Tidal Volume Lower than 6 ml/kg Enhances LungProtection Role of Extracorporeal Carbon Dioxide Removal

TIDAL VOLUME LOWER THAN SIX MILLILITER/KILOGRAM ENHANCES LUNG PROTECTION: ROLE OF EXTRACORPOREAL CARBON DIOXIDE REMOVAL

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Running head: Carbon dioxide removal and protective ventilation

Summary Statement: Tidal volume lower than 6 milliliter/kilogram minimizes *ventilator induced lung injury* when plateau pressure ranges between 28 and 30 cmH_2O; extracorporeal carbon dioxide removal may manage consequent respiratory acidosis

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Abstract

Background: Tidal hyperinflation may occur in patients with acute respiratory distress syndrome that ventilated with a tidal volume (V_T) of 6 ml/kg of predicted body weight develop a plateau pressure (P_{PLAT}) of $28 \leq P_{PLAT} \leq 30$ cmH_2O. We verified if $V_T < 6$ 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 (broncho-alveolar lavage) were assessed in 32 patients ventilated with a V_T of 6 ml/kg. Data are provided as mean ± standard deviation or median and interquartile (25 and 75 percentile) range. In patients with $28 \leq P_{PLAT} \leq 30$ cmH_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 cmH_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 hours.

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] hours. The improvement of morphological markers of lung protection and the reduction of pulmonary cytokines concentration ($P<0.01$) were observed after 72 hours 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.

Introduction

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 cmH_2O represents the gold standard for mechanical ventilation of patients with acute respiratory distress syndrome (ARDS)[1,2]. However, recent studies found that (a) tidal hyperinflation may occur in some patients despite limiting V_T to 6 mL/kg and P_{PLAT} to 30 cmH_2O[3]; (b) ARDS patients may benefit from V_T reduction even if they already have $P_{PLAT} < 30$ cmH_2O[4] .

Extracorporeal assist separating carbon dioxide removal from oxygen uptake has been proposed by Gattinoni and coworkers[5]. With this technique, carbon dioxide is removed by a pump driven veno-venous bypass while oxygenation is accomplished by high levels of positive end-expiratory pressure (PEEP) and three-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 and coworkers proposed the concept of removing "*only a portion of* carbon dioxide *production*" to allow less traumatic ventilator settings[10]. The present 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.

Material 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 ≥ 18 years; diagnosis of ARDS[11]. Exclusion criteria were: > 3 days since they met ARDS criteria; pulmonary artery occlusion pressure > 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 > 30; pregnancy; intracranial abnormality[12].

The institutional review board (Comitato Etico Interaziendale, Regione Piemonte, Turin), approved the study. As the patients at study entry were incompetent, consent was delayed. The family was informed of the study (although not required) and the study was performed. Written permission for using collected data was 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 that met inclusion and exclusion criteria were treated for 72 hours according to the "*ARDSNet*" strategy[2]. A detailed description of the protocol can be found in the *supplemental digital content*.

After 72 hours of ventilation according to the "*ARDSNet*" strategy[2], P_{PLAT} was recorded for a period of one hour with an half–second inspiratory pause keeping ventilator setting constant and abolishing spontaneous respiratory muscles activity by (***a***) reaching a Ramsay score of sedation 5 (midazolam up to 0.15 mg/kg/hour, morphine up to 0.03 mg/kg/hour, and

propofol up to 2 mg/kg/hr)[14]; (***b***) increasing, if required before measurements, doses of midazolam (up to 10 mg/h) and/or propofol (150mg/h increments every 10 min)[15,16].

In the patients that had $25<P_{PLAT}<28$ cmH_2O, the "*ARDSNet*" strategy[2] was maintained at least for the following 72 hours (**Figure 1**). In patients that had $28 \leq P_{PLAT} \leq 30$ cmH_2O the following strategy was implemented and maintained for at least the following 72 hours (**Figure 1**): (***a***) V_T was stepwise reduced (1 ml/kg of PBW every four hours) until P_{PLAT} $25<P_{PLAT}<28$ cmH_2O; (***b***) to manage the re-absorption 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]; (***c***) respiratory rate was increased up to 40 breaths/min and bicarbonate infused up to 20 mEq/hr; (***d***) if pH was $\leq$ 7.25, extracorporeal carbon dioxide removal was initiated 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)** (**Figure 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 non-occlusive 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 re-circulated through the membrane lung by a peristaltic pump (0-155 ml/min).

