

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

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ABSTRACT

Background: Guidelines suggest a plateau pressure (P_{PLAT}) of 30 cm H₂O or less for patients with acute respiratory distress syndrome, but ventilation may still be injurious despite adhering to this guideline. The shape of the curve plotting airway pressure *versus* time ($STRESS\ INDEX$) may identify injurious ventilation. The authors assessed accuracy of P_{PLAT} and $STRESS\ INDEX$ to identify morphological indexes of injurious ventilation.

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What We Already Know about This Topic

- A plateau pressure of less than or equal to 30 cm H₂O does not identify all patients at risk of lung injury due to mechanical ventilation

What This Article Tells Us That Is New

- Using computed tomography references for morphologic indexes in both a training and a validation group of patients, a P_{PLAT} greater than 25 cm H₂O and a $STRESS\ INDEX$ greater than 1.05 were found to be the best thresholds for identifying 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} of greater than 30 cm H₂O were 0.06 (95% CI, 0.002–0.30) and 1.0 (95% CI, 0.87–1.00). P_{PLAT} of greater than 25 cm H₂O and a $STRESS\ INDEX$ of greater than 1.05 best identified morphological markers of injurious ventilation. Sensitivity and specificity of these values were 0.75 (95% CI, 0.35–0.97) and 0.75 (95% CI, 0.43–0.95) for P_{PLAT} greater than 25 cm H₂O *versus* 0.88 (95% CI, 0.47–1.00) and 0.50 (95% CI, 0.21–0.79) for $STRESS\ INDEX$ greater than 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 $P_{PLAT,RS}$ greater than 25 cm H₂O and $STRESS\ INDEX,RS$ greater than 1.05. Although a substantial discrepancy between $P_{PLAT,RS}$ and $P_{PLAT,L}$ occurs, $STRESS\ INDEX,RS$ reflects $STRESS\ INDEX,L$.

THE acute respiratory distress syndrome (ARDS) is a type of pulmonary inflammatory response to various

inciting events characterized by hypoxemia and bilateral radiographic opacities¹ with nonaerated regions in the dependent lung and relatively normally aerated regions in the nondependent lung.²⁻⁴ Inappropriate ventilatory settings may overdistend the normally aerated lung and/or continuously open and close the nonaerated regions causing ventilator-induced lung injury.⁵

Current guidelines recommend keeping end-inspiratory plateau airway pressure (P_{PLAT}) of 30 cm H₂O or less,^{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 cm H₂O decreased absolute mortality by 9%.⁸ However, these recommendations are challenged by results of recent studies showing that (1) patients with ARDS may be exposed to forces which can induce injurious ventilation despite values of P_{PLAT} of 30 cm H₂O or less⁹⁻¹¹; (2) impairment of chest wall mechanics compromises the ability of P_{PLAT} to reflect overdistension.¹²⁻¹⁴ Another approach to assess the propensity for injurious ventilation is to assess the *STRESS INDEX* based on the shape of the curve plotting airway pressure *versus* time during constant flow.¹⁵⁻¹⁸ Although used in clinical studies¹⁹⁻²² 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. We used indexes of lung aeration (computerized tomography [CT]) associated with injurious ventilation as standards.^{9,10} In a separate patient cohort, we examined the impact of chest wall mechanics on the use 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. Because the patients were incompetent, they 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: aged 18 years or more; diagnosis of ARDS.²⁶ Exclusion criteria were: more than 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;

preexisting chronic obstructive pulmonary disease; pregnancy; and known intracranial abnormality. Measurements were interrupted and patients withdrawn from the study if any of the following *a priori* defined conditions occurred: (1) presence of inspiratory efforts during measurement of respiratory mechanics despite infusion of sedatives and respiratory muscle paralytics; (2) decrease in arterial oxygen saturation of less than 80%; (3) decrease in mean arterial pressure of greater than 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 10 mg/h) and/or propofol (150 mg/h increments every 10 min)^{27,28} or use of neuromuscular blockade (*cis*-atracurium besylate 2-8 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Absence of spontaneous effort was confirmed by inspecting flow and airway pressure traces during an end-expiratory pause of 4-5 s.^{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 (PAW; Special Instruments Digima-Clic \pm 100 cm H₂O; Nordlingen, Germany) were measured as previously described.^{16,18,29} In a subset of 50 patients, intrathoracic 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 \pm 100 cm H₂O).³¹

