An Objective Analysis of the Pressure-Volume Curve in the Acute Respiratory Distress Syndrome

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To assess the interobserver and intraobserver variability in the clinical evaluation of the quasi-static pressure-volume (P-V) curve, we analyzed 24 sets of inflation and deflation P-V curves obtained from patients with ARDS. We used a recently described sigmoidal equation to curve-fit the P-V data sets and objectively define the point of maximum compliance increase of the inflation limb ($P_{mci,i}$) and the true inflection point of the deflation limb ($P_{inf,d}$). These points were compared with graphic determinations of lower Pflex by seven clinicians. The graphic and curve-fitting methods were also compared for their ability to reproduce the same parameter value in data sets with reduced number of data points. The sigmoidal equation fit the P-V data with great accuracy ($R^2 = 0.9992$). The average of Pflex determinations was found to be correlated with $P_{mci,i}$ (R = 0.89) and $P_{inf,d}$ (R = 0.76). Individual determinations of Pflex were less correlated with the corresponding objective parameters (R = 0.67 and 0.62, respectively). Pflex + 2 cm H_2O was a more accurate estimator of $P_{inf,d}$ (2 SD = ±6.05 cm H_2O) than Pflex was of $P_{mci,i}$ (2 SD = ±8.02 cm H_2O). There was significant interobserver variability in Pflex, with a maximum difference of 11 cm H_2O for the same patient (SD = 1.9 cm H_2O). Clinicians had difficulty reproducing Pflex in smaller data sets with differences as great as 17 cm H_2O (SD = 2.8 cm H_2O). In contrast, the curve-fitting method reproduced $P_{mci,i}$ with great accuracy in reduced data sets (maximum difference of 1.5 cm H_2O and SD = 0.3 cm H_2O). We conclude that Pflex rarely coincided with the point of maximum compliance increase defined by a sigmoid curve-fit with large differences in Pflex seen both among and within observers. Calculating objective parameters such as $P_{mci,i}$ or $P_{inf,d}$ from curve-fitted P-V data can minimize this large variability. Harris RS, Hess DR, Venegas JG. An objective analysis of the pressure-volume curve in the acute respiratory distress syndrome. AM J RESPIR CRIT CARE MED 2000;161:432–439.

The inspiratory limb of the quasi-static pressure-volume (P-V) curve of the total respiratory system has been used to guide mechanical ventilation in the acute respiratory distress syndrome (ARDS) (1, 2). The form of the curve is sigmoidal, with upward concavity at low inflation pressures and downward concavity at higher inflation pressures (3). The pressure at which a rapid increase in compliance occurs is thought to reflect recruitment of atelectatic alveolar units (1). Beyond this point, the "linear" portion of the curve is thought to reflect alveolar compliance. It has thus been postulated that setting PEEP above a point on the inspiratory limb of the P-V curve termed "Pflex" or "lower inflection point" (LIP) might optimize alveolar recruitment (4). In fact, by setting PEEP = Pflex + 2 cm H_2O in a pressure-limited, "open lung" ventilator strategy in ARDS, Amato and colleagues (5) demonstrated reduced barotrauma, a higher weaning rate, and improved survival at 28 d when compared with a "conventional" ventilator strategy without guidance from P-V curves.

Despite these encouraging results, there are few theoretical or experimental reasons to justify the clinical use of Pflex to optimize alveolar recruitment. First, PEEP is conceptually used to prevent derecruitment after a sustained inflation maneuver. Because derecruitment is a deflation phenomenon, it seems reasonable that it would be best identified on the deflation, and not the inflation, limb of the P-V curve (6). Second, there is most likely not a single pressure where recruitment or derecruitment occurs, but rather a distribution of pressures around which the phenomenon progressively takes place. These points have been recognized by other investigators (7). Holzapfel and colleagues (8) compared the reduction in shunt fraction with features of the inflation and deflation P-V curves as PEEP was progressively increased in patients with ARDS. They found that the maximum reduction in shunt correlated best with the *true* inflection point (the point where concavity changes direction) of the deflation limb of the P-V curve. It has also been shown by nitrogen washout studies in anesthetized patients that the deflation limb of the P-V curve can be used to estimate the pressure required to raise FRC above its closing volume (9). Others have shown with mathematical models that alveolar collapse may occur before the true inflection point has been reached (10). These studies provide support for

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the concept that the deflation, rather than the inflation, limb of the P-V curve could be used for titration of PEEP.

In addition, analysis of the P-V curve has generally been done by eye from a graph, a method that may be affected by large interobserver and intraobserver variability. In an attempt to describe the point where compliance increases rapidly, lower Pflex has been defined in several ways in the literature (Table 1). This makes it difficult to compare values from different studies (5, 11–16). Furthermore, the lack of rigorous definitions of terms such as lower Pflex, upper Pflex, inflection point, lower inflection point (LIP), and upper inflection point (UIP) has added confusion to the subject. Inflection point is a mathematical term that refers to the point of a function where the concavity changes direction. Lower Pflex (or LIP) and upper Pflex (or UIP) are used in the critical care literature to describe a rapid change in the slope of the P-V curve, often referred to as a "knee" in the curve, although clinically the change is typically more gradual. It is not clear whether the methods used to calculate these points give a point of maximum compliance increase (where the second derivative reaches a maximum), but it would appear that these graphic approaches are attempts to do so. Part of the objectives of this study was to see how close the lower Pflex, assessed by clinicians using the conventional method, reproduced the point of maximum compliance increase of the P-V curve. We will use lower Pflex to refer to any of the graphic methods to determine the lower "knee" of the curve, and reserve points of maximum compliance increase or decrease and inflection points to refer to the strict mathematical definitions. These definitions are detailed in Table 1.