The membrane lung and the hemofilter were coupled in series in order to: (a) 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]; (b) minimize the need for heparin by diluting the blood entering the membrane lung by re-circulating the plasmatic water separated by the hemofilter[21]; (c) enhance the performance of the extracorporeal device extracting the carbon dioxide dissolved in the plasmatic water separated by the hemofilter and re-circulated through the membrane lung[22] (**Figure 2**).

Pressure developed by the roller pump (arterial pressure) was measured and limited to 120-150 mmHg. Re-infusion pressure (venous pressure), and the pressure gradient across the membrane lung and the hemofilter (drop pressure: pre-membrane 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/kg/h infusion) was delivered using a syringe 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 hours 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 with these ventilator settings P_{PLAT} remained for more that 3 hours < than 28 cmH_2O, extracorporeal carbon dioxide removal was interrupted and conventional "*ARDSNet*" ventilatory strategy re-established.

MEASUREMENTS

Underlying disease responsible for ARDS, clinical status and laboratory data on admission (the worst value within 24 hours 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 hours of ventilation according to the conventional "*ARDSNet*" strategy and, in those patients that had $28 \leq P_{PLAT} \leq 30$ cmH_2O, after lowering V_T and before initiating carbon dioxide removal (***baseline***), and after 60-90 minutes ($\boldsymbol{T_{1.5}}$), 24 ($\boldsymbol{T_{24}}$), 48 ($\boldsymbol{T_{48}}$) and 72 ($\boldsymbol{T_{72}}$) hours after initiation of carbon dioxide removal. Blood flow during carbon dioxide removal was recorded at $\boldsymbol{T_{1.5}}$, $\boldsymbol{T_{24}}$ $\boldsymbol{T_{48}}$ $\boldsymbol{T_{72}}$.

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 two hours 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 > 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 ≥ 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 recorded during the period the **LOWER "*ARDSNet*"/CARBON DIOXIDE REMOVAL** strategy was recorded.

Lung morphology

A pulmonary CT scan of the whole lung was performed in all patients after study enrollment. The CT scan was repeated after approx 72 hours of ventilation with the **LOWER "*ARDSNet*"/CARBON DIOXIDE REMOVAL** strategy in those patients that had $28 \leq P_{PLAT} \leq 30$ cmH_2O, and after approx 72 hours of ventilation with the conventional "*ARDSNet*" strategy in some of the patients that had $25 < P_{PLAT} < 28$ cmH_2O (**Figure 1**). A detailed description of the methods used can be found in the *supplemental digital content*[3].

Weight and volume of the entire lungs and of the *non-aerated*, *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 *non-aerated* compartment**" was defined as the volume of the *non-aerated* compartment at end-expiration minus the volume at end-inspiration. All were expressed as % of the total tidal inflation-related

change in CT lung volume[3,24].

Pulmonary inflammatory response

A broncho-alveolar lavage was performed in all patients after study enrollment[25]. The broncho-alveolar lavage was repeated after approx 72 hours of ventilation with the **LOWER "*ARDSNet*"/CARBON DIOXIDE REMOVAL** strategy in the patients that had $28 \leq P_{PLAT} \leq 30$ cm H_2O, and after approx further 72 hours of ventilation with the conventional "*ARDSNet*" strategy in some of the patients that had $25 < P_{PLAT} < 28$ cmH_2O (**Figure 1**). Interleukin 6 (IL-6), interleukin 8 (IL-8) and interleukin 1 (IL-1b) and IL-1 receptor antagonist (IL-1Ra) were measured. A detailed description of the methods used can be found in the *supplemental digital content*[25].

STATISTICAL ANALYSIS

Data are expressed as mean ± standard deviation of the mean or median and inter-quartile (25 and 75 percentile) range as appropriate. To evaluate differences between the two groups, the Fisher's exact test for categorical variables, and the t-test with unequal variance for continuous variables were used. Data at different time during carbon dioxide removal were compared by analysis of variance (ANOVA) for repeated measures 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 hours ventilation according to the "*ARDSNet*" strategy using a paired t-test as modified by Dunnett. All tests were two tailed. Analysis was carried out using the SPSS software package (SPSS Inc. Chicago, IL).

Results

Of the 32 patients that matched study criteria, 22 patients had $25<P_{PLAT}<28$ cmH_2O and 10 patients had a $28\leq P_{PLAT}\leq 30$ cmH_2O. Patients characteristics are shown in **Table 1**. Age, gender, Simplified Acute Physiology Score II and underlying diseases responsible for ARDS did not differ between the two groups; PaO_2/FiO_2 ratio was lower in patients with $28 \leq P_{PLAT}\leq 30$ cmH_2O than in patients with $25<P_{PLAT}<28$ cmH_2O ($P<0.01$).

