Cardiorespiratory Effects of Positive End-expiratory Pressure during Progressive Tidal Volume Reduction (Permissive Hypercapnia) in Patients with Acute Respiratory Distress Syndrome

V. Marco Ranieri, M.D., Luciana Mascia, M.D., Tommaso Fiore, M.D., Francesco Bruno, M.D., Antonio Brienza, M.D., Rocco Giuliani, M.D.

Background: In patients with acute respiratory distress syndrome (ARDS), the ventilatory approach is based on tidal volume (VT) of 10–15 ml/kg and positive end-expiratory pressure (PEEP). To avoid further pulmonary injury, decreasing VT and allowing Pao2 to increase (permissive hypercapnia) has been suggested. Effects of 10 cmH2O of PEEP on respiratory mechanics, hemodynamics, and gas exchange were compared during mechanical ventilation with conventional (10–15 ml/kg) and low (5–8 ml/kg) VT.

Methods: Nine sedated and paralyzed patients were studied. VT was decreased gradually (50 ml every 20–30 min). Static volume-pressure (V–P) curves, hemodynamics, and gas exchange were measured.

Results: During mechanical ventilation with conventional VT, V–P curves on PEEP 0 (ZEEP) exhibited an upward convexity in six patients reflecting a progressive reduction in compliance with inflating volume, whereas PEEP resulted in a volume displacement along the flat part of this curve. After VT reduction, V–P curves in the same patients showed an upward concavity, reflecting progressive alveolar recruitment with inflating volume, and application of PEEP resulted in alveolar recruitment.

The other three patients showed a V–P curve with an upward concavity; VT reduction increased this concavity, and application of PEEP induced greater alveolar recruitment than during conventional VT. With PEEP, cardiac index decreased by, respectively, 31% during conventional VT and 11% during low VT (P < 0.01); Pao2 increased by 32% and 71% (P < 0.01), respectively, whereas right-to-left venous admixture (Qs/Qt) decreased by 11% and 40%, respectively (P < 0.01). The greatest values of Pao2, static compliance, and oxygen delivery and the lowest values of Qs/Qt (best PEEP) were obtained during application of PEEP with low VT (P < 0.01).

Conclusions: Although PEEP induced alveolar hyperinflation in most patients during mechanical ventilation with conventional VT, at low VT, there appeared to be a significant alveolar collapse, and PEEP was able to expand these units, improving gas exchange and hemodynamics. (Key words: Acute respiratory distress syndrome, Alveolar recruitment, Gas exchange, Hemodynamics, Permissive hypercapnia, Positive end-expiratory pressure.)

In patients with acute respiratory distress syndrome (ARDS), a ventilatory strategy based on larger tidal volumes (VT) and PEEP has been proposed.1-4 Tidal volumes (VT) of 10–15 ml/kg are used to prevent the microatelectasis that accompanies shallow breathing, adjusting respiratory rate to normalize pH and/or arterial carbon dioxide tension (Paco2). Sufficient levels of positive end-expiratory pressure (PEEP) to recruit previously collapsed alveoli and ensure arteriovenous oxygenation at an inspiratory oxygen fraction (FIO2) that does not cause oxygen toxicity have also been suggested.

In experimental animals,6-9 mechanical ventilation with high peak airway pressure and large VT results in pulmonary edema, severe alterations in permeability, and diffuse alveolar damage very similar to the pathologic findings observed in patients with ARDS. Bearing in mind these experimental findings6-9 and a retrospective review of clinical data,10 the recent Consensus Conference on Mechanical Ventilation11 recommended that, end-inspiratory static airway pressure ideally should be maintained at less than 35 cmH2O during ventilatory treatment of ARDS patients. To accomplish this goal, the Consensus Conference suggested reducing VT to as low as 5 ml/kg, allowing Pao2 to increase (permissive hypercapnia) provided there was no pres...
LOW Vᵣ AND PEEP IN ARDS

Table 1. Clinical Data of Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Weight (kg)</th>
<th>Sex</th>
<th>F₁O₂</th>
<th>PaO₂* (mmHg)</th>
<th>Cdyn* (L/cmH₂O)</th>
<th>Days†</th>
<th>Underlying Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>M</td>
<td>0.8</td>
<td>85</td>
<td>0.041</td>
<td>8</td>
<td>Intestinal volvulus, laparotomy, sepsis</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>M</td>
<td>1.0</td>
<td>95</td>
<td>0.037</td>
<td>2</td>
<td>Multiple trauma, aspiration, sepsis</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>M</td>
<td>0.7</td>
<td>88</td>
<td>0.045</td>
<td>3</td>
<td>Burns, sepsis</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>M</td>
<td>0.7</td>
<td>86</td>
<td>0.044</td>
<td>12</td>
<td>Peritonitis, laparotomy, sepsis</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>M</td>
<td>0.7</td>
<td>82</td>
<td>0.045</td>
<td>3</td>
<td>Multiple trauma, aspiration, sepsis</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>F</td>
<td>1.0</td>
<td>84</td>
<td>0.046</td>
<td>4</td>
<td>Peritonitis, laparotomy, sepsis</td>
</tr>
<tr>
<td>7</td>
<td>75</td>
<td>M</td>
<td>1.0</td>
<td>88</td>
<td>0.045</td>
<td>3</td>
<td>Intestinal obstruction, laparotomy, sepsis</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>M</td>
<td>0.8</td>
<td>78</td>
<td>0.041</td>
<td>3</td>
<td>Peritonitis, laparotomy, sepsis</td>
</tr>
<tr>
<td>9</td>
<td>75</td>
<td>M</td>
<td>0.8</td>
<td>81</td>
<td>0.044</td>
<td>4</td>
<td>Multiple trauma, aspiration, sepsis</td>
</tr>
</tbody>
</table>

F₁O₂ = inspired O₂ fraction; Q₂/O₂ = right-to-left venous admixture; Cdyn* = static compliance of the respiratory system.

