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Lower tidal volume strategy (≈ 3 ml/kg) combined with extracorporeal CO₂ removal versus ‘conventional’ protective ventilation (6 ml/kg) in severe ARDS

The prospective randomized Xtravent-study

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Abstract *Background:* Acute respiratory distress syndrome is characterized by damage to the lung caused by various insults, including ventilation itself, and tidal hyperinflation can lead to ventilator induced lung injury (VILI). We investigated the effects of a low tidal volume (V_T) strategy ($V_T \approx 3$ ml/kg/predicted body weight [PBW]) using pumpless extracorporeal lung assist in established ARDS. *Methods:* Seventy-nine patients were enrolled after a ‘stabilization period’ (24 h with optimized therapy and high PEEP). They were randomly assigned to receive a low V_T ventilation (≈ 3 ml/kg) combined with extracorporeal CO₂ elimination, or to a ARDSNet strategy (≈ 6 ml/kg) without the extracorporeal device. The primary outcome was the 28-days and 60-days ventilator-free days (VFD).

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Secondary outcome parameters were respiratory mechanics, gas exchange, analgesic/sedation use, complications and hospital mortality.

Results: Ventilation with very low V_T 's was easy to implement with extracorporeal CO_2 -removal. VFD's within 60 days were not different between the study group (33.2 ± 20) and the control group (29.2 ± 21 , $p = 0.469$), but in more hypoxemic patients ($\text{PaO}_2/\text{FIO}_2 \leq 150$) a post hoc

analysis demonstrated significant improved VFD-60 in study patients (40.9 ± 12.8) compared to control (28.2 ± 16.4 , $p = 0.033$). The mortality rate was low (16.5 %) and did not differ between groups.

Conclusions: The use of very low V_T combined with extracorporeal CO_2 removal has the potential to further reduce VILI compared with a 'normal' lung protective management. Whether this strategy will

improve survival in ARDS patients remains to be determined (Clinical trials NCT 00538928).

Keywords

Lung protective ventilation · Pumpless extracorporeal lung support · Carbon dioxide removal · Acute respiratory distress syndrome · Ultrprotective ventilation

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by damage to the lung parenchyma, caused by either indirect or direct insults, including ventilation itself [1]. Tidal hyperinflation and cyclic alveolar recruitment/derecruitment during mechanical ventilation can lead to an entity called ventilator induced lung injury (VILI) [2, 3]. A multi-centered clinical trial demonstrated that a lung protective strategy with tidal volumes (V_T 's) of 6 ml/kg predicted body weight (PBW), and plateau pressures ≤ 30 cmH₂O decreased mortality by a relative 22 % compared to control [4]. A post hoc analysis of this study [5] found that the lower the plateau pressure (P_{plat}), the better the patient's chances of survival, even for P_{plat} substantially < 30 cmH₂O, and these data suggested that even lower tidal volumes might further improve survival. Grasso and colleagues [6] demonstrated that many ARDS patients ventilated using the ARDSNet strategy with table-based PEEP have a stress index indicating alveolar hyperinflation.

These data would suggest the use of even lower tidal volumes, but in severe ARDS the implementation of such a strategy may be limited by a therapeutic dilemma due to the increased likelihood of more severe hypercapnia and acidosis. The impact of hypercapnia on lung injury or on systemic effects including remote organ damage (myocardial insufficiency, renal failure, and hepatic/intestinal ischemia) is somewhat controversial [7, 8], delaying or preventing the implementation of adequate lung-protective strategies [9].

In the last few years, extracorporeal, pumpless arteriovenous approaches to CO_2 removal using an artificial membrane lung have been developed and tested for clinical use retrospectively in 90 patients [10] demonstrating marked carbon dioxide removal and moderate oxygenation improvement. Additionally, in a prospective cohort study Terragni and coworkers [11] used a CO_2 removal device to reduce tidal volume lower than 6 ml/kg and observed an improvement of morphological markers of lung protection. However, their study was not a

randomized clinical trial and there was no concurrent control group. We set out to investigate the effects of combining a very low V_T (3 ml/kg PBW) with arteriovenous extracorporeal CO_2 -elimination (avECCO₂-R) in patients suffering from established ARDS.

