Positive end-expiratory pressure titration in acute respiratory distress syndrome patients: Impact on right ventricular outflow impedance evaluated by pulmonary artery Doppler flow velocity measurements

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Objective: **Positive end-expiratory pressure (PEEP) titration in acute respiratory distress syndrome patients remains debatable. We used two mechanical approaches, calculation of the compliance of the respiratory system and determination of the lower inflexion point of the pressure-volume curve of the respiratory system, to identify specific PEEPs ($PEEP_S$ and $PEEP_A$) whose impact on right ventricular (RV) outflow was compared with Doppler analysis of pulmonary artery flow velocity.**

Design: **Prospective, open, clinical study.**

Setting: **Medical intensive care unit of a university hospital.**

Patients: **Sixteen consecutive ventilator-dependent acute respiratory distress syndrome patients.**

Interventions: **Two PEEPs were determined: $PEEP_S$ was the highest PEEP associated with the highest value of respiratory compliance, and $PEEP_A$ was the coordinate of the lower inflexion point of the inspiratory pressure-volume curve on the pressure axis plus 2 cm H_2O.**

Measurements and Main Results: **We observed a large difference between the two PEEPs, with $PEEP_A$ (13 + 4 cm H_2O) > $PEEP_S$ (6 + 3 cm H_2O). Changes in RV outflow impedance produced by tidal ventilation with zero end-expiratory pressure (ZEEP) and after application of these two PEEPs were assessed by Doppler study of pulmonary artery flow velocity obtained by a transesophageal approach, with particular reference to the end-expiratory and end-inspiratory pulmonary artery velocity-time integral, as reflecting RV stroke output, and mean acceleration as reflecting RV outflow impedance during an unchanged flow period. A significant inspiratory reduction in pulmonary artery velocity-time integral (from 11.8 + 0.3 to 10.0 + 0.3 cm) and mean acceleration (from 11.9 + 0.9 to 8.0 + 0.9 m/sec^2) was observed with ZEEP, showing a reduction in RV stroke index (from 29.0 + 0.9 to 26.0 + 0.6 cm^3/m^2) by a sudden increase in outflow impedance during tidal ventilation. Application of $PEEP_A$, which improved Pa_{O_2} (102 + 40 vs. 65 + 18 torr with ZEEP), worsened the inspiratory drop in RV stroke index (21.6 + 0.8 cm^3/m^2), resulting in a significant reduction in cardiac index compared with ZEEP (from 3.0 + 1.0 to 2.7 + 1.1). Application of $PEEP_S$, which also significantly improved Pa_{O_2} (81 + 21 torr), was associated with a lesser impact on RV outflow impedance (inspiratory mean acceleration: 9.5 + 1 m/sec^2) and cardiac index (3.2 + 1.0) than $PEEP_A$.**

Conclusion: **RV outflow impedance evaluated by the Doppler technique appeared sensitive to PEEP titration. Application of $PEEP_A$ worsened RV systolic function impairment produced by tidal ventilation. Conversely, application of $PEEP_S$ reduced RV systolic function impairment, suggesting an association with a lower pulmonary vascular resistance. (Crit Care Med 2001; 29:1154–1158)**

KEY WORDS: acute respiratory distress syndrome; positive end-expiratory pressure titration; total respiratory system compliance; pressure-volume curve; right ventricular function

The clinical description of acute respiratory distress syndrome (ARDS) in 1967 (1) was rapidly followed by the observation that mechanical ventilation with positive end-expiratory pressure (PEEP) improved arterial oxygenation in these patients (2). However, after 30 yrs, the "optimum" PEEP required in a given patient and how it should be determined remain thorny issues. Measurements of C_{RS} were first advocated by Suter et al. (3), in 1975, as a useful tool to determine optimum PEEP, and were recently re-emphasized by Amato et al. (4), using slope changes in the inspiratory pressure-volume (P/V) curve of the total respiratory system, which reflect changes in C_{RS}.