* Values obtained on zero end-expiratory pressure during standard mechanical ventilation before the study.
† Number of days elapses from the beginning of mechanical ventilation.

peence or risk of increased intracranial pressure. At the same time, PEEP should be applied (values of approximately 10–12 cmH₂O) to avoid end-expiratory collapse of alveolar units. ¹¹

In isolated lavaged rat lungs, Muscedere et al.¹² found that ventilation at low airway pressure caused a significant decrease in lung compliance and progressive lung injury. Recent studies have also shown that, in patients with ARDS, the application of PEEP may result in a volume displacement along the flat part of the static volume-pressure (V-P) relationship obtained on PEEP 0 (ZEEP) with no alveolar recruitment and overdistention of the functional lung units.¹³,¹⁴

Despite recent editorials that suggest limiting airway pressure by decreasing V₁,¹⁵–¹⁹ there are no controlled studies assessing either clinical use or the consequences on respiratory mechanics, hemodynamics, and gas exchange of such a ventilatory strategy in patients with ARDS. We investigated the hypothesis that, although PEEP may induce hyperdistention of alveolar units already recruited by large V₁, it may reverse the alveolar derecruitment concomitant to V₁ reduction.

Methods

Nine patients (eight men) with severe ARDS of varying etiologies admitted to the intensive care unit of the Policlinico Hospital (University of Bari, Bari, Italy) were studied. Patient selection for the study was based on the criteria of ARDS as recently proposed by the American-European Consensus Conference on ARDS: acute onset, presence of hypoxemia (arterial oxygen tension (PaO₂)/FiO₂ ≤ 200 mmHg regardless of PEEP level), bilateral and diffuse opacities seen on frontal chest x-ray film, and absence of left ventricular failure with a pulmonary arterial occluded pressure (PAOP) ≤ 18 mmHg.²⁰ None of the patients had a history of previous lung disease. Sex, weight, individual values of FiO₂, PaO₂, right-to-left venous admixture (Qs/Qt), static compliance of the respiratory system (Cst.rs) obtained on zero end-expiratory pressure (ZEEP), days of mechanical ventilation, and causes of ARDS are shown in table 1. Applied PEEP before the study and PAOP amounted to 11 ± 1 cmH₂O and 12 ± 1 mmHg, respectively (mean ± SEM).

Flow (V) was measured with a heated pneumotachograph (Fleisch no. 2, Lausanne, Switzerland), connected to a differential pressure transducer (Validyne MP 45 ± 2 cmH₂O; Validyne, Northridge, CA), which was inserted between the y-piece of the ventilator circuit and the endotracheal tube. The pneumotachograph was linear over the experimental range of flow. Equipment dead space (not including the endotracheal tube) was 70 ml. Airway opening pressure (Pao) was measured proximal to the endotracheal tube with a pressure transducer (Validyne MP 45 ± 100 cmH₂O). To reduce the effects of compliance and resistance of the system connecting the endotracheal tube to the ventilator circuit, a single length of standard low compliance tubing supplied with the ventilator was used (2 cm ID, 60 cm long). During the measurements, the humidifier was disconnected from the inspiratory tubing. All patients had an intratracheal (radial artery) and a pulmonary artery catheter (7 Fr, Abbott, North Chicago, IL). All the above variables were recorded on an eight-channel pen recorder (7718 A Hewlett-Packard) and on a personal computer via a 12-bit analog-to-digital converter at a
sample rate of 100 Hz for subsequent data analysis. Volume was determined by digital integration of the flow signal. Cardiac output was measured by thermodilution (3300 Cardiac Output Computer, Abbott). Blood samples (arterial and mixed venous) were analyzed with an ABL 300 analyzer (Radiometer, Copenhagen, Denmark). The patients were nasotracheally intubated (Portex® cuffed endotracheal tube) with the inner diameter varying from 8 to 9 mm and were mechanically ventilated with a Siemens Servo Ventilator 900C (Siemens Elema AB, Berlin, Germany).

The investigation was performed in supine patients after sedation (0.1–0.2 mg/kg diazepam and 2–3 µg/kg fentanyl) and paralysis (0.1–0.2 mg/kg pancuronium bromide). Two levels of tidal volumes were used: conventional Vₚ of 10–15 ml/kg and low Vₚ of 5–8 ml/kg. Conventional Vₚ was adjusted to maintain a PaO₂ level of 35–45 mmHg. The baseline value used in the study was 10.39 ± 0.55 ml/kg (table 2). Low Vₚ was obtained by halving Vₚ, reducing the inspiratory time and duty cycle but leaving respiratory rate and inspiratory flow unchanged; the baseline value amounted to 5.50 ± 0.20 ml/kg (table 2). For each Vₚ, PEEP levels of 0 and 10 cmH₂O were applied. We chose 10 cmH₂O because this was the PEEP level used before the study.

The experimental design decreed that Vₚ be decreased from conventional to low Vₚ, whereas PEEP levels be randomized. Changes in Vₚ were achieved by progressively decreasing the previous Vₚ by 50 ml every 20–30 min. Measurements after reduction in Vₚ were obtained after 2–3 h, whereas effects of changes in PEEP level were evaluated after 30–40 min. The entire experimental procedure lasted 7–8 h. All measurements of respiratory mechanics, hemodynamics, and gas exchange were made during the last 5–10 min of each experimental condition. Application of the two Vₚ levels was not randomized for two reasons: first because in clinical practice permissive hypercapnia is always implemented from normocapnic conditions, and second, because random changes in Vₚ would have considerably increased the duration of the study. The protocol was approved by the ethics committees, and written informed consent was obtained from each patient or next of kin. A physician not involved in the experimental procedure was always present to provide patient care.

Experimental Procedure

Intrinsic PEEP. Whenever the time required to complete passive expiration is greater than the expiratory duration set by the ventilator, the end-expiratory lung volume (EELV) will exceed the relaxation volume (V₀) of the respiratory system during mechanical ventilation, and the respiratory system will exert positive static pressure at end-expiration. This pressure is termed intrinsic PEEP (PEEPi). To measure PEEPi, we measured the pressure increase during passive expiration of the respiratory system (PEEPi) was measured by pressing the end-expiratory hold knob on the ventilator during a baseline ventilatory cycle. If PEEPi is present, Pao increases after airway occlusion until a plateau is reached, corresponding to PEEPi. This plateau pressure usually was reached in 3–4 s.

