

# Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome\*

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**Objective:** Both prone position and high-frequency oscillatory ventilation (HFOV) have the potential to facilitate lung recruitment, and their combined use could thus be synergetic on gas exchange. Keeping the lung open could also potentially be lung protective. The aim of this study was to compare physiologic and proinflammatory effects of HFOV, prone positioning, or their combination in severe acute respiratory distress syndrome (ARDS).

**Design:** Prospective, comparative randomized study.

**Setting:** A medical intensive care unit.

**Patients:** Thirty-nine ARDS patients with a  $\text{PaO}_2/\text{FiO}_2$  ratio  $<150$  mm Hg at positive end-expiratory pressure  $\geq 5$  cm  $\text{H}_2\text{O}$ .

**Interventions:** After 12 hrs on conventional lung-protective mechanical ventilation (tidal volume 6 mL/kg of ideal body weight, plateau pressure not exceeding the upper inflection point, and a maximum of 35 cm  $\text{H}_2\text{O}$ ; supine-CV), 39 patients were randomized to receive one of the following 12-hr periods: conventional lung-protective mechanical ventilation in prone position (prone-CV), HFOV in supine position (supine-HFOV), or HFOV in prone position (prone-HFOV).

**Measurements and Main Results:** Prone-CV (from  $138 \pm 58$  mm Hg to  $217 \pm 110$  mm Hg,  $p < .0001$ ) and prone-HFOV (from

$126 \pm 40$  mm Hg to  $227 \pm 64$  mm Hg,  $p < 0.0001$ ) improved the  $\text{PaO}_2/\text{FiO}_2$  ratio whereas supine-HFOV did not alter the  $\text{PaO}_2/\text{FiO}_2$  ratio (from  $134 \pm 57$  mm Hg to  $138 \pm 48$  mm Hg). The oxygenation index ( $[\text{mean airway pressure} \times \text{FiO}_2 \times 100]/\text{PaO}_2$ ) decreased in the prone-CV and prone-HFOV groups and was lower than in the supine-HFOV group. Interleukin-8 increased significantly in the bronchoalveolar lavage fluid (BALF) in supine-HFOV and prone-HFOV groups compared with prone-CV and supine-CV. Neutrophil counts were higher in the supine-HFOV group than in the prone-CV group.

**Conclusions:** Although HFOV in the supine position does not improve oxygenation or lung inflammation, the prone position increases oxygenation and reduces lung inflammation in ARDS patients. Prone-HFOV produced similar improvement in oxygenation like prone-CV but was associated with higher BALF indexes of inflammation. In contrast, supine-HFOV did not improve gas exchange and was associated with enhanced lung inflammation. (Crit Care Med 2005; 33:2162–2171)

**KEY WORDS:** acute respiratory distress syndrome; prone position; high-frequency oscillatory ventilation; oxygenation; interleukin-8 neutrophils

Despite recent clinical trials showing improved outcome in acute respiratory distress syndrome (ARDS) and acute lung injury (1), controversy still exists regarding the optimal approach to ventilate these patients. It has been concluded from animal studies that lung injury occurs from large distending volume asso-

ciated with excessive transpulmonary pressure or resulting from (in a volume-cycle mode) repetitive opening and closing of unstable lung units (2–7). To avoid ventilator-associated lung injury, current recommendations focus on the avoidance of both alveolar overdistention and alveolar collapse and re-expansion as well as achieving and maintaining alveolar recruitment.

One strategy uses conventional mechanical ventilation with decreased tidal volume and increased positive end-expiratory pressure (PEEP) adjusted on the basis of an initial pressure-volume curve (8). Ranieri and coworkers (9) reported that this strategy resulted in a decrease in pulmonary and systemic cytokines. More recently, the ARDS Net investigators reported a 22% decrease in the relative risk of death of patients with ARDS using a protective conventional

strategy with a small tidal volume and a PEEP that averaged  $\sim 9$  cm  $\text{H}_2\text{O}$  (1).

High-frequency oscillatory ventilation (HFOV) is a ventilation method that has the potential to achieve all of the goals of lung-protective ventilation (10, 11) by avoiding alveolar overdistention, cyclic alveolar collapse, and re-expansion and by maintaining open recruited alveoli. There are convincing animal data indicating that HFOV improves gas exchange, facilitates uniform lung inflation, and reduces lung injury (7, 12, 13). High-frequency oscillatory ventilation is also associated with reduced inflammatory mediators and granulocytes in lung lavage samples when compared with conventional ventilation (14–17). High-frequency oscillation has been used for years in neonates, and six observational series (18–23) and one randomized controlled trial (24) have suggested that

\*See also p. 2407.

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Table 1. Patient characteristics

	Supine-HFOV	Prone-CV	Prone-HFOV
Age, yrs, mean $\pm$ SD	55 $\pm$ 15	51 $\pm$ 9	51 $\pm$ 12
Gender, M/F	8/5	6/7	9/4
Ideal body weight, kg	62 $\pm$ 10	59 $\pm$ 11	65 $\pm$ 13
SOFA score at admission, mean $\pm$ SD	7.5 $\pm$ 3.0	8.5 $\pm$ 4.1	7.7 $\pm$ 3.1
SAPS II score at admission, mean $\pm$ SD	43 $\pm$ 13	44 $\pm$ 21	36 $\pm$ 14
McCabe and Jackson classification			
Nonfatal underlying disease	6	6	8
Ultimately fatal underlying disease	4	6	4
Rapidly fatal underlying disease	3	1	1
ICU mortality, n	5	4	3
SOFA score at inclusion, mean $\pm$ SD	10.0 $\pm$ 3.0	9.7 $\pm$ 3.0	8.9 $\pm$ 2.0
PaO <sub>2</sub> /Fio <sub>2</sub> ratio at inclusion, mm Hg	106 $\pm$ 31	103 $\pm$ 41	101 $\pm$ 22
Oxygenation index at inclusion	18.3 $\pm$ 6.1	20.4 $\pm$ 7.7	19.8 $\pm$ 9.2
Fio <sub>2</sub> at inclusion	0.70 $\pm$ 0.21	0.72 $\pm$ 0.21	0.73 $\pm$ 0.18
Lung Injury Score at inclusion	3.2 $\pm$ 0.3	3.0 $\pm$ 0.4	3.0 $\pm$ 0.5
Pulmonary ARDS, n	11	9	11
Lower inflection point, cm H <sub>2</sub> O (n)	10 $\pm$ 4 (8)	11 $\pm$ 4 (10)	10 $\pm$ 5 (10)
Cause of ARDS, n			
Aspiration	5	5	4
Community-acquired pneumonia	4	3	4
Pneumonia in immunocompromised patients	2	1	2
Septic shock	2	1	2
Peritonitis	0	3	0
Nosocomial pneumonia	0	0	1
Scanographic infiltrates, n			
Diffuse	7	7	7
Lobar	4	3	5
Patchy	2	3	1
PEEP on inclusion, cm H <sub>2</sub> O	11 $\pm$ 5	11 $\pm$ 4	12 $\pm$ 4
Tidal volume on inclusion, mL $\cdot$ kg <sup>-1</sup>	6.4 $\pm$ 0.9	6.5 $\pm$ 0.7	6.2 $\pm$ 0.6