We hypothesized mechanical ventilation using lower tidal volumes (3 ml/kg) assisted by avECCO₂-R would enhance lung protection and hence increase 28-day and 60-day ventilator-free days, compared with mechanical ventilation using conventional tidal volumes (6 ml/kg).

Methods

Patients

The study was approved by the ethics committee of the Regensburg University Hospital (reference 07/012), and the ethics committees of all involved study centers. Before enrolment, written informed consent was obtained from the legal proxy of each patient. Patients were enrolled from September 2007 through December 2010 at eight intensive care units (ICU) in Germany and two ICU's in Austria.

Entry criteria were: (1) presence of ARDS according to the American-European Consensus Conference [12] defined by bilateral infiltrates on chest X-ray, and a $\text{PaO}_2/\text{FIO}_2 < 200$ present for at least 2 h. At the time of screening patients could not have any evidence of left ventricular failure; (2) age ≥ 18 years; (3) history of mechanical ventilation < 7 days; (4) plateau pressure > 25 cmH₂O at defined ventilator settings (PEEP/ FIO_2 -table + $V_T = 6$ ml/kg); (5) absence of severe hemodynamic instability with high demand for vasopressors (mean arterial pressure ≥ 70 mmHg with continuous norepinephrine infusion ≤ 0.4 $\mu\text{g}/\text{kg}/\text{min}$). Exclusion criteria were: decompensated heart insufficiency, acute coronary syndrome, severe chronic obstructive pulmonary disease, advanced malignancy with life expectancy < 6 months, chronic dialysis treatment, lung transplant

patients, proven heparin-induced thrombocytopenia (HIT), morbid obesity (body mass index $>40 \text{ kg/m}^2$), cirrhosis of the liver Child Class $\geq B$ (Child–Pugh scores ≥ 7), or acute fulminant hepatic failure, severe peripheral arterial occlusive disease, absence of limb doppler pulse, and acute brain injury (Glasgow Coma Scale ≤ 9).

To identify patients presenting with established ARDS and to help further rule out patients with acute cardiogenic pulmonary edema, the screening was followed by a stabilization period for 24 h, characterized by lung protective mechanical ventilation with high PEEP ($\geq 12 \text{ cmH}_2\text{O}$), the use of supportive measures, and hemodynamic evaluation (echocardiography). Patients who had ARDS criteria ($\text{PaO}_2/\text{FIO}_2 < 200$) after 24 h despite optimal supportive treatment were identified as those with established ARDS [13], and were randomized through phone hot line by a random number table generated by the involved statistician with respect to the stratum pulmonary/non-pulmonary ARDS (Fig. 1). The principal investigator (TB) performed visits aimed at information and supervision of the study protocol in the participating centers. An independent Data Safety Monitoring Board monitored the study.

Treatment of the study group

The intensive care management in both groups followed the ‘best clinical evidence’ recommended by the European Society of Intensive Care Medicine [14]. The daily monitoring included the assessment of awakesness/sedation (Richmond Agitation Sedation Scale [RASS])

and the daily evaluation of the Sequential Organ Failure Assessment (SOFA) and the Simplified Acute Physiology Score (SAPS-II).