We have recently described a new equation to characterize the P-V curve in terms of objective parameters (17). The objectives of the present study were: (*1*) to test the ability of that equation to prospectively characterize the total respiratory system P-V curve in patients with ARDS, (*2*) to compare objective parameters obtained from inflation and deflation P-V curves with Pflex obtained graphically by clinicians in intensive care units, and (*3*) to assess the interobserver and intraobserver variability of the graphically derived Pflex.

METHODS

Study Population

Patients were enrolled from the medical or surgical intensive care units at Massachusetts General Hospital (Boston, MA). Approval for this study was obtained from the Institutional Review Board with consent waived. All patients fulfilled the American-European Consensus Conference criteria for ARDS/ALI (acute onset, $Pa_{O_2}/FI_{O_2} \leqslant 300$, bilateral infiltrates on chest radiograph, and no clinical evidence for left atrial hypertension) and were older than 18 yr of age. Patients were heavily sedated or paralyzed and sedated without spontaneous breaths. Exclusion criteria included those who were too hemodynamically unstable (mean arterial pressure [MAP] $\leqslant$ 60 mm Hg or pulse $>$ 140 beats/min) to be removed from the ventilator, those with leaks around their endotracheal tube or tracheostomy tube, those with pneumothorax or bronchopleural fistulae, and those with recent head injury or cerebral edema.

Procedure

Once the inclusion and exclusion criteria were met and demographic information obtained, the patient was ventilated with 100% O_2 for approximately 10 min and then disconnected from the ventilator. After allowing the lungs to reach functional residual capacity (approximately 5 s), the patient's airway was connected to a 3-liter calibration syringe previously filled with 100% O_2. The inflation curve was obtained by sequentially adding 50- to 100-ml incremental volumes in a stepwise fashion until a pressure of 35 cm H_2O was reached. Four seconds were allowed between steps. The patient was then reconnected to the ventilator at the original settings for approximately 5 min. Pilot data showed that 5 min was an adequate time to reestablish the volume history of the lungs in this patient population. The patient was again removed from the ventilator and after allowing the lungs to reach functional residual capacity, the syringe was reconnected to the patient and the lungs rapidly inflated to 35 cm H_2O (approximately 2 to 3 s). After a pause of approximately 4 s, volumes were then withdrawn in 50- to 100-ml decrements, waiting at each step until the pressure signal reached a quasi-steady-state level (approximately 4 s). The procedure was stopped when a pressure of 0 cm H_2O was reached.

Measurements

A 3-liter calibration syringe was fitted with linear displacement and pressure transducers with outputs connected to a personal computer data acquisition system. Dedicated software was developed using LabVIEW (National Instruments Corp., Austin, TX) to acquire, display, save, and analyze pressure and volume signals as the syringe was manually inflated in incremental steps. The user manually accepted each data point when the pressure signal had reached a quasi-steady-state level. Volume and pressure values were saved in a spreadsheet file.

Inflation volume data were not corrected for changes in temperature and humidity or oxygen consumption since these effects have been found to cancel out during inflation in the time taken by the procedure (18). For the deflation limb, the volume was corrected for changes in temperature, humidity, and oxygen consumption. Loss of volume caused by oxygen consumption was assumed to be 95 ml/min, the average rate of loss in thoracic gas volume measured in patients by Dall'ava-Santucci and colleagues (18).

Data Analysis

Only complete data sets, including both inflation and deflation, were analyzed. P-V data were fitted with the equation:

$$V = a + b/(1 + e^{-(P - c)/d}) \quad (1)$$

TABLE 1

DEFINITIONS OF TERMS

Term	Definition
Lower Pflex, LIP*	A term for a graphically or numerically derived point on the inflation limb of the P-V curve. Some reported methods are listed below: • The pressure at the intersection of two lines, one drawn through the low compliance region and the other through the high compliance region of the inflation P-V curve (12, 13). • The lower point where the curve first deviates from its "linear portion" (14). • The pressure corresponding to the point at which the curve becomes straight (15). • The zone of lowest elastance (highest compliance) determined by step-by-step regression analysis (16).
$P_{inf,i}$, $P_{inf,d}$	The pressure (cm H_2O) at the inflection point (where concavity changes direction) for either inflation (i) or deflation (d).
$P_{mci,i}$, $P_{mci,d}$	The pressure (cm H_2O) at the point of maximum compliance increase for either inflation (i) or deflation (d).
$P_{mcd,i}$, $P_{mcd,d}$	The pressure (cm H_2O) at the point of maximum compliance decrease for either inflation (i) or deflation (d).

* Lower inflection point.

that has been previously reported (17). This equation has four fitting parameters: *a*, in units of volume, representing the lower asymptote; *b*, in units of volume, representing the distance from *a* to the upper asymptote, or inspiratory capacity; *c*, in units of pressure, representing the true inflection point (where concavity changes direction); *d*, in units of pressure, representing the distance from *c* of the zone of high compliance (Figure 1). Using the program DeltaGraph (SPSS Inc., Chicago, IL), the equation was fitted to the P-V data using the Levenberg-Marquardt iterative algorithm to minimize the sum of squared residuals. The algorithm was set to run until the resulting sum of squared residuals changed by < 0.0001, yielding estimates of the parameters *a*, *b*, *c*, and *d* and the best-fit coefficient R^2. Initial guess coefficients were $a = 0$ L, $b = 3$ L, $c = 20$ cm H_2O, $d = 10$ cm H_2O. The point of maximum compliance increase (P_{mci}, where the rate of change of upward slope is maximal or where the second derivative of the function has a maximum) is: c-1.317d (17). Points of maximum compliance increase or decrease falling outside the range of data collected ($<$ 0 cm H_2O or $>$ the highest data point collected in cm H_2O) were not included in the analysis.

