Accuracy of Plateau Pressure and Stress Index to Identify Injurious Ventilation in Patients with Acute Respiratory Distress Syndrome.

ACCURACY OF PLATEAU PRESSURE AND STRESS INDEX TO IDENTIFY INJURIOUS VENTILATION IN PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME[1]

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Abstract

Background: Guidelines suggest plateau pressure (P_{PLAT})≤30 cmH_2O for patients with acute respiratory distress syndrome but ventilation may still be injurious despite adhering to this guideline. The shape of the airway pressure vs. time curve (*STRESS INDEX*) may identify injurious ventilation. We assessed accuracy of P_{PLAT} and *STRESS INDEX* to identify morphological indexes of injurious ventilation.

Methods: Indexes of lung aeration (computerized-tomography) associated with injurious ventilation were used as a "***reference standard***". Threshold values of P_{PLAT} and *STRESS INDEX* were determined assessing the receiver-operating characteristics ("***training set***" *N=30*). Accuracy of these values was assessed in a second group of patients ("***validation set***" *N=20*). P_{PLAT} and *STRESS INDEX* were partitioned between respiratory system ($P_{PLAT,RS}$ and *STRESS INDEX,RS*) and lung ($P_{PLAT,L}$ and *STRESS INDEX,L*) (esophageal pressure; "***physiological set***" *N=50*).

Results: Sensitivity and specificity of P_{PLAT}>30 cmH_2O were 0.06 (95% CI: [0.002 to 0.30]) and 1.0 (95% CI: [0.87 to 1.00]). P_{PLAT}>25cmH_2O and a *STRESS INDEX*>1.05 best identified morphological indexes associated with injurious ventilation. Sensitivity and specificity of these values were 0.75 (95% CI:[0.35 to 0.97]) and 0.75 (95% CI:[0.43 to 0.95]) for P_{PLAT}>25cmH_2O vs. 0.88 (95% CI:[0.47 to 1.00]) and 0.50 (95% CI:[0.21 to 0.79]) for *STRESS INDEX*>1.05. $P_{PLAT,RS}$ did not correlate with $P_{PLAT,L}$ (R^2=0.0099); *STRESS INDEX,RS* and *STRESS INDEX,L* were correlated (R^2=0.762).

Conclusions: The best threshold values for discriminating morphological indexes associated with injurious ventilation were $P_{PLAT,RS}$>25 cmH_2O and *STRESS INDEX,RS*>1.05. While a substantial discrepancy between $P_{PLAT,RS}$ and $P_{PLAT,L}$ occurs, *STRESS INDEX,RS* reflects *STRESS*

INDEX,L.

Introduction

The acute respiratory distress syndrome (ARDS) is a type of pulmonary inflammatory response to various inciting events characterized by hypoxemia and bilateral radiographic opacities[1] with non-aerated regions in the dependent lung and relatively normally aerated regions in the non-dependent lung[2-4]. Inappropriate ventilatory settings may over-distend the normally aerated lung and/or continuously open and close the non-aerated regions causing ventilator-induced lung injury[5].

Current guidelines recommend keeping end-inspiratory plateau airway pressure (P_{PLAT}) $\leq$30 cmH_2O[6,7], based on a randomized clinical trial demonstrated that limiting tidal volume (V_T) to 6 ml/kg predicted body weight and P_{PLAT} to 30 cmH_2O decreased absolute mortality by 9%[8]. However, these recommendations are challenged by results of recent studies showing that (a) ARDS patients may be exposed to forces which can induce injurious ventilation despite values of P_{PLAT} $\leq$30 cmH_2O[9-11]; (b) impairment of chest wall mechanics compromises the ability of P_{PLAT} to reflect over-distension[12-14]. Another approach to assess the propensity for injurious ventilation is to assess the *STRESS INDEX* based on the shape of the airway pressure vs. time curve during constant flow[15-18]. Although used in clinical studies[19-22] and implemented in a commercially available ventilator[23], the accuracy of the *STRESS INDEX* to assess the propensity for injurious ventilation has not been tested in humans, and has been questioned in the context of impairment in chest wall mechanics[24,25].