ΔEELV. ΔEELV is the difference between EELV during mechanical ventilation (with or without PEEP) and V0 on ZEEP. It was assessed by reducing respiratory rate to the lowest value during a baseline breath, while removing PEEP when present. This way, sufficient time elapsed to complete expiration to V₀. To check that V₀ had been reached, the expiratory tubing of the ventilator was occluded by pressing the end-expiratory hold button at the end of the prolonged expiration: if, after 3–4 s of occlusion, there was no increase in Pao, V₀ had been reached.

Static Inflation V-P Curve. Static inflation V-P curve was obtained, as previously described, by performing single-breath occlusions at different Vₚ. Different inflation volumes were achieved by changing the respiratory frequency of the ventilator, while maintaining inspiratory flow at baseline level. Each occlusion was maintained until an apparent plateau in Pao was observed. This plateau pressure, which usually was reached in about 3–4 s, represents the static end-inspiratory alveolar pressure (Pst,s). After each test breath, baseline ventilation was resumed until Pao returned to its pretest configuration (usually in fewer than four breaths). Inflation volume was varied in ran-

| Table 2. Baseline Breathing Pattern during the Two Experimental Conditions |
|-----------------------------|-----------------------------|
| Vₚ (ml/kg)                  | Vₚ (ml/kg)                  |
| Vₚ (ml/kg)                  | Vₚ (ml/kg)                  |
| 10.39 ± 0.55                | 5.50 ± 0.20*                |
| Tₑ (s)                      | 0.91 ± 0.05                 |
| Tₑ/Tₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑᵉ |
| Tₑ/Tₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑᵉ | 0.12 ± 0.01*                |
| RR (min⁻¹)                  | 14.96 ± 0.11                |
| Flow (l/s)                  | 0.89 ± 0.07                 |

Vₚ = tidal volume; Tₑ = inspiratory time; Tₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑᵉ; RR = respiratory rate.

Data are mean ± SEM.

* P < 0.0001, standard Vₚ versus low Vₚ, paired t test.

Anesthesiology, V 83, N 4, Oct 1995
LOW V T AND PEEP IN ARDS

The static inflation V-P curves were constructed by plotting the different inflation volumes against the corresponding values of Pst,rs. Because ∆ELV was known, the V-P curves were related to V T. A second-order polynomial equation was fitted to the experimental points obtained above ∆V = 0.13:

\[ \Delta V = a + b \text{Pst,rs} + c \text{Pst,rs}^2 \]  

(1)

where a, b, and c are constants. The nonlinear coefficient in equation 1 was used to describe the shape of the inspiratory V-P curve.13,14 Positive values indicate upward concavity and a progressive increase in slope (i.e., compliance) with increasing volume, whereas negative values indicate upward convexity and a progressive decrease in slope (i.e., compliance) with inflating volume.13,14

Alveolar Recruitment. The recruitment of previously collapsed alveoli consequent to application of PEEP (recruited volume) was identified as the upward shift along the volume axis of the V-P curve on PEEP relative to the curve on ZEEP and was quantified as the increase in volume with PEEP at the same Pst,rs (20 cmH 2O; figs. 1 and 2).15,16,21 Tension changes and stress relaxation, besides alveolar recruitment, must be considered in explaining the volume shift of the V-P curve with PEEP.15,16,21 so that our estimation of alveolar recruitment with PEEP should be taken as the maximum estimate of the actual recruited volume.

Alveolar Hyperinflation. Hyperinflation of already ventilated alveoli consequent to application of PEEP was identified when the V-P curve on PEEP was displaced along the flat part of the curve on ZEEP.15,14

Static Compliance of the Respiratory System. Static compliance of the respiratory system (Cst,rs) was computed dividing the baseline inflation volume by the corresponding value of end-inspiratory Pst,rs—(PEEP + PEEP) 15

Hemodynamics and Gas Exchange. Intravascular pressure measurements were obtained over several respiratory cycles. End-expiratory pressure measurements were recorded. These values were referred to atmospheric pressure. Cardiac output was measured and blood samples (arterial and mixed venous) were collected at each level of PEEP, immediately before measurements of respiratory mechanics. Cardiac output was determined by the thermodilution technique using injection of 5 ml cold (<8°C) 5% dextrose solution. Five serial determinations were taken regardless of the respiratory cycle. Variance of individual thermodilution cardiac output at each level of PEEP was always <10%.

Heart rate was monitored. Cardiac index was computed by dividing cardiac output by the body surface area. Arterial (Cao 2) and mixed venous (Cvo 2) oxygen contents were calculated, respectively, from PaO 2 , PVO 2 , and measured arterial (SaO 2 ) and venous (SvO 2 ) oxygen saturation using the formula: oxygen content (ml/dl) = (fractional saturation · hemoglobin concentration · 1.39) + (0.003 · PaO 2 ). Oxygen delivery (Do 2 ) was computed as the product of Cao 2 and cardiac index (CI). Oxygen consumption (Vo 2 ) was calculated as: Vo 2 = CI · (Cao 2 - Cvo 2 ). Qs/Qt was calculated using the equation: Qs/Qt = (Cao 2 - Cvo 2 )/(Cao 2 - Cvo 2), where Cao 2 (oxygen content of alveolar capillary blood) was calculated assuming capillary oxygen tension to be equal to the alveolar oxygen tension calculated using the alveolar gas equation.