We have long observed that the mechanical conditions of respiratory support, particularly PEEP and tidal ventilation, have a negative impact on right ventricular (RV) systolic function (5, 6). Recently, we have used Doppler assessment of pulmonary artery flow velocity to show changes in RV outflow impedance related to tidal ventilation (7). The aim of the present study was to determine, in a group of ARDS patients, the exact impact of optimum PEEP, determined by the methods of both Suter and Amato, on RV outflow impedance.

PATIENTS AND METHODS

Between January 1999 and December 1999, 16 consecutive patients (12 men, 4 women; mean age 51 ± 14 yrs) were submitted to mechanical respiratory support (controlled mode) for ARDS of various causes, with Pa_{O_2}/F_{IO_2} <150 and bilateral chest infiltrates. Cardiogenic pulmonary edema was excluded using bedside Doppler echocardiography. The

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exclusion criteria were demonstration of an acute or chronic cardiopathy by two-dimensional echocardiography, associated with a high filling pressure pattern on the Doppler mitral flow examination. ARDS resulted from septic shock with multiple organ failure (six cases), extensive bacterial pneumonia (four cases), aspiration pneumonia (three cases), viral pneumonia (one case), near drowning (one case), and diffuse alveolar hemorrhage (one case). Average lung injury severity score was 2.7 ± 0.5. Final recovery occurred in ten cases, giving a mortality rate of 38% in this small group. All patients were investigated during the first or second day of respiratory support. At the time of the study, all patients were hemodynamically stable with invasive systolic arterial pressure >105 mm Hg, heart rate <110 beat/min, and central venous pressure ≥12 mm Hg. At this time, patients were sedated with a continuous venous infusion of midazolam and sufentanil, and paralyzed with vecuronium. This sedation was not modified during the study.

Hemodynamic measurements, which are performed in our unit with transesophageal echocardiography (TEE) in mechanically ventilated patients, were considered a part of routine clinical practice and no informed consent was obtained from the patients' next of kin. This procedure was approved by the Clinical Research Ethics Committee of the French Intensive Care Society.

Respiratory Measurements

Tidal volume ($\dot{V}T$) and airway pressure were obtained from the respirator (Puritan Bennet 7200, Puritan Bennet, Carlsbad, CA). During the study period, the respiratory rate was unchanged (15 cycles/min), inspiratory flow was constant, and an end-inspiratory pause of 0.6 secs was preset. These settings were those used for supportive purposes, with a $\dot{V}T$ of 8 mL/kg, an inspiration/expiration ratio of 1:2, and an average FIO_2 of 0.75 ± 0.19 at the time of the study. No patient had intrinsic PEEP, as evidenced by lack of change in airway pressure during a brief end-expiratory occlusion. Total quasi-static compliance (Crs) was calculated by dividing $\dot{V}T$ by the difference between plateau and end-expiratory airway pressures. The increase in functional residual capacity produced by PEEP was measured as the difference between the first expiratory volumes when PEEP was abruptly removed and the preceding expiratory volume (8).

PEEP Titration

Determination of Suter's PEEP ($PEEP_S$). PEEP was first applied in increments of 3 cm of H_2O without changing the $\dot{V}T$ (8 mL/kg), and Crs was calculated at each PEEP. $PEEP_S$ was the highest PEEP coinciding with the highest value of Crs (3)

Determination of Amato's PEEP ($PEEP_A$). The P/V relationship of the total respiratory system was obtained from the ventilator software, the tracings being recorded by connecting an Epson LX-300 printer to the respirator (Fig. 1). The inspiration/expiration curve was recorded during a single inspiration of a 12 mL/kg volume at a constant inspiratory flow of 10 L/min, as described by Lu et al. (9), and after fitting a special device to the expiratory port to obtain a low expiratory flow (<10 L/min). A typical inspiratory curve comprised a first portion concave toward the volume axis, a second intermediate linear portion, and a third portion concave toward the pressure axis (Fig. 1). From the recording obtained, we determined manually the lower inflexion point (LIP) of the curve by tracing two straight lines tangentially to the two initial portions of the inspiratory curve: the LIP was computed as the pressure corresponding to the intersection between these lines (Fig. 1). $PEEP_A$ was determined by adding 2 cm H_2O to the LIP (4).

