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$_A$ and PEEP$_S$) 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$_A$ was the highest PEEP associated with the highest value of respiratory compliance, and PEEP$_S$ was the coordinate of the lower inflexion point of the inspiratory pressure-volume curve on the pressure axis plus 2 cm H$_2$O.

Measurements and Main Results: We observed a large difference between the two PEEPs, with PEEP$_A$ (13 + 4 cm H$_2$O) > PEEP$_S$ (6 + 3 cm H$_2$O). 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$_S$, which improved PaO$_2$ (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$_A$, which also significantly improved PaO$_2$ (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 Cts 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 Cts.

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 PaO$_2$/FiO$_2$ <150 and bilateral chest infiltrates. Cardiogenic pulmonary edema was excluded using bedside Doppler echocardiography. The
exclusion criteria were demonstration of an acute or chronic cardiopathy by two-dimen-
sional 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), ve-
ri nal 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 ven-
tilated 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 (Vt) 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 Vt of 8 mL/kg, an inspiration/expiration ratio of 1:2, and an average Fio2 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 occlu-
sion. Total quasi-static compliance (Crs) was calculated by dividing Vt 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 vol-
umes when PEEP was abruptly removed and the preceding expiratory volume (8).

**PEEP Titration**

**Determination of Suter’s PEEP (PEEPₙ).** PEEP was first applied in increments of 3 cm of H₂O without changing the Vt (8 mL/kg), and Crs was calculated at each PEEP. PEEPₙ was the highest PEEP coinciding with the highest value of Crs (3).

**Determination of Amato’s PEEP (PEEPₐ).** 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 de-
termined 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). PEEPₐ was deter-
mined by adding 2 cm H₂O to the LIP (4).

**Pressure Hysteresis Measurement.** As il-
lustrated in Figure 1, the vertical line drawn from PEEPₐ 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 (To-
shima, Otawarashi, Japan). Using the signal from the respirator, airway pressure was dis-
payed on the screen of the echo-Doppler de-
vice, 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 oc-
curring 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 acceler-
ation (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 pul-
monary artery cross-sectional area. RV stroke output was calculated by multiplying pulmonary artery velocity-time integral (PAVTI) by cross-sectional area (10), and was expressed as stroke index after dividing by body surface area. Cardiac index was calcu-
lated by multiplying RV stroke output, aver-
aged by beat-to-beat measurement within three successive respiratory cycles, by heart rate.

**Protocol**

Respiratory measurements, hemodynamic measurements, and blood gas analysis were...
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 PEEP$_A$, tidal ventilation was reduced to 6 mL/kg with PEEP$_S$, 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 Cts (PEEP$_S$). This PEEP was 6 ± 3 cm H$_2$O (range 3–9 cm H$_2$O). Above this level, an additional increment of PEEP of 3 cm H$_2$O worsened Cts.

All patients studied had an inspiratory airway pressure;ctotal compliance; $\Delta$FRC, increase in functional residual capacity produced by PEEP.

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

<table>
<thead>
<tr>
<th></th>
<th>ZEEP</th>
<th>PEEP$_S$</th>
<th>PEEP$_A$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pao$_2$, torr</td>
<td>65 ± 18</td>
<td>81 ± 21$^a$</td>
<td>102 ± 40$^{a,b}$</td>
</tr>
<tr>
<td>Paco$_2$, torr</td>
<td>51 ± 13</td>
<td>50 ± 14</td>
<td>56 ± 15$^a$</td>
</tr>
<tr>
<td>Plateau, cm H$_2$O</td>
<td>18 ± 4</td>
<td>21 ± 6$^a$</td>
<td>30 ± 8$^{a,b}$</td>
</tr>
<tr>
<td>PEEP, cm H$_2$O</td>
<td>0</td>
<td>6 ± 3$^a$</td>
<td>13 ± 4$^{a,b}$</td>
</tr>
<tr>
<td>TV, mL</td>
<td>533 ± 82</td>
<td>533 ± 82</td>
<td>457 ± 109$^a$</td>
</tr>
<tr>
<td>CT, mL/cm H$_2$O</td>
<td>30.6 ± 7.9</td>
<td>35.5 ± 8.8$^a$</td>
<td>27.3 ± 8.2$^a$</td>
</tr>
<tr>
<td>$\Delta$FRC, mL</td>
<td>0</td>
<td>169 ± 94$^a$</td>
<td>485 ± 224$^{a,b}$</td>
</tr>
</tbody>
</table>

$^{a}$p < .05, compared with ZEEP; $^{b}$p < .05, compared with PEEP$_S$.

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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 loops 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, $V_{max}$, 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 $A_{mean}$, which was unchanged during PEEP$_A$. 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.

Average pressure hysteresis was different from PEEP$_A$, measurements producing by tidal ventilation.

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**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 acute respiratory distress syndrome patients undergoing mechanical ventilation.
ARDS patients (7). Doppler measurement of an inspiratory decrease in pulmonary artery $A_{\text{mean}}$, 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 in the two different PEEP—the 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$_S$ was always higher than PEEP$_A$ in a given patient, and we have found a nonlinear action on RV outflow impedance of these different PEEP$_S$ whereas ZEEP and PEEP$_S$ were associated with an increased RV outflow impedance during tidal ventilation, as demonstrated by a reduced $A_{\text{mean}}$ 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 PV 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.

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**

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