To assess interobserver variability in the determination of Pflex, critical care clinicians were asked to analyze plots of P-V data without patient identifiers and without knowing the results of the curve-fitting analysis. Clinicians were asked to calculate lower Pflex as they normally would in the intensive care units. It was made clear to them to find the lower "knee" of the curve and not the points where concavity changes direction or the upper "knee" (upper Pflex). The clinicians were familiar with the concept of lower Pflex since it is frequently used to set PEEP in patients with ARDS in our intensive care units. Inflation P-V data of all patients and corresponding sets where every other data point was deleted were mixed in random order and given to the clinicians without revealing which data sets came from the same patient.

Overall goodness-of-fit of the equation to the data was assessed by normalizing each P-V data set by the corresponding fitting parameters yielding the dimensionless variables $(V - a)/b$ and $(P - c)/d$. These dimensionless variables allow the points of all curves to be plotted on the same *x*- and *y*-axis. Normalized P-V data were pooled for all curves, analyzed, plotted, and fitted by the equation: $(V - a)/b = 1/(1 + e^{-(P - c)/d})$. Also, for all the data sets, the mean values of Pflex among all observers and Pflex were plotted against the corresponding values of $P_{mci,i}$ and $P_{inf,d}$ and the correlation coefficient between them obtained. The accuracy of Pflex in estimating $P_{mci,i}$ and $P_{inf,d}$ and $P_{mci,i}$ in estimating $P_{inf,d}$ was assessed by bias and precision plots (19). Pflex was also analyzed for interobserver variability in the form of bias versus observer plots. The difference between Pflex and $P_{mci,i}$ was analyzed in the same fashion. The subjective and curve-fitting methods were compared for their ability to reproduce Pflex or $P_{mci,i}$ with reduced data points using bias and precision plots (19).

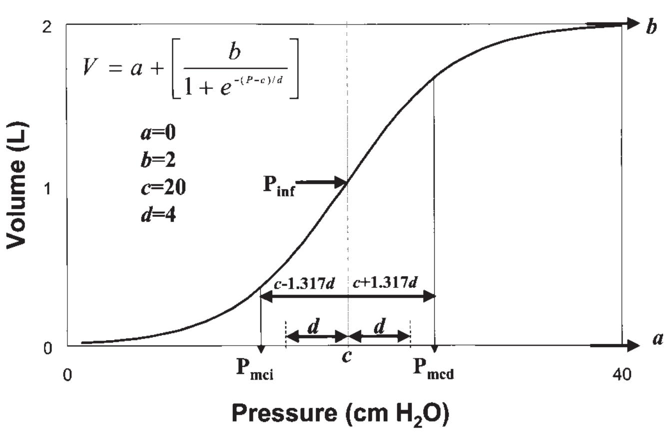

Figure 1. An example of the sigmoid equation used for curve-fitting P-V data. The equation (*top left* of the figure) with the coefficients $a = 0$ L, $b = 2$ L, $c = 20$ cm H_2O, $d = 4$ cm H_2O is shown plotted as the solid line. The inflection point (P_{inf}) is equal to *c*, and the points of maximum compliance increase (P_{mci}) and decrease (P_{mcd}) can be calculated as shown. For further description, *see* text.

RESULTS

Complete sets of inflation and deflation P-V curves were obtained from 18 patients. In four patients, P-V curves were repeated at different times giving a total of 24 sets used for analysis. The mean Murray Lung Injury Score for the 18 patients was 2.98 ± 0.42 SD. P-V data were obtained at times ranging from 1 to 50 d postintubation (median, 6.5 d). All but three patients had P-V curves done within 3 wk of intubation. In one inflation P-V curve, all seven clinicians agreed there was no Pflex. In two other inflation P-V curves, one of seven clinicians and four of seven clinicians, respectively, reported no Pflex. All other curves had Pflex values $>$ 0 cm H_2O for all clinicians. The diagnoses were pneumonia in nine, sepsis in eight, aspiration in five, pancreatitis in one, and lymphangitic spread of tumor in one. The sigmoidal Equation 1 had excellent fit (Figure 2), yielding R^2 values ranging from 0.9965 to 0.9999 for both inflation (mean, 0.9992 ± 0.0005 SD) and deflation (mean, 0.9993 ± 0.0010 SD). When inflation and deflation data points (547 points) were pooled for all curves analyzed and normalized by their corresponding curve-fitting parameters in a plot of $(V - a)/b$ versus $(P - c)/d$, they clustered tightly along the sigmoidal curve, with an R^2 of 0.9992 (Figure 3).

For three inflation curves, $P_{mci,i}$ was less than zero, and these were not used to compare with Pflex. All other curves had calculated parameters within the data set. Graphically determined Pflex by the seven clinicians correlated poorly with $P_{mci,i}$ and $P_{inf,d}$ ($R = 0.67$ and 0.62, respectively). However, when the seven Pflex determinations for each curve were averaged, there was a stronger correlation with $P_{mci,i}$ ($R = 0.89$) (Figure 4A). The average Pflex tended to overestimate $P_{mci,i}$ at low pressures and underestimate $P_{mci,i}$ at higher pressures. The average of the clinician's Pflex also correlated well with $P_{inf,d}$ ($R = 0.76$) (Figure 4B), but consistently underestimated it. Linear regression analysis yielded the following relationship: $P_{inf,d} = 0.91 \times$ average Pflex + 3.2 cm H_2O.