HFOV, high-frequency oscillatory ventilation; CV, conventional mechanical ventilation; SOFA, Sequential Organ Failure Assessment score; SAPS, Simplified Acute Physiology Score; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure.

There was no difference between the three groups.

HFOV can be applied successfully to adults.

Prone positioning is another adjunct to a lung-protective strategy that may promote lung recruitment by decreasing regional pleural pressure gradients (25, 26). However, its use was not associated with a reduction in mortality rate when used with a mean tidal volume of 10.3  $\pm$  2.7 mL/kg (27). In a *post hoc* analysis, the authors showed that prone position was associated with a decreased mortality rate when a tidal volume >12 mL/kg was used (27). As suggested by the accompanying editorial of this latter study, it is reasonable to use ventilation at a low tidal volume with the patient in the prone position (28). Finally, both prone position and HFOV have the potential to facilitate lung recruitment, and their combined use could therefore be synergetic on gas exchange. Keeping the lung open also has the potential to be lung protective. This association has only been reported in a case report (29). Thus, the physiologic rationale for the combined use of HFOV and prone position would appear to be attractive. Therefore, the primary physi-

ologic goal of this prospective, randomized study was to compare the effects of prone position, HFOV, and their combination on gas exchange in severe ARDS patients. Secondary end points were a) the evolution of inflammatory mediators; and b) the number of complications (mucus obstruction, pulmonary air leak, vasopressor requirements).

## MATERIALS AND METHODS

### Study Population

Thirty-nine patients admitted to the medical intensive care unit (ICU) of Sainte-Marguerite University Hospital in Marseille, France, were investigated early in the course of ARDS (<24 hrs) after written informed consent was obtained from each patient's next of kin. The study was approved by our Ethics Committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Marseille) and supported by l'Assistance Publique des Hôpitaux de Marseille. Patient characteristics on inclusion (before the beginning of the optimization period: see study design section) are summarized in Table 1.

There was no difference between the three groups. The ICU mortality rate of the entire group was 31%.

### Inclusion Criteria

Eligible patients met the following criteria: PaO<sub>2</sub>/Fio<sub>2</sub> ratio  $\leq$ 150 mm Hg while on PEEP  $\geq$ 5 cm H<sub>2</sub>O, bilateral radiographic pulmonary infiltrates, and pulmonary artery occlusion pressure of  $\leq$ 18 mm Hg.

### Exclusion Criteria

Exclusion criteria were patients younger than 18 yrs old, lack of informed consent, moribund status, severe chronic respiratory insufficiency requiring long-term oxygen therapy or long-term mechanical ventilation, head injury, unstable pelvic or vertebral fracture, extra-alveolar air in the chest radiograph, or a chest tube in place with persistent air leak, or patients who had participated in other investigational trials within 30 days.

### Study Design

The study design is detailed in Figure 1. After an optimization period (supine-CV) of 12 hrs using conventional lung-protective mechanical ventilation (tidal volume, 6 mL/kg of ideal body weight; plateau pressure  $\leq$ 35 cm H<sub>2</sub>O or the value of the upper inflection point, PEEP set at 2 cm H<sub>2</sub>O above the lower inflection point), patients were assigned to one of the three following ventilatory modalities: a) conventional lung-protective mechanical ventilation in prone position (prone-CV); b) HFOV in supine position (supine-HFOV); or c) HFOV in prone position (prone-HFOV). The patients were assigned to one group using opaque sealed envelopes.

As shown in Figure 1, a bronchoalveolar lavage (BAL) and a blood sample (for cytokine determination) were performed after the optimization period and after the randomized ventilatory modality.

### Instrumentation and Measurements

**Hemodynamic Monitoring.** All patients had a radial artery catheter and a pulmonary artery catheter. Cardiac index (obtained by a continuous method), oxygen delivery index, and venous admixture were calculated using standard formulas. These measurements were performed just before blood and BAL sampling.

**Blood Gas Analysis.** Blood gases were monitored via a continuous arterial sensor system. The Paratrend 7 (Diametrics Medical, St. Paul, MN) sensor is comprised of two optodes for the measurements of pH and PaCO<sub>2</sub>, a miniaturized Clark electrode for the measurement of PaO<sub>2</sub>, and a thermocouple for the

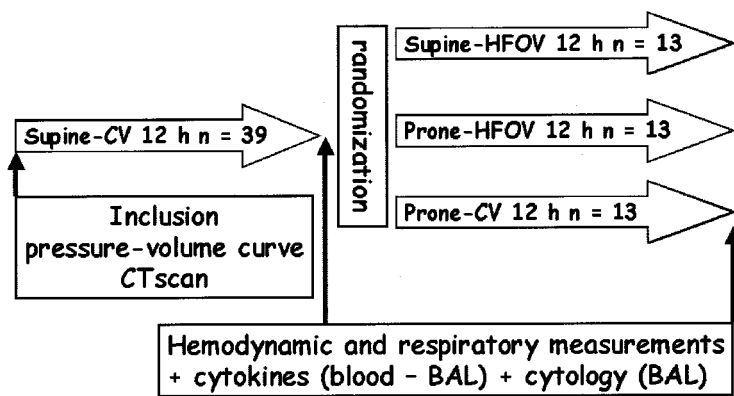


Figure 1. Study design. CV, conventional lung-protective mechanical ventilation; HFOV, high-frequency oscillatory ventilation; CT, computed tomography; BAL, bronchoalveolar lavage.

measurement of temperature. The sensing elements are housed in a single unit with a 0.5-mm diameter and located in the distal 4 cm of the sensor. Before insertion, the sensor requires computer-controlled calibration performed by diffusing precision gases of fixed concentration in a tonometer solution for 30 mins.