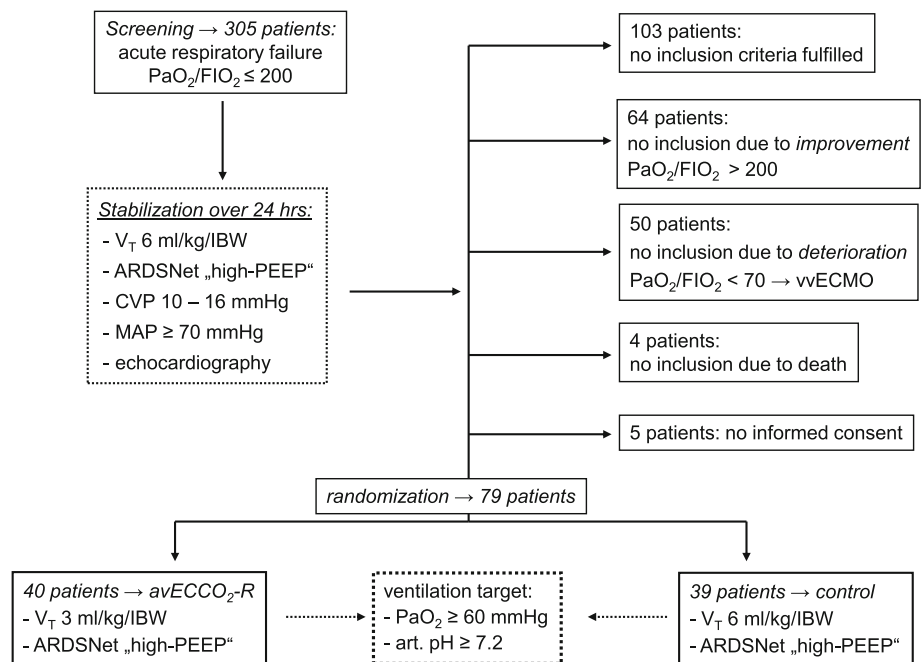
After randomization to the treatment group, percutaneous cannulation and initiation of pumpless extracorporeal lung assist (iLA AV, Novalung, Heilbronn, Germany) was performed. Unlike ‘classic’ pump-driven extracorporeal carbon dioxide removal, iLA does not require a blood pump, because the extremely low resistance of this circuit allows flows of about 1–2 l/min with normal arterial pressures (for more detailed description: [10, 15]). Evaluation, cannulation and clinical monitoring for avECCO₂-R can be found in electronic supplementary material (ESM).

After initiation of avECCO₂-R, adaptation of the ventilation strategy according to study protocol was performed as follows: a rapid titration down to V_T 3 ml/kg/PBW, PEEP following ARDSNet ‘high-PEEP/FIO₂’ table [16], respiratory rate 10–25/min with an inspiratory/expiratory ratio of 1:1. Termination of the avECCO₂-R therapy and decannulation was performed according to a defined algorithm (see ESM).

Treatment of the control group

The ventilatory management followed the algorithm of the study group except for the use of a $V_T = 6 \text{ ml/kg/PBW}$. The target blood gases for both groups were: $\text{PaO}_2 \geq 60 \text{ mmHg}$ and arterial pH ≥ 7.2 . The use of buffering (tris-(hydroxymethyl) aminomethane [TRIS]) was permitted if the patient had hypercapnia and respiratory acidosis (pH < 7.2).

Fig. 1 Screening, randomization and follow-up according to study protocol. V_T tidal volume, CVP central venous pressure, MAP mean arterial pressure, vvECMO veno-venous ECMO



Weaning and extubation procedures

In both groups daily screening was performed as a pre-condition for carrying out a spontaneous breathing trial (SBT): ability to breathe spontaneously ($\text{FIO}_2 \leq 0.4$, $\text{SaO}_2 \geq 90\%$, $\text{PEEP} \leq 8 \text{ cmH}_2\text{O}$, hemodynamic stability, RASS score ≥ -1 , body temperature $< 38.5^\circ$).

SBT was carried out over 1 h with augmented spontaneous breathing (ASB) $5 \text{ cmH}_2\text{O}$ with an active humidifier or, $10 \text{ cmH}_2\text{O}$ with HME filter ($\text{PEEP} \leq 8 \text{ cmH}_2\text{O}$, flow trigger $< 3 \text{ l/min}$). Patients were extubated when no deterioration was observed over a 1 h period.