In the current study we assessed the diagnostic accuracy of P_{PLAT} and *STRESS INDEX* to identify ventilator settings likely to produce injurious ventilation. As standards we used indexes of lung aeration (computerized-tomography) associated with injurious ventilation[9,10]. In a separate patient cohort, we examined the impact of chest wall mechanics on the utility of P_{PLAT} and *STRESS INDEX* to identify propensity for injurious ventilation.

Material and Methods

The institutional review board (Comitato Etico Interaziendale AUO S. Giovanni Battista e CTO di Torino, Italy) approved the study. As the patients were incompetent, patients were included into the study and consent was delayed. The family was informed of the study (although not required). Written permission for using collected data was hence obtained from the patient (if competent) or from the family (in case of death or if the patient remained incompetent)[2].

Patients admitted from January 2007 to February 2012 to the intensive care units of the Molinette (Turin) and Policlinico (Bari) hospitals were considered for enrollment when the following criteria were met: age ≥18 years; diagnosis of ARDS[26]. Exclusion criteria were: >3 days elapsed since ARDS criteria were met and mechanical ventilation was initiated; history of ventricular fibrillation or tachyarrhythmia, unstable angina or myocardial infarction within preceding month; chest tube with persistent air leak; pre-existing chronic obstructive pulmonary disease; pregnancy; known intracranial abnormality. Measurements were interrupted and patients withdrawn from the study if any of the following *a priori* defined conditions occurred: (a) presence of inspiratory efforts during measurement of respiratory mechanics despite infusion of sedatives and respiratory muscle paralytics; (b) drop in arterial oxygen saturation <80%; (c) decrease in mean arterial pressure >10% of baseline despite 500 ml intravenous bolus.

MEASUREMENTS

All patients were ventilated (SERVOi, Maquet, Lund, Sweden) according to the "*ARDSNet*" protective ventilatory strategy[8]. Measurements were performed during absence of spontaneous respiratory muscle effort obtained by increasing doses of midazolam (up to

10mg/h) and/or propofol (150mg/h increments every 10 min)[27,28] or use of neuromuscular blockade (cis-atracurium besylate 2-8 gamma/kg/min). Absence of spontaneous effort was confirmed by inspecting flow and airway pressure traces during an end-expiratory pause of 4-5 seconds[27,28].

RESPIRATORY MECHANICS

Flow (heated pneumotachograph Fleisch No. 2; Fleisch, Lausanne, Switzerland and differential pressure transducer; Diff-Cap, Special Instruments, Nordlingen, Germany), volume and airway opening pressure (P_{aw}) (Special Instruments Digima-Clic ± 100 cmH_2O; Nordlingen, Germany) were measured as previously described[16,18,29]. In a subset of 50 patients, intra-thoracic pressure was evaluated by assessment of esophageal pressure (P_{ES})[30] using a thin latex balloon-tipped catheter system (Microteck Medical B.V., Zutphen, Netherlands) connected by a polyethylene catheter to a pressure transducer (Special Instruments Digima-Clic ± 100 cmH_2O; Nordlingen, Germany)[31].

All the described variables were displayed and collected for 5 minutes on a personal computer through a 12-bit analog-to-digital converter board (National Instrument DAQCard 700; Austin, TX, USA) at a 200 Hz sample rate of (KleisTEK Engineering; Bari, Italy). End-expiratory and end-inspiratory occlusions were performed. Signals were averaged and smoothed by a filter that averaged the signal over a 120 ms time window[18].