Pflex was less precise at predicting $P_{mci,i}$ than $P_{inf,d}$ (Figure 5). The difference between Pflex and $P_{mci,i}$ showed less bias (−0.61 cm H_2O) (Figure 5A), but a large scatter (2 SD = ±8.02 cm H_2O). In contrast, the difference between Pflex and $P_{inf,d}$ showed more bias (−2.33 cm H_2O) (Figure 5B), but less scatter (2 SD = ±6.05 cm H_2O). $P_{mci,i}$ was also less precise than Pflex at predicting $P_{inf,d}$ (Figure 6). The difference between $P_{mci,i}$ and $P_{inf,d}$ showed a bias of −1.5 cm H_2O and a large scatter (2 SD = ±7.95 cm H_2O).

The difference between Pflex and $P_{mci,i}$ for each observer ranged from −9.1 to 9.2 cm H_2O (SD = 1.9 cm H_2O) (Figure 7A). The interobserver variability of Pflex among the seven clinicians ranged between −6.6 and 6.6 cm H_2O (SD = 1.9 cm H_2O) (Figure 7B). In two curves, the clinicians differed by as much as 11 cm H_2O in estimating Pflex. When every other data point in each P-V data set was deleted, the clinician's ability to reproduce Pflex in that curve was poor (Figure 8A). The difference between Pflex obtained with sparse data and Pflex obtained with all data ranged between −17.0 and 12.5 cm H_2O (SD = 2.8 cm H_2O). In contrast, the curve-fitting method was much better at reproducing the estimated parameters in the presence of a reduced data set (Figure 8B). The difference between $P_{mci,i}$ obtained with sparse data and $P_{mci,i}$ obtained with all data ranged between −0.7 and 1.5 cm H_2O (SD = 0.6 cm H_2O).

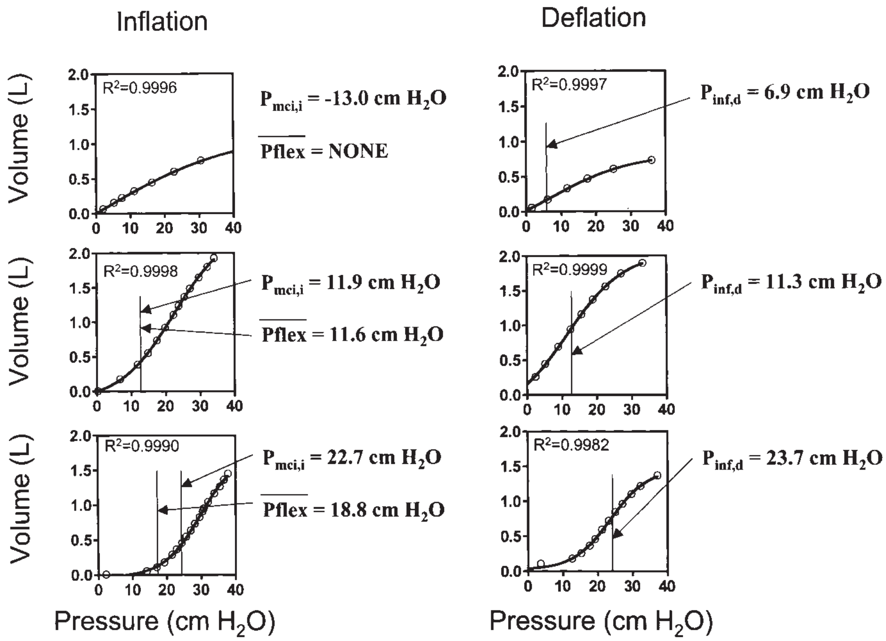

Figure 2. Inflation (*left panel*) and deflation (*right panel*) P-V curves are shown for three patients. The *open circles* are the data points and the thick *solid line* is the equation curve-fitted to the data. The values for $P_{mci,i}$ and mean Pflex are shown for the inflation curves and the value for $P_{inf,d}$ is shown for deflation. These patients were chosen to illustrate a patient with no Pflex (*top*), a mean Pflex in the middle range (*middle*), and the maximum mean Pflex (*bottom*) of all of the 18 patients.

In comparing objective parameters from inspiratory and expiratory data sets, there was a good correlation between $P_{inf,d}$ and $P_{mci,i}$ ($R = 0.76$), and a poorer correlation between $P_{inf,i}$ and $P_{inf,d}$ ($R = 0.57$). $P_{inf,d}$ was generally greater than $P_{mci,i}$ at lower $P_{mci,i}$, but they became closer as $P_{mci,i}$ increased (Figure 9A). $P_{inf,i}$ was always higher than $P_{inf,d}$, and this difference tended to increase with increasing $P_{inf,i}$ (Figure 9B).

