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Tidal Volume Lower than 6 ml/kg Enhances Lung Protection

Role of Extracorporeal Carbon Dioxide Removal

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Background: **Tidal hyperinflation may occur in patients with acute respiratory distress syndrome who are ventilated with a tidal volume (V_T) of 6 ml/kg of predicted body weight develop a plateau pressure (P_{PLAT}) of 28 ≤ P_{PLAT} ≤ 30 cm H_2O. The authors verified whether V_T lower than 6 ml/kg may enhance lung protection and that consequent respiratory acidosis may be managed by extracorporeal carbon dioxide removal.**

Methods: **P_{PLAT}, lung morphology computed tomography, and pulmonary inflammatory cytokines (bronchoalveolar lavage) were assessed in 32 patients ventilated with a V_T of 6 ml/kg. Data are provided as mean ± SD or median and interquartile (25th and 75th percentile) range. In patients with 28 ≤ P_{PLAT} ≤ 30 cm H_2O (n = 10), V_T was reduced from 6.3 ± 0.2 to 4.2 ± 0.3 ml/kg, and P_{PLAT} decreased from 29.1 ± 1.2 to 25.0 ± 1.2 cm H_2O (P < 0.001); consequent respiratory acidosis ($Paco_2$ from 48.4 ± 8.7 to 73.6 ± 11.1 mmHg and pH from 7.36 ± 0.03 to 7.20 ± 0.02; P < 0.001) was managed by extracorporeal carbon dioxide removal. Lung function, morphology, and pulmonary inflammatory cytokines were also assessed after 72 h.**

Results: **Extracorporeal assist normalized $Paco_2$ (50.4 ± 8.2 mmHg) and pH (7.32 ± 0.03) and allowed use of V_T lower than 6 ml/kg for 144 (84–168) h. The improvement of morphological markers of lung protection and the reduction of pulmonary cytokines concentration (P < 0.01) were observed after 72 h of ventilation with V_T lower than 6 ml/kg. No patient-related complications were observed.**

Conclusions: **V_T lower than 6 ml/Kg enhanced lung protection. Respiratory acidosis consequent to low V_T ventilation was safely and efficiently managed by extracorporeal carbon dioxide removal.**

LIMITATION of tidal volume (V_T) to 6 ml/kg predicted body weight (PBW) and of end-inspiratory plateau pressure (P_{PLAT}) to a maximum of 30 cm H_2O represents the standard for mechanical ventilation of patients with acute respiratory distress syndrome (ARDS).[1,2] However, recent studies found that (1) tidal hyperinflation may occur in some patients despite limiting V_T to 6 ml/kg and P_{PLAT} to 30 cm H_2O[3], (2) ARDS patients may benefit from V_T reduction even if they already have P_{PLAT} < 30 cm H_2O.[4]

Extracorporeal assist separating carbon dioxide removal from oxygen uptake has been proposed by Gattinoni *et al.*[5] With this technique, carbon dioxide is removed by a pump-driven veno-venous bypass, and oxygenation is accomplished by high levels of positive end-expiratory pressure (PEEP) and three to five sighs every minute.[5] Although effective,[5] negative results of a clinical trial,[6] the extensive amount of required resources,[7] and the high incidence of side effects[8] restricted the use of extracorporeal carbon dioxide removal as "rescue" therapy for the most severe case of ARDS.[9]

To reduce complexity, expenses, and side effects of extracorporeal lung assistance, Pesenti *et al.* proposed the concept of removing "only a portion of carbon dioxide production" to allow less traumatic ventilator settings.[10] The current study set up to examine the hypothesis that a modified renal replacement circuit incorporating a neonatal membrane lung coupled in series with a hemofilter may safely remove the amount of carbon dioxide sufficient to buffer the respiratory acidosis associated to V_T lower than 6 ml/kg and allow more protective ventilatory settings.

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Materials and Methods

Patient Selection

Patients admitted from July 2006 to September 2007 in the intensive care units of the S. Giovanni Battista-Molinette hospital (University of Turin, Turin, Italy) were enrolled. Inclusion criteria were age of at least 18 yr and diagnosis

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of ARDS.[11] Exclusion criteria were more than 3 days since they met ARDS criteria, pulmonary artery occlusion pressure greater than 18 mmHg, history of ventricular fibrillation, tachyarrhythmia, unstable angina, or myocardial infarction within preceding month, chronic obstructive pulmonary disease, chest wall abnormalities, chest tube, abdominal distension, body mass index greater than 30, pregnancy, intracranial abnormality.[12]

The institutional review board (Comitato Etico Interaziendale, Regione Piemonte, Turin) approved the study. If the patient was incompetent at study entry, consent was delayed, the family was informed of the study (although not required), and the study was performed. Written permission for using collected data were hence obtained from the patient (if competent) or from the family (in case of death or if the patient remained incompetent).[13]

Study Protocol

All consecutive patients who met inclusion and exclusion criteria were treated for 72 h according to the *ARDSNet* strategy.[2] A detailed description of the protocol can be found in the Supplemental Digital Content (see text file, Supplemental Digital Content 1, http://links.lww.com/ALN/A542).

After 72 h of ventilation according to the *ARDSNet* strategy,[2] P_{PLAT} was recorded for a period of 1 h with 0.5-s inspiratory pause keeping ventilator setting constant and abolishing spontaneous respiratory muscles activity by (1) reaching a Ramsay score of sedation 5 (midazolam up to 0.15 $mg \cdot kg^{-1} \cdot h^{-1}$, morphine up to 0.03 $mg \cdot kg^{-1} \cdot h^{-1}$, and propofol up to 2 $mg \cdot kg^{-1} \cdot h^{-1}$)[14]; (1) increasing, if required before measurements, doses of midazolam (up to 10 mg/h) and/or propofol (150 mg/h increments every 10 min).[15,16]

In the patients who had $25 < P_{PLAT} < 28$ cm H_2O, the *ARDSNet* strategy[2] was maintained at least for the subsequent 72 h (fig. 1). In patients who had $28 \leq P_{PLAT} \leq 30$ cm H_2O, the following strategy was implemented and maintained for at least the next 72 h (fig. 1): (1) V_T was stepwise reduced (1 ml/kg of PBW every 4 h) until $25 < P_{PLAT} < 28$ cm H_2O; (2) to manage the reabsorption atelectasis that may occur during mechanical ventilation with low V_T,[17,18] PEEP-FiO_2 combination was set according to the "higher PEEP" arm of the ALVEOLI study[12]; (3) respiratory rate was increased up to 40 breaths/min, and bicarbonate was infused up to 20 mEq/h; (4) if pH was no more than 7.25, extracorporeal carbon dioxide removal was initiated by using a modified continuous veno-venous hemofiltration system equipped with a membrane lung with a total membrane surface of 0.33 m^2 (Decap®, Hemodec, Salerno, Italy)[19] (Lower *ARDSNet*/Carbon Dioxide Removal; fig. 2).