All the described variables were displayed and collected for 5 min on a personal computer through a 12-bit analog-to-digital converter board (DAQCard 700; National Instrument, Austin, TX) 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_{PLATRS}) was the value of PAW 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_{PLATL}) were estimated as $P_{PLATRS} - P_{PLAT_{CW}}$.¹²⁻¹⁴

Stress Index. The software identified the beginning and the end of each recorded breath by means of a threshold value (0.1 l/s) on the flow signal.¹⁷⁻¹⁹ Transpulmonary pressure (Pl) was calculated as $PAW - P_{ES}$.¹²⁻¹⁴ Individual flow, PAW,

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 $\pm 3\%$.^{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 PAW–time and P_L –time curves encompassed in the time interval *time 0*–*time 1* was fitted to the equations:

$$P_{aw} = a_{aw} \cdot (\text{time}_0 - \text{time}_1)^{b_{aw}} + c_{aw} \quad (1)$$

$$P_L = a_L \cdot (\text{time}_0 - \text{time}_1)^{b_L} + c_L \quad (2)$$

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 PAW–time and of the P_L –time curves. Values of coefficient b less than 1 indicate that elastance decreases with time, whereas elastance increases with time for values of coefficient b greater than 1. Finally, $b = 1$ indicates a constant elastance during tidal inflation (fig. 1).^{17–19}

CT Assessment of “Ventilator-induced Lung Injury”. As soon as targets of the ventilatory protocols were reached and respiratory and hemodynamic parameters (measured at 20- to 30-min intervals) were stable, patients were transferred to the CT scan facility. During the transport and the examination, 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) 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. *Nonaerated* (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 *nonaerated* 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 percentage of total tidal inflation–related changes in CT lung volume.

Pulmonary Inflammatory Response. Five to 10 min after CT and respiratory mechanics measurements, a bronchoalveolar lavage was performed and stored at -80°C , as previously described.^{9,10,33} Assay for tumor necrosis factor- α soluble receptors, interleukin-6, interleukin-8 and interleukin-1 β and interleukin-1 receptor antagonist were carried out using a solid-phase enzyme-linked immunosorbent assay method (Diaclone, Milan, Bender Med Systems, Milan, Italy and BioSource International Inc., Camarillo, CA).^{9,10,33}

Study Design

In *Phase 1*, we evaluated the diagnostic accuracy of *Pplat,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 *Pplat,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 *Pplat,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* were 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 *Pplat,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 by assessing the receiver-operating characteristics curve.³⁶

The area under the receiver-operating characteristics curve for *Pplat,RS* and *STRESS INDEX,RS* was calculated and CIs 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.