Values were expressed as mean ± SEM. Regression analysis was performed with the least-square method. Values obtained at different tidal volumes and levels of PEEP were compared using the repeated measures two-way analysis of variance (ANOVA), the factors being tidal volume and PEEP. If significant (P ≤ 0.05), the values obtained at different tidal volumes and PEEP levels were compared with those obtained during mechanical ventilation with V T at 10–15 ml/kg and ZEEP using the paired t test as modified by Dunnott.22

Results

During mechanical ventilation with conventional V T (fig. 1), in patients 1–4, 6, and 8, static inflation V-P curves on ZEEP exhibited a convex shape and a progressive decrease in slope with increasing inflation volume, as reflected by the negative values of nonlinear coefficients in equation 1 (table 3). In these patients, application of PEEP resulted in a volume displacement along the static V-P curves obtained on ZEEP, with a progressive straightening of the V-P curves. In the remaining patients (5, 7, and 9), static inflation V-P curves exhibited a concave shape on ZEEP with a progressive increase in slope and positive values for the nonlinear coefficient in equation 1 (table 3). An upward shift along the volume axis of the static inflation V-P curves was observed with PEEP in these patients.

In patients 1–4, 6, and 8, the static V-P curves on ZEEP during mechanical ventilation with low V T (fig. 2) became curvilinear toward the horizontal axis (fig. 2) as indicated by the positive values of the nonlinear coefficients in equation 1 (table 3). V-P curves on PEEP appeared raised along the volume axis with respect to
Fig. 1. Static inflation volume-pressure relationships of the total respiratory system in nine patients with acute respiratory distress syndrome during mechanical ventilation with tidal volume \(V_t\) of 10–15 ml/kg during zero end-expiratory pressure (ZEEP; open circles) and 10 cmH\(_2\)O of positive end-expiratory pressure (PEEP; closed circles). \(\Delta V\) = changes in lung volume relative to the elastic equilibrium point of the respiratory system \(V_e\); Pst.rs = static elastic recoil pressure. Total PEEP (intrinsic PEEP + externally applied PEEP) values and the corresponding increase in end-expiratory lung volume relative to \(V_e\) (EELV) are indicated on ZEEP (closed squares) and on 10 cmH\(_2\)O of applied PEEP (open squares). Equation 1 was fitted to the experimental points above \(\Delta V = 0\).

Fig. 2. Static inflation volume-pressure relationships of the total respiratory system in nine patients with ARDS during mechanical ventilation with tidal volume \(V_t\) of 5–8 ml/kg during zero end-expiratory pressure (ZEEP; open circles) and 10 cmH\(_2\)O of positive end-expiratory pressure (PEEP; closed circles). Details and abbreviations as in figure 1.

LOW V\textsubscript{T} AND PEEP IN ARDS

Table 3. Nonlinear Coefficients in Equation 1, \(\Delta EELV\) and Recruited Volume on 10 cmH\textsubscript{2}O of PEEP during Mechanical Ventilation with Standard and Low V\textsubscript{T}

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Nonlinear Coefficient (Equation 1) (t)</th>
<th>(\Delta EELV) (L)</th>
<th>Recruited Volume (L)</th>
<th>Recruited Volume/(\Delta EELV) (%)</th>
<th>Nonlinear Coefficient (Equation 1) (t)</th>
<th>(\Delta EELV) (L)</th>
<th>Recruited Volume (L)</th>
<th>Recruited Volume/(\Delta EELV) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.00230</td>
<td>0.40</td>
<td>0.08</td>
<td>22.1</td>
<td>0.014</td>
<td>1.27</td>
<td>0.06</td>
<td>43.8</td>
</tr>
<tr>
<td>2</td>
<td>-0.00052</td>
<td>0.46</td>
<td>0.09</td>
<td>19.5</td>
<td>0.010</td>
<td>0.73</td>
<td>0.04</td>
<td>55.4</td>
</tr>
<tr>
<td>3</td>
<td>-0.00012</td>
<td>0.28</td>
<td>0.03</td>
<td>10.9</td>
<td>0.015</td>
<td>0.98</td>
<td>0.06</td>
<td>57.3</td>
</tr>
<tr>
<td>4</td>
<td>-0.00141</td>
<td>0.90</td>
<td>0.08</td>
<td>9.2</td>
<td>0.018</td>
<td>1.77</td>
<td>0.04</td>
<td>41.8</td>
</tr>
<tr>
<td>5</td>
<td>-0.00587</td>
<td>1.12</td>
<td>0.38</td>
<td>34.0</td>
<td>0.015</td>
<td>1.76</td>
<td>0.75</td>
<td>42.3</td>
</tr>
<tr>
<td>6</td>
<td>-0.00013</td>
<td>0.40</td>
<td>0.01</td>
<td>0.3</td>
<td>0.022</td>
<td>1.41</td>
<td>1.20</td>
<td>85.3</td>
</tr>
<tr>
<td>7</td>
<td>0.0052</td>
<td>0.87</td>
<td>0.17</td>
<td>19.5</td>
<td>0.019</td>
<td>1.31</td>
<td>1.06</td>
<td>80.9</td>
</tr>
<tr>
<td>8</td>
<td>-0.00033</td>
<td>0.60</td>
<td>0.05</td>
<td>8.6</td>
<td>0.015</td>
<td>0.90</td>
<td>0.55</td>
<td>61.4</td>
</tr>
<tr>
<td>9</td>
<td>0.0088</td>
<td>1.25</td>
<td>0.65</td>
<td>52.1</td>
<td>0.016</td>
<td>1.34</td>
<td>0.97</td>
<td>72.0</td>
</tr>
</tbody>
</table>

\(ZEEP\) = zero end-expiratory pressure; PEEP = positive end-expiratory pressure; \(\Delta EELV\) = increase in end-expiratory lung volume due to the combined effects of intrinsic and externally applied PEEP.

*Values obtained fitting Equation 1 to static inflation V-P curve on ZEEP.
†Values obtained at 10 cmH\textsubscript{2}O of applied PEEP.

the V-P curves on ZEEP (fig. 2). In patients 5, 7, and 9, the inspiratory V-P curve on ZEEP appeared more arched than during conventional \(V_T\), as indicated by the more positive values of the nonlinear coefficients in equation 1 (table 3). Application of PEEP resulted in a larger upward displacement along the volume axis than during mechanical ventilation with conventional \(V_T\) (table 3).