Femoral vein was accessed *via* a double lumen catheter (14 F; Arrow International Inc. Reading, PA) inserted with the Seldinger technique and connected with the extracorporeal circuit. Blood flow was driven through the circuit by a roller nonocclusive low-flow pump (0–500 ml/min) through a membrane lung (Polystan SAFE; Maquet, Rastatt, Germany) that was connected to a fresh gas flow source delivering 100% oxygen at a constant rate of 8 l/min. Exiting the membrane lung, blood was driven to a hemofilter (Medica D200, Medolla, Italy). The resulting plasmatic water was recirculated through the membrane lung by a peristaltic pump (0–155 ml/min).

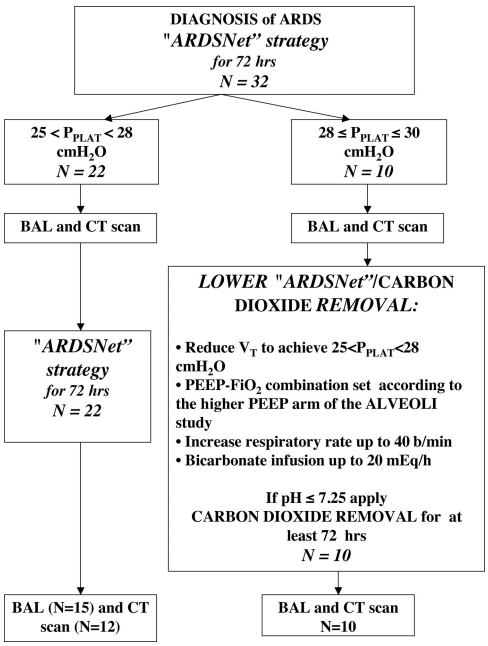

Fig. 1. Study design. ARDS = acute respiratory distress syndrome; ARDS network strategy = *ARDSNet* strategy; BAL = bronchoalveolar lavage; CT = computed tomography; F_{IO2} = inspired O_2 fraction; PEEP = positive end-expiratory pressure; P_{PLAT} = end-inspiratory plateau pressure; V_T = tidal volume. All patients in the Lower *ARDSNet*/Carbon Dioxide Removal arm met pH criteria for carbon dioxide removal and were therefore connected to the veno-venous bypass.

The membrane lung and the hemofilter were coupled in series to: (1) increase the pressure inside the membrane lung by adding the downstream resistance exerted by the hemofilter and therefore reduce the risk of air bubble formation[20]; (2) minimize the need for heparin by diluting the blood entering the membrane lung by recirculating the plasmatic water separated by the hemofilter[21]; (3) enhance the performance of the extracorporeal device extracting the carbon dioxide dissolved in the plasmatic water separated by the hemofilter and recirculated through the membrane lung[22] (fig. 2).

Pressure developed by the roller pump (arterial pressure) was measured and limited to 120–150 mmHg. Reinfusion pressure (venous pressure) and the pressure gradient across the membrane lung and the hemofilter (drop pressure = premembrane lung pressure – venous pressure) were also measured. Detectors of leaks and bubbles were inserted within the circuit. The circuit, including the membrane lung was primed with saline with a volume that ranged between 140 and 160 ml.

A starting dose of heparin (80 IU/kg bolus and 18 IU $\cdot kg^{-1} \cdot h^{-1}$ infusion) was delivered by using a syringe

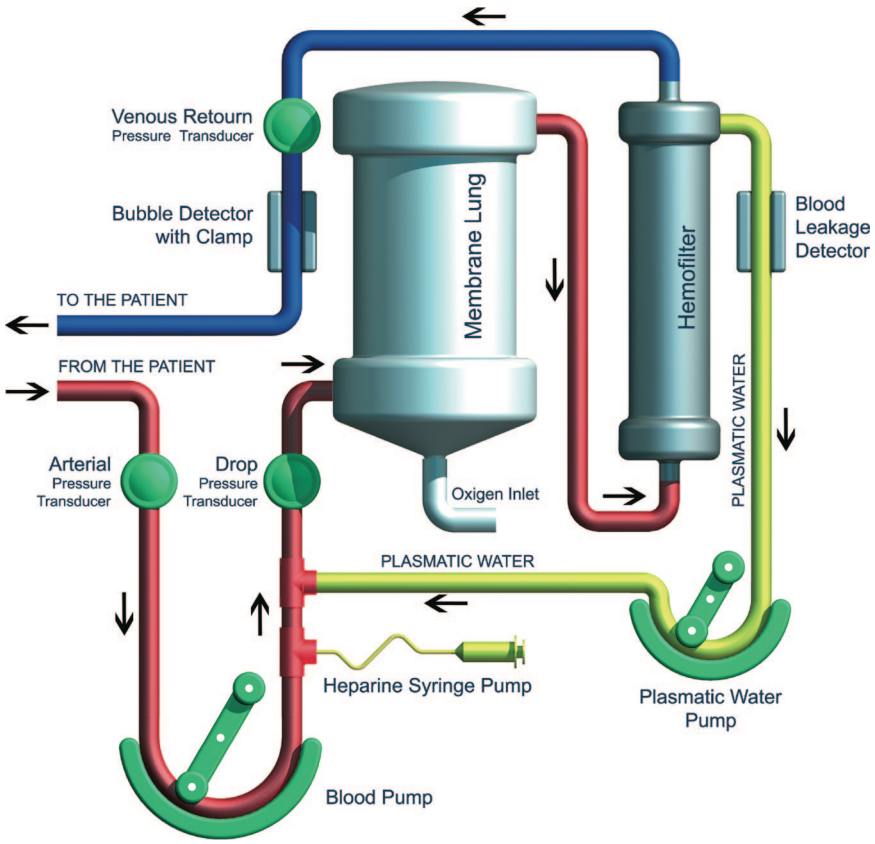

Fig. 2. Extracorporeal carbon dioxide removal device used in the study. The system consisted of a standard continuous veno-venous hemofiltration system equipped with a membrane lung with a total membrane surface of 0.33 m^2.

pump included in the system. Heparin continuous infusion was hence titrated to maintain the activated partial thromboplastine time ratio to approximately 1.5.