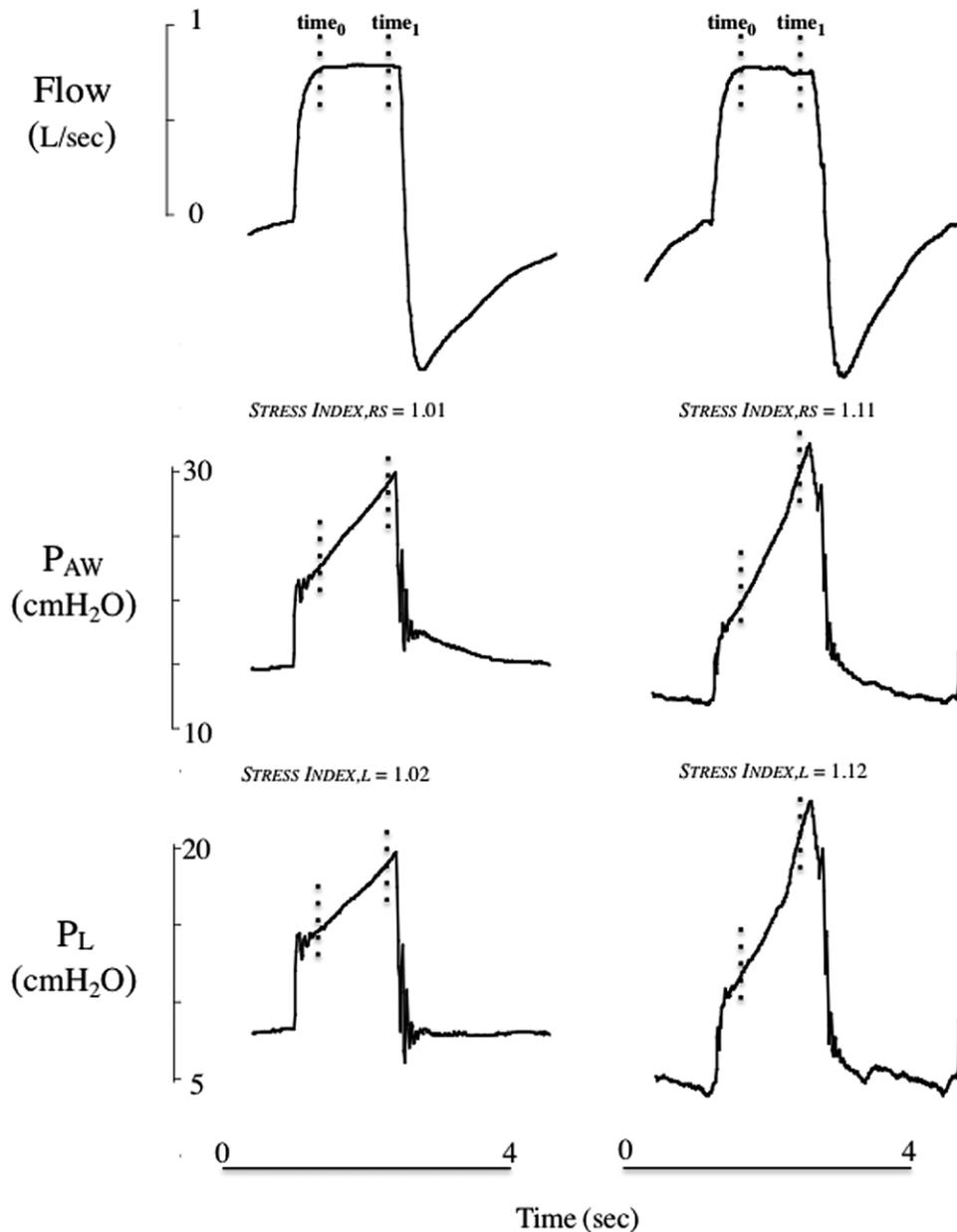


Fig. 1. Flow, airway pressure (PAW), and transpulmonary pressure (PL) in two representative patients. Signals were collected for 5 min and hence averaged and smoothed by a filter that averaged the signal over a 120-ms time window. Dotted vertical lines indicate the beginning (*time 0*) and the end (*time 1*) of the constant flow portion. The corresponding portion on the PAW–time (PAW–*t*) curve encompassed in the time interval (*time 0*–*time 1*) was fitted to the equations: $P_{aw} = a_{aw} \cdot (time_0 - time_1)^{b_{aw}} + c_{aw}$ $P_L = a_L \cdot (time_0 - time_1)^{b_L} + c_L$. The coefficients b_{aw} (*STRESS INDEX,RS*) and b_L (*STRESS INDEX,L*) are dimensionless number that describes the shape of the PAW–*t* and of the PL–*t* curves. Values of coefficient $b < 1$ indicate that compliance increases with time, whereas compliance decreases with time for values of coefficient $b > 1$. Finally, $b = 1$ indicates a constant compliance during tidal inflation.

The predictive power of the previously selected values of $P_{plat,RS}$ and *STRESS INDEX,RS* was estimated using the previously selected cutoff values, which 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 \pm SD; *P* value less than 0.05 was considered significant. Comparisons of continuous and categorical data among groups were performed using unpaired *t* tests and chi-square tests. Regression was performed using least-squares. Because values of cytokine concentrations were not normally distributed, \log_{10} transformation was performed before applying parametric statistics.