The upward displacement of the V-P curves with PEEP indicates recruitment of previously closed lung units. It was quantified in terms of the increase in volume at \(Pst_{rs}\) of 20 cmH\textsubscript{2}O. The recruited volume with PEEP and the corresponding changes in \(\Delta EELV\) at both \(V_T\) levels are shown in table 3. During mechanical ventilation with conventional \(V_T\), recruited volume amounted to 0.17 ± 0.07 L versus 0.75 ± 0.09 L with low \(V_T\) \((P < 0.0001)\). The average percentage volume recruited to \(\Delta EELV\) was 19 ± 5% during mechanical ventilation with conventional \(V_T\) and increased to 60 ± 5% during mechanical ventilation with low \(V_T\) \((P < 0.0001)\).

During baseline mechanical ventilation with conventional \(V_T\), end-inspiratory \(Pst_{rs}\) on ZEEP amounted to 23.4 ± 1.0 cmH\textsubscript{2}O. Application of PEEP increased \(Pst_{rs}\) up to 39.2 ± 1.0 cmH\textsubscript{2}O \((P < 0.001)\). During baseline mechanical ventilation with low \(V_T\), end-inspiratory \(Pst_{rs}\) amounted to 11.4 ± 1.7 and 21.0 ± 1.7 cmH\textsubscript{2}O \((P < 0.001)\) on ZEEP and on 10 cmH\textsubscript{2}O of applied PEEP, respectively. On ZEEP, \(Pst_{rs}\) during conventional \(V_T\) was significantly higher than during low \(V_T\) \((P < 0.001)\). Cst.\(rs\) during baseline mechanical ventilation with conventional \(V_T\) amounted on ZEEP to 0.041 ± 0.004 L/cmH\textsubscript{2}O and decreased \((P < 0.0001)\) to 0.031 ± 0.003 L/cmH\textsubscript{2}O with 10 cmH\textsubscript{2}O of applied PEEP. During baseline mechanical ventilation with low \(V_T\) and ZEEP, Cst.\(rs\) was significantly lower \((P < 0.01)\) than during conventional \(V_T\), amounting to 0.033 ± 0.003 L/cmH\textsubscript{2}O. Application of PEEP significantly \((P < 0.0001)\) increased Cst.\(rs\) up to 0.066 ± 0.008 L/cmH\textsubscript{2}O.

The effects of PEEP on hemodynamics during mechanical ventilation with conventional and low \(V_T\) are shown in table 4. Cardiac index and SVI decreased \((P < 0.001)\), whereas MPAP increased \((P < 0.05)\) with PEEP during conventional \(V_T\); during mechanical ventilation, low \(V_T\), and PEEP, they remained unchanged. Cardiac index and SVI were significantly \((P < 0.05)\) higher during low \(V_T\) than during conventional \(V_T\) ventilation at both PEEP levels. \(V_T\) reduction did not affect MPAP either on ZEEP or on PEEP. PAOP and RAP significantly \((P < 0.01)\) increased with PEEP during both conventional and low \(V_T\) and were higher \((P < 0.01)\) during conventional than during low \(V_T\) at both PEEP levels. Tidal volume reduction and application of PEEP did not modify heart rate or MBP. These effects of PEEP on hemodynamics, when expressed as a percentage of the values on ZEEP, were systematically greater during mechanical ventilation with conventional than with low \(V_T\).

Table 5 shows the effects of PEEP on gas exchange during mechanical ventilation with conventional and
low Vt. PEEP significantly increased PaO2 and SâO2, whereas Qs/Q̇t decreased with both Vt (P < 0.001).

With PEEP, during conventional Vt, PaO2 and SâO2 remained unchanged, whereas they increased (P < 0.001) during low Vt, DvO2 and SâO2 increased (P < 0.001) with PEEP during conventional Vt, whereas during low Vt, DvO2 increased (P < 0.001) and SâO2 remained unchanged with 10 cmH2O of PEEP. PaCO2 and arterial pH on ZEEP amounted to 41 ± 1 mmHg and 7.42 ± 0.04, respectively, during mechanical ventilation with conventional Vt and remained unchanged with 10 cmH2O of applied PEEP. During low Vt, PaCO2 and arterial pH on ZEEP amounted to 64 ± 5 mmHg and 7.24 ± 0.02 (P < 0.0001), respectively. Application of PEEP significantly (P < 0.01) decreased PaCO2 and increased arterial pH. On ZEEP, Vt reduction significantly (P < 0.05) increased Qs/Q̇t, PaO2, SâO2, and DvO2 and decreased PaCO2, SâO2, and Vt. The effects of PEEP on gas exchange relative to ZEEP values are shown in table 5.

As can be seen, PEEP can significantly improve gas exchange during low Vt ventilation.

Discussion

Since the original description of ARDS,1 the use of large tidal volume and the application of PEEP to restore functional residual capacity and improve arterial oxygenation by the recruitment of collapsed alveoli has become the conventional ventilatory treatment.2,4 The presence of massive extraalveolar air1,25 and the cardiovascular depression24 due to positive pressure breathing were the only clinical side effects pointed out during such ventilatory therapy. However, in normal animals, mechanical ventilation with high peak airway pressure and large Vt resulted in pulmonary edema and alveolar damage.5-8 Furthermore, mechanical ventilation aggravated previous injury to animal lungs due to increased shear stress in the bronchioles and alveoli caused by repeated opening and closing of alveolar units and by regional overdilatation produced by uneven distribution of the time constants.25-27