After 72 h of Lower *ARDSNet*/Carbon Dioxide Removal strategy, the following weaning trial was conducted once a day: flow through the circuit was set to the lowest value (50 ml/min), V_T was increased to 6 ml/kg PBW, and PEEP-FIO_2 combination was set according to the conventional *ARDSNet* strategy.[2] If P_{PLAT} with these ventilator settings remained for more that 3 h at less than 28 cm H_2O, extracorporeal carbon dioxide removal was interrupted, and conventional *ARDSNet* ventilatory strategy reestablished.

Measurements

Underlying disease responsible for ARDS, clinical status, and laboratory data on admission (the worst value within 24 h after admission) were recorded for calculation of the Simplified Acute Physiology Score II.[23]

Clinical Variables

Clinical variables (P_{PLAT}, V_T, respiratory rate, PEEP, minute ventilation, PaO_2/FIO_2 ratio, $PaCO_2$, pH, continuous cardiac output [Vigileo system; Edwards LifeScience, Irvine, CA], heparin doses, and activated partial thromboplastine time ratio) were prospectively collected at the following scheduled times: after 72 h of ventilation according to the conventional *ARDSNet* strategy and, in those patients who had $28 \leq P_{PLAT} \leq 30$ cm H_2O, after lowering V_T and before initiating carbon dioxide removal (baseline) and after 60–90 min ($T_{1.5}$), 24 h (T_{24}), 48 h (T_{48}), and 72 h (T_{72}) after initiation of carbon dioxide removal. Blood flow during carbon dioxide removal was recorded at $T_{1.5}$, T_{24}, T_{48}, and T_{72}.

Potential complications during the procedure were prospectively classified as mechanical (cannula problems, membrane lung failure, clots in the circuit, air in the circuit, pump malfunction, tubing rupture, catheter displacement, system leaks) and patient-related (vein perforation, significant bleeding [*i.e.*, any bleeding event that required the administration of 1 unit of packed red cells], hemodynamic instability [*i.e.*, 80–90 mmHg increase or a 30–40 mmHg decrease in systolic blood pressure relative to the baseline value or need for inotropic drugs for at least 2 h to maintain systolic blood pressure higher than 85 mmHg or electrocardiogram evidence of ischemia or significant ventricular arrhythmias] ischemic/gangrenous bowel, pneumothorax, renal complications [*i.e.*, occurrence after initiation of carbon dioxide removal of creatinine greater than 1.5 mg/dl], infectious complications [*i.e.*, occurrence after initiation of carbon dioxide removal of culture proven new infection], metabolic [*i.e.*, occurrence after initiation of carbon dioxide removal of glucose of at least 240 mg/dl or hyperbilirubinemia], thromboembolic complications [*i.e.*, occurrence after initiation of deep venous thrombosis or

pulmonary embolus], and neurologic complications [*i.e.*, occurrence after initiation of carbon dioxide removal of cerebral infarction, or clinical seizure, or cerebral hemorrhage or cerebral edema]), and their occurrence was recorded during the period that the Lower *ARDSNet*/Carbon Dioxide Removal strategy was recorded.

Lung Morphology

A pulmonary computed tomography (CT) scan of the whole lung was performed in all patients after study enrollment. The CT scan was repeated after approximately 72 h of ventilation with the Lower *ARDSNet*/Carbon Dioxide Removal strategy in those patients who had $28 \leq P_{PLAT} \leq 30$ cm H_2O and after approximately 72 h of ventilation with the conventional *ARDSNet* strategy in some of the patients who had $25 < P_{PLAT} < 28$ cm H_2O (fig. 1). (See text file, Supplemental Digital Content 1, which is a detailed description of the methods used, http://links.lww.com/ALN/A542).[3]

Weight and volume of the entire lungs and of the nonaerated, poorly aerated, normally aerated, and hyperinflated compartments were assessed.[13,24] Protected tidal inflation and tidal hyperinflation were defined as the volume of the normally aerated and hyperinflated compartment at end-inspiration minus the volume of the normally aerated and hyperinflated compartment at end-expiration, respectively. Tidal recruitment of the nonaerated compartment was defined as the volume of the nonaerated compartment at end-expiration minus the volume at end-inspiration. All were expressed as percent of the total tidal inflation-related change in CT lung volume.[3,24]

Pulmonary Inflammatory Response

A bronchoalveolar lavage was performed in all patients after study enrollment.[25] The bronchoalveolar lavage was repeated after approximately 72 h of ventilation with the Lower *ARDSNet*/Carbon Dioxide Removal strategy in the patients who had $28 \leq P_{PLAT} \leq 30$ cm H_2O and after approximately further 72 h of ventilation with the conventional *ARDSNet* strategy in some of the patients who had $25 < P_{PLAT} < 28$ cm H_2O (fig. 1). Interleukin 6 (IL-6), IL-8, IL-1b, and IL-1 receptor antagonist (IL-1Ra) were measured. (See text file, Supplemental Digital Content 1, which is a detailed description of the methods used, http://links.lww.com/ALN/A542).[25]

Statistical Analysis

Data are expressed as mean ± SD of the mean or median and interquartile (25th and 75th percentile) range as appropriate. To evaluate differences between the two groups, the Fisher exact test for categorical variables and the *t* test with unequal variance for continuous variables were used. Data at different times during carbon dioxide removal were compared by analysis of variance (ANOVA) for repeated measures by using a Bonferroni correction. If significant ($P \leq 0.05$), the values at baseline, $T_{1.5}$, T_{24}, T_{48}, and T_{72} were compared with those obtained after 72 h of ventilation according to the *ARDSNet* strategy by using a paired *t* test as modified by Dunnett. All tests were two tailed. Analysis was carried out by using the SPSS software package (SPSS Inc. Chicago, IL).