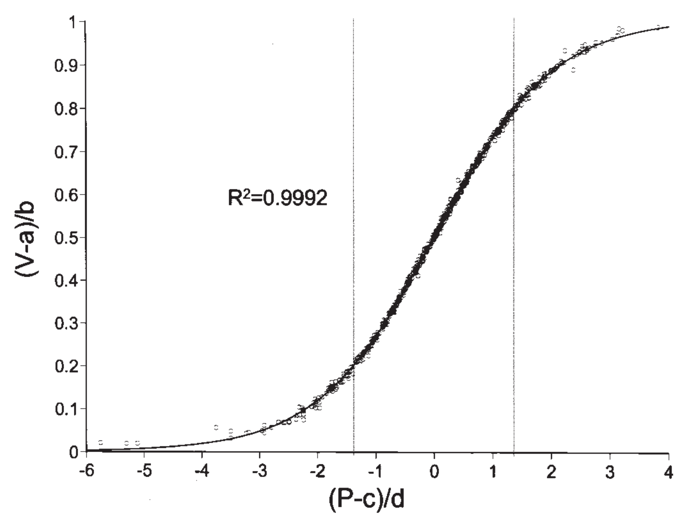

Figure 3. *Open circles* are the pooled 547 P-V data points from both inflation and deflation normalized by their curve-fitting parameters and plotted as $(V - a)/b$ versus $(P - c)/d$. The equation $(V - a)/b = 1/(1 + e^{-(P - c)/d})$ is the *solid line* drawn through the data points. The *dotted lines* represent P_{mci} and P_{mcd}, respectively. The R^2 for the curve-fit is 0.9992.

DISCUSSION

The main findings of this study were: (*1*) The sigmoidal Equation 1 fits P-V data from patients with ARDS remarkably well, (*2*) graphically determined Pflex correlated poorly with $P_{mci,i}$ and $P_{inf,d}$, but an average of clinician's Pflex determinations improved the correlations, (*3*) graphically determined Pflex + 2 cm H_2O was better at predicting $P_{inf,d}$ than Pflex at predicting $P_{mci,i}$, (*4*) there was substantial interobserver variability in estimating Pflex, (*5*) objective parameters derived using Equation 1 avoided intraobserver and interobserver variability and were robust even with reduced data sets, (*6*) $P_{mci,i}$ correlated better than $P_{inf,i}$ with $P_{inf,d}$, and (*7*) $P_{inf,i}$ is systematically higher than $P_{inf,d}$.

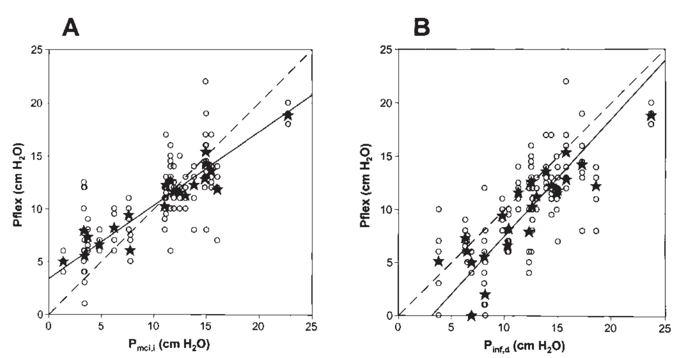

Figure 4. (*Panel A*) Pflex versus $P_{mci,i}$. (*Panel B*) Pflex versus $P_{inf,d}$. The open circles are the individual data points from the seven clinicians and the *solid stars* are the average Pflex of the seven clinicians for each P-V curve. A regression line for average Pflex versus $P_{mci,i}$ or $P_{inf,d}$ (*solid line*) and the line of identity (*dashed line*) are also shown.

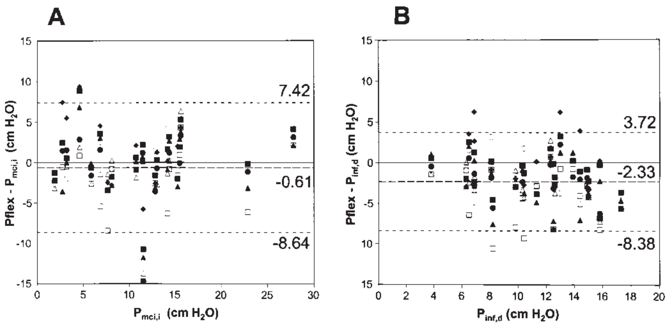

Figure 5. (*Panel A*) Difference between Pflex and $P_{mci,i}$ versus $P_{mci,i}$. (*Panel B*) difference between Pflex and $P_{inf,d}$ versus $P_{inf,d}$. Each clinician's differences are represented by a unique symbol. No difference is represented by the *solid line*, and the bias and two standard deviations from the bias are represented by the *dashed lines*. For *panel A*, 2 SD = ±8.02 cm H_2O; for *panel B*, 2 SD = ±6.05 cm H_2O. The values for bias and precision are shown next to the *dashed lines*.

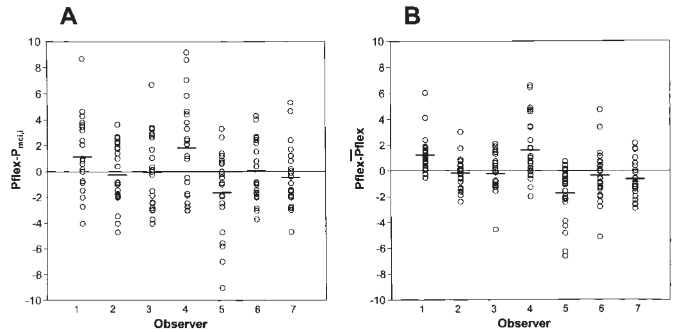

Figure 7. (*Panel A*) Pflex-$P_{mci,i}$ versus observer. (*Panel B*) Pflex-mean Pflex versus observer. The *open circles* are the individual data points for each P-V curve and the *horizontal line* segments are the means for each observer's data points.