Pressure Hysteresis Measurement. As illustrated in Figure 1, the vertical line drawn from $PEEP_A$ perpendicular to the x-axis crossed the inflation curve at a point *A*. The horizontal line traced from this point to the y-axis crossed the expiratory curve at a point *B*. We measured pressure hysteresis as the pressure difference between *A* and *B*.

Doppler-Echocardiographic Measurements

Echo-Doppler studies were performed with a Toshiba "Corevision" model SSA-350A (Thoshiba, Otawarashi, Japan). Using the signal from the respirator, airway pressure was displayed on the screen of the echo-Doppler device, allowing accurate timing of cardiac events during the respiratory cycle. Four beats were selected for measurements: an end-expiratory beat defined as the last beat occurring before mechanical lung inflation (beat 1), a beat occurring during the dynamic phase of lung inflation (beat 2), an end-inspiratory beat defined as the last beat occurring during the end-inspiratory pause (beat 3), and a beat occurring at the start of exhalation (beat 4).

The multiplane TEE transducer (5–7 MHz) was positioned in the upper esophagus in a 30°–40° plane and the ultrasonic beam parallel to the long axis of the pulmonary artery. The Doppler sample volume was placed beyond the pulmonary valve in the mid-lumen of the pulmonary artery, to record the RV outflow. From the pulsed Doppler velocity profile recorded at a high speed of 5 cm/sec, we measured peak velocity, acceleration time from the beginning of the profile to the peak velocity, flow period, and velocity-time integrals. Mean acceleration (Ac_{mean}) was calculated as peak velocity/acceleration time. Pulmonary artery systolic diameter was measured on the same view, after enhanced contrast by color Doppler. From this diameter, we calculated the pulmonary artery cross-sectional area. RV stroke output was calculated by multiplying pulmonary artery velocity-time integral (PA_{VTI}) by cross-sectional area (10), and was expressed as stroke index after dividing by body surface area. Cardiac index was calculated by multiplying RV stroke output, averaged by beat-to-beat measurement within three successive respiratory cycles, by heart rate.

Protocol

Respiratory measurements, hemodynamic measurements, and blood gas analysis were

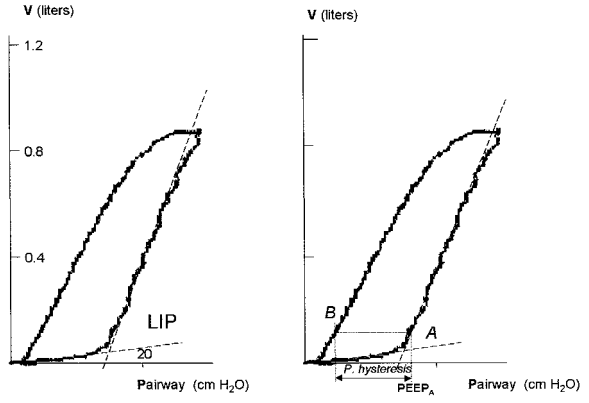

Figure 1. An example of a low-flow, inspiratory-expiratory, pressure-volume curve, the inspiratory curve comprising a first portion concave to the volume axis, an intermediate linear portion, and a final portion concave to the pressure axis. The lower inflexion point (*LIP*) was manually determined by drawing tangents to the first and second parts of the curve (*left panel*). From this point (*right panel*) we determined Amato's positive end-expiratory pressure ($PEEP_A$). We also measured pressure hysteresis (*P. hysteresis*) as the pressure difference between points *A* and *B*. *Pairway*, airway pressure.

Table 1. Blood gas analysis and mechanical data during the three periods of the study

	ZEEP	$PEEP_S$	$PEEP_A$
Pao_2, torr	65 ± 18	81 ± 21[a]	102 ± 40[a,b]
$Paco_2$, torr	51 ± 13	50 ± 14	56 ± 15[a]
Plateau, cm H_2O	18 ± 4	21 ± 6[a]	30 ± 8[a,b]
PEEP, cm H_2O	0	6 ± 3[a]	13 ± 4[a,b]
TV, mL	533 ± 82	533 ± 82	457 ± 109[a]
CT, mL/cm H_2O	30.6 ± 7.9	35.5 ± 8.8[a]	27.3 ± 8.2[b]
ΔFRC, mL	0	169 ± 94[a]	485 ± 224[a,b]

ZEEP, zero end-expiratory pressure; *PEEP,* positive end-expiratory pressure; *plateau,* end-inspiratory airway pressure; *TV,* tidal volume; *CT,* total compliance; *ΔFRC,* increase in functional residual capacity produced by PEEP.