A true positive was defined when PPLAT and STRESS INDEX predicted *tidal hyperinflation* or *tidal recruitment* and CT scan analysis was confirmatory. A true-negative was defined when PPLAT and STRESS INDEX predicted absence of *tidal hyperinflation* or *tidal recruitment* and CT scan analysis was confirmatory. A false positive was defined when PPLAT and STRESS INDEX value predicted presence of *tidal hyperinflation* or *tidal recruitment* and CT scan was not confirmatory. A false negative was defined when PPLAT 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, NC; MedCalc version 11.1.1; MedCalc Software bvba, Ostend, Belgium).

Results

Some of the results reported in the current investigation include data obtained from patients who enrolled in previously published studies.^{1,9,10,20} Of the 110 patients enrolled, 10 were excluded for the following reasons: more than 3 days elapsed since mechanical ventilation initiation (N = 5); chest tube with persistent air leak (N = 2); unilateral lung disease (N = 2); and spontaneous respiratory effort during physiological measurements (N = 1). Of the remaining 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 two clusters of patients. In a cluster of 28 patients (16 in the training set and 12 in the validation set), *tidal hyperinflation* was $8.36 \pm 5.51\%$ (training set) and $9.91 \pm 4.31\%$ (validation set), whereas *protected ventilation* was $71.20 \pm 8.05\%$ (training set) and $75.68 \pm 8.01\%$ (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 $53.76 \pm 7.92\%$ (training set) and $50.91 \pm 21.78\%$ (validation set), and *protected ventilation* was $28.55 \pm 16.33\%$ (training set) and $25.91 \pm 14.71\%$ (validation set) of the total tidal inflation–associated change in CT lung compartments. These patients were considered relatively not protected from injurious ventilation (“*NONPROTECTED*”). *Tidal recruitment* was $20.44 \pm 7.03\%$ (training set) and $14.81 \pm 7.73\%$ (validation set) in *PROTECTED* and $17.69 \pm 8.15\%$ (training set) and $23.18 \pm 9.32\%$ (validation set) in the *NONPROTECTED*. As such, *tidal recruitment* could not be identified in the cluster analysis as a distinct entity that could define a *PROTECTED* versus a *NONPROTECTED* ventilator setting and therefore could not be used as an additional criterion to define a nonprotected tidal inflation.

Ventilator settings and biological variables in the *PROTECTED* and “*NONPROTECTED*” clusters are shown in table 2. Pulmonary concentrations of the inflammatory cytokines were lower in *PROTECTED* than in *NONPROTECTED* ($P < 0.05$).

The areas under the receiver-operating characteristics curves for *Pplat, Rs* and *STRESS INDEX, RS* (0.833 ; 95% CI, 0.621 – 0.954 and 0.917 ; 95% CI, 0.724 – 0.990 , respectively;

Table 1. Characteristics of the Study Population

	Training Set (N = 30)	Validation Set (N = 20)	Physiological Study (N = 50)
Demographics			
Age, yr	67 ± 11	64 ± 9	60 ± 15
Male/female	13/10	17/3	27/21
SAPS II	52 ± 20	44 ± 12	45 ± 12
Respiratory variables			
V _T , ml/kg IBW	6.8 ± 0.8	6.9 ± 0.8	7.2 ± 2.3
P _{plat, Rs} , cm H ₂ O	26.3 ± 2.2	24.5 ± 4.1	24.8 ± 5.4
PEEP, cm H ₂ O	13 ± 3	14 ± 4	10.8 ± 4.8
P _{aO₂} /F _{iO₂}	152 ± 37	149 ± 54	150 ± 50
V _E , l/min	16.6 ± 5.3	15.1 ± 5.6	12.0 ± 4.4
P _{aCO₂} , mmHg	52.4 ± 13.2	51 ± 15	46 ± 11
Arterial pH	7.38 ± 0.07	7.40 ± 0.08	7.40 ± 0.08
Causes of lung injury			
Pneumonia, no. (%)	11 (48)	10 (50)	19 (39)
Sepsis, no. (%)	10 (43)	9 (45)	22 (46)
Trauma, no. (%)	2 (9)	1 (5)	7 (15)

Data are mean ± SD.