Results

Of the 32 patients who matched study criteria, 22 patients had $25 < P_{PLAT} < 28$ cm H_2O and 10 patients had a $28 \leq P_{PLAT} \leq 30$ cm H_2O. Patient characteristics are shown in table 1. Age, gender, Simplified Acute Physiology Score II, and underlying diseases responsible for ARDS did not

Table 1. Characteristics of the Study Population

	Overall Population (n = 32)	*ARDSNet* $25 < P_{PLAT} < 28$ (n = 22)	*ARDSNet* $8 \leq P_{PLAT} \leq 30$ (n = 10)	*P* Value
Demographics				
Age, yrs	65.8 ± 12.2	65.2 ± 13.2	64.1 ± 13.5	NS
Male/female	22/10	15/7	7/3	NS
SAPS II	48 ± 20	43 ± 17	56 ± 23	NS
Respiratory variables				
Tidal volume (ml/kg predicted body weight)	6.3 ± 0.7	6.3 ± 0.3	6.3 ± 0.2	NS
Plateau pressure (cm H_2O)	27.6 ± 1.8	25.2 ± 0.5	29.1 ± 1.2	0.01
PEEP (cm H_2O)	11.4 ± 2.8	10.3 ± 2.3	12.1 ± 2.5	0.01
Pao_2/FIo_2, mmHg	147 ± 56	185 ± 60	136 ± 30	0.003
Minute ventilation (l/min)	10.4 ± 2.6	9.5 ± 2.8	11.5 ± 1.6	0.01
$Paco_2$, mmHg	48.9 ± 7.1	43.5 ± 6.4	48.4 ± 8.7	NS
Arterial pH	7.37 ± 0.02	7.38 ± 0.01	7.36 ± 0.03	NS
Causes of lung injury				
Pneumonia, n (%)	11 (34)	8 (36)	4 (40)	NS
Sepsis, n (%)	16 (50)	10 (45)	5 (50)	NS
Trauma, n (%)	5 (16)	4 (18)	1 (10)	NS

Data are mean ± SD.

FIo_2 = inspiratory O_2 fraction; $Paco_2$ = arterial CO_2 partial pressure; Pao_2 = arterial O_2 partial pressure; PEEP = positive end-expiratory pressure; SAPS = simplified acute physiological score.

Table 2. Quantitative CT Scan of the Study Population

		ARDSNet 25 < P_{PLAT} < 28		*ARDSNet* 28 ≤ P_{PLAT} ≤ 30	
	Overall Population (n = 32)	Study Entry (n = 22)	After 72 h of Conventional *ARDSNet* (n = 12)	Study Entry (n = 10)	After 72 h of Lower *ARDSNet*/Carbon Dioxide Removal (n = 10)
Lung weight, g	1.661 ± 466	1.488 ± 513	1.143 ± 234§	1.919 ± 402*	1.519 ± 106#
End inspiratory CT lung compartments, % total lung volume					
Non-aerated (+100 and –100 HU)	16.2 ± 7.8	12.6 ± 8.7	3.1 ± 1.1§	23.2 ± 7.0*	12.3 ± 2.6#
Poorly aerated (–101 and –500 HU)	14.3 ± 6.1	11.2 ± 6.5	1.1 ± 0.3§	16.3 ± 2.8*	11.4 ± 6.7#
Normally aerated (–501 and –900 HU)	58.7 ± 10.5	72.3 ± 10.1	94.5 ± 3.8§	40.1 ± 9.5*	75.5 ± 8.8#
Hyperinflated (–901 and –1,000 HU)	10.8 ± 8.5	3.9 ± 3.4	1.3 ± 0.2§	20.4 ± 4.4*	0.8 ± 0.7#

Data are mean ± SD.

* $P < 0.001$ *ARDSNet* 25 <P_{PLAT} < 28 cm H_2O at study entry *vs. ARDSNet* 28 ≤ P_{PLAT} ≤ 30 cm H_2O at study entry; § $P < 0.05$ *ARDSNet* 25 < P_{PLAT} < 28 cm H_2O, study entry *vs.* after 72 h of conventional *ARDSNet*; # $P < 0.001$ *ARDSNet* 28 ≤ P_{PLAT} ≤ 30 cm H_2O, study entry *vs.* 72 h of Lower *ARDSNet*/Carbon Dioxide Removal.

CT = computed tomomography.

differ between the two groups; Pa_{CO_2}:F_{IO_2} ratio was lower in patients with 28 ≤ P_{PLAT} ≤ 30 cm H_2O than in patients with 25 < P_{PLAT} < 28 cm H_2O ($P < 0.01$).

Lungs were heavier, and the extent of the hyperinflated, nonaerated, and poorly aerated CT lung compartments was larger and the extent of the normally aerated compartment was smaller in patients with 28 ≤ P_{PLAT} ≤ 30 cm H_2O than in patients with 25 < P_{PLAT} < 28 cm H_2O (all $P < 0.001$) (table 2). Protected tidal inflation was smaller and tidal hyperinflation was larger in patients who had 28 ≤ P_{PLAT} ≤ 30 cm H_2O than in the patients who had 25 < P_{PLAT} < 28 cm H_2O (19 ± 6 *vs.* 81 ± 6 and 67 ± 5 *vs.* 11 ± 4% of the total tidal inflation-associated change in CT lung compartments, respectively; $P < 0.01$). Tidal recruitment of the poorly aerated compartment did not differ between the two groups of patients.

In the patients who had 28 ≤ P_{PLAT} ≤ 30 cm H_2O, V_T was decreased from 6.3 ± 0.2 to 4.2 ± 0.3 ml/kg PBW and P_{PLAT} decreased from 29.1 ± 1.2 to 25.0 ± 1.2 cm H_2O (all $P < 0.001$). Despite the increase in respiratory rate (from 31.2 ± 2.3 to 37.0 ± 1.9 breaths/min; $P < 0.001$) and bicarbonate infusion (20.2 ± 0.8 mEq/h), the reduction in minute ventilation (from 12.03 ± 2.77 to