[a] $p < .05$, compared with ZEEP; [b] $p < .05$, compared with $PEEP_S$.

first obtained at baseline with zero end-expiratory pressure (ZEEP), and were repeated after application of $PEEP_S$. When this level was different from $PEEP_A$, measurements were repeated after application of $PEEP_A$. Whereas $\dot{V}_T$ (8 mL/kg) was unchanged with ZEEP and $PEEP_S$, it was reduced to 6 mL/kg with $PEEP_A$, to limit end-inspiratory (plateau) pressure when $PEEP_A > PEEP_S$.

Statistical Analysis

Statistical calculations were performed using the Statgraphics plus package (Manugistics, Rockville, MD). Data are expressed as mean ± SD, unless otherwise specified. Respiratory and global hemodynamic changes between the three periods and hemodynamic changes within the respiratory cycle were analyzed using an analysis of variance for repeated measurements, followed by a Fisher's least significant difference test when significant changes were individualized. A test giving a p value $< .05$ was considered as statistically significant.

RESULTS

In all patients studied, we found a PEEP that did not change or improve CRS ($PEEP_S$). This PEEP was 6 ± 3 cm H_2O (range 3–9 cm H_2O). Above this level, an additional increment of PEEP of 3 cm H_2O worsened CRS.

All patients studied had an inspiratory (P/V) relationship of the total respiratory system exhibiting a clear intermediate linear part with a LIP (11 ± 4 cm H_2O). Average $PEEP_A$ was thus computed as 13 ± 4 cm H_2O (range, 6–17cm H_2O).

In each case, $PEEP_A > PEEP_S$. The average difference was 6 ± 4 cm H_2O. A strong linear correlation between the two PEEPs was observed, with $PEEP_A = 1.28\ PEEP_S + 4.68$, ($r = 0.87$, $p = .0002$). Average pressure hysteresis was 6 ± 4 cm H_2O, strictly similar to the average difference between $PEEP_A$ and $PEEP_S$.

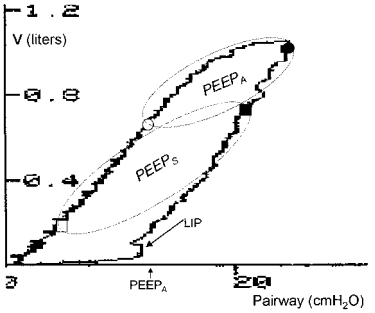

Figure 2. An example of the influence of the two positive end-expiratory pressures (PEEPs) (*$PEEP_S$*: Suter's PEEP, *squares*; *$PEEP_A$*: Amato's PEEP, *circles*) of the diagrammatic pressure-volume loops, constructed with end-expiratory (*open symbols*) and end-inspiratory (*filled symbols*) pressures and volumes measured in an individual patient. *LIP,* lower inflexion point.

Average changes in mechanical data and blood gas analysis produced by the application of the two PEEPs, compared with the baseline value with ZEEP, are presented in Table 1. An individual example of P/V loop changes produced by the two PEEPs is diagrammatically illustrated in Figure 2.