Several clinical investigations have questioned the ability of a ventilatory procedure based on large Vt and PEEP to improve respiratory mechanics and gas exchange.15,16,27,28,29 and pointed out the potential for harm.30 Studies comparing conventional ventilation with low Vt for the same PEEP level have shown a systematic increase in cardiac index and DvO2.28,29 On the other hand, PEEP resulted in alveolar recruitment only in those patients who had a PâO2 value on ZEEP lower than 25 cmH2O.14 In addition, Rouby et al.30 reported that parenchymal air cysts and emphysema-like lesions were found in 86% of the post mortem lungs of ARDS patients previously ventilated with a Vt amounting to 12 ± 3 ml/kg. These lesions were found to be more evident in the healthy, normally aerated lung regions.30 Lec et al.31 reported the results of a study in which 103 patients were randomized to receive mechanical ventilation with PEEP using a conventional Vt (12 ml/kg) and a low Vt (6 ml/kg). A lower rate of pulmonary infections as well as a shorter duration of intubation and intensive care unit stay associated with low Vt. In a study32 indicated that limits set by reducing Vt and decreasing predicted hospital mortality, in view of these experimental studies,15,16,27,28,29 several new articles have shown that attempts to control Vt and PâO2 are not sufficient. However, the effects on respiratory mechanics and gas exchange of a reduction in Psâs has been investigated in patients who did not tolerate the use of tidal volume reduction and decreased oxygenation.15 PEEP had little effect in most patients ventilated in the supine position because these patients were already inflating their lungs. If on the other hand, the use values, there was still no doubt if PEEP was able to recruit.

With the exception of mechanical ventilation, static inflation V-P curve toward the horizontal increase in compliance.


Table 4. Effects of PEEP on Hemodynamics during Mechanical Ventilation with the Two Different Vt

<table>
<thead>
<tr>
<th></th>
<th>ZEEP</th>
<th>PEEP 10</th>
<th>ΔZEEP-PEEP (%)</th>
<th>ZEEP</th>
<th>PEEP 10</th>
<th>ΔZEEP-PEEP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (min⁻¹)</td>
<td>95 ± 6</td>
<td>98 ± 7</td>
<td>3.2 ± 0.1</td>
<td>95 ± 7</td>
<td>98 ± 7</td>
<td>3.2 ± 0.1</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>88 ± 2</td>
<td>84 ± 4</td>
<td>-5.1 ± 0.4</td>
<td>89 ± 6</td>
<td>85 ± 2</td>
<td>-7.2 ± 0.5</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>192 ± 23</td>
<td>232 ± 27</td>
<td>-5.1 ± 0.4</td>
<td>217 ± 14</td>
<td>221 ± 23</td>
<td>-7.2 ± 0.5</td>
</tr>
<tr>
<td>PAOP (mmHg)</td>
<td>119 ± 14</td>
<td>157 ± 17</td>
<td>-28.5 ± 11</td>
<td>95 ± 10</td>
<td>115 ± 11</td>
<td>17.4 ± 11.2</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>76 ± 6</td>
<td>120 ± 6</td>
<td>-3.6 ± 0.6</td>
<td>64 ± 22</td>
<td>74 ± 6</td>
<td>3.6 ± 0.6</td>
</tr>
<tr>
<td>CI (L/min⁻¹·m²)</td>
<td>4.8 ± 0.4</td>
<td>3.3 ± 0.4</td>
<td>-31.3 ± 1.5</td>
<td>5.9 ± 0.6</td>
<td>5.3 ± 0.6</td>
<td>-10.8 ± 1.4</td>
</tr>
<tr>
<td>SVI (m²/m³)</td>
<td>52.0 ± 2.7</td>
<td>34.2 ± 2.6</td>
<td>-35.4 ± 1.1</td>
<td>56.1 ± 3.1</td>
<td>53.8 ± 2.0</td>
<td>-4.1 ± 1.0</td>
</tr>
</tbody>
</table>

Vt = tidal volume; ZEEP = zero end-expiratory pressure; PEEP = positive end-expiratory pressure; HR = heart rate; MPAP = mean pulmonary arterial pressure; PAOP = pulmonary artery occlusion pressure; RAP = right atrial pressure; CI = cardiac index; SVI = stroke volume index.

Data are mean ± SEM.

* P < 0.01.
† P < 0.001.
‡ P < 0.001, Vt = 10–15 ml/kg versus Vt = 5–8 ml/kg.
§ P < 0.001, Vt = 10–15 ml/kg versus Vt = 5–8 ml/kg.
LOW \( V_T \) AND PEEP IN ARDS

Table 5. Effects of PEEP on Gas Exchange during Mechanical Ventilation with the Two Different \( V_T \)

<table>
<thead>
<tr>
<th>( V_T = 10−15 ) ml/kg</th>
<th>( V_T = 5−8 ) ml/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta ZEEP−\text{PEEP} (%) )</td>
<td>( \Delta ZEEP−\text{PEEP} (%) )</td>
</tr>
<tr>
<td>( P_{a_0} (\text{mmHg}) )</td>
<td>88 ± 4</td>
</tr>
<tr>
<td>( S_{ao_2} (%) )</td>
<td>95 ± 1</td>
</tr>
<tr>
<td>( P_{vo_2} (\text{mmHg}) )</td>
<td>34 ± 2</td>
</tr>
<tr>
<td>( S_{vo_2} (\text{mmHg}) )</td>
<td>67 ± 3</td>
</tr>
<tr>
<td>( P_{aco_2} (\text{mmHg}) )</td>
<td>41 ± 1</td>
</tr>
<tr>
<td>( pH )</td>
<td>7.42 ± 0.04</td>
</tr>
<tr>
<td>( Q_O2/Q_CO2 )</td>
<td>0.44 ± 0.11</td>
</tr>
<tr>
<td>( D_{O2} (\text{ml}−\text{min}^{-1}−\text{m}^{-2}) )</td>
<td>487 ± 91</td>
</tr>
<tr>
<td>( V_{co} (\text{ml}−\text{min}^{-1}−\text{m}^{-2}) )</td>
<td>139 ± 14</td>
</tr>
</tbody>
</table>

Standard \( V_T \) = tidal volume equal to 10−15 ml/kg; low \( V_T \) = tidal volume equal to 5−8 ml/kg; ZEEP = zero end-expiratory pressure; PEEP = positive end-expiratory pressure; \( P_{ao_2} \) = arterial \( O_2 \) tension; \( S_{ao_2} \) = arterial \( O_2 \) saturation; \( P_{vo_2} \) = mixed venous \( O_2 \) tension; \( S_{vo_2} \) = mixed venous \( O_2 \) saturation; \( P_{aco_2} \) = arterial carbon dioxide tension; \( Q_O2/Q_CO2 \) = right-to-left venous admixture; \( D_{O2} \) = oxygen delivery; \( V_{co} \) = oxygen consumption.

