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 (Pplat) 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 Pplat and STRESS INDEX to identify morphological indexes of injurious ventilation.

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 Pplat 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 Pplat 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). Pplat and STRESS INDEX were partitioned between respiratory system (Pplat,Rs and STRESS INDEX,Rs) and lung (Pplat,L and STRESS INDEX,L; esophageal pressure; “physiological set,” N = 50).

Results: Sensitivity and specificity of Pplat of greater than 30 cm H2O were 0.06 (95% CI, 0.002–0.30) and 1.0 (95% CI, 0.87–1.00). Pplat 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 Pplat 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. Pplat,Rs did not correlate with Pplat,L (R² = 0.0099); STRESS INDEX,Rs and STRESS INDEX,L were correlated (R² = 0.762).

Conclusions: The best threshold values for discriminating morphological indexes associated with injurious ventilation were Pplat,Rs greater than 25 cm H2O and STRESS INDEX,Rs greater than 1.05. Although a substantial discrepancy between Pplat,Rs and Pplat,L occurs, STRESS INDEX,Rs reflects STRESS INDEX,L.

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

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

Current guidelines recommend keeping end-inspiratory plateau airway pressure (Pplat) of 30 cm H2O or less, based on a randomized clinical trial demonstrated that limiting tidal volume (VT) to 6 ml/kg predicted body weight and Pplat to 30 cm H2O decreased absolute mortality by 9%. 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 Pplat of 30 cm H2O or less; (2) impairment of chest wall mechanics compromises the ability of Pplat to reflect overdistension.

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. Although used in clinical studies and implemented in a commercially available ventilator, 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.

In the current study, we assessed the diagnostic accuracy of Pplat 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. In a separate patient cohort, we examined the impact of chest wall mechanics on the use of Pplat 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).

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. 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. 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) or use of neuromuscular blockade (cis-atracurium besylate 2–8 gamma·kg−1·min−1). Absence of spontaneous effort was confirmed by inspecting flow and airway pressure traces during an end-expiratory pause of 4–5 s.

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 ± 100 cm H2O; Nordlingen, Germany) were measured as previously described. In a subset of 50 patients, intrathoracic pressure was evaluated by assessment of esophageal pressure (PES) using a thin latex balloon-tipped catheter system (Microtek Medical B.V., Zutphen, Netherlands) connected by a polyethylene catheter to a pressure transducer (Special Instruments Digima-Clic ± 100 cm H2O). 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.

End-inspiratory Plateau Pressure. Pplat of the respiratory system (PplatRS) was the value of PAW after an end-inspiratory occlusion. In the subset of patients in whom PES was measured, end-inspiratory chest wall plateau pressure (PplatCW) was measured as the variation in PES between end-expiratory and end-inspiratory occlusions; end-inspiratory plateau pressure of the lung (PplatLI) was estimated as PplatRS – PplatCW.

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. Transpulmonary pressure (Pt) was calculated as PAW – PES. Individual flow, PAW,
and \( P_t \) 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 \( \pm 3\% \). 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 offset after the beginning \(( t = 0)\) and before the end \(( t = 1)\) of the constant flow portion. The portion of the mean \( PAW \)-time and \( P_L \)-time curves encompassed in the time interval \( t = 0 \text{--} t = 1 \) was fitted to the equations:

\[
P_{aw} = a_{aw} \times \text{time}_0^{b_{aw}} + c_{aw} \tag{1}
\]

\[
P_L = a_L \times \text{time}_0^{b_L} + c_L \tag{2}
\]

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 \( Stress\ Index,rl \)) are dimensionless numbers that describe the shape of the \( PAW \)-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 ventilation \( R^2 \) was prospectively assessed in a second group of patients \( ("validation set") \) 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 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 \( P_{plat} \), \( RS \) 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 by assessing the receiver-operating characteristics curve.\(^{36}\)

Accuracy of \( P_{plat} \) and \( Stress\ Index \). 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 over-distension.\(^9\)\(^{10}\) 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 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.

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The area under the receiver-operating characteristics curve for \( P_{plat} \), \( RS \) 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.
The predictive power of the previously selected values of $P_{\text{plat}},R_s$ and $\text{Stress Index},R_s$ 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 $\text{Stress Index},L$ and $P_{\text{plat}},L$ 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; $P$ 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 $P_{\text{plat}}$ and Stress Index predicted tidal hyperinflation or tidal recruitment and CT scan analysis was confirmatory. A true-negative was defined when $P_{\text{plat}}$ and Stress Index predicted absence of tidal hyperinflation or tidal recruitment and CT scan analysis was confirmatory. A false positive was defined when $P_{\text{plat}}$ and Stress Index value predicted presence of tidal hyperinflation or tidal recruitment and CT scan was not confirmatory. A false negative was defined when $P_{\text{plat}}$ and Stress Index value predicted absence of tidal hyperinflation or tidal recruitment and CT scan analysis was not confirmatory.

Standard formulæ 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. 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.

Ventricular 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 $P_{\text{plat}}$, $R_s$ and Stress Index, $R_s$ (0.833; 95% CI, 0.621–0.954) and 0.917; 95% CI, 0.724–0.990, respectively;
The correlation coefficients relating Stress Index,rs versus Stress Index,l and of Pplat,Rs versus Pplat,l were 0.762 and 0.0099, respectively (fig. 3).