Cyclic changes in hemodynamic parameters obtained by pulmonary artery Doppler flow analysis are presented in Table 2. Heart rate (103 ± 6 beat/min) was unchanged during the study. A significant reduction in peak velocity, Ac_{mean}, and PA_{VTI} at end-inspiration compared with preinflation (beat 3 vs. beat 1), was observed with ZEEP. Similar changes were observed with $PEEP_S$, except for Ac_{mean}, which was unchanged during $PEEP_S$. With $PEEP_A$, tidal ventilation produced earlier (beat 2) and more pronounced (beat 3) changes in pulmonary artery flow velocity. Flow period was unaffected throughout the study. An example of a Doppler recording is presented in Figure 3. Cyclic changes in right ventricular stroke index (RVSI) calculated by combining PA_{VTI} and echographic measurement of pulmonary artery diameter are also presented in Table 2. The changes were similar to changes in PA_{VTI}. In particular, with $PEEP_A$, the drop in RVSI produced by tidal ventilation was earlier (beat 2) and more marked (beat 3). As a result, cardiac index was significantly reduced with $PEEP_A$ compared with ZEEP (2.7 ± 1.1 vs. 3.0 ± 1.0 L/min/m^2), whereas it was maintained with $PEEP_S$ (3.2 ± 1.0).

The present study demonstrates that right ventricular systolic function is sensitive to end-expiratory pressure in acute respiratory distress syndrome patients undergoing mechanical ventilation.

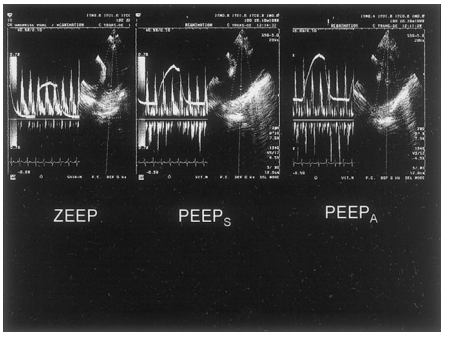

Figure 3. An example of a pulmonary artery Doppler flow recording at the three airway pressures. In these low-speed recordings, a large amplitude of cyclic change in peak velocity (V_{max}) was observed with zero end-expiratory pressure (*ZEEP*) and Amato's positive end-expiratory pressure (*$PEEP_A$*), whereas this amplitude was reduced with Suter's PEEP (*$PEEP_S$*).

DISCUSSION

An important point that was addressed in this study was the relation between PEEP titration and changes in RV outflow impedance. Recently, we have illustrated the practical value of Doppler TEE in evaluating changes in RV outflow impedance produced by tidal ventilation in

Table 2. Doppler measurement of pulmonary artery flow velocity during the three periods of the study

	Period	Preinflation (Beat 1)	Mid-inflation (Beat 2)	End-inflation (Beat 3)	Start-exhalation (Beat 4)
V_{MAX}, m/sec	ZEEP	0.84 ± 0.02	0.81 ± 0.02	0.73 ± 0.02[a]	0.78 ± 0.02
	$PEEP_S$	0.82 ± 0.02	0.82 ± 0.02	0.73 ± 0.02[a]	0.75 ± 0.02[a]
	$PEEP_A$	0.80 ± 0.02	0.75 ± 0.02[b]	0.60 ± 0.02[a,b,c]	0.71 ± 0.02[a,b]
AT, msec	ZEEP	92 ± 01	88 ± 01	94 ± 01	98 ± 01
	$PEEP_S$	83 ± 01	87 ± 01	95 ± 01	99 ± 01
	$PEEP_A$	89 ± 01	86 ± 01	98 ± 01	103 ± 01
FP, msec	ZEEP	219 ± 5	210 ± 5	216 ± 5	220 ± 5
	$PEEP_S$	219 ± 4	223 ± 4	224 ± 4	216 ± 4
	$PEEP_A$	213 ± 7	203 ± 7	208 ± 7	214 ± 7
Ac_{mean}, m/sec^2	ZEEP	11.9 ± 0.9	10.6 ± 0.9	8.6 ± 0.9[a]	8.9 ± 0.9
	$PEEP_S$	11.7 ± 1.0	10.0 ± 1.0	9.5 ± 1.0	8.2 ± 1.0[a]
	$PEEP_A$	11.1 ± 1.0	9.3 ± 1.0	7.0 ± 1.0[a]	7.6 ± 1.0[a]
VTI, cm	ZEEP	11.8 ± 0.3	11.5 ± 0.3	10.3 ± 0.3[a]	11.1 ± 0.3
	$PEEP_S$	12.2 ± 0.4	12.0 ± 0.4	10.9 ± 0.4[a]	10.8 ± 0.4[a]
	$PEEP_A$	11.5 ± 0.3	10.3 ± 0.3[a,b,c]	8.7 ± 0.3[a,b,c]	9.9 ± 0.3[a,b]
SI, cm^3/m^2	ZEEP	29.0 ± 0.9	27.9 ± 0.6	26.0 ± 0.6[a]	27.5 ± 0.6
	$PEEP_S$	29.9 ± 0.9	29.9 ± 0.9	27.0 ± 0.9[a]	26.7 ± 0.9[a]
	$PEEP_A$	28.3 ± 0.8	25.7 ± 0.8[c]	21.6 ± 0.8[a,b,c]	24.5 ± 0.8[a]