Data are mean ± SEM.

* \( P < 0.001 \).
† \( P < 0.01 \).
‡ \( P < 0.05 \) vs. \( V_T = 10−15 \) ml/kg.
§ \( P < 0.01 \) vs. \( V_T = 5−8 \) ml/kg.

In these patients, the increase in functional residual capacity due to PEEP resulted in displacement of the V-P curve along the upper flat part of the V-P curve on ZEEP (fig. 1). In patients 5, 7, and 9, the V-P curve during mechanical ventilation with conventional \( V_T \) and ZEEP showed a convexity toward the volume axis, indicating that compliance increased with PEEP. In these patients, PEEP caused a shift along the V-P curve, suggesting that alveolar recruitment or other changes in lung properties had occurred (fig. 1). On the other hand, when our patients were mechanically ventilated with a \( V_T \) of 5−8 ml/kg, the static V-P curve showed concavity toward the volume axis; in all patients, the application of PEEP resulted in alveolar recruitment of previously collapsed alveoli (fig. 2).

To explain the clinical and physiologic implications of these results, the complex relationship between airway pressure and lung volume must be discussed. The interpretation of our experimental findings is based on the assumption that a static V-P curve with downward concavity represents lungs with all available alveoli recruited and becoming overdistended, whereas V-P curves with upward concavity indicate that alveoli are being progressively recruited. During baseline mechanical ventilation with conventional \( V_T \), patients who had V-P curves with a downward concavity on ZEEP...
(patients 1–4, 6, and 9) had an end-inspiratory PST.r value amounting to 21.9 ± 0.1 cmH2O. They were therefore close to their maximal volume, i.e., in the flat part of the static V-P curve. Conventional Vt was thus able to recruit and even hyperinflated the recruitable lung zones through the concomitant increase in end-inspiratory PST.r. In this case, the application of PEEP caused further hyperinflation of the alveoli already recruited by large tidal volumes. After reduction of Vt to 5–8 ml/kg, the V-P curves of patients 1–4, 6, and 8 showed upward concavity and end-inspiratory PST.r amounted to 11.4 ± 1.7 cmH2O during baseline ventilation. Under these circumstances, an alveolar derecruitment related to the lower inflating pressure can be attributed to Vt reduction. In this case, the application of PEEP elicited a larger increase in recruited volume compared with higher baseline inflation volume and was able to counteract the alveolar derecruitment induced by low-Vt ventilation. During baseline ventilation, conventional Vt and ZEEP, patients 5, 7, and 9 had lower PST.r values (17.5 ± 0.1 vs. 21.9 ± 0.1 cmH2O) than the other patients. In these, conventional Vt did not inflate the lung along the flat part of the V-P curve (fig. 1), and hence application of PEEP resulted in alveolar recruitment. Tidal volume reduction enhanced this behavior in the sense that tidal inflation on ZEEP occurred along the initial part of the static inflation V-P curve, characterized by a more rapid progressive increase in compliance. Moreover, application of PEEP induced a larger amount of alveolar recruitment (table 3). More than 15 yr ago, Suter et al.24 noted that “optimum” compliance in ARDS was jointly determined by PEEP and tidal volume. Pelosi et al.33 extended that observation with elegant computed tomography studies demonstrating differences in gas/tissue ratios at the extremes of the conventional tidal cycle that are eliminated by 10–15 cmH2O of PEEP. A direct correlation between CST.r measurements and the amount of aerated lung regions quantified with the computed tomography scan technique was demonstrated by Pelosi et al. and Gattinoni et al.33,34 Our data show that the greater number of aerated alveoli, i.e., the highest values of CST.r, was observed during mechanical ventilation with conventional Vt on ZEEP and during mechanical ventilation with low Vt and PEEP. The application of PEEP during conventional Vt and the Vt reduction on ZEEP decreased CST.r, indicating that, during such conditions, normal and recruited alveoli were hyperinflated or minimized, respectively.

In our patients, the reduction in Vt induced a decrease in the hemodynamic consequences of PEEP. Cardiac index and SVI fell with PEEP by 30 ± 2 and 54 ± 1 %, respectively, during conventional Vt, and 9 ± 1 and 4 ± 1 %, respectively, during low Vt. These results can be explained by the lower values of end-inspiratory PST.r obtained when PEEP was applied during mechanical ventilation with low Vt. These lower PST.r values thus could have minimized the amount of alveolar pressure transmitted to intrathoracic vasculature (preload effect) and/or the increase in alveolar pressure relative to pericardial pressure (afterload effect).

35,36 Whereas, during conventional Vt, PEEP decreased the pressure gradient for venous return by increasing RAP by 65 ± 3 % of its value on ZEEP, an increase of 16 ± 1 % of RAP value on ZEEP was observed when PEEP was applied during mechanical ventilation with low Vt. MPAP, routinely used as an index of right ventricular afterload, increased with PEEP by 21 ± 2 % of its values on ZEEP during mechanical ventilation with conventional Vt, whereas it is only 11 ± 1 % during mechanical ventilation with low Vt. However, the right ventricle is exposed to the same intrathoracic pressure as the pulmonary artery so that accepting a single downstream pressure value regardless of flow as a legitimate index of “afterload” is a gross oversimplification. Only more accurate measurements can assess the hemodynamic consequences of low-Vt ventilation.