**Discussion**

The main findings of the current investigation are: (1) the value of Pplat,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 Pplat,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 Pplat,Rs versus Pplat,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. Accordingly to these methods (1) we included a study population representative of patients with ARDS 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 variables; (3) we developed threshold values of Pplat,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,
Tidal Hyperinflation

Table 3. Accuracy of the Threshold Values of \textit{Stress Index,rs} and \textit{Pplat,Rs} Used to Identify Patients with and without CT Scan Evidence of Tidal Hyperinflation

<table>
<thead>
<tr>
<th>\textit{Stress Index,rs}</th>
<th>Present = 8</th>
<th>Absent = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.05 (N = 13)</td>
<td>TP = 7</td>
<td>FP = 6</td>
</tr>
<tr>
<td>≤1.05 (N = 7)</td>
<td>FN = 1</td>
<td>TN = 6</td>
</tr>
<tr>
<td>\textit{Pplat,rs}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25 cm H\textsubscript{2}O (N = 9)</td>
<td>TP = 6</td>
<td>FP = 3</td>
</tr>
<tr>
<td>≤25 cm H\textsubscript{2}O (N = 11)</td>
<td>FN = 2</td>
<td>TN = 9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Stress Index,rs} &gt;1.05</td>
<td>0.88</td>
<td>0.50</td>
<td>0.54</td>
</tr>
<tr>
<td>\textit{Pplat} &gt;25 cm H\textsubscript{2}O</td>
<td>0.75</td>
<td>0.75</td>
<td>0.67</td>
</tr>
</tbody>
</table>

CT = computed tomography; FN = false negative; FP = false positive; NPV = negative predictive value; \textit{Pplat,Rs} = end-inspiratory plateau pressure of the respiratory system; PPV = positive predictive value; TN = true negative; TP = true positive; \textit{Stress Index,rs} = \textit{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, 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, this may be a marker of severity of ARDS and not solely reflect the degree of hyperinflation.

A clinical trial and observational studies have demonstrated that limiting \(V_t\) to 6 ml/kg predicted body weight and \(P_{plat,Rs}\) to 30 cm H\textsubscript{2}O improves survival. Our data show that the threshold value that best identified protected patients was \(P_{plat,Rs}\) greater than 30 cm H\textsubscript{2}O but \(P_{plat,Rs}\) greater than 25 cm H\textsubscript{2}O. 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 cm H\textsubscript{2}O.

Previous studies proposed analyzing the PAW–time curve during constant flow to assess the mechanical properties of the respiratory system of patients with ARDS. 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, and can be described by a power equation (pressure = \(a\) \(t^{\text{expiration}} + \epsilon\)). 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 \textit{Stress Index}) could be used to detect tidal hyperinflation or tidal recruitment during mechanical ventilation. Although subsequent experimental studies challenged these findings, the use of \textit{Stress Index} to detect injurious ventilation has been tested in clinical studies and implemented in a commercially available ventilator. We found that a \textit{Stress Index} greater than 1.05 best identified patients nonprotected from injurious ventilation. The area under the receiver-operating characteristics curve for \textit{Stress Index,rs} and \textit{Pplat,Rs} were not statistically different. However, in the validation set, sensitivity of \textit{Pplat,Rs} greater than 25 cm H\textsubscript{2}O was slightly lower than sensitivity of \textit{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 \textit{Pplat,Rs} to estimate \textit{Pplat,l, Stress Index,ls} closely reflects \textit{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. \textit{Pplat,Rs} as a measure of \textit{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. The \textit{Stress Index} reflects the changes with volume of the elastance of the respiratory system (PAW \(v.s.\) time) or of the lung (\(P_L\) \(v.s.\) time). In the range of changes of lung volume associated with a low tidal volume strategy, the volume–pressure relationship of the chest wall is linear, and hence the \textit{Stress Index} should largely reflect the mechanical properties of the lung.

In conclusion, the current study demonstrates that the value of \textit{Pplat,Rs} currently recommended by guidelines...
(≤30 cm H₂O) does not accurately discriminate patients with CT scan indexes of tidal hyperinflation. The threshold values of $P_{\text{plat,rs}}$ and of $\text{Stress Index,rs}$ that correspond to CT scan indexes of tidal hyperinflation are less than 25 cm H₂O and less than 1.05. Although a substantial discrepancy between $P_{\text{plat,rs}}$ and $P_{\text{plat,l}}$ occurs, $\text{Stress Index,rs}$ reflects $\text{Stress Index,l}$ with reasonable accuracy. Clinical trials are required to test whether ventilator settings targeting $P_{\text{plat,rs}}$ of 25 cm H₂O or less and/or a $\text{Stress Index,rs}$ of 1.05 or less will improve clinical outcomes.

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Accuracy of Pplat and Stress Index


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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 1883, 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 photoporation of Dr. Bryant, he has signed his name (right) as “Joseph D. Bryant.” (Copyright © the American Society of Anesthesiologists, Inc.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA’s Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio, UJYC@aol.com.