Systemic and pulmonary arterial blood samples were simultaneously withdrawn within 3 mins of hemodynamic measurements. Arterial pH,  $P_{aO_2}$ , mixed venous oxygen tension,  $P_{aCO_2}$ , hemoglobin concentration, and arterial and mixed venous oxygen saturations were measured using a blood gas analyzer (Synthesis 15, Instrumentation Laboratory, Lexington, MA). Arterial and mixed venous blood gases were analyzed at 37°C and corrected to core temperature. Values from the arterial blood gases withdrawn at the end of each 12-hr period were used to calculate the  $P_{aO_2}/F_{IO_2}$  ratio and the oxygenation index, where oxygenation index = (mean airway pressure  $\times F_{IO_2} \times 100)/P_{aO_2}$ .

**Lung Mechanics.** Static inflation pressure-volume curves in supine position were obtained before the beginning of the period of the conventional lung-protective mechanical ventilation in supine position. Pressure-volume curve was performed using a 2-L syringe. The endotracheal tube was disconnected from the ventilator to allow functional residual capacity to be reached. Then, 100-mL increments of oxygen were given with a 2-sec pause at the end of each inflation. Inspiratory and expiratory flow were measured with a heated pneumotachograph (adult size, Hans-Rudolf 3700; Hans-Rudolf, Kansas City, KS) and a differential pressure transducer. Airway pressures were measured by another differential pressure transducer. Volume changes were obtained by integration of the flow signal recorded on the MP100 data acquisition system (Biopac Systems, Goleta CA) and analyzed using AcqKnowledge software program (Biopac Systems). A pressure-volume curve was constructed permitting the determination of the lower inflection point computed as the

pressure corresponding to the intersection between starting compliance and compliance of the respiratory system lines (30). The upper inflection point was identified according to the criteria defined by Roupie et al. (31) (i.e., the first upper point above which the curve consistently deviates from the linear part of the curve at high lung volume). Auto-PEEP was measured by pressing (5 secs) the end-expiratory hold knob on the ventilator.

**Blood and Bronchoalveolar Lavage Sampling.** Ten milliliters of blood specimens were placed in a vacuumed bottle containing EDTA just before performing BAL. Following centrifugation (4500 rpm at 4°C for 10 mins), multiple aliquots of serum were frozen at -80°C until analysis.

BAL was performed by one of only two designated clinicians to ensure consistency of technique. The two BAL procedures were performed in the supine position with the same ventilator settings as those used during the optimization period. Patients were preoxygenated with an  $F_{IO_2}$  of 1.0 for 10 mins. A fiberoptic bronchoscope was placed via the endotracheal tube into the upper airways. We first performed a meticulous aspiration of airway secretions with a first fiberoptic bronchoscope. We used a second bronchoscope to perform the BAL. The right middle lobe (or the left lower lobe when there was a right predominance of the infiltrates) was identified and the tip of the bronchoscope wedged. Sterile saline was instilled into the right middle lobe in aliquots of 50 mL. After one respiratory cycle, 20–30 cm  $H_2O$  suction was applied. This was repeated until either 15 mL of instillate had been recovered or a total of 100 mL had been instilled. The recovered lavage fluid was pooled into a polypropylene tube (Falcon, Rockfalls, NJ), filtered, and placed on ice. Bronchoalveolar lavage fluid (BALF) was centrifuged (4500 rpm at 4°C for 10 mins) to remove cellular material and the supernatant stored at -80°C for subsequent analysis. The time between the end of the BAL procedure and freezing was not allowed to exceed 10 mins, and samples were kept at 4°C until this

time. The supernatants were aliquot into cups and frozen at -80°C until analysis.

**Calculation of Recovered Pulmonary Epithelial Lining Fluid Volume.** Concentrations of tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\beta$ , IL-6, and IL-8 in the pulmonary epithelial lining fluid were then calculated by the following formula: concentration of cytokine in the epithelial lining fluid = concentration of cytokine in BALF  $\times$  (urea serum/urea BALF) and are shown as picograms per milliliter of epithelial lining fluid.

**Measurement of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-8.** Concentrations of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-8 in BALF as well as in serum were determined by double-antibody (sandwich) enzyme-linked immunosorbent assay kits (Human TNF $\alpha$  Quantikine, Human IL-1 $\beta$  Quantikine HS, and Human IL-8 Quantikine, R&D Systems, Minneapolis, MN; for technical details see <http://www.rndsystems.com>) and IL-6 enzyme-linked immunosorbent assay (Immuno-tech-Beckman, Marseille, France; minimum detectable dose, 3 pg·mL<sup>-1</sup>).

**Cell Count in BALF and Cytospin Preparations.** After centrifugation of BALF, the cell pellet was resuspended in 2 mL of normal saline solution and the cells were counted in a Neubauer improved (Brand, Wertheim, Germany) hemocytometer. Cyto centrifuge preparations were made on a Shandon Cytospin II (Shandon Instruments, Sewickley, PA) using 100- $\mu$ L aliquots of the previously described cell suspension. White blood cell differentiation was made by May-Grunwald and Giemsa stains. Five hundred cells were counted on each slide.