F_{iO₂} = inspiratory oxygen fraction; IBW = ideal body weight; P_{aCO₂} = arterial carbon dioxide partial pressure; P_{aO₂} = arterial oxygen partial pressure; PEEP = positive end-expiratory pressure; P_{plat, Rs} = end-inspiratory plateau pressure of the respiratory system; SAPS = simplified acute physiological score; V_E = minute ventilation; V_T = tidal volume.

Table 2. Ventilatory and Biological Variables Concentration of Pulmonary Concentration of Inflammatory Cytokines in the Selected Two Clusters

	Tidal Hyperinflation		P Value
	Absent	Present	
V_T , ml/kg IBW	6.8±0.7	7.0±0.9	
PEEP, cm H ₂ O	11.6±2.9	14.0±2.5	0.0411
P_{aO_2}/F_{iO_2}	175±45	126±37	0.0489
$P_{plat,RS}$, cm H ₂ O	24.8±2.3	27.5±2.7	0.0353
$STRESS\ INDEX_{RS}$, cm H ₂ O	1.06±0.09	1.14±0.09	0.0005
TNF-asR55, pg/ml	1,060±629	5,787±2,611	0.0001
TNF-asR75, pg/ml	2,178±1,322	9,539±6,191	0.0001
IL-6, pg/ml	1,078±863	23,751±14,586	0.0001
IL-8, pg/ml	5,696±7,646	23,494±30,141	0.007
IL-1 β , pg/ml	1,557±1,869	14,266±21,689	0.005
IL-1Ra, pg/ml	9,099±15,899	142,527±264,870	0.004

Data are mean \pm SD.

F_{iO_2} = inspiratory oxygen fraction; IBW = ideal body weight; IL = interleukin; IL-1Ra = interleukin-1 receptor antagonist receptor antagonist; P_{aCO_2} = arterial carbon dioxide partial pressure; P_{aO_2} = arterial oxygen partial pressure; PEEP = positive end-expiratory pressure; $P_{plat,RS}$ = end-inspiratory plateau pressure of the respiratory system; TNF-asR55 and TNF-asR75 = tumor necrosis factor- α soluble receptors; V_E = minute ventilation; V_T = tidal volume.

fig. 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 cm H₂O) were 0.06 (95% CI, 0.002–0.30) and 1.0 (95% CI, 0.87–1.00), respectively. The threshold value of $P_{plat,RS}$ that best identified *NONPROTECTED* patients was 25 cm H₂O; sensitivity and specificity were 0.82 (95% CI, 0.48–0.98) and 0.67 (95% CI, 0.35–0.90), respectively. A threshold value of $STRESS\ INDEX_{RS}$ greater than 1.05 best identified *NONPROTECTED* patients; sensitivity and specificity were 0.82 (95% CI, 0.48–0.98) and 0.83 (95% CI, 0.52–0.98), respectively.

Sensitivity and specificity of $P_{plat,RS}$ greater than 25 cm H₂O to identify *NONPROTECTED* patients were 0.75 (95% CI, 0.35–0.97) and 0.75 (95% CI, 0.43–0.95), respectively. Sensitivity and specificity of a $STRESS\ INDEX_{RS}$ greater than 1.05 to identify *NONPROTECTED* patients were 0.88 (95% CI, 0.47–1.00) and 0.50 (95% CI, 0.21–0.79); table 3).

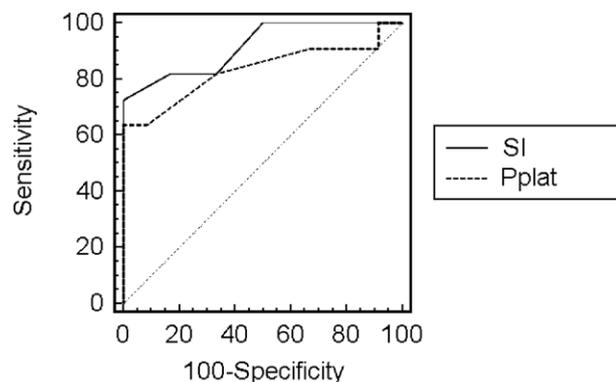


Fig. 2. Receiver-operating characteristics curve for the end-inspiratory plateau pressure ($P_{plat,RS}$) and stress index ($STRESS\ INDEX_{RS}$) of the respiratory system. SI = Stress Index.