Data collection

At the time of screening (24 h prior to randomization) physiologic data were recorded and relevant laboratory, radiographic and clinical findings were collected. Throughout the complete study period, data on ventilator settings, laboratory, physiologic, radiographic and interventional data were recorded. Relevant data of the ventilation management (V_T , PEEP , P_{plat} , minute ventilation, proportion of spontaneous ventilation on minute ventilation, arterial oxygen saturation) as well as results of the blood gas analyses (PaO_2 , PaCO_2 , pH) were recorded three times daily (8 a.m., 2 p.m., 10 p.m.) and the mean values of repeated measures were used for further analysis. SOFA score, SAPS-II and RASS scores were calculated daily (8 a.m.).

In addition, in a subgroup of study patients of the Regensburg University Hospital, depending on 'in-the-daytime'-availability of requested lab values, the levels of proinflammatory cytokines (tumour necrosis factor [TNF], interleukin 6 [IL-6] and interleukin 8 [IL-8]) were assessed from serum probes of avECCO₂-R-patients ($n = 20$) and control patients ($n = 15$) at various time points during the study, since the measurement of these parameters is part of the routine laboratory program in this hospital. Furthermore, in all participating centers the daily cumulative doses of vasopressors (norepinephrine, adrenaline, dobutamine), sedative and analgesic agents (sufentanil, propofol, midazolam) and net fluid balances were calculated in each patient and recorded.

Primary outcome

The primary outcome parameter was the proportion of days without assisted ventilation in a 28-day period ("ventilator-free" days within 28 days [28-VFD]) and in a 60 days period ("ventilator-free" days within 60 days [60-VFD]) [17].

Secondary outcomes

Secondary outcomes were: inspiratory plateau pressure levels (P_{plat}), the proportion of spontaneous breathing as a

percentage of the minute ventilation (automatically calculated by the ventilator's software), the RASS score, hemodynamic changes, the incidence of complications or adverse reactions, the frequency and duration of other adjunctive therapeutic measures, transfusion requirements [packed red blood cell transfusions (units), fresh frozen plasma units, platelet transfusion], the daily cumulative doses of analgesic and sedative agents, cumulative catecholamine requirements/24 h throughout the study period, frequency and duration of renal replacement therapy, the number of failing organs, the "organ-failure-free days" within 28 days after randomisation, and "in-hospital" mortality.

Statistical analysis

Assuming an increase in 28-VFD from 6.0 ± 10 (control group) to 11.0 ± 8 (study group [13]), we estimated that 53 patients would be needed per group for a power of 0.8 and an alpha of 0.05 (calculation by Charité Centrum für Therapieforschung, Berlin, Germany). We assumed a "drop-out-rate" of 10 % and we calculated that 120 patients would need to be enrolled. However, after an interim analysis with 56 patients by the Data Safety Monitoring Board, it was decided to limit the study period to 3 years, since a statistical significant difference was not expected in a longer study period.

We used a Student's *t*-test, the Wilcoxon test, the chi-square test or Fisher's exact test to assess differences between the groups, as appropriate. A Kaplan–Meier curve was calculated and plotted to assess the days until successful weaning from the ventilator. Furthermore, a nonparametric analysis of longitudinal data in factorial experiments was performed. Changes in interesting clinical outcomes with respect to time were analyzed using multivariate nonparametric analysis of longitudinal data in a two-factorial design (1st [independent] factor: groups, 2nd [dependent] factor: repetitions in time). Therefore, all the time points were simultaneously compared on the corresponding response curves (analysis according to Brunner [Brunner-analysis 18]). Additionally, a post hoc analysis was performed in patients with greater hypoxemia ($\text{PaO}_2/\text{FIO}_2 \leq 150$) regarding primary outcome parameters. The reported *P* values are two-sided and significance was set at $P < 0.05$.