## Protocol

**Ventilator Settings During Conventional Lung-Protective Mechanical Ventilation.** All patients were supported with volume-assist/control ventilation (Puritan Bennett 840, Carlsbad, CA). Tidal volume was kept at 6 mL/kg of ideal body weight, and the plateau pressure was maintained at a level not exceeding 35 cm  $H_2O$  or the value of the upper inflection point if it was <35 cm  $H_2O$ . The PEEP level was set at 2 cm  $H_2O$  above the lower inflection point. Whenever a lower inflection point could not be determined on the pressure-volume static curve, a PEEP level of 10 cm  $H_2O$  was initiated. If necessary,  $F_{IO_2}$  was adjusted to maintain a  $P_{aO_2}$  measured by the continuous arterial sensor system >60 mm Hg and/or  $SpO_2 > 88\%$ . These settings were also used during the prone position period of the prone-CV group.

**High-Frequency Oscillatory Ventilation Settings.** During periods with HFOV, the 3100B high-frequency oscillatory ventilator was used (SensorMedics, Yorba Linda, CA). After we performed a recruitment maneuver (mean airway pressure of 45 cm  $H_2O$  for 40 secs), HFOV was initiated at the following settings:  $F_{IO_2}$  1.00, oscillation frequency 5 Hz, percent inspiratory time 33%, and bias flow 20

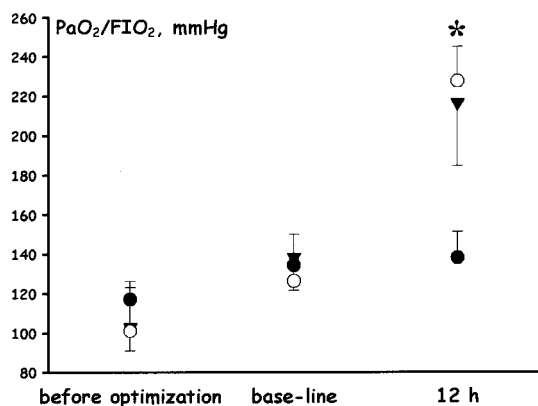


Figure 2. Evolution of PaO<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> ratio. Mean ± SEM. Filled circles, high-frequency oscillatory ventilation in the supine position. Open circles, high-frequency oscillatory ventilation in the prone position. Filled triangles, conventional lung-protective mechanical ventilation in the prone position. \**p* < .0001 vs. baseline and *p* < .001 vs. high-frequency oscillatory ventilation in the supine position.

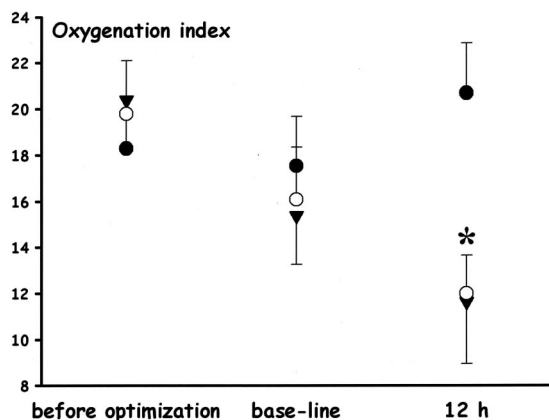


Figure 3. Evolution of the oxygenation index. Mean ± SEM. Filled circles, high-frequency oscillatory ventilation in the supine position. Open circles, high-frequency oscillatory ventilation in the prone position. Filled triangles, conventional lung-protective mechanical ventilation in the prone position. \**p* < .05 vs. baseline and *p* < .001 vs. high-frequency oscillatory ventilation in the supine position.

L/minute. Mean airway pressure was set at 5 cm H<sub>2</sub>O greater than mean airway pressure measured at the end of the conventional lung-protective mechanical ventilation in supine position. The pressure amplitude of oscillation was initially set to achieve a PaCO<sub>2</sub> close to the PaCO<sub>2</sub> measured after the 12-hr period of conventional lung-protective mechanical ventilation in supine position. The pressure amplitudes of oscillation and oscillation frequency were sequentially adjusted to achieve PaCO<sub>2</sub> within the target range and maintain a pH >7.15. If the maximum pressure amplitude of oscillation (110 cm H<sub>2</sub>O) was insufficient to achieve a pH in the target range, the oscillation frequency was decreased to 4 Hz. If the PaCO<sub>2</sub> remained higher than expected, a cuff leak was used. The mean airway pressure providing the higher PaO<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> ratio was used by decreasing or increasing it in increments of 2–3 cm H<sub>2</sub>O every 20–30 mins to a maximum corresponding to the plateau pressure measured at the end of conventional lung-

protective mechanical ventilation in supine position.

**Prone Position.** Patients were positioned flat on special air mattresses with a dynamic alternating cell design and automatic adjustment for patient weight (ProNimbus, Huntleigh Healthcare, Luton, UK). No cushion was used to facilitate abdominal movement. In the prone position, the arms were laid parallel to the body. Attention was paid to avoid eye damage or any nonphysiologic movement of the limbs during posture changes.

**General Measures.** All patients were sedated and paralyzed throughout the study period with a continuous infusion of sufentanil, midazolam, and cisatracurium. The target PaCO<sub>2</sub> was 40–80 torr with a pH >7.15. Tracheal suctioning was achieved by placing an in-line suction catheter (Ballard Trach Care, 16-Fr, Ballard Medical Products, Draper UT). Suction was prohibited in the 30-min period preceding hemodynamic and gas exchange measurements. Additional ARDS cointerven-

tions (inhaled nitric oxide or prostacycline, administration of almitrine or steroids) were not allowed during the study period. It was suggested to the clinician in charge of the patient to prefer the use of norepinephrine rather than fluids when mean arterial pressure was <70 mm Hg.

## Classification of Infiltrates

A computed tomographic exam was performed in the 12-hr period preceding measurements. Infiltrates were classified into three groups (32): lobar, patchy, and diffuse.