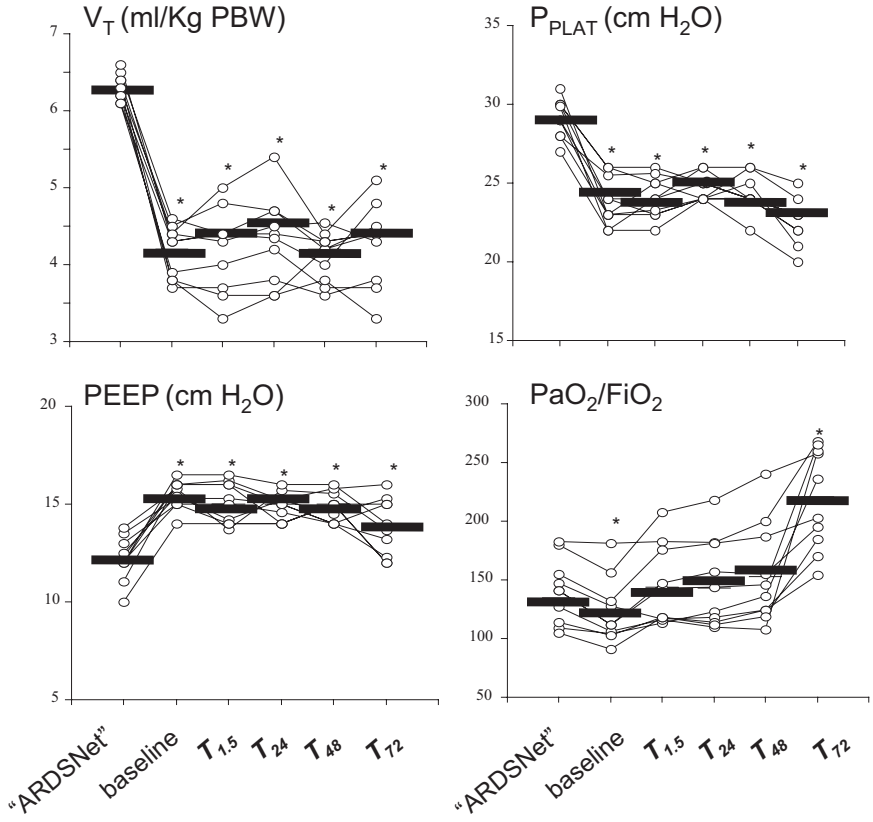

Fig. 3. Individual and average (*horizontal bar*) values of tidal volume (V_T), plateau pressure (P_{PLAT}) positive end expiratory pressure (PEEP), and arterial to inspired O_2 fraction ration (Pa_{O_2}/F_{IO_2}) during acute respiratory distress syndrome network (*"ARDSNet"*) strategy after lowering V_T and before initiating carbon dioxide removal (baseline), and 60–90 min ($T_{1.5}$), 24 h (T_{24}), 48 h (T_{48}), and 72 (T_{72}) after initiation of carbon dioxide removal. * $P < 0.01$ *versus ARDSNet* strategy.

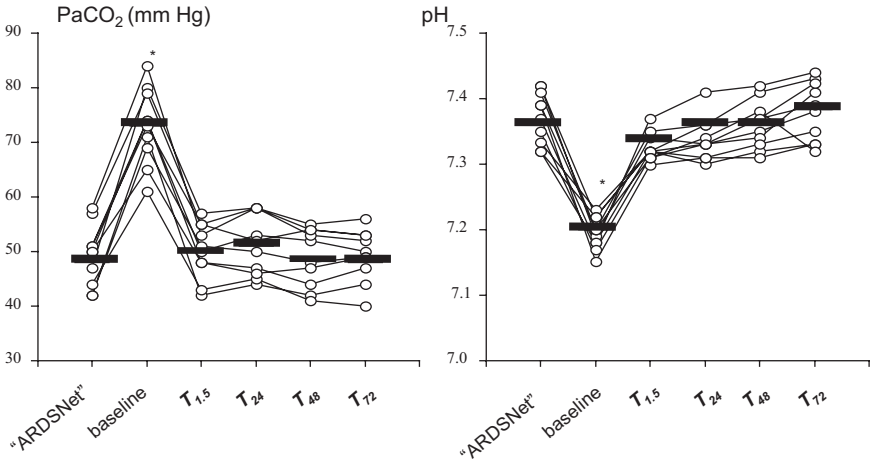

Fig. 4. Individual and average (*horizontal bar*) values of arterial carbon dioxide partial pressure ($Paco_2$) and arterial pH during acute respiratory distress syndrome network (*ARDSNet*) strategy after lowering tidal volume and before initiating carbon dioxide removal (baseline), and 60–90 min ($T_{1.5}$), 24 h (T_{24}), 48 h (T_{48}), and 72 h (T_{72}) after initiation of carbon dioxide removal. * $P < 0.001$ *versus ARDSNet* ventilation.

9.03 ± 1.18 l/min; $P < 0.001$) increased $Paco_2$ (from 48.4 ± 8.7 to 73.6 ± 11.1 mmHg; $P < 0.001$) and decreased pH (from 7.36 ± 0.03 to 7.20 ± 0.02; $P < 0.001$). The increase in PEEP (from 12.1 ± 2.5 cm H_2O to 15.2 ± 0.8 cm H_2O, $P < 0.001$) attenuated the reduction in Pao_2/Fio_2 (from 135 ± 30 to 124 ± 29; $P < 0.01$) associated to the lowering of V_T (fig. 3). All patients met pH criteria for carbon dioxide removal and were therefore connected to the veno-venous bypass.

Sixty to ninety minutes of veno-venous bypass decreased $Paco_2$ to 50.4 ± 8.2 mmHg and increased arterial pH to 7.32 ± 0.03 ($P < 0.001$). After 72 h of extracorporeal support, $Paco_2$ and arterial pH were 47.2 ± 8.6 mmHg and 7.38 ± 0.04, respectively ($P < 0.001$; fig. 4). The extracorporeal veno-venous carbon dioxide removal device was used for 144 (84, 168) h. The pump-driven blood flow through the circuit ranged between 191 and 422 ml/min (5–10% of cardiac output; table 3). Heparin infusion ranging between 3 and 19 IU/kg was needed to maintain activated partial thromboplastine time ratio between 1.1 and 1.7 (table 3).

No patient-related complications were observed. Mechanical complications are reported in table 4. In three cases, the 14-French double-lumen catheter had to be replaced by two 8-French simple-lumen catheters (one for each femoral vein) due to recirculation issues (two cases) and catheter kinking (one case). None of the reported malfunctions impaired patient status during the procedure. The membrane clotting observed in three patients did not result in additional transfusion. The Lower *ARDSNet*/Carbon Dioxide Removal strategy did not require any increase in nursing resources. A technician with expertise in the Decap® system was present (9 AM–5 PM) during the treatment of the first five patients.

Average lung density histograms of tidal changes in CT lung compartments in patients who had $28 \leq P_{PLAT} \leq 30$ cm H_2O during the *ARDSNet* strategy are shown at study entry (fig. 5A, left) and after 72 h of Lower *ARDSNet*/Carbon Dioxide Removal strategy (fig. 5A, right). Ventilation with the Lower *ARDSNet*/Carbon Dioxide Removal was associated with: (1) the reduction of lung weight and of the extent of hyperinflated, nonaerated, and poorly aerated CT lung compartments and an increase of the extent of normally aerated lung compartments ($P < 0.001$; table 2); (2) increase of protected tidal inflation (from 19 ± 6% to 86 ± 8% of the total tidal inflation-associated change in CT lung compartments; $P < 0.01$); (3) the reduction of tidal hyperinflation (from 67 ± 5% to 5 ± 4% of the total tidal inflation-associated change in CT lung compartments; $P < 0.01$); (4) a significant improvement of Pao_2/Fio_2 (from 136 ± 30 to 221 ± 56; $P < 0.001$) (fig. 3). Same data for the patients who during the *ARDSNet* strategy had $25 < P_{PLAT} < 28$ cm H_2O are shown at study entry (fig. 5B, left). In 12 of the 22 patients, CT scans were obtained after further 72 h of conventional *ARDSNet* strategy (fig. 5B, right); these data were retrospectively obtained by using CT scan performed for other studies or for clinical reasons. Relative to