Lungs were heavier and the extent of the *hyperinflated*, *non-aerated* and *poorly aerated* CT lung compartments were larger, and of the *normally aerate*d compartment smaller in patients with $28\leq P_{PLAT}\leq 30$ cmH_2O than in patient with $25<P_{PLAT}<28$ cmH_2O (all $P<0.001$) (**Table 2**). "***Protected tidal inflation***" was smaller and "***tidal hyperinflation***" was larger in patients that had $28\leq P_{PLAT}\leq 30$ cmH_2O than in the patients that had $25<P_{PLAT}<28$ cmH_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 that had $28\leq P_{PLAT}\leq 30$ cmH_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 cmH_2O (all $P<0.001$). Despite the increase in respiratory rate (from 31.2±2.3 to 37.0±1.9 b/min; $P<0.001$) and bicarbonate infusion (20.2±0.8 mEq/hr), the reduction in minute ventilation (from 12.03±2.77 to 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 cmH_2O to 15.2±0.8 cmH_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 (**Figure 3**). All patients met pH criteria for carbon dioxide removal and were therefore connected to the veno-venous bypass.

Sixty-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 hours of extracorporeal support, $PaCO_2$ and arterial pH were 47.2±8.6 mmHg and 7.38±0.04, respectively (P<0.001) (**Figure 4**). The extracorporeal veno-venous carbon dioxide removal device was used for 144 hours [84,168]. The pump-driven blood flow through the circuit ranged between 191-422 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 F double lumen catheter had to be replaced by two 8 F 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's 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 a.m.- 5 p.m.) during the treatment of the first five patients.

Average lung density histograms of tidal changes in CT lung compartments in patients that during the "*ARDSNet*" strategy had $28 \leq P_{PLAT} \leq 30$ cmH_2O are shown at study entry (**Figure 5A, *left***) and after 72 hours of **LOWER "*ARDSNet*"/CARBON DIOXIDE REMOVAL** strategy (**Figure 5A, *right***). Ventilation with the **LOWER "*ARDSNet*"/CARBON DIOXIDE REMOVAL** was associated to: (***a***) the reduction of lung weight and of the extent of the *hyperinflated*, *non-*

aerated and *poorly aerated* CT lung compartments and the increase of the extent of the *normally aerate*d lung compartments (P<0.001) (**Table 2**); (***b***) the 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); (***c***) 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); (***d***) a significant improvement of PaO_2/FiO_2 (from 136±30 to 221±56; P<0.001) (**Figure 3**). Same data for the patients that during the "*ARDSNet*" strategy had $25<P_{PLAT}<28$ cmH_2O are shown at study entry (**Figure 5B, *left***). In 12 of the 22 patients CT scan were obtained after further 72 hours of conventional "*ARDSNet*" strategy (**Figure 5B, *right***); these data were retrospectively obtained using CT scan performed for other studies or for clinical reasons. Relative to study entry, further 72 hours of conventional "*ARDSNet*" strategy were also associated to the reduction of lung weight and of the extent of the *hyperinflated*, *non-aerated* and *poorly aerated* CT lung compartments and the increase of the extent of the *normally aerate*d lung compartments (P<0.05) (**Table 2**) with no changes in amount of "***protected tidal inflation***" and "***tidal hyperinflation***" (**Figure 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 that during the "*ARDSNet*" strategy had $25<P_{PLAT}<28$ cmH_2O than in patients that had $28\leq P_{PLAT}\leq 30$ cmH_2O. In the former, further 72 hours of conventional "***ARDSNet***" strategy did not modify concentration of pulmonary inflammatory cytokines (data were retrospectively obtained in 15 of the 22 patients using broncho-alveolar lavage performed for other studies). In the latter, the use of the **LOWER "*ARDSNet*"/CARBON DIOXIDE**

REMOVAL strategy was associated to a significantly reduced concentration of pulmonary inflammatory cytokines (P = 0.001) (**Figure 6**). Broncho-alveolar 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 that during "*ARDSNet*" ventilation had $28 \leq P_{PLAT} \leq 30$ cmH_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 using a modified renal replacement device incorporating a membrane lung.