END-INSPIRATORY PLATEAU PRESSURE

P_{PLAT} of the respiratory system ($P_{PLAT_{RS}}$) was the value of P_{aw} after an end-inspiratory occlusion. In the subset of patients in whom P_{ES} was measured, end-inspiratory chest wall plateau pressure ($P_{PLAT_{CW}}$) was measured as the variation in P_{ES} between end-expiratory and

end-inspiratory occlusions; end-inspiratory plateau pressure of the lung (P_{PLAT_L}) were estimated as $P_{PLAT_{RS}}$-$P_{PLAT_{CW}}$[12-14].

STRESS INDEX

The software identified the beginning and the end of each recorded breath by means of a threshold value (0.1 liter/second) on the flow signal[17-19]. Trans-pulmonary pressure (P_L) was calculated as P_{AW}-P_{ES} [12-14]. Individual flow, P_{aw} and P_L signals were averaged and smoothed by a filter that averaged the signal over a 120 ms time window. On the resulting mean flow, the software first identified the steady flow level and then the largest portion of flow signal that was considered to be steady flow ±3%[17-19]. The beginning and the end of this constant portion were marked by cursors. To eliminate on and off flow transient, the constant flow portion was further narrowed by adding a 50 ms offsets after the beginning (**time $_0$**) and before the end (**time $_1$**) of the constant flow portion. The portion of the mean P_{aw}-time and P_L–time curves encompassed in the time interval **time $_0$-time $_1$** was fitted to the equations:

$$P_{aw} = a_{aw} \cdot (\textbf{time}_0\textbf{-time}_1)^{b_{aw}} + c_{aw}$$

$$P_L = a_L \cdot (\textbf{time}_0\textbf{-time}_1)^{b_L} + c_L$$

using the *Levenberg-Marquardt* algorithm[17-19]. Values of R^2 were computed and displayed. The coefficients b_{aw} and b_L (*STRESS INDEX,RS* and *STRESS INDEX,L*) are dimensionless number that describe the shape of the P_{aw}-time and of the P_L-time curves. Values of coefficient $b < 1$ indicate that elastance decreases with time, whereas elastance increases with time for values of coefficient $b > 1$. Finally, $b = 1$ indicates a constant elastance during tidal inflation (**Figure 1**)[17-19].

COMPUTERIZIED TOMOGRAPHY ASSESSMENT OF "VENTILATOR INDUCED LUNG INJURY"

As soon as targets of the ventilatory protocols were reached and respiratory and hemodynamic parameters (measured at 20-30-min intervals) were stable, patients were transferred to the computerized tomography (CT) scan facility. During the transport and the exam, the ventilator and the ventilator settings were the one used for the clinical management; particular attention was paid to avoid ventilator disconnection[9,10]. Lung scanning was performed from the apex to the base using a Light Speed Qx/i (General Electric Medical System, Milwaukee, WI, USA) at the end of end-expiratory and end-inspiratory occlusions[9,10]. The ventilator settings were identical to those previously set. The CT scanner was set as previously described[9,10]. Each section of the right and left lung was chosen by manually drawing the outer boundary along the inside of the ribs and the inner boundary along the mediastinal organs. Pleural effusions were excluded. *Non-aerated* (density between +100 and –100 Hounsfield units), *poorly aerated* (density between –101 and –500 Hounsfield units), *normally aerated* (density between –501 and –900 Hounsfield units), and *hyperinflated* (density between –901 and –1000 Hounsfield units) lung compartments were identified as previously described[3,4,32].

Volume of the entire lungs (i.e. the sum of gas plus tissue volume) and of each compartment at end-expiration and end-inspiration was measured for each slice as: [(size of the pixel)^2 multiplied by the number of pixels in each compartment] multiplied by the thickness of the CT lung slice[3,4,32]. "***Tidal hyperinflation***" was defined as the volume of the *hyperinflated* compartment at end-inspiration minus the volume of the *hyperinflated* compartment at end-expiration[9,10]. "***Tidal recruitment***" was defined as the volume of the *non-aerated* and of the *poorly aerated* compartments at end-expiration minus the volume at end-inspiration[9,10]. "***Protected tidal inflation***" was the volume of the *normally aerated* compartment at end-inspiration minus the volume of the *normally aerated* compartment at

end-expiration[9,10]. All were expressed as % of total tidal inflation-related changes in CT lung volume.