V_{MAX}, peak velocity of pulmonary artery flow; *AT,* acceleration time; *FP,* flow period; *Ac_{mean},* mean acceleration; *VTI,* velocity-time integral; *SI,* stroke index.

[a] $p < .05$, vs. beat 1 at the same PEEP; [b] $p < .05$ vs. the same beat at ZEEP; [c] $p < .05$ vs. the same beat at $PEEP_S$. Values are mean ± SEM.

ARDS patients (7). Doppler demonstration of an inspiratory decrease in pulmonary artery Ac_{mean}, provided no change occurred in flow period at the same time, permitted detection of increased RV outflow impedance (7). In the present study, we have examined changes in RV outflow impedance at two specific PEEPs—$PEEP_S$, determined by Crs measurements, as recommended 25 yrs ago by Suter (3), and $PEEP_A$, determined by the LIP of the inspiratory (P/V) curve, as recommended more recently by Amato (4). We have observed that $PEEP_A$ was always higher than $PEEP_S$ in a given patient, and we have found a nonlinear action on RV outflow impedance of these different PEEPs: whereas ZEEP and $PEEP_A$ were associated with an increased RV outflow impedance during tidal ventilation, as demonstrated by a reduced Ac_{mean} at end inflation, this association disappeared with $PEEP_S$. As a beneficial effect, cardiac output was preserved with $PEEP_S$ despite a probable increase in pleural pressure, whereas it was reduced by $PEEP_A$. An explanation for this nonlinear effect of PEEP on cardiac output may be found in the shape of the relationship between lung volume and pulmonary vascular resistance, which is curvilinear (11).

As previously stated, a mechanical concept to determine the optimal PEEP necessary for a given ARDS patient was first used by Suter (3) in a simple approach, assuming that Crs improvement by a given PEEP signified a positive balance between beneficial recruitment and detrimental inflation. A more sophisticated approach was proposed by Amato (4): in addition to increased elastance of the respiratory system, loss of lung volume in ARDS results in an inflation PV curve with two inflexion points (IP), lower (L) and upper (U), which delineate a lung volume range over which respiratory system elastance is minimal. An explanation is usually given, which is that the LIP is produced by the sudden opening of a "closed volume" and that the UIP is produced by a sudden increase in pressure when the total pulmonary volume is attained. However, there is increasing evidence that the LIP simply represents the beginning of recruitment on the inflation P/V curve, and that recruitment, at least in some patients, continues well above the LIP (12), a sudden reduction in recruitment producing the UIP (13). For these reasons, and also because for a given lung area the "opening pressure" is usually greater than the "closing pressure" (14), Amato's approach is debatable.