## Statistical Methods

All statistics were performed using SPSS 12.0 software (SPSS, Chicago, IL). We selected a sample size of 39 subjects because it would allow us to detect a difference of 70 ± 60 mm Hg in the mean PaO<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> ratio, assuming a two-tailed test and α = 0.05 and β = 0.80. Data are expressed as mean ± SD or median with interquartile range (IQR) according to the distribution of the data. Statistically significant differences were analyzed using the chi-square test or the Fisher's exact test for categorical variables and the Student's *t*-test or the Mann-Whitney rank sum test for unpaired comparisons. The paired Student's *t*-test or a Wilcoxon signed rank test was used for comparisons of paired continuous variables; the chi-square test or the Fisher's exact test was used for categorical variables. We performed two-way repeated-measures analyses of variance (with the factors being time and group) for all gas exchange and hemodynamic variables. *Post hoc* pairwise multiple comparison procedures using Holm-Sidak method were used. Correlation between neutrophil count and IL-8 was analyzed using Pearson test. We considered *p* < .05 to indicate significance.

## RESULTS

### Effects of HFOV and Prone Positioning on Oxygenation Variables

Prone-CV and prone-HFOV groups produced a similar significant improvement in PaO<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> (from 138 ± 58 mm Hg to 217 ± 110 mm Hg, *p* < .0001; and from 126 ± 40 mm Hg to 227 ± 64 mm Hg, *p* < .0001, respectively, Fig. 2) and oxygenation index (Fig. 3). In contrast, supine-HFOV improved neither PaO<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> (from 134 ± 57 mm Hg to 138 ± 48 mm Hg, Fig. 2) nor oxygenation index. There was a greater increase in PaO<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> from measurements performed at the end of the optimization period (supine-CV) in

Table 2. Main ventilatory settings and gas exchange

	Baseline Supine-CV <i>n</i> = 39	Supine-HFOV <i>n</i> = 13	Prone-CV <i>n</i> = 13	Prone-HFOV <i>n</i> = 13
Tidal volume, mL · kg <sup>-1</sup>	6.4 ± 0.7	NA	6.4 ± 0.8	NA
Respiratory rate, cycles · min <sup>-1</sup>	26 ± 6	280 ± 47	24 ± 5	277 ± 46
Plateau pressure, cm H <sub>2</sub> O	25 ± 6	NA	26 ± 7	NA
Mean airway pressure, cm H <sub>2</sub> O	19 ± 4 <sup>a</sup>	25 ± 5	19 ± 5 <sup>a</sup>	25 ± 6
Applied PEEP, cm H <sub>2</sub> O	12 ± 4	NA	12 ± 4	NA
Auto-PEEP, cm H <sub>2</sub> O	0.9 ± 1.3	NA	0.6 ± 0.7	NA
Pressure amplitude of oscillation, cm H <sub>2</sub> O	NA	78 ± 17	NA	80 ± 20
Paco <sub>2</sub> , mm Hg	50 ± 11	52 ± 13	47 ± 9	52 ± 12

HFOV, high-frequency oscillatory ventilation; CV, conventional mechanical ventilation; NA, not applicable; PEEP, positive end-expiratory pressure.

<sup>a</sup>*p* < .01 vs. supine-HFOV and prone-HFOV.

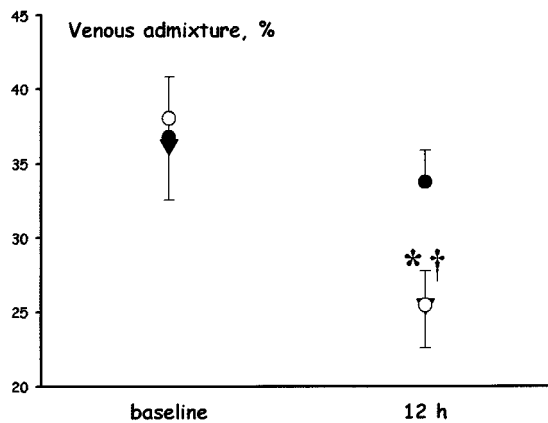


Figure 4. Evolution of the venous admixture. Mean ± SEM. Filled circles, high-frequency oscillatory ventilation in the supine position. Open circles, high-frequency oscillatory ventilation in the prone position. Filled triangles, conventional lung-protective mechanical ventilation in the prone position. \**p* < 0.0001 and *p* < .05 for high-frequency oscillatory ventilation in the prone position vs. baseline and vs. high-frequency oscillatory ventilation in the supine position, respectively. †*p* < .001 and *p* < .05 for prone positioning vs. baseline and vs. high-frequency oscillatory ventilation in the supine position, respectively.

the prone-CV or prone-HFOV groups (median increase 60%, IQR 14–96%, and median increase 45%, IQR 31–57%, respectively) than in patients randomized to receive supine-HFOV (median increase 3%, IQR –12 to 30%, *p* < .01 and *p* < .001, respectively).

### Effects of HFOV and Prone Positioning on Respiratory Variables

As shown in Table 2, tidal volume, mean airway and plateau pressures, and applied and auto-PEEP remained unchanged in the prone-CV group. As expected, mean airway pressure was higher when using HFOV than when lung-protective ventilation was used, whatever the posture. The mean airway pressure when HFOV was used was not different from the plateau pressure used during the periods that patients were ventilated

using a conventional lung-protective mechanical ventilation strategy (Table 2). Respiratory rate was decreased below 5 Hz during HFOV in four patients included in the supine-HFOV group and in three patients included in the prone-HFOV group to correct hypercapnia.

### Effects of HFOV and Prone Positioning on the Venous Admixture, the Other Hemodynamic Variables, and Gas Exchange

As shown in Figure 4, the two-way analysis of variance showed that prone position (*p* < .0001) and HFOV (*p* < .001) reduced the venous admixture. Moreover, the venous admixture calculated in patients treated using prone positioning (combined or not with HFOV) was significantly reduced compared with

the venous admixture calculated in the supine-HFOV group (*p* < .05). Except for a slight increase in right atrial pressure in all groups (from 9.4 ± 3.9 to 10.9 ± 4.1 mm Hg with prone positioning, from 9.0 ± 3.2 to 11.1 ± 4.5 mm Hg with HFOV, and from 9.2 ± 2.8 to 11.2 ± 4.7 mm Hg in patients who received HFOV in the prone position), the other hemodynamic variables (including cardiac index) remained unchanged (data not shown). No significant modification of Paco<sub>2</sub> was observed throughout the duration of the protocol (Table 2).