PULMONARY INFLAMMATORY RESPONSE

Five-ten min after CT and respiratory mechanics measurements, a broncho-alveolar lavage was performed and stored at -80 ^{o}C. as previously described[9,10,33]. Assay for tumor necrosis factor-α soluble receptors, interleukin 6, interleukin 8 and interleukin 1β and interleukin-1 receptor antagonist were carried out using a solid-phase enzyme-linked immunoabsorbent assay (ELISA) method (Diaclone, Milan, Bender Med Systems, Milan, ITALY and BioSource International Inc., Camarillo, USA)[9,10,33].

STUDY DESIGN

In ***Phase 1***, we evaluated the diagnostic accuracy of $P_{PLAT,RS}$ and *STRESS INDEX,RS* to identify the propensity for injurious ventilation using CT criteria to assess the degree of overdistension[9,10]. Accuracy of $P_{PLAT,RS}$ and *STRESS INDEX,RS* was determined in a first group of patients ("***training set***") to select the threshold values that discriminated best between patients with and without the condition of interest; the accuracy of these values was prospectively assessed in a second group of patients ("***validation set***")[34]. In ***Phase 2***, we addressed the question of how chest wall mechanics affects interpretation of $P_{PLAT,RS}$ and of the *STRESS INDEX,RS* ("***physiological set***")[12-14]. In this phase, we did not use CT scan or pulmonary concentration of inflammatory cytokines. Patients were assigned to the different data sets depending on the chronological order in which they entered the study.

The maximal degrees of association between CT scan evidence of "***protected tidal inflation***", "***tidal hyperinflation*** or "***tidal recruitment***" was identified using cluster analysis with cubic clustering criteria[9]. Cluster analysis entails grouping similar objects into distinct,

mutually exclusive subsets referred to as *clusters*; elements within a cluster share a high degree of "natural association," whereas the clusters are relatively distinct from one another[35].

Values of $P_{PLAT,RS}$ and $STRESS\ INDEX_{,RS}$ that best differentiated the patients who were ventilated with CT scan evidence of "***protected tidal inflation***" from those in whom tidal volume and pressure limitation caused CT scan evidence of "***tidal hyperinflation"*** or "***tidal recruitment***" were determined assessing the receiver-operating-characteristics curve[36].

The area under the receiver-operating characteristics curve for $P_{PLAT,RS}$ and $STRESS\ INDEX_{,RS}$ was calculated and confidence intervals (CI) reported. The selected threshold values were those that minimized false negative classifications (i.e. patients who were thought to be protected when in fact they were not) with a specificity value not lower than 0.5. This decision was based on the assumption that from a clinical perspective, a false negative result is worse than a false positive.

The predictive power of the previously selected values of $P_{PLAT,RS}$ and $STRESS\ INDEX_{,RS}$ was estimated using the previously selected cut-off values that best discriminated patients with CT scan evidence of "***protected tidal inflation***" from "***tidal hyperinflation"*** or "***tidal recruitment***".

Values of $STRESS\ INDEX_{,RS}$ and $P_{PLAT,RS}$, and values of $STRESS\ INDEX_{,L}$ and $P_{PLAT,L}$ were compared in a third set of patients ventilated according to the "*ARDSNet*" protective ventilator strategy[8].

STATISTICAL ANALYSIS

Results are expressed as mean±SD; $P<0.05$ was considered significant. Comparisons of continuous and categorical data between groups were performed using unpaired t-tests and chi-squared tests. Regression was performed using least-squares. Since values of cytokine

concentrations were not normally distributed, $\log_{10}$ transformation was performed prior to applying parametric statistics.