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 since: (***a***) the confounding effect of time on the observed improvement of physiological, radiographic and inflammatory parameters before and after 72 hours of **LOWER "*ARDSNet*"/CARBON DIOXIDE REMOVAL** strategy can't be ruled out since we don't have a control group of patients with $28 \leq P_{PLAT} \leq 30$ cmH_2O who received usual care without **LOWER "*ARDSNet*"/CARBON DIOXIDE REMOVAL**. Moreover, the study design prevents us for knowing what the respective effect of decreasing V_T, increasing PEEP and applying carbon dioxide removal. (***b***) 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 since measurements of extracorporeal carbon dioxide transfer and of total body carbon dioxide production were not performed. (***c***) Studies in experimental models suggest that un-buffered respiratory acidosis may reduce ventilator induced lung injury[26]. It is therefore possible that physiological, morphological and inflammatory variables would have improved as much or more if we reduced V_T and P_{PLAT} without carbon dioxide removal. (***d***) None of the patients that during "*ARDSNet*" ventilation had $28 \leq P_{PLAT} \leq 30$ cmH_2O was 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 in three patients V_T was reduced more than required since in these patients P_{PLAT} before initiating extracorporeal carbon dioxide removal was 24.2, 23.3 and 24.1 cmH_2O, values that are lower that the target P_{PLAT}. Moreover tris-hydroxymethyl aminomethane, a non- carbon dioxide generating buffers that was recently showed to efficiently manage respiratory acidosis[27,28] was not used in the present study.

Gattinoni and coworkers hypothesized that "to rest the lung", oxygenation *via* mechanical ventilation could be dissociated from decarboxylation *via* extracorporeal carbon dioxide removal[5]. In Gattinoni's study, mechanical ventilation was limited to apneic oxygenation and to 3-5 sighs every minute with peak inspiratory pressure not higher than 35-45 cmH_2O; PEEP ranged between 15 and 25 cmH_2O. carbon dioxide removal was performed 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 therefore raised regarding the standard use of extracorporeal support[6,29] because of the high incidence of serious complications such as hemorrhage, hemolysis, and neurological impairments[8]. Extracorporeal carbon dioxide removal has been therefore 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 that already had P_{PLAT} < 30 cm H_2O[4]. Moreover, physiological[32] and morphological[3] evidences of *tidal hyperinflation* have been described in patients in whom the "*ARDSNet*" strategy resulted in $28 \leq P_{PLAT} \leq 30$ cmH_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 and coworkers 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 and coworkers 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 present study, carbon dioxide removal was performed through a dedicated pump-driven extracorporeal venous-venous circuit with a neonatal membrane lung and a hemofilter coupled in series (**Figure 2**). The main elements that characterize and differentiate this system are: (*a*) a blood flow lower than the one used in standard carbon dioxide removal [191-422 ml/min (5-10 % of cardiac output) vs. 1.5-2.0 L/min (20-30 % of cardiac output][5,6,36]; (*b*) 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]; (*c*) the use of 14 F double lumen catheters instead of large 21-28 F double or single

lumen catheters[9]; (*d*) a priming volume smaller than currently used [(140-160 ml vs. 1500-1800 mL)[37]]; (*e*) a relatively small infusion rate of heparin (3-19 IU/Kg) and less hypo-coagulation 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 neurological complications were observed during the 141±69 hours in which the device was in clinical use. However, since the level of blood flow required to normalize arterial pH (up to 422 ml/hr) was relatively high for a circuit like the one used in the present study[38], the 14 F double lumen catheter had to be replaced in three cases by two 8 F simple-lumen catheters (one for each femoral vein).

Re-absorption 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 and coworkers randomized animals with ARDS to be ventilated for 24 hours 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 pump-less 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 present study, after 72 hours of **LOWER "*ARDSNet*"/CARBON DIOXIDE REMOVAL** strategy we observed (*a*) the reduction of lung weight and of the extent of the *non-aerated* and *poorly aerated*; (*b*) the increase of the extent of the *normally aerate*d CT lung compartments lung (**Table 2**), (*c*) a significant improvement of PaO_2/FiO_2 (from 136±30 to 221±56; P<0.001) (**Figure 5**). These differences may be explained by the fact that while in Dembinsky's study, PEEP was set to 5 cmH_2O in both group, in our study PEEP was increased from 12.1±2.5 cm H_2O to 15.2±0.8 c 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 that, ventilated with the "*ARDSNet*" ventilation have a P_{PLAT} ranging between 28 and 30 cmH_2O. 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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