### Effects of HFOV and Prone Positioning on Cytokines and Cell Differential Counts

The median percentage of epithelial cells in the BAL was 0% (IQR 0–2%). Median values and IQR for the cytokines assayed are displayed in Tables 3 (BALF) and 4 (blood). IL-8 increased significantly in BALF in patients who were randomized to receive HFOV in either supine or prone position compared with the concentration of IL-8 measured in BALF after the 12-hr period of optimization. When compared with the IL-8 concentration measured in the prone-CV group, HFOV (in either position) was associated with a higher IL-8 concentration determined on BALF. IL-1β slightly (but significantly) decreased in the prone-CV group. The other cytokines evaluated in BALF and all cytokines evaluated in blood were not modified by HFOV and/or prone positioning. The differential cytology demonstrated that neutrophils counts were higher in the supine-HFOV group (median 475,000·mL<sup>-1</sup>, IQR 290,000–875,000·mL<sup>-1</sup>) than after prone-CV

**Table 3.** Levels of interleukin (IL)-8, IL-1 $\beta$ , IL-6, and tumor necrosis factor (TNF)- $\alpha$  in bronchoalveolar lavage fluid after a 12-hr period of conventional lung-protective mechanical ventilation in the supine position and after 12 hrs in the randomized ventilation mode

	Prone-CV Group (n = 13)		Supine-HFOV Group (n = 13)		Prone-HFOV Group (n = 13)	
	Supine-CV	Prone-CV	Supine-CV	Supine-HFOV	Supine-CV	Prone-HFOV
IL-8 pg/mL	2985 (1119–11,550)	1583 (693–7523)	2390 (2098–9176)	16893 (1602–26,204) <sup>a,b</sup>	2294 (620–8934)	15420 (6224–46,749) <sup>b,c</sup>
IL-1 $\beta$ pg/mL	36 (11–137)	0 (0–13) <sup>a</sup>	22 (5–67)	16 (0–41)	27 (4–1267)	102 (5–326) <sup>b</sup>
IL-6 pg/mL	8114 (3794–22,561)	6905 (3051–18,975)	4885 (616–23,917)	5062 (3090–34,031)	3340 (477–9061)	4217 (2293–10,290)
TNF- $\alpha$ pg/mL	0 (0–66)	0 (0–93)	0 (0–38)	51 (0–531)	0 (0–128)	113 (0–370)

CV, conventional lung-protective mechanical ventilation; HFOV, high-frequency oscillatory ventilation.

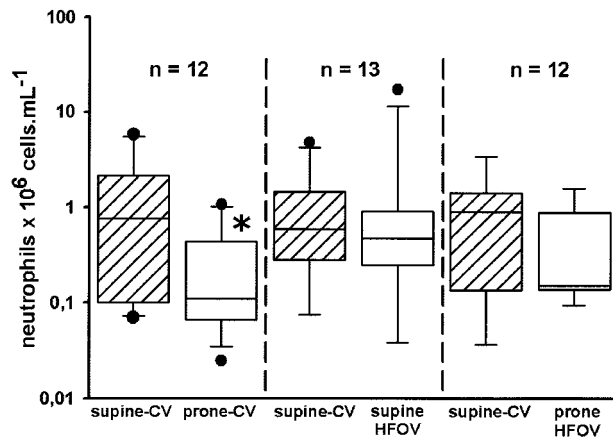
<sup>a</sup> $p < .05$  (Wilcoxon's signed-rank test) vs. supine-CV; <sup>b</sup> $p < .05$  (Mann-Whitney rank sum test) vs. prone-CV; <sup>c</sup> $p < .01$  (Mann-Whitney rank-sum test) vs. supine-CV. Results are presented as median (with interquartile range).

**Table 4.** Levels of interleukin (IL)-8, IL-1 $\beta$ , IL-6, and tumor necrosis factor (TNF)- $\alpha$  in blood after a 12-hr period of protective ventilation in the supine position and after 12 hrs in the randomized ventilation mode

	Prone-CV Group (n = 13)		Supine-HFOV Group (n = 13)		Prone-HFOV Group (n = 13)	
	Supine-CV	Prone-CV	Supine-CV	Supine-HFOV	Supine-CV	Prone-HFOV
IL-8 pg/mL	54 (31–83)	38 (17–105)	59 (31–108)	53 (20–80)	33 (17–53)	21 (20–54)
IL-1 $\beta$ pg/mL	0.55 (0.40–0.74)	0.36 (0.20–0.48)	0.92 (0.25–1.62)	0.42 (0.20–1.08)	0.46 (0.28–0.74)	0.36 (0.24–0.73)
IL-6 pg/mL	170 (42–618)	118 (20–199)	157 (61–536)	112 (43–196)	162 (72–277)	60 (20–157)
TNF- $\alpha$ pg/mL	8 (0–9)	8 (7–12)	12 (0–20)	8 (0–15)	0 (0–10)	0 (0–11)

CV, conventional lung-protective mechanical ventilation; HFOV, high-frequency oscillatory ventilation.

Results are presented as median (with interquartile range).



**Figure 5.** Neutrophil counts in the bronchoalveolar lavage fluid after a 12-hr period of conventional lung-protective mechanical ventilation in the supine position and after 12 hrs of the randomized ventilation mode. Median values (25th, 50th, and 75th percentiles), largest and smallest values that are not outliers are reported. Outliers (cases with values between 1.5 and 3 box-lengths from the upper or lower edge of the box) are presented as closed circles. CV, conventional lung-protective mechanical ventilation; HFOV, high-frequency oscillatory ventilation. \* $p < .05$  vs. supine-CV (Wilcoxon signed rank test) and vs. supine-HFOV (Mann-Whitney rank sum test).

(median 110,000·mL<sup>-1</sup>, IQR 72,000–310,000·mL<sup>-1</sup>;  $p < 0.05$  by Mann-Whitney rank sum test, Fig. 5). This increase coincided with the elevated BALF IL-8 concentrations observed after HFOV in supine position. Finally, neutrophil count was correlated with BAL IL-8 level at baseline and after all

12-hr periods ( $r^2 = .45$ ,  $p < .001$  and  $r^2 = .61$ ,  $p < .0001$ , respectively).