The correlation coefficients relating $STRESS\ INDEX_{RS}$ versus $STRESS\ INDEX_{L}$ and of $P_{plat,RS}$ versus $P_{PLAT,L}$ were 0.762 and 0.0099, respectively (fig. 3).

Discussion

The main findings of the current investigation are: (1) the value of $P_{plat,RS}$ recommend by current guidelines (≤ 30 cm H₂O) does not accurately discriminate patients with CT scan indexes of tidal hyperinflation; (2) the discriminating threshold values that best associate $P_{plat,RS}$ and $STRESS\ INDEX_{RS}$ to CT pattern of tidal hyperinflation are less than 25 cm H₂O and greater than 1.05, respectively; (3) although $STRESS\ INDEX_{RS}$ represents a reasonable reflection of $STRESS\ INDEX_{L}$, there is substantial discrepancy when using $P_{plat,RS}$ versus $P_{PLAT,L}$.

Rigorous statistical methods have been developed to evaluate the degree of agreement between a test and the best available method for establishing the presence or absence of the condition of interest.³⁷ Accordingly to these methods (1) we included a study population representative of patients with ARDS²⁶ excluding only those patients who were mechanically ventilated for more than 72 h or in whom measurements of respiratory mechanics could not be performed; (2) we used previously established methods to measure physiological variables³¹; (3) 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); (4) 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,

Table 3. Accuracy of the Threshold Values of *STRESS INDEX_{RS}* and *Pplat,RS* Used to Identify Patients with and without CT Scan Evidence of Tidal Hyperinflation

	Tidal Hyperinflation		PPV	NPV
	Present = 8	Absent = 12		
<i>STRESS INDEX_{RS}</i>				
>1.05 (N = 13)	TP = 7	FP = 6		
≤1.05 (N = 7)	FN = 1	TN = 6		
<i>PPLAT, RS</i>				
>25 cm H ₂ O (N = 9)	TP = 6	FP = 3		
≤25 cm H ₂ O (N = 11)	FN = 2	TN = 9		
	Sensitivity	Specificity		
<i>STRESS INDEX</i> >1.05	0.88	0.50	0.54	0.86
<i>PPLAT</i> >25 cm H ₂ O	0.75	0.75	0.67	0.82

CT = computed tomography; FN = false negative; FP = false positive; NPV = negative predictive value; *Pplat,RS* = end-inspiratory plateau pressure of the respiratory system; PPV = positive predictive value; TN = true negative; TP = true positive; *STRESS INDEX_{RS}* = *STRESS INDEX* of the respiratory system.

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 because tidal recruitment could not be addressed by cluster analysis, the terms *PROTECTED* and *NONPROTECTED* should be referred only to tidal hyperinflation. Moreover, although we found a concentration of inflammatory mediators higher in patients included in the *NONPROTECTED* 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 trial⁸ and observational studies^{39,40} have demonstrated that limiting V_T to 6 ml/kg predicted body weight and *Pplat,RS* to 30 cm H₂O improves survival. Our data show that the threshold value that best identified *NONPROTECTED* patients was not *Pplat,RS* greater than 30 cm H₂O but *Pplat,RS* greater than 25 cm H₂O. 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 *Pplat,RS* to 30 cm H₂O.^{9–11}

Previous studies proposed analyzing the PAW–time curve during constant flow to assess the mechanical properties of the respiratory system of patients with ARDS.^{15,16} This approach is based on the concept that at constant flow, the rate of change of PAW 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 (pressure = a time ^{b} + c).¹⁶ A coefficient $b = 1.0$ indicates a linear PAW–time curve and an unchanging elastance during inflation; coefficient b less than 1.0 indicates decreasing elastance during inflation; and coefficient b greater than

1.0 indicates an 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}* greater than 1.05 best identified patients *NONPROTECTED* 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* greater than 25 cm H₂O was slightly lower than sensitivity of *STRESS INDEX_{RS}* greater than 1.05 (0.75; 95% CI, 0.35–0.97) versus 0.88 (95% CI, 0.47–1.00; table 3).