A true-positive was defined when P_{PLAT} and *STRESS INDEX* predicted "***tidal hyperinflation***" or "***tidal recruitment***" and CT scan analysis was confirmatory. A true-negative was defined when P_{PLAT} and *STRESS INDEX* predicted absence of "***tidal hyperinflation***" or "***tidal recruitment***" and CT scan analysis was confirmatory. A false-positive was defined when P_{PLAT} and *STRESS INDEX* value predicted presence of "***tidal hyperinflation***" or "***tidal recruitment***" and CT scan was not confirmatory. A false-negative was defined when P_{PLAT} and *STRESS INDEX* value predicted absence of "***tidal hyperinflation***" or "***tidal recruitment***" and CT scan analysis was not confirmatory.

Standard formulae were used to calculate sensitivity, specificity, and positive and negative predictive values. Positive and negative likelihood ratios were calculated (SAS software, version 9.1.3; SAS Institute, Cary, North Carolina, USA; MedCalc version 11.1.1, MedCalc software BVBA, Ostend, Belgium).

Results

Some of the results reported in the present investigation include data obtained from patients enrolled in previously published studies [1,9,10,20].

Of the 110 patients enrolled, 10 were excluded for the following reasons: >3 days since mechanical ventilation initiation (N=5); chest tube with persistent air leak (N=2); unilateral lung disease (N=2); spontaneous respiratory effort during physiological measurements (N=1). Of the remaining patients 100 patients, 50 patients were included in ***PHASE 1*** (30 in the "training set" and 20 in the "validation set"), and 50 patients were included in ***PHASE 2*** (**Table 1**).

The volume of "***protected ventilation***" and of "***tidal hyperinflation***" identified 2 clusters of patients. In a cluster of 28 patients (16 in the "training set" and 12 in the "validation set"), "***tidal hyperinflation***" was 8.36±5.51 ("training set") and 9.91±4.31% ("validation set"), while "***protected ventilation***" was 71.20±8.05 ("training set") and 75.68±8.01% ("validation set") of the total tidal-inflation associated change in CT lung compartments. These patients were considered relatively protected from injurious ventilation ("*PROTECTED"*). In a cluster of 22 patients (14 in the "training set" and 8 in the "validation set"), "***tidal hyperinflation*** was 53.76±7.92 ("training set") and 50.91±21.78% ("validation set"), and "***protected ventilation***" was 28.55±16.33 ("training set") and 25.91±14.71% ("validation set") of the total tidal-inflation associated change in CT lung compartments. These patients were considered relatively not protected from injurious ventilation ("*NON PROTECTED"*). "***Tidal recruitment***" was 20.44±7.03 ("training set") and 14.81±7.73% ("validation set") in *"PROTECTED"* and 17.69±8.15 ("training set") and 23.18±9.32% ("validation set") in the "*NON-PROTECTED"*. As such, "***tidal recruitment***" could not be identified in the cluster analysis as a distinct entity that could define a "protected" vs. a "non-

protected" ventilator setting and therefore could not be used as additional criterion to define a non-protected tidal inflation.

Ventilator settings, and biological variables in the "*PROTECTED"* and "*NON PROTECTED"* clusters are shown in **Table 2**. Pulmonary concentrations of the inflammatory cytokines were lower in *PROTECTED* than in *NON-PROTECTED* ($P < 0.05$).