Table 3. Coagulation Parameters and Blood Flow

	$T_{1.5}$	T_{24}	T_{48}	T_{72}
aPTT ratio*	1.3 ± 0.2	1.4 ± 0.1	1.5 ± 0.2	1.4 ± 0.2
Heparin, IU/kg*	8 ± 5	11 ± 7	11 ± 8	11 ± 7
Blood flow through CO_2 removal device, ml/min*	348 ± 74	357 ± 75	329 ± 78	282 ± 91
Cardiac output, ml/min*	5.8 ± 1.3	5.6 ± 1.2	5.7 ± 1.1	6.4 ± 2.3
Fluid balance, ml†	530 (–420, 1,545)	–215 (–2,944, 2,041)	648 (–220, 1,100)	119 (–1,062, 625)

Data are * mean ± standard deviation or † median and interquartile (25th and 75th percentile) range.

aPPT = activated partial thromboplastine time ratio; CO_2 = carbon dioxide; IU = international units.

Table 4. Total Number of Mechanical Complications Occurring during the 144 (84, 168)* Hours of Treatment

	Frequency (n)
Pump malfunction	1
Membrane lung/hemofilter clotting	3
Catheter displacement	1
Cannula problems, *i.e.* need for two cannulas instead of a single double-lumen	3

* Median and interquartile (25th and 75th percentile).

study entry, further 72 h of conventional *ARDSNet* strategy were also associated to the reduction of lung weight and of the extent of the hyperinflated, nonaerated, and poorly aerated CT lung compartments and the increase of the extent of the normally aerated lung compartments ($P < 0.05$; table 2) with no changes in amount of protected tidal inflation and tidal hyperinflation (fig. 5B, left); a significant improvement of Pao_2/Fio_2 (from 185 ± 60 to 301 ± 42; $P < 0.001$) was also observed.

Pulmonary concentration of inflammatory cytokines at study entry were lower ($P = 0.001$) in patients who during the *ARDSNet* strategy had $25 < P_{PLAT} < 28$ cm H_2O than in patients who had $28 \leq P_{PLAT} \leq 30$ cm H_2O. In the former, further 72 h of conventional *ARDSNet* strategy did not modify concentration of pulmonary inflammatory cytokines (data were retrospectively obtained in 15 of the 22 patients by using bronchoalveolar lavage performed for other studies). In the latter, the use of the Lower *ARDSNet*/Carbon Dioxide Removal strategy was associated with a significantly reduced concentration of pulmonary inflammatory cytokines ($P = 0.001$; fig. 6). Bronchoalveolar lavage procedure did not cause complications in any of the studied patients.

Discussion

Use of V_T lower than 6 ml/kg PBW in patients who during *ARDSNet* ventilation had $28 \leq P_{PLAT} \leq 30$ cm H_2O was associated to a significant reduction of inflammatory and morphological markers of ventilator-induced lung injury. Respiratory acidosis consequent to further V_T reduction was effectively and safely corrected by using a modified renal replacement device incorporating a membrane lung.