Before discussing the impact of the above results, it is important to acknowledge some technical limitations of our methods. The supersyringe method for obtaining P-V curves has the problem of oxygen consumption and changes in temperature and water vapor pressure as the gas is introduced and withdrawn from the lungs (18). The change in temperature and water vapor pressure are known and can be used to correct the volume read from the syringe, but changes caused by oxygen consumption must be assumed. We used the average rate of fall in thoracic gas volume found by Dall'ava-Santucci and colleagues (18) during supersyringe P-V maneuvers. To examine the effect of this correction on our parameters, we compared $P_{inf,d}$ when derived from data with no correction versus those derived from data corrected using the highest rate of change of thoracic gas volume of 190 ml/min found by Dall'ava-Santucci and colleagues (18). The mean difference between $P_{inf,d}$ derived from uncorrected and corrected data was only 0.98 cm H_2O (SD = 2.8 cm H_2O). This suggests there is little effect of corrections for oxygen consumption on our derived parameters. This may be because we collected inflation and deflation data in separate maneuvers and therefore the time for each maneuver was short.

The sigmoidal Equation 1 did well at characterizing the data, as previously reported for retrospectively obtained data from animals and humans and without the use of computer data acquisition (17). The R^2 for the pooled data was 0.9992, suggesting that only 0.08% of the variance was not accounted by the function. One possible reason for such a good fit is that the data sets often did not contain enough data along one of the asymptotes of the sigmoid. Such a lack of data, however, should mostly affect the parameters *a* or *b* (the upper and lower asymptotes of the curve), and these parameters are not used in the calculation of $P_{mci,i}$ or $P_{inf,d}$. In our experience, adding or deleting data at the extremes of the data range does affect the parameter *d*, but to a lesser extent than *a* or *b*. As long as one is careful to disregard calculated parameters that fall outside of the range of available data, the other parameters appear to be quite robust.

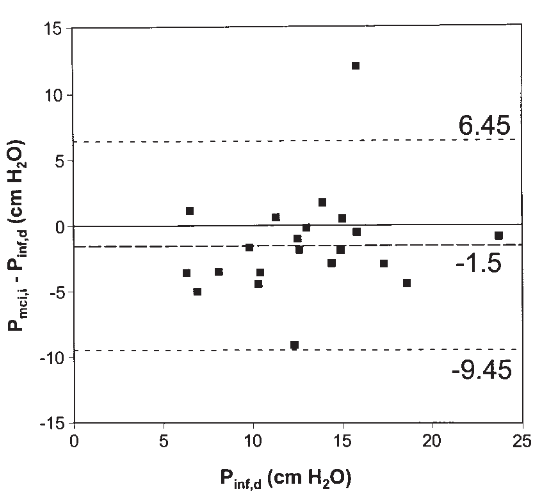

Figure 6. Difference between $P_{mci,i}$ and $P_{inf,d}$ versus $P_{inf,d}$. No difference is represented by the *solid line* and the bias and 2 SD from the bias are represented by the *dashed lines*. 2 SD = ±7.95 cm H_2O. The values for bias and precision are shown next to the *dashed lines*.

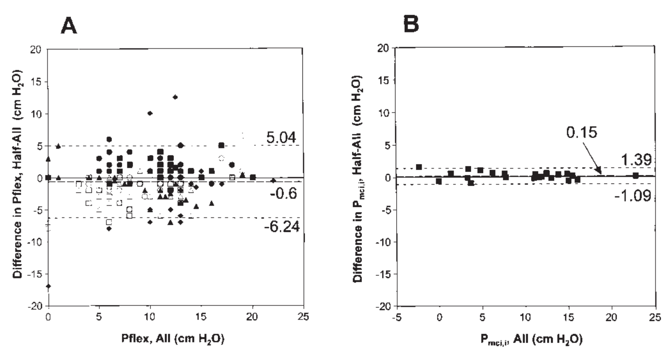

Figure 8. (*Panel A*) Pflex determined graphically by the clinicians. The difference between Pflex determined with all of the data points versus half of the data points is plotted against the Pflex calculated with all of the points. Each observer is represented by a different symbol. (*Panel B*) $P_{mci,i}$ determined by curve-fitting. The difference between the calculation done with all of the data points and half of the data points is plotted against $P_{mci,i}$ calculated with all of the points. No difference is represented by the *solid lines*, and the bias and 2 SD from the bias are represented by the *dashed lines*. For *panel A*, 2 SD = ±5.64 cm H_2O; for *panel B*, 2 SD = ±1.24 cm H_2O. The values for bias and precision are shown next to the *dashed lines*.

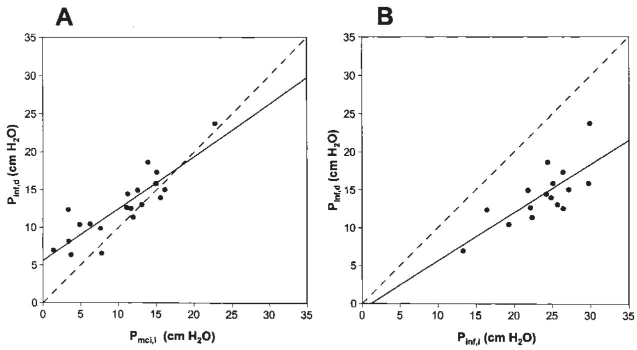

Figure 9. (*Panel A*) $P_{inf,d}$ versus $P_{mci,i}$. (*Panel B*) $P_{inf,d}$ versus $P_{inf,i}$. The data points (*closed circles*) are shown with a regression line drawn through them (*solid line*). The line of identity (*dashed line*) is also shown.