The areas under the receiver-operating characteristics curves for $P_{PLAT,RS}$ and *STRESS INDEX,RS* (0.833; 95% CI:[0.621 to 0.954] and 0.917; 95%CI:[0.724 to 0.990], respectively) (**Figure 2**) were both significantly (P=0.001) larger than that of an arbitrary test that would be expected *a priori* to have no discriminatory value. Sensitivity and specificity of the value of $P_{PLAT,RS}$ currently suggested by guidelines (>30 cmH_2O) were 0.06 (95% CI: [0.002 to 0.30]) and 1.0 (95% CI: [0.87 to 1.00]), respectively. The threshold value of $P_{PLAT,RS}$ that best identified *NON-PROTECTED* patients was 25 cmH_2O; sensitivity and specificity were 0.82 (95% CI: [0.48 to 0.98]) and 0.67 (95% CI: [0.35 to 0.90]), respectively. A threshold value of *STRESS INDEX,RS* >1.05 best identified *NON-PROTECTED* patients; sensitivity and specificity were 0.82 (95% CI: [0.48 to 0.98]) and 0.83 (95% CI: [0.52 to 0.98]), respectively.

Sensitivity and specificity of $P_{PLAT,RS}$ >25 cmH_2O to identify "*NON-PROTECTED"* patients were 0.75 (95% CI: [0.35 to 0.97]) and 0.75 (95% CI: [0.43 to 0.95]), respectively. Sensitivity and specificity of a *STRESS INDEX,RS* >1.05 to identify *"NON-PROTECTED"* patients were 0.88 (95% CI: [0.47 to 1.00]) and 0.50 (95% CI: [0.21 to 0.79]) (**Table 3**).

The correlation coefficients relating *STRESS INDEX,RS* vs. *STRESS INDEX,L* and of $P_{PLAT,RS}$ vs. $P_{PLAT,L}$ were 0.762 and 0.0099, respectively (**Figure 3**).

Discussion

The main findings of the present investigation are: (*a*) the value of $P_{PLAT,RS}$ recommend by current guidelines (≤ 30 cmH_2O) does not accurately discriminate patients with CT-scan indexes of tidal hyperinflation; (*b*) the discriminating threshold values that identify associate $P_{PLAT,RS}$ and $STRESS\ INDEX_{,RS}$ to CT pattern of lung aeration related to tidal hyperinflation are <25 cmH_2O and not greater than 1.05, respectively; (*c*) while $STRESS\ INDEX_{,RS}$ represents a reasonable reflection of $STRESS\ INDEX_{,L}$, there is substantial discrepancy when using $P_{PLAT,RS}$ vs. $P_{PLAT,L}$.

Rigorous statistical methods have been developed to evaluate the degree of agreement between a test and the best available method for establishing the presence/absence of the condition of interest[37]. Accordingly to these methods, (***a***) we included a study population representative of ARDS patients[26] excluding only those patients that were mechanically ventilated for >72 hours or in whom measurements of respiratory mechanics could not be performed; (***b***) we used previously established methods to measure physiological variables[31]; (***c***) we developed threshold values of $P_{PLAT,RS}$ and $STRESS\ INDEX_{,RS}$ through the analysis of the receiver-operating characteristics curves obtained in a training set (30 patients) and then evaluated their accuracy in a validation set (20 patients); (***c*)** we selected threshold values giving priority to those that optimized sensitivity minimizing false negative classifications (i.e. patients who were thought to be protected when in fact they were not). This decision was based on the assumption that from a clinical perspective, a false negative result is less acceptable than a false positive. However our use of CT scan indexes of lung aeration as a "***reference standard***" for injurious ventilation has some weaknesses. We used CT scan evidence of "***protected tidal inflation***" and "***tidal hyperinflation*** to select a cluster characterized by a predominant "***protected tidal inflation***" and a cluster characterized by

predominant "***tidal hyperinflation***". These two clusters may represent different ranges of a continuum [4,38]) and, since tidal recruitment could not be addressed by cluster analysis, the terms "*PROTECTED*" and "*NON PROTECTED*" should be referred only to tidal hyperinflation. Moreover, although we found a concentration of inflammatory mediators higher in patients included in the *NON-PROTECTED* cluster than in patients included in the *PROTECTED* cluster[9,10], this may be a marker of severity of ARDS and not solely reflect the degree of hyperinflation.