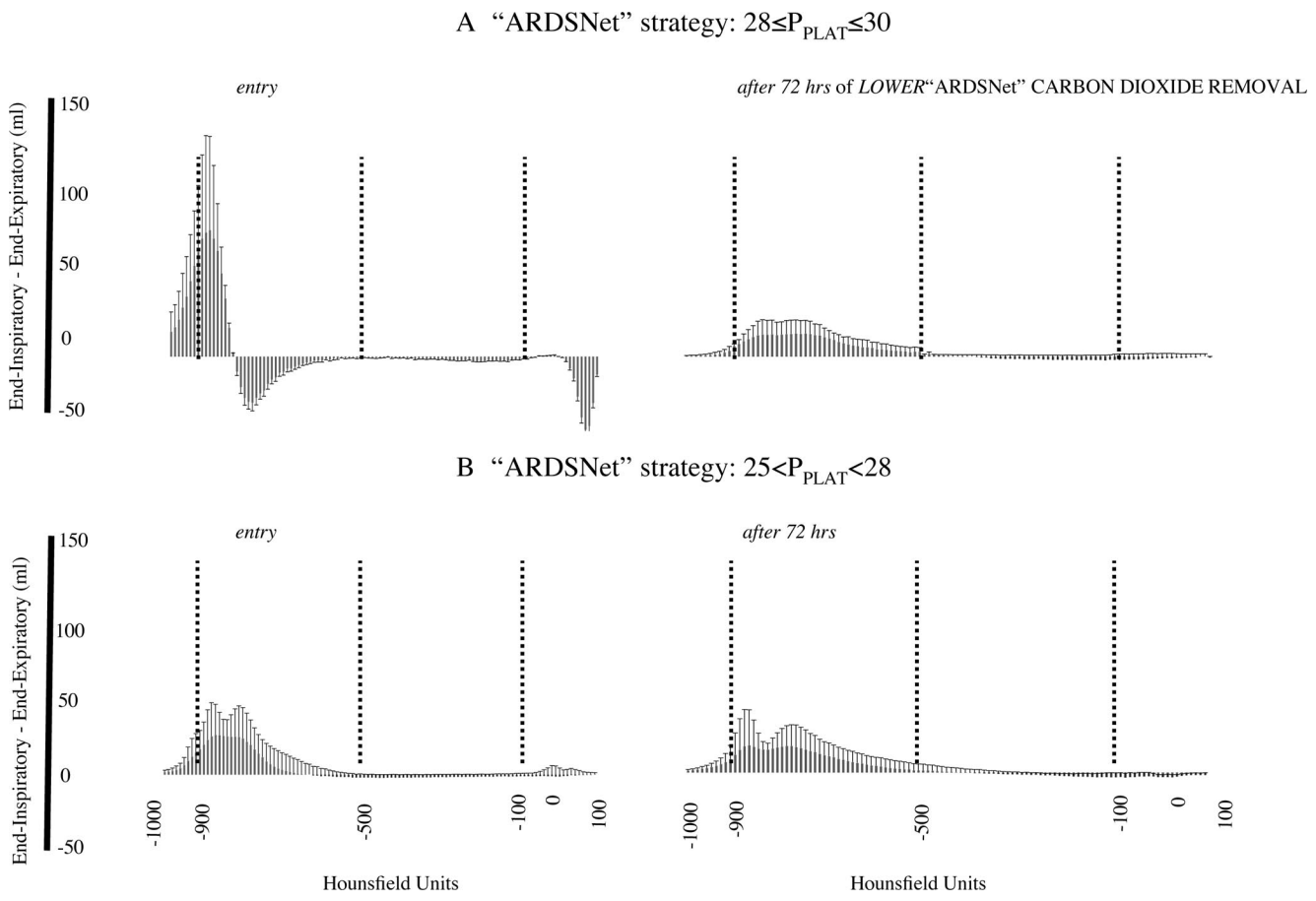

Fig. 5. Average lung density histograms of tidal changes in computed tomography of lung compartments in patients who during the acute respiratory distress syndrome network (*ARDSNet*) strategy had $28 \leq P_{PLAT} \leq 30$ cm H_2O are shown at study entry (*A*, *left*) and after 72 h of Lower *ARDSNet*/Carbon Dioxide Removal strategy (*A*, *right*). Same data for the patients who during the *ARDSNet* strategy had $25 < P_{PLAT} < 28$ cm H_2O are shown at study entry (*B*, *left*) and after further 72 h of conventional *ARDSNet* strategy (*B*, *right*).

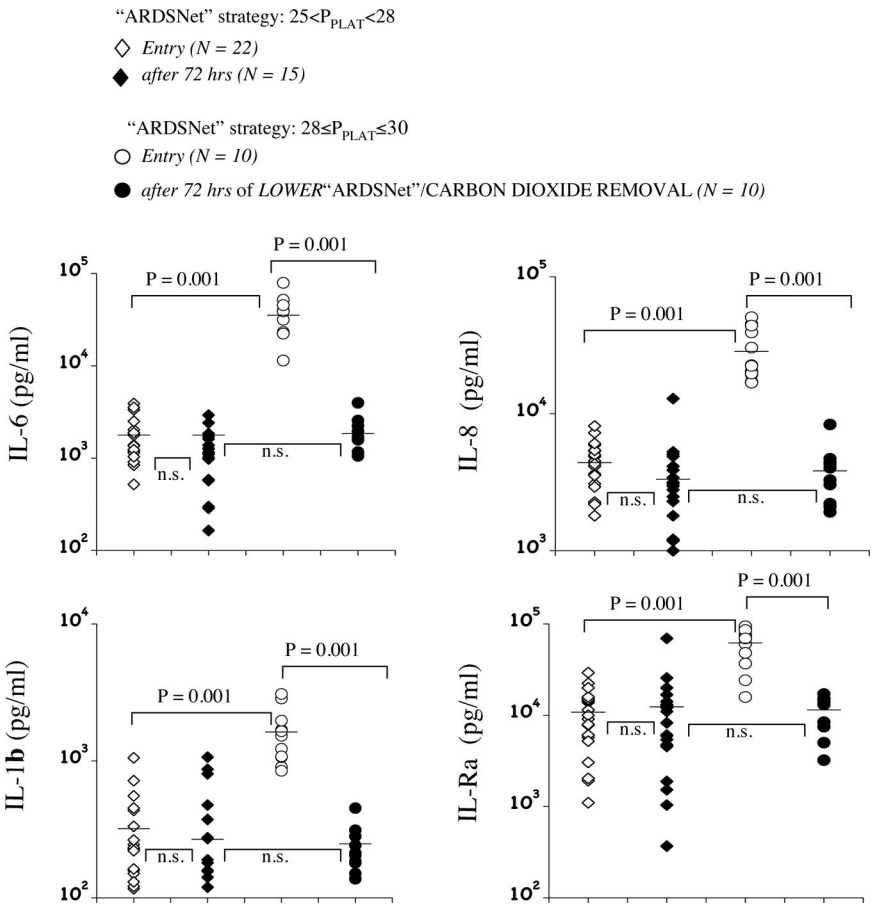

Fig. 6. Individual and average (*horizontal bar*) values of pulmonary concentration of inflammatory mediators in patients who at study entry had 25 < P_{PLAT} < 28 cm H_2O and 28 ≤ P_{PLAT} ≤ 30 cm H_2O during acute respiratory distress syndrome network (*ARDSNet*) strategy. Values of inflammatory cytokines in the former, after further 72 h of *ARDSNet* strategy, and in the latter after 72 h of Lower *ARDSNet*/Carbon Dioxide Removal strategy are also presented. IL-1b = interleukin 1b; IL-1Ra = IL-1 receptor antagonist; IL-6 = interleukin 6; IL-8 = interleukin 8.

These results support the use of extracorporeal carbon dioxide removal as a tool that, integrated with conventional ventilation, allows more protective ventilator settings.[9] However, these data can only be used as proof of principle for the following reasons. (1) The confounding effect of time on the observed improvement of physiologic, radiographic, and inflammatory parameters before and after 72 h of Lower *ARDSNet*/Carbon Dioxide Removal strategy cannot be ruled out because we don't have a control group of patients with 28 ≤ P_{PLAT} ≤ 30 cm H_2O who received usual care without Lower *ARDSNet*/Carbon Dioxide Removal. Moreover, the study design prevents us from knowing what the respective effect of decreasing V_T, increasing PEEP, and application of carbon dioxide removal. (2) We could not assess weather the observed substantial decrease in $Paco_2$ with the limited blood flow was exclusively related to the device used in the study; measurements of extracorporeal carbon dioxide transfer and of total body carbon dioxide production were not performed. (3) Studies in experimental models suggest that unbuffered respiratory acidosis may reduce ventilator-induced lung injury.[26] It is therefore possible that physiologic, morphological, and inflammatory variables would have improved as much or more if we reduced V_T and P_{PLAT} without carbon dioxide removal. (4) None of the patients who had 28 ≤ P_{PLAT} ≤ 30 cm H_2O during "*ARDSNet*" ventilation were able to reach the target P_{PLAT} values (25–28 cm H_2O) with the increase in respiratory rate and bicarbonate infusion. This may be because V_T in three patients was reduced more than required; P_{PLAT} in these patients before initiating extracorporeal carbon dioxide removal was 24.2, 23.3, and 24.1 cm H_2O, values that are lower than the target P_{PLAT}. Moreover tris-hydroxymethyl aminomethane, a non-carbon dioxide-generating buffer that was recently shown to efficiently manage respiratory acidosis,[27,28] was not used in the current study.