As pointed out in our previous report (17), the sigmoidal Equation 1 is symmetric around the true inflection point. There is no physiologic reason why the shape of the P-V curve must have such symmetry. In fact, if the upward concavity reflects recruitment of alveoli, whereas the downward concavity reflects nonlinear tissue elasticity, there is no reason why these should be the same. It is therefore intriguing that a symmetric equation fitted the clinical data so well. A possible answer is that the data sets included mostly points at one end of the sigmoid: inflation P-V curves with pressures < 40 cm H_2O included mostly data to the left of $P_{inf,i}$, and deflation curves included mostly data to the right of $P_{inf,d}$. We have recently modified our model to include a sigmoidal recruitment function and an exponential elasticity function (20). We found that this new model can fit much better data covering both ends of the sigmoid (with inflation pressures $\geqslant 40$ cm H_2O). However, for data sets with pressures < 40 cm H_2O, the simple sigmoid fitted the data as well as the new model. Therefore, we expect that errors introduced by imposing a symmetric model on the data are small.

Finally, this sigmoidal curve-fitting process does not define a local point of maximum compliance increase within the discrete data set but rather the point of maximum compliance increase of the fitted function. For example, when the point of maximum compliance increase of the fitted function occurs at negative pressures, the graphic method could still identify a positive Pflex. There were three patients with negative values of $P_{mci,i}$, and these were not included in the analysis. In one of these patients, all clinicians agreed there was no identifiable Pflex. In the other two patients, one and four of the seven clinicians, respectively, stated that there was no lower Pflex. Therefore, in most cases where $P_{mci,i}$ was negative, many clinicians agreed there was no Pflex. More interesting, however, was that some clinicians *did* find a lower Pflex when $P_{mci,i}$ was negative. The real issue is whether a lower Pflex is of clinical value when $P_{mci,i}$ is negative. If $P_{mci,i}$ corresponds to the maximum rate of recruitment of alveoli, it is plausible that the lungs of some patients, and most normal subjects, may already be above the maximum rate of recruitment at FRC, and a positive lower Pflex in those patients would not represent the maximum rate of recruitment of alveoli, but either a data sampling artifact caused by an insufficient data range or simply a meaningless graphic feature.

Pflex has been described as the point where compliance suddenly changes to become "straight" or the "knee" of the curve (4, 15). This has been interpreted as the pressure above which recruitment has been completed (1, 21). However, usually there is not a true linear segment in the P-V curve, but rather a gradual change from upward concavity to downward, and recruitment may be taking place all along the P-V curve (6, 17, 22). The remarkably good curve-fitting of our clinical data to the sigmoid curve is additional evidence that a gradual, rather than an abrupt, change in slope describes the compliance properties of the ARDS lung. As we pointed out earlier (17), this sigmoid is the integral of a bell-shaped function that closely approximates a normal distribution. This may indicate that the sigmoidal shape of the P-V curve could be due in part to progressive recruitment of alveolar units with normally distributed opening pressures. Thus, it may be more useful to think of inspiratory P-V curves as *recruitment* functions, rather than as compliance curves.

In addition to the theoretical problems with the use of Pflex, one practical problem is defining it. There have been multiple definitions of Pflex in the literature (Table 1). One popular method uses the intersection of two lines, one drawn through the compliance of the first 100 ml and another through the most compliant zone (12). This may be a graphic attempt to define the point where the compliance is changing most rapidly. In general, inflation data sets with low $P_{mci,i}$ include few data points around that point, and Pflex tended to overestimate $P_{mci,i}$ (Figure 4A). Extreme examples of this are the three inflation P-V curves with $P_{mci,i}$ less than zero. We found that Pflex systematically overestimated $P_{mci,i}$ at low pressures and underestimated it at high pressures. A possible explanation for this finding may be an unconscious bias on the part of the clinicians to define a Pflex within clinically acceptable values. Thus, clinicians may have biased their graphic interpolation to increase Pflex when it seemed low, and to decrease it when it seemed high. It is curious that the regression line intersects the identity line at approximately 12 cm H_2O, a commonly used level of PEEP for ARDS.

Another possible explanation for the systematic differences in $P_{mci,i}$ and Pflex could be that they represent different features of the curve. Pflex may not be the point of maximum compliance increase (where the second derivative of the function reaches a maximum), but rather the point of maximum curvature (or point with the minimum radius of curvature).* This point is defined by a maximum change in slope per unit arc length instead of per unit of pressure, which defines P_{mci}. A problem with using the point of maximum curvature to characterize the P-V curve is that its location is highly dependent on the scale used in the plotting coordinates. In contrast, the location of P_{mci} is scale-independent. Given the differences between Pflex and $P_{mci,i}$ (Figure 5A), it seems clear that any individual determination of Pflex is not a reliable estimator of the point of maximum compliance increase of the P-V curve.

The study by Amato and colleagues (5) reported an improved survival at 28 d, a higher rate of weaning from mechanical ventilation, and a lower rate of barotrauma in patients with acute respiratory distress syndrome when PEEP was set at Pflex + 2 cm H_2O. Curiously, Pflex + 2 cm H_2O appeared to be a better estimator of a feature of the deflation limb, $P_{inf,d}$ (Figure 5B) than of $P_{mci,i}$. There is no clear mechanistic reason why Pflex, a feature of the inflation curve, should be related to

* Curvature for a function $y = f(x)$ plotted with equal scales is mathematically defined as $k(x) = |f''(x)|/(1 + [f'(x)]^2)^{3/2}$ and is expressed in units of radians per unit of arc length. As can be seen from this equation, when compliance is lower than unity, the point of maximum curvature approaches the point of maximum compliance increase (P_{mci}), but when compliance is higher than unity, the point of maximum curvature deviates from P_{mci}.