A clinical trial[8] and observational studies[39,40] have demonstrated that limiting V_T to 6 ml/kg predicted body weight and $P_{PLAT,RS}$ to 30 cmH_2O improves survival. Our data show that the threshold value that best identified *NON-PROTECTED* patients was not $P_{PLAT,RS}$ >30 cmH_2O but $P_{PLAT,RS}$ >25 cmH_2O. These data are in accord with previous studies demonstrating that ***tidal hyperinflation*** may occur despite limiting V_T to 6 ml/kg predicted body weight and $P_{PLAT,RS}$ to 30 cmH_2O[9-11].

Previous studies proposed analyzing the P_{AW}-t curve during constant flow to assess the mechanical properties of the respiratory system of ARDS patients[15,16]. This approach is based on the concept that at constant flow, the rate of change of P_{AW} with time corresponds to the rate of change of elastance of the respiratory system during tidal inflation[15], and can be described by a power equation ($\mathbf{pressure} = a \cdot \mathbf{time}^{b+c}$)[16]. A coefficient b=1.0 indicates a linear Paw-t curve and an unchanging elastance during inflation; coefficient b<1.0 indicates decreasing elastance during inflation; coefficient b>1.0 indicates a increasing elastance. Experimental studies demonstrated that markers of injurious ventilation were minimized using ventilator settings associated with $0.9<b<1.1$ and therefore concluded that the coefficient b (called *STRESS INDEX*) could be used to detect tidal hyperinflation or tidal recruitment during mechanical ventilation[17,18,41-43]. Although subsequent experimental studies challenged these findings[24,44], the use of *STRESS INDEX* to detect injurious ventilation has been tested in clinical studies[19-22] and implemented in a commercially available ventilator[23]. We found that a $STRESS\ INDEX_{,RS}$ >1.05 best identified patients *NON PROTECTED* from injurious

ventilation. The area under the receiver-operating characteristics curve for *STRESS INDEX,RS* and *PPLAT,RS* were not statistically different. However, in the validation set, sensitivity of *PPLAT,RS* >25 cmH_2O was slightly lower than sensitivity of *STRESS INDEX,RS*>1.05 (0.75 (95% CI:[0.35-0.97] vs. 0.88 (95% CI: [0.47-1.00]) (**Table 3**).

Our data demonstrate that while alterations of chest wall mechanics may substantially impair the ability of *PPLAT,RS* to estimate *PPLAT,L*, *STRESS INDEX,RS* closely reflects *STRESS INDEX,L*. These results may be explained by partitioning the volume-pressure relationship of the respiratory system between the lung and the chest wall[45-47]. *PPLAT,RS* as a measure of *PPLAT,L* is directly related to the stiffness of the chest wall at the end of an inspiration, which may be substantial in patients with ARDS[12-14]. The *STRESS INDEX* reflects the *changes* with volume of the elastance of the respiratory system (P_{AW} vs. time) or of the lung (P_L vs. time). In the range of changes of lung volume associated with a low tidal volume strategy[8], the volume-pressure relationship of the chest wall is linear[12,45,48], and hence the *STRESS INDEX* should largely reflect the mechanical properties of the lung.

In conclusion, the present study demonstrates that the value of *PPLAT,RS* currently recommend by guidelines (≤ 30 cmH_2O) does not accurately discriminate patients with CT-scan indexes of tidal hyperinflation. The threshold values of *PPLAT,RS* and of *STRESS INDEX,RS* that correspond to CT-scan indexes of tidal hyperinflation are < 25 cmH_2O and < 1.05. While a substantial discrepancy between *PPLAT,RS* and *PPLAT,L* occurs, *STRESS INDEX,RS* reflects *STRESS INDEX,L* with reasonable accuracy. Clinical trials are required to test whether ventilator settings targeting *PPLAT,RS* ≤25 cmH_2O and/or a *STRESS INDEX,RS* ≤1.05 will improve clinical outcomes.

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