### Protocol Compliance

We found a compliance of 98% with the gas exchange and ventilator settings strategy during the 24-hr period of the protocol.

### Complications

In one patient, mucus plugging requiring endotracheal tube change occurred in the group of patients randomized to receive HFOV in the supine position. No pulmonary air leak was diagnosed in any patient during the study period. Only six patients did not receive inotropic or vasopressive agents throughout the study period. Norepinephrine was the most widely used agent. Twenty-eight patients were receiving norepinephrine at the end of the optimization period (median 0.45  $\mu\text{g}\cdot\text{kg}\cdot\text{min}^{-1}$ , IQR 0.22, and 0.90  $\mu\text{g}\cdot\text{kg}\cdot\text{min}^{-1}$ ). There was no modification of the infusion rate of norepinephrine throughout the study period in all groups (or in the three groups, at baseline and at the end of the 12-hr period).

### DISCUSSION

This prospective randomized study compared the effects of HFOV and conventional lung-protective mechanical ventilation in either supine and prone position during ARDS. Both prone-CV and prone-HFOV produced similar significant improvements in oxygenation over a 12-hr study interval. In contrast, supine-HFOV did not improve oxygenation. Moreover, we reported that prone posi-

tioning reduced IL-8 levels and the amount of neutrophils in BAL fluid compared with HFOV in the supine position.

Numerous studies have suggested that HFOV reduces ventilator-induced lung injury and lung biotrauma in small animal models (14, 33–36). In inhomogeneous lungs with some very long inspiratory time constants (as in primary ARDS), HFOV theoretically appears valuable because pressure swings are dampened during transmission to the alveoli, and the sustained high mean airway pressure may open slow-recruiting compartments while keeping the fast-collapsing portions of the lungs open (37). In experimental models of lung injury, it has been shown that prone position improved oxygenation by homogenizing the ventral-dorsal distribution of ventilation, thereby improving ventilation of the dorsal lung regions (25, 26, 38, 39) whereas perfusion remained predominant in the dorsal regions whichever the position (38, 40). As a consequence, a synergy (or at least an additive effect) between HFOV and prone position was expected in regard to gas exchange.

### **Effects of HFOV and Conventional Lung-Protective Mechanical Ventilation on Physiologic Variables**

We found that, compared with supine-CV, prone-CV produced a greater increase in oxygenation than did HFOV in supine position. Moreover, we did not find any synergistic or at least additive effect between HFOV and the prone position.

Derdak et al. (24) found that  $\text{PaO}_2/\text{FIO}_2$  was significantly higher at 8 and 16 hrs in patients receiving HFOV compared with ARDS patients receiving conventional mechanical ventilation. As compared with the present study, the patients studied by Derdak et al. (24) were ventilated using a higher tidal volume ( $8 \pm 2$  mL/kg of actual body weight), a similar PEEP level, and a similar variation in mean airway pressure between HFOV and conventional mechanical ventilation (5–6 cm  $\text{H}_2\text{O}$ ). HFOV is considered by its users as a “rescue” therapy that “theoretically achieves the goals of lung protective ventilation” (23). Experimental studies in animals support this hypothesis. However, the very few studies in adult humans have involved small numbers of patients. The article on the Toronto experience reported on HFOV in a total of 156 patients treated over 4 yrs in three ICUs (23).

Improvement in oxygenation was assessed but not compared with a control group. Furthermore, in this article, pneumothorax occurred in 21.8% of the patients, which does not support a protective effect of HFOV.

As observed in the present work and in the study by Derdak et al. (24), there was no difference in oxygenation index after 12 hrs between supine-CV and supine-HFOV, whereas we observed a decrease in oxygenation index with prone-CV and prone-HFOV. We chose to evaluate the effects of each strategy after a 12-hr period of conventional lung-protective mechanical ventilation for several reasons. First, an early improvement in oxygenation with a peak after 12 hrs of HFOV but a slight decrease after 24 hrs of HFOV has been reported (23, 41). Therefore, the 12-hr study period of both strategy used in the present study would have favored HFOV. The second reason is that a duration of prone position of  $\geq 12$  hrs is widely used (42). The severity of ARDS in the patients included in the present study is suggested not only by the  $\text{PaO}_2/\text{FIO}_2$  on inclusion but also by the fact that whereas we observed the same mortality rate as that reported for ARDS patients included in the small tidal volume arm of the ARDS Network study (1), the mean airway pressure when patients were receiving conventional lung-protective mechanical ventilation was slightly higher in the present study ( $19 \pm 4$  cm  $\text{H}_2\text{O}$ ) than in the ARDS Network trial ( $17 \pm 13$  cm  $\text{H}_2\text{O}$ ).

### **Effects of HFOV and Conventional Lung-Protective Mechanical Ventilation on Neutrophil Counts and Cytokines**

We report in the present study that neutrophil counts decreased when patients were ventilated with prone-CV compared with supine-CV and supine-HFOV. This persistent increase in neutrophils coincided with the increased BALF IL-8 concentrations in patients receiving HFOV. However, in contrast with the results on BALF, there was a (nonsignificant) trend to lower blood levels of IL-8, IL-6, and TNF- $\alpha$  in the prone-HFOV group. Several studies have suggested that the presence of neutrophils, their infiltration in the lung (16, 33), and their activation with the subsequent release of proteases could be an important mechanism in ventilator-induced lung injury

(43). It has recently been confirmed (44) that there is a role for neutrophils in the mechanically overstretched lung *in vivo*. HFOV has been found to be associated with less activation of neutrophils (15, 16).