This latter concern about Amato's approach, which produced the greatest impairment in RV systolic function, was reinforced by an original finding of the present study. We actually found a perfect analogy between $PEEP_S$ and $PEEP_A$ when subtracting pressure hysteresis from the latter. This finding demonstrated that, whereas $PEEP_A$ was determined by the inspiratory PV curve, $PEEP_S$ always fell on the expiratory P/V curve. The goal with Amato's open lung approach is to have the tidal inflation and deflation on the linear part of the P/V curve (4). But this strategy simultaneously shifts the inflation curve upward and leftward, and presumably produces lung distension, as illustrated on Figure 2. Koutsoukou et al. (15) recently did a mechanical study of expiratory flow limitation in ARDS. These authors differentiated two major goals required for "optimal" airway pressure settings in ARDS: recruitment of atelectatic alveoli and prevention of cyclic reopening and closure of small airways (15). In particular, they demonstrated that the PEEP required for this prevention is low, identical to the $PEEP_S$ of the present study, at least in one patient (15). Finally, one can consider that recruitment is an inspiratory goal, achieved by an adequate setting of end-inspiratory pressure, whereas prevention of derecruitment is an expiratory goal, achieved by an "optimal" PEEP, which is low (15). It is noteworthy that this original approach was associated in our study with a better preservation of RV systolic function, suggesting concordance with the lowest level of pulmonary vascular resistance.

In conclusion, the present study demonstrates that RV systolic function is sensitive to end-expiratory pressure in ARDS patients undergoing mechanical ventilation. By examining changes in RV outflow impedance together with mechanical changes produced by PEEP, we observed that the lowest value of RV outflow impedance was associated with the better value of Crs. This might be an argument for a new concept in PEEP titration, focused on prevention of airway closure and leaving out all consideration of recruitment.

REFERENCES

1. Ashbaugh D, Bigelow D, Petty T, et al: Acute respiratory distress in the adult. *Lancet* 1967; ii:319–323
2. Ashbaugh D, Petty T, Bigelow D, et al: Continuous positive-pressure breathing in adult

respiratory distress syndrome. *J Thorac Cardiovasc Surg* 1969; 57:31–41
3. Suter P, Fairley H, Isenberg M: Optimum end-expiratory airway pressure in patients with acute lung disease. *N Engl J Med* 1975; 292: 284–289
4. Amato M, Barbas C, Medeiraos D, et al: Beneficial effect of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995; 152:1835–1846
5. Jardin F, Farcot JC, Boisante L, et al: Influence of positive end-expiratory pressure on left ventricular performance. *N Engl J Med* 1981; 304:387–392
6. Jardin F, Delorme G, Hardy A, et al: Reevaluation of hemodynamic consequences of positive pressure ventilation: Emphasis on cyclic right ventricular afterloading by mechanical lung inflation. *Anesthesiology* 1990; 72: 966–970
7. Vieillard-Baron A, Loubières Y, Schmitt JM, et al: Cyclic changes in right ventricular output impedance during mechanical ventilation. *J Appl Physiol* 1999; 87:1644–1650
8. Jardin F, Genevray B, Brun-Ney D, et al: Influence of lung and chest wall compliances on transmission of airway pressure to the pleural space in critically ill patients. *Chest* 1985; 88: 653–658
9. Lu Q, Vieira R, Richecoeur J, et al: A simple method for measuring pressure-volume curves during mechanical ventilation. *Am J Respir Crit Care Med* 1999; 159:275–282
10. Maslow A, Communale M, Haering J, et al: Pulsed wave Doppler measurement of cardiac output from the right ventricular outflow tract. *Anesth Analg* 1996; 83:466–471
11. Mead J, Whittenberger J: Lung inflation and hemodynamic. *In:* Hamilton W, Dow P (Eds). Handbook of Physiology. Vol. III. Washington, DC, American Physiological Society, 1965, pp 477–486
12. Jonson B, Richard JC, Strauss C, et al: Pressure-volume curves and compliance in acute lung injury. Evidence of recruitment above the lower inflexion point. *Am J Respir Crit Care Med* 1999; 159:1172–1178
13. Hickling K: The pressure-volume curve is greatly modified by recruitment. A mathematical model of ARDS lung. *Am J Respir Crit Care Med* 1998; 158:194–202
14. Mead J, Whittenberger J, Radford E: Surface tension as a factor in pulmonary volume-pressure hysteresis. *J Appl Physiol* 1957; 10: 191–196
15. Koutsoukou A, Armangadis A, Stravrakaki-Kallergi C, et al: Expiratory flow limitation and intrinsic positive end-expiratory pressure at zero positive end-expiratory pressure in patients with adult respiratory distress syndrome. *Am J Respir Crit Care Med* 2000; 161:1590–1596