Results

Between September 2007 and December 2010, 40 patients were randomized to avECCO₂-R and 39 patients to control. Baseline data are given in Table 1. Patients did not differ with respect to age and body mass index, but in the avECCO₂-R-group there were more patients with

Table 1 Baseline characteristics of the patients

	avECCO ₂ -R (n = 40)	Control (n = 39)
Age (years)	49.8 ± 12	48.7 ± 17
Gender (male/female)	38/2	30/9
Lung Injury Score (Murray)	2.8 ± 0.7	2.7 ± 0.8
Body mass index (kg/m ²)	28.6 ± 5	28.8 ± 5
Source of ARDS		
Pulmonary/non-pulmonary	31/9	37/2
ARDS		
<i>Non-pulmonary</i>		
SIRS/Sepsis	5	1
Massive transfusion	1	0
Trauma	3	1
<i>Pulmonary</i>		
Pneumonia	24 (58 % bacterial)	21 (62 % bacterial)
Aspiration	1	6
Lung contusion	6	9
Inhalation	1	0
Comorbidities		
Diabetes mellitus	2	3
COPD	5	3
Arterial hypertension	10	7
Coronary artery disease	1	1
Chronic renal impairment	2	0
Other	19	15
Atrial fibrillation	3	2
Alcohol use disorder	2	3
Obesity	2	3

The data are presented as mean ± standard deviation or absolute numbers

Table 2 Ventilation parameters and gas exchange after 24-h stabilization period at randomization

	avECCO ₂ -R (n = 40)	Control (n = 39)	<i>p</i>
PaO ₂ /FIO ₂	152 ± 37	168 ± 37	0.044
PaCO ₂ (mmHg)	57.3 ± 12	54.3 ± 9	0.352
Arterial pH	7.34 ± 0.07	7.36 ± 0.07	0.317
V _T (ml/kg, PBW)	5.9 ± 1.2	6.0 ± 0.6	0.495
Minute ventilation (l/min)	9.9 ± 1.6	9.8 ± 2.4	0.745
Frequency/min	22.4 ± 3	22.7 ± 3.5	0.854
PEEP (cmH ₂ O)	16.1 ± 3	16.0 ± 3	0.898
Plateau pressure (cmH ₂ O)	29.0 ± 5	28.0 ± 7	0.384
Delta (PEEP-Plateau) (cmH ₂ O)	12.9 ± 4	12.4 ± 4	0.475
FIO ₂	0.62 ± 0.2	0.53 ± 0.1	0.028

The data are presented as mean ± standard deviation

secondary ARDS. Ventilatory and gas exchange data are shown in Table 2.

Initially all patients were ventilated with high PEEP and low tidal volume according to the ARDSNet protocol, and had moderate hypercapnia. At randomization there were no significant differences regarding mean arterial

pressure, heart rate or demand vasopressor uses (data not shown). However, there was a significantly lower PaO₂/FIO₂-ratio in the intervention arm. The mean duration of iLA-treatment was 7.4 ± 4 days with a mean blood flow of 1.3 ± 0.2 l/min throughout the treatment period.

Primary outcome results

We found no statistical differences in VFD-28 or VFD-60 between groups, (Table 3), but a post hoc analysis demonstrated that surviving patients with greater hypoxemia (PaO₂/FIO₂ ≤ 150 at randomization) treated with avECCO₂-R had a significantly shorter period of ventilation (VFD-60 = 40.9 ± 12.8) compared to control (28.2 ± 16.4, *p* = 0.033) Fig. 2). Non-pulmonary organ failure free days within 60 days, intensive care and hospital days were not statistically different between groups.

Secondary outcome results

After insertion of pumpless extracorporeal lung assist, a V_T of 3 ml/kg PBW was achieved in most patients which increased moderately (as spontaneous breathing increased) to day 6 after randomization (Fig. 3), while in control patients V_T increased from 6 ml to 8 ml/kg/PBW (*p* < 0.001 between groups). Minute ventilation was significantly decreased, and the difference between plateau pressure and PEEP (*P*_{plat} – PEEP) was significantly reduced in study patients compared to control.

The fractional amount of augmented spontaneous breathing as a percent of total minute ventilation was significantly increased from day 3 in avECCO₂-R compared to control (Fig. 4).