The neutrophil chemotactic cytokine IL-8 is produced by alveolar macrophages and is the predominant chemoattractant in ARDS BALF (45). It has been reported that IL-8 concentration correlated with neutrophil concentrations (45–47). IL-8 is up-regulated when epithelial cells (48) and alveolar macrophages (49) are subjected to cyclic overstretching. Ranieri et al. (9) found that patients who received the lung-protective strategy had a decrease in BALF concentrations of IL-1 $\beta$  and IL-8. In the present study, we observed that HFOV was associated with an increased level of IL-8 when compared with conventional lung-protective mechanical ventilation. Evaluating the concentration of IL-8 in epithelial lining fluid, Wiedermann et al. (50) recently showed that IL-8 in BALF from ARDS patients correlated with neutrophil count in BALF, suggesting that there is a prominent role of IL-8 for recruitment of neutrophils in the lung in the early phase of ARDS. The present study corroborates this latter result. In ARDS there could be extensive lung areas in which collapsed lung units are adjacent to open lung units. Mead et al. (51) suggested that tissue tensions at the boundaries of expanding and collapsed alveoli could be several-fold higher than those experienced in the free wall of the open unit. Therefore, the external traction resulting from alveolar pressures related to HFOV could generate transvascular pressures in the lung sufficient to exceed the tension threshold for pulmonary capillary stress failure (52, 53). Moreover, high regional transpulmonary pressures are able to overstretch open alveoli. This deleterious effect should have been provoked by HFOV, explaining the increase in inflammatory mediators observed in the present study. Evaluating the relative contributions of mean airway pressure and tidal volume to ventilator-induced injury, Broccard et al. (54) showed that mean airway pressure induces more lung hemorrhage and permeability alterations than tidal volume. Moreover, all experimental data favoring the use of HFOV have been obtained in models of acute lung injury that are highly able to be recruited as in the surfactant depletion injury (55). In contrast, in the setting of pneumonia-

**A**lthough high-frequency oscillatory ventilation in the supine position does not improve oxygenation or lung inflammation, the prone position increases oxygenation and reduces lung inflammation in acute respiratory distress syndrome patients.

caused (“primary”) ARDS, only 5–10% of consolidated lung tissue can be reopened (56). In the present study, 79% of the patients presented primary ARDS. The beneficial effect of prone position on ventilator-induced lung injury was suggested by Broccard et al. (57, 58), who showed that histologic lesions were more severe in dogs ventilated in the supine than in the prone position.

### Study Limitations

The choice of lung lobe to perform BAL (dependent vs. nondependent) could have made significant differences in recovered BALF white blood cells and cytokine levels. The right middle lobe is dependent in the prone position and could be expected to have increased pulmonary blood flow during a 12-hr period in the prone position and an increased amount of secretions when the patients are turned back to the supine position to perform the BAL. However, if it is an important variable, this would have indirectly favored all measurements performed after 12 hrs of supine position (the increase in blood flow would have facilitated white blood cell influx and the increase of the amount of airway secretions would have increased the white blood cell count and cytokine levels after a 12-hr period of prone positioning). It could be therefore postulated that the difference in inflammatory lung indexes is possibly greater than reported in the present study and finally that the prone position is less injurious for the lungs. From a methodological point of view, it would have been highly questionable to

perform two BALs (baseline during supine-CV and in the two prone groups) in different lung lobes, especially when nearly all patients presented with primary ARDS. As frequently reported in the literature using a similar design (9), we did not discard the first aliquot of the BAL. It could have modified the cytokines and cell differential count evaluation.

The lack of a control group to evaluate BALF and blood cytokines and cytology did not allow us to definitely conclude if prone position is associated with a reduction of markers of lung inflammation compared with supine-CV. Indeed, as suggested by a recently published study (59), the supine-CV was able to attenuate the circulating plasma levels of IL-6 and IL-8 during the first 3 days after randomization. Therefore, it is possible that the decrease of the inflammatory mediators observed in the present study after prone positioning was the natural evolution of these mediators and not a protective effect of the postural treatment.

The mean airway pressure used during the present study is slightly lower than in the study by Derdak et al. (24). Our main objective was to evaluate the effects on oxygenation. It was therefore evident that comparable “pressures” must have been used during HFOV and during CV. However, by limiting mean airway pressure in HFOV to the value of the plateau pressure observed during CV, transpulmonary pressure was probably higher during HFOV but not associated with improved oxygenation. It is also possible that a better strategy could have consisted in the early use of cuff leak to avoid high pressure swing. The use of a bias flow set at 20 L·min<sup>-1</sup> is probably not a serious limitation. Indeed, a sufficient pressure was reached in all patients. Hypercapnia necessitated a decrease in the respiratory rate in four patients in the supine-HFOV group and in three patients included in the prone-HFOV group. It was never necessary to deflate the cuff to correct hypercapnia.

The present study completely supports the conclusions of the recently published article by Mehta et al. (23), who considered that HFOV should be considered as a rescue therapy. Prone positioning can also be considered as a rescue therapy. Indeed, Gattinoni and coworkers (27) reported a decreased mortality rate for the more severely hypoxemic patients in a *post hoc* analysis. It is for this reason that we decided to include only ARDS patients presenting a PaO<sub>2</sub>/F<sub>IO</sub><sub>2</sub> <150 mm Hg with

a PEEP of ≥5 cm H<sub>2</sub>O. Finally, mean PaO<sub>2</sub>/F<sub>IO</sub><sub>2</sub> on inclusion was 107 ± 32 mm Hg with a PEEP level of 11–12 cm H<sub>2</sub>O. However, it was difficult to propose including more severely hypoxemic patients because the design of the present study included two BALs.

### CONCLUSIONS

In ARDS patients with a PaO<sub>2</sub>/F<sub>IO</sub><sub>2</sub> <150 mm Hg, prone-HFOV produced improvement in oxygenation that was similar to that of prone-CV but was associated with higher BALF indexes of inflammation. In contrast, supine-HFOV did not improve gas exchange and was associated with enhanced lung inflammation.

Further investigation should be performed that evaluates the effect of HFOV in maintaining adequate oxygenation in ARDS patients who are responders to prone positioning, when they are returned to the supine position. There is still controversy regarding how to best optimize HFOV to achieve optimal gas exchange and lung-protective strategy. HFOV is therefore not ready for prime time, and more needs to be learned before it can be safely used. Finally, other investigations should be performed to evaluate if prone positioning alone or in association with HFOV is able to modify the outcome of the more severely hypoxemic patients.

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