$P_{inf,d}$, a feature of the deflation P-V curve. In fact, the better predictive value of Pflex + 2 cm H_2O for $P_{inf,d}$ could be purely chance, or could reflect some relationship between the distributions of opening and closing pressures of alveolar units in the ARDS lung. Perhaps by setting PEEP to Pflex + 2 cm H_2O, clinicians are approximating $P_{inf,d}$, serendipitously preventing derecruitment. It is possible, however, that choosing a feature of the deflation limb, such as $P_{inf,d}$, could further improve the prevention of derecruitment in a patient-specific manner.

Because alveolar derecruitment is a deflation phenomenon, ideally the deflation limb of the P-V curve should be used to identify the best PEEP to prevent derecruitment. Holzapfel and colleagues (8) reported that the greatest reduction in shunt fraction occurred in patients with ARDS when PEEP was set at a value that corresponded to the *true* inflection point of the deflation ($P_{inf,d}$) P-V curve. Further support for the use of the deflation limb comes from nitrogen washout experiments in anesthetized patients. It has been shown that rapid airway closure occurs during a lower "knee" of the deflation limb (9). Also, using modeling techniques, airway closure was shown to potentially occur throughout the deflation limb of the P-V curve (10). Although it is still not clear what feature of the P-V curve to use to set PEEP, our results point out the difficulty in comparing studies using Pflex. If we were setting PEEP in this study, patients could have had PEEP settings that varied by 11 cm H_2O with the same P-V data set. O'Keefe and colleagues (23) reported differences between observers of 9 cm H_2O. In that study, clinicians were instructed on the method to determine Pflex, whereas in our study, in order to simulate actual clinical conditions, clinicians were not instructed on the method to determine Pflex. Despite not getting explicit instructions for finding lower Pflex, the clinicians in our study appeared to be finding a similar feature of the P-V curve. The average difference between each clinician's Pflex and the mean of the group was always within about 2 cm H_2O (Figure 7B). However, there was a slightly larger bias of Observers 1, 4, and 5 (Figure 7B), suggesting that these observers may have potentially used a different algorithm for obtaining lower Pflex. Despite the methodologic differences, the interobserver variability in the study of O'Keefe and colleagues was comparable to ours.

When clinicians were given the same patient's data but with only every other point, their ability to reproduce Pflex was poor, with differences as high as 17 cm H_2O (SD = 2.8 cm H_2O). The curve-fitting was much better at reproducing $P_{mci,i}$ with the sparse data sets (SD = 0.3 cm H_2O). This finding has important implications in the clinical analysis of P-V curves, particularly in unstable patients where it is not advisable to keep the patient apneic for prolonged periods. In those patients, the curve-fitting method would allow a robust analysis of the P-V curve with a lower number of points.

Although we did not give the clinicians the same data set more than once, the differences caused by reducing the number of points provides an estimate of the magnitude of intraobserver variability. The total variance in Pflex determinations between full and reduced data sets should be equal to the sum of the variance caused by intrasubject variability and the variance caused by the difference in the data sets. If so, then the small standard deviation in the parameters obtained by the curve-fitting method suggests that the variance caused by the differences in the data sets was small and thus most of the increased variability in the clinician's determinations of Pflex reflect intraobserver variability. Taken together, our data suggest that determining Pflex is quite variable both among and within observers.

$P_{inf,i}$ was found to be systematically higher than $P_{inf,d}$, with differences ranging from 5 to 15 cm H_2O that tended to increase for higher values of $P_{inf,i}$ (Figure 9B). This difference, reflecting hysteresis of the P-V loop, may be attributed to factors such as alveolar recruitment, surfactant, tissue plasticity, air-trapping, oxygen uptake, or errors in volume correction for BTPS. In this study, hysteresis was less likely to be explained by errors in the estimation of oxygen uptake or BTPS corrections since data correction for BTPS using an excessive loss of thoracic gas volume of 190 ml/min did not change significantly the recovered value of $P_{inf,d}$. It is more likely that in these patients with ARDS, the hysteresis of the P-V curve reflected distributions of opening pressures with higher mean values than the corresponding distributions of closing pressures. This hypothesis is consistent with data from animals using implanted pleural capsules (24). This notion is important because it suggests that the pressure (PEEP) required to prevent derecruitment may be substantially lower than that required to recruit.

In summary, the sigmoidal Equation 1 was able to fit P-V data from patients with ARDS remarkably well up to inflation pressures of 40 cm H_2O. Lower Pflex did not predict well the point of maximum compliance increase ($P_{mci,i}$) defined by a sigmoid curve, and Pflex + 2 cm H_2O was better at estimating $P_{inf,d}$ than at estimating $P_{mci,i}$. There was substantial interobserver and intraobserver variability in the determination of Pflex. $P_{inf,i}$ was always higher than $P_{inf,d}$, consistent with the expected hysteresis in patients with ARDS. The wide variability in determining Pflex graphically can be reduced by curve-fitting a sigmoidal equation to the P-V data. Although the clinical usefulness of the quasi-static P-V curve in guiding ventilator settings remains to be determined, it is important that in future studies definitions and analysis methods of the P-V curve be standardized and objective.

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