Our data demonstrate that although alterations in 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 (PAW 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 current study demonstrates that the value of *Pplat,RS* currently recommend by guidelines

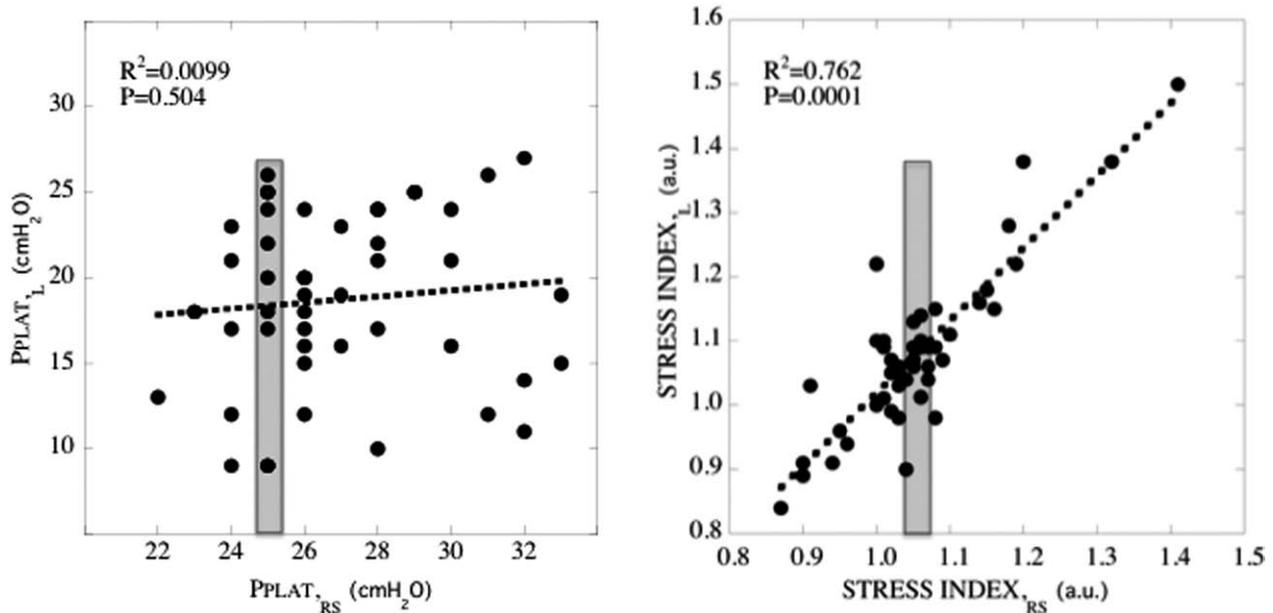


Fig. 3. Relationship between end-inspiratory plateau pressure of the respiratory system ($P_{plat,RS}$) and of the lung ($P_{PLAT,L}$) and stress index of the respiratory system ($STRESS\ INDEX_{RS}$) and of the lung ($STRESS\ INDEX_{L}$). Shaded bar indicates the threshold values of $P_{plat,RS}$ (25 cm H_2O) and $STRESS\ INDEX_{RS}$ (1.05) previously found to provide the optimal predictive power for tidal hyperinflation.

(≤ 30 cm H_2O) does not accurately discriminate patients with CT scan indexes of tidal hyperinflation. The threshold values of $P_{plat,RS}$ and of $STRESS\ INDEX_{RS}$ that correspond to CT scan indexes of tidal hyperinflation are less than 25 cm H_2O and less than 1.05. Although a substantial discrepancy between $P_{plat,RS}$ and $P_{PLAT,L}$ occurs, $STRESS\ INDEX_{RS}$ reflects $STRESS\ INDEX_{L}$ with reasonable accuracy. Clinical trials are required to test whether ventilator settings targeting $P_{plat,RS}$ of 25 cm H_2O or less and/or a $STRESS\ INDEX_{RS}$ of 1.05 or less will improve clinical outcomes.