Because Do3 is the product of cardiac index and CaO2, the effects of PEEP during the different Vt used in this study represent the balance of the effects of the two different ventilatory strategies on these factors. During mechanical ventilation with conventional Vt, CaO2 increased from 10.35 ± 0.21 to 13.61 ± 0.70 ml/dl (P < 0.0001; 32 ± 2%). However, this increase was unable to compensate for the 30 % reduction in cardiac index due to PEEP, and hence, Do3 significantly fell when PEEP was applied. Instead, the reduction in cardiac index with PEEP with low Vt amounted only to 9 ± 1 %, whereas CaO2 increased by 23 ± 2 % of the values on ZEEP (from 10.37 ± 0.31 to 12.70 ± 0.65 ml/dl on ZEEP and 10 cmH2O of applied PEEP, respectively, P < 0.001). This increase in CaO2 was able to counterbalance the reduction in cardiac index, so that PEEP increased Do3 during mechanical ventilation with low Vt.

The effects of acute hypercapnia on pulmonary and systemic circulation have been evaluated extensively in experimental models.37,38 In intact animals, acute hypercapnia causes pulmonary hypertension and increases heart rate, cardiac output, and systemic arterial pressure. Studies in patients with neurogenic or iatrogenic hypercapnia induced by halving the mechanical ventilation baseline level. In their study, 60–90 min after Vt reduction in PaCO2 from 38 ± 2 to 30 ± 3 decreased significantly in arterial blood gases, 22 ± 0.02 mmHg was observed. Reduction in Vt from 655 to 245 ml/kg resulted in hypercapnia, induced a significant increase in pulmonary and systemic arterial pressures, and concentrations of noradrenaline. These conditions were obtained by a volume stepwise by 50 ml/kg, and the procedure lasted 205 min. In our study, the reduction induced a significant decrease in arterial pH (table 4). However, changes in heart rate or pulmonary pressures (table 4) do not depend on the degree of pCO2. In our study, patients were divided into two groups, those with mild or those with severe hypercapnia. Carbon dioxide acts extracellularly and intracellularly on the alveolar and pulmonary circulation and results in similar effects. However, changes in arterial pH are due to changes in bicarbonate levels, and changes in the level of arterial pCO2 are due to changes in the level of pCO2. The level of arterial pCO2 is due to changes in the level of arterial pCO2. The level of arterial pCO2 is due to changes in the level of arterial pH.
LOW VT AND PEEP IN ARDS

VT induced a decrease in pulmonary vascular resistance by 30 ± 2 and 
ventilatory Vt and partial pressure of arterial PCO2 were 
both lowered. These values were obtained in patients with 
normal values of cardiac index and pulmonary artery pressures. 
Puybasset et al. studied the effects of permissive hypercapnia in 11 consecutive 
ARDS patients in whom the increase in PaCO2 was rapidly induced by halving the minute ventilation from 
the baseline level. In their study, measurements were obtained 60–90 min after VT reduction. A significant increase in PaCO2 from 38 ± 2 to 65 ± 5 mmHg and a 
significant decrease in arterial pH from 7.41 ± 0.01 to 
7.22 ± 0.02 were observed as a consequence of the reduction in VT from 655 ± 40 to 530 ± 28 ml. Acute hypercapnia induced a significant increase in systemic and pulmonary artery pressures, heart rate, and plasma concentrations of norepinephrine. In our study, low 
VT conditions were obtained by decreasing the minute ventilation 
by 21 ± 2 and the conventional VT was increased by only 
11 ± 5 ml/min with low VT. The changes in systemic and pulmonary artery pressures were obtained after 170 ± 25 min. In our 
study, VT reduction induced increases in PaCO2 and decreases in arterial pH (table 5) similar to those reported in Puybasset et al.’s study. However, we observed no 
changes in heart rate or pulmonary and systemic arterial pressures (table 4). The differences between the effects of permissive hypercapnia in Puybasset et al.’s study and our study can be explained by the longer time used to reduce VT in our study. Many concerns regarding hypercapnia are related to the prolonged extracellular acidosis with which it is associated. However, the majority of effects of acute hypercapnia are mediated by 
intracellular pH. It is now apparent that the changes in intracellular pH have a markedly different time course to those of extracellular pH after acute hypercapnia. Carbon dioxide spreads freely through both extracellular and intracellular spaces, and acute hypercapnia results in similar PCO2 and pH changes in both spaces. However, intracellular pH returns to 90% of normal within 3 h, whereas extracellular renal pH correction occurs slowly and is still incomplete after 3 days. It may be assumed that, in our patients, the compensation for the fall in intracellular pH occurred during the slow step-by-step reduction in VT and the following 2–3 h, so that the adrenergic mediated effects of acute hypercapnia were minimized. Only direct measurements of plasma catecholamine concentrations, not performed in our study, could confirm this assumption.

In our patients, the pulmonary vascular resistance index (PVRI) during conventional VT ventilation and ZEEP was 121 ± 11 dyne·s·cm⁻⁵ and increased significantly (P < 0.01) to 138 ± 10 dyne·s·cm⁻⁵ with progressive VT reduction. These values are close to those found in normal subjects and are substantially lower than those reported in Puybasset et al.’s study. Therefore, considering the normally flat PAP-flow relationship in our patients, hypercapnia-induced increase in cardiac index resulted in a significant and marked increase in PAP because of the more pronounced slope of the PAP-flow relationship.

In conclusion, our data show that application of PEEP during mechanical ventilation with a VT of 10–15 ml/kg induced hyperinflation of alveoli already recruited by tidal inflation, whereas PEEP applied during mechanical ventilation with a VT of 5–8 ml/kg induced alveolar recruitment counteracting the alveolar collapse induced by the low VT. Although these results confirm the clinical applicability of permissive hypercapnia, randomized controlled studies are required to prove its capacity to improve outcome in patients with ARDS.

The authors thank the physicians and nursing staff of Policlinico Hospital for their cooperation. They also thank M. Pinsky, M.D., and J. J. Rouby, M.D., for their suggestions and criticisms, and Mary V. C. Pragnell, B.A., for help in revising the manuscript.

References