress index and the P_{L} stress index showed a linear correlation. The P_{aw} stress index could be substituted for the P_{L} stress index, which reflects changes in lung mechanics.

Our study showed that the P_{aw} stress index was equal to the P_{L} stress index when chest wall elastance/respiratory system elastance >30%, this result suggests that chest wall elastance changes had no effects on respiratory system elastance in the high chest wall elastance group. This result was the same in Mergoni’s study, in which Mergoni et al.\(^{[22]}\) found that chest wall elastance did not change with the increase in P_{aw} in patients with ARF. However, when the P_{L} stress index was too low, the P_{aw} stress index may not be equal to the P_{L} stress index. The reason could be related to the impact of the lower inflection point of the chest wall P-V curve on the respiratory system P-V curve. This reason could explain why the P_{aw} stress index was not equal to the P_{L} stress index in the high chest wall elastance group in Chiumello’s study.\(^{[3]}\)

Limitations in our study are as follows: (1) respiratory P-V curves are not monitored in our study. (2) Patients involved were not administered lung-recruited and PEEP titration. The purpose of the study was to observe the physiological effects of the chest wall on MV patients and the relationship between the stress index of P_{L} and P_{aw}. The effects of lung recruitment and PEEP on the results were not observed. (3) Patients with suspected high intra-abdominal pressure were not involved in our study. Therefore, the results could not explain the relationship between the stress index of P_{L} and P_{aw} in high intra-abdominal-pressure patients with a stiff chest wall.

In conclusion, high chest wall elastance plays a role in lung mechanics; however, high chest wall elastance did not work on P_{aw} stress index in respiratory failure patients in this study. It is worth remarking, however, that this physiological study was performed on a limited number of patients and that further studies on the stress index of P_{L} and P_{aw} in patients with a stiff chest wall are clearly necessary to ascertain whether the advantage suggested by our data is reliable.

**Financial support and sponsorship**

This study was supported by the grants from the National Natural Science Foundation of China (No. 81300043, No. 81370180, and No. 81501705), and the Natural Science Foundation of Jiangsu Province (No. H201434).
Conflicts of interest
There are no conflicts of interest.

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