Gattinoni *et al.* hypothesized that, "to rest the lung," oxygenation *via* mechanical ventilation could be dissociated from decarboxylation *via* extracorporeal carbon dioxide removal.[5] In that study, mechanical ventilation was limited to apneic oxygenation and to 3–5 sighs every minute with peak inspiratory pressure not higher than 35–45 cm H_2O; PEEP ranged between 15 and 25 cm H_2O. carbon dioxide removal was performed by using a pump-driven veno-venous bypass, allowing blood flow to pass through two membrane lungs (9 m^2 total membrane surface area). Extracorporeal blood flow was progressively raised from 200 to 300 ml/min to the selected maintenance flow (20–30% of cardiac output). Although the observed mortality rate was lower than expected, several episodes of severe bleeding were reported.[5] A subsequent randomized clinical trial did not confirm these data.[6] Concerns have been raised regarding the

standard use of extracorporeal support[6,29] because of the high incidence of serious complications such as hemorrhage, hemolysis, and neurologic impairments.[8] As a result, extracorporeal carbon dioxide removal has been restricted to the sickest patients in whom all other treatments have failed[30] and to centers with large expertise.[31]

Retrospective evaluation of the *ARDSnet* database suggested that V_T reduction would have improved outcome, even in patients who already had $P_{PLAT} < 30$ cm H_2O.[4] Moreover, physiologic[32] and morphological[3] evidences of tidal hyperinflation have been described in patients in whom the *ARDSNet* strategy resulted in $28 \leq P_{PLAT} \leq 30$ cm H_2O. These data have therefore challenged the view of extracorporeal support only as rescue therapy[33,34,35] and have generated the hypothesis that extracorporeal carbon dioxide removal may be incorporated in a lung protective strategy to allow further reduction of V_T and P_{PLAT}.[9]

The concept originally developed by Pesenti *et al.* of removing "only a portion of carbon dioxide production"[10] has been recently implemented in new devices that may reduce side effects, complexity, and costs of extracorporeal carbon dioxide removal.[19,33] Bein *et al.* recently reported the use of a pump-less extracorporeal device in ARDS patients.[34] Retrospective analysis of 90 patients demonstrated that using this device was possible to obtain physiologic values of $Paco_2$ (31–42 mmHg) and pH (7.38–7.50) despite ventilation with low V_T (320–470 ml). However, the authors reported a complication rate of 24%, including limb ischemia, compartment syndrome, and intracranial hemorrhage. In addition, continuous intravenous infusion of norepinephrine was needed to maintain the pressure gradient between arterial and venous blood.

In the current study, carbon dioxide removal was performed through a dedicated pump-driven extracorporeal veno-venous circuit with a neonatal membrane lung and a hemofilter coupled in series (fig. 2). The main elements that characterize and differentiate this system are: (1) a blood flow lower than the one used in standard carbon dioxide removal (191–422 ml/min [5–10% of cardiac output] *versus* 1.5–2.0 l/min [20–30% of cardiac output])[5,6,36]; (2) a small neonatal membrane lung (0.33 m^2) instead of two large adult membrane lung (3–4.5 m^2 each)[5,6,36]; (3) the use of 14-French double-lumen catheters instead of large 21- to 28-French double- or single-lumen catheters[9]; (4) a priming volume smaller than currently used (140–160 ml *vs.* 1,500–1,800 ml)[37]; (5) a relatively small infusion rate of heparin (3–19 IU/kg) and less hypocoagulation than used in previous studies (activated partial thromboplastine time ratio of 1.1–1.7 *vs.* 2.0–2.5).[5,6]

Seventy-two hours of use of this extracorporeal bypass was associated to a 33.6 ± 6.3% reduction of $Paco_2$ (from 73.6 ± 11.1 to 48.5 ± 6.3 mmHg, $P < 0.001$) sufficient to normalize arterial pH (from 7.20 ± 0.02 to 7.38 ± 0.04, $P < 0.001$) while ventilating patients with V_T ranging between 167 and 340 ml (3.7–4.6 ml/Kg PBW) and minute ventilation ranging between 8.1 and 11.9 l/min. No adverse events in terms of vein perforation, significant bleeding, hemodynamic instability, ischemic/gangrenous bowel, pneumothorax, and renal, infectious, metabolic, thromboembolic, and neurologic complications were observed during the 141 ± 69 h in which the device was in clinical use. However, the level of blood flow required to normalize arterial pH (up to 422 ml/h) was relatively high for a circuit like the one used in the current study[38]; therefore, the 14-French double-lumen catheter had to be replaced in three cases by two 8-French simple-lumen catheters (one for each femoral vein).

Reabsorption atelectasis may occur during mechanical ventilation with low V_T, depending on the Fio_2, the regional ventilation/perfusion ratios and the end-expiratory lung volume.[17] In a recent study, Dembinsky *et al.* randomized animals with ARDS to be ventilated for 24 h with a V_T of 3 ml/kg or with a V_T of 6 ml/kg; consequent respiratory acidosis was managed in the former group removing carbon dioxide *via* a pumpless system.[18] The study showed that, despite a significant reduction of P_{PLAT}, organ function and organ injury assessment did not reveal significant improvements when compared with conventional strategy. On the contrary, pulmonary gas exchange was impaired because of increased pulmonary ventilation/perfusion mismatch. In the current study, after 72 h of Lower *ARDSNet*/Carbon Dioxide Removal strategy, we observed (1) the reduction of lung weight and of the extent of the nonaerated and poorly aerated; (2) the increase of the extent of the normally aerated CT lung compartments lung (table 2); (3) a significant improvement of Pao_2/Fio_2 (from 136 ± 30 to 221 ± 56; $P < 0.001$) (fig. 5). These differences may be explained by the fact that, whereas PEEP was set to 5 cm H_2O in both groups in the Dembinsky *et al.* study, PEEP in our study was increased from 12.1 ± 2.5 cm H_2O to 15.2 ± 0.8 cm H_2O ($P < 0.001$).[12,39]

In conclusion, this study suggests that further reduction of V_T minimizes tidal hyperinflation and attenuates pulmonary inflammation in ARDS patients who have a P_{PLAT} ranging between 28 and 30 cm H_2O when ventilated with the *ARDSNet* ventilation. Extracorporeal carbon dioxide removal effectively and safely managed the respiratory acidosis consequent to V_T lower than 6 l/kg PBW and reestablished a normal arterial pH. This proof of concept study provides preliminary clinical evidence that extracorporeal lung support may integrate conventional care and allow the use of more protective ventilator settings. Additional clinical studies are required to further confirm these results.

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