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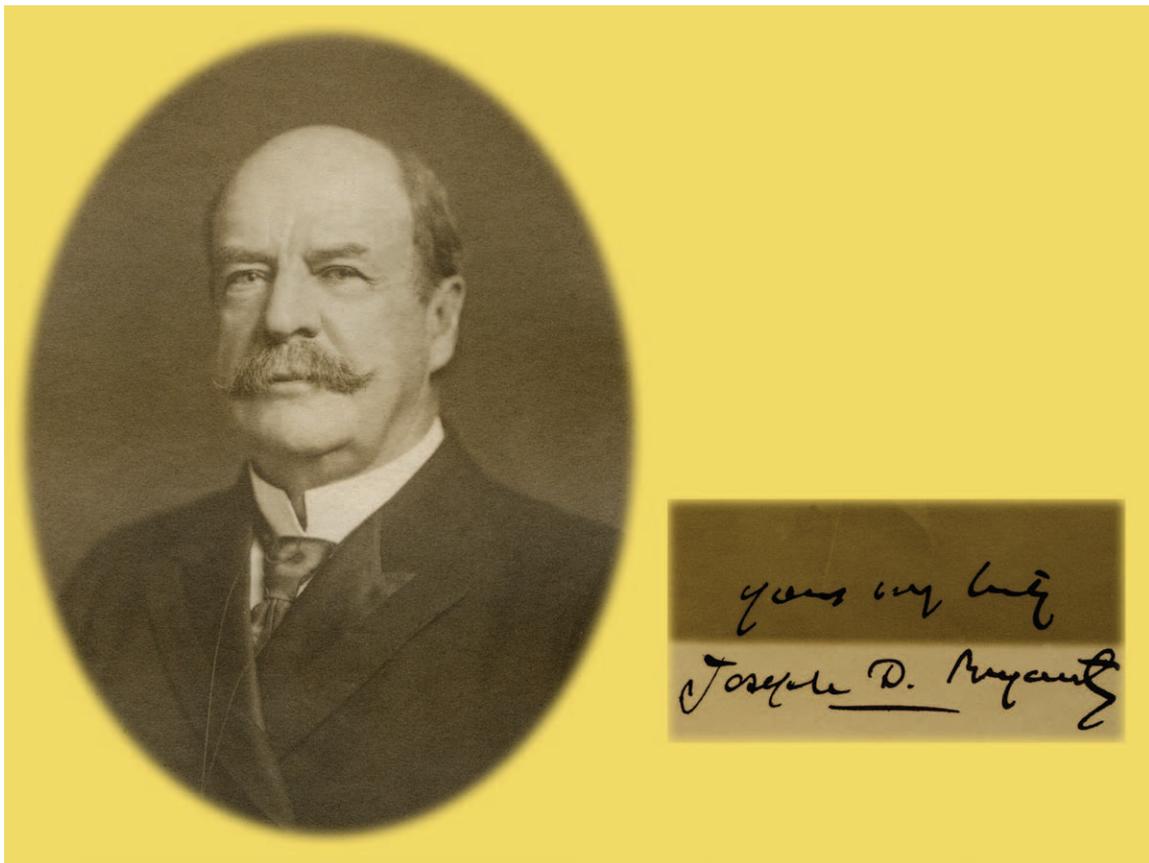
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Dr. Joseph Bryant's Role in President Grover Cleveland's Secret Anesthesia and Surgery



As the yacht *Oneida* steamed slowly along the Long Island Sound in July of 1893, U.S. President Grover Cleveland underwent oral cancer surgery which removed most of "his left upper jaw." The secret operation was coordinated by Cleveland's personal surgeon Joseph G. Bryant (*left*). Dr. Bryant arranged for his assistant surgeons William Keene and John Erdmann, for dentist-anesthetist Ferdinand Hasbrouck (nitrous oxide administrator), and for physicians Robert O'Reilly (etherist) and Edward Janeway (pulse monitor) to each embark and disembark from random ports—to both fool the press corps and guard the president's privacy. On the Wood Library-Museum's photoportrait of Dr. Bryant, he has signed his name (*right*) as "Joseph D. Bryant." (Copyright © the American Society of Anesthesiologists, Inc.)

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