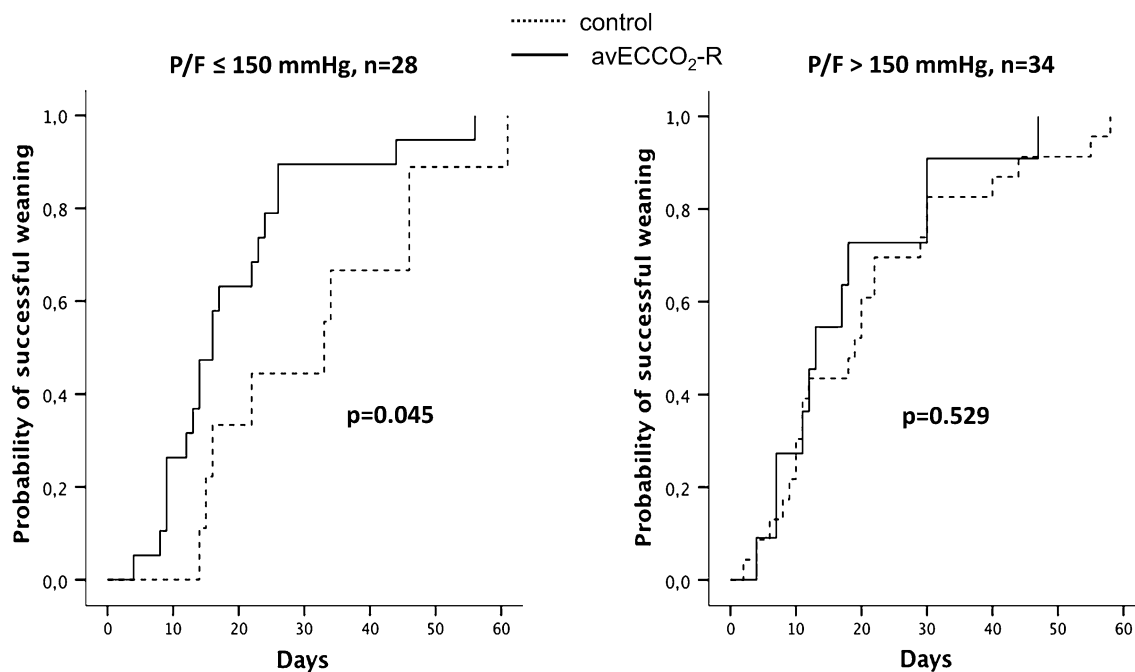
In line with previous data, extracorporeal CO₂ removal required higher FIO₂ which is thought to be due to the lower partial pressure of alveolar oxygen (PAO₂) secondary to a decreased lung respiratory quotient [19], and due to a reduction in functional residual capacity with a V_T of 3 ml/kg compared to 6 ml/kg [20]. PaCO₂-values, arterial pH, and mean respiratory rates/min were similar between groups, but mean PEEP levels tended to be elevated in the study group. During the study period, patients with avECCO₂-R had a modest reduction in MAP without increased demand for continuous norepinephrine infusion.

The cumulative amount of opioid (sufentanil) and benzodiazepine infusion (midazolam) was significantly lower in the study group, but mean RASS-scores were not different between groups during the study period (Fig. 5, ESM).

The number of units of red blood cells transfused was significantly higher in the avECCO₂-R -group in the period between randomization and day 10 (3.7 ± 2.4 units RBC) compared with control (1.5 ± 1.3, *p* < 0.05). The

Table 3 Outcome parameters of the study

	All patients			Subgroup: PaO ₂ /FIO ₂ <150		
	avECCO ₂ -R	Control	<i>p</i>	avECCO ₂ -R	Control	<i>p</i>
Ventilator-free-days-28	10.0 ± 8	9.3 ± 9	0.779	11.3 ± 7.5	5.0 ± 6.3	0.033
Ventilator-free-days-60	33.2 ± 20	29.2 ± 21	0.469	40.9 ± 12.8	28.2 ± 16.4	0.033
Non-pulmonary organ failure free days-60	21.0 ± 14	23.9 ± 15	0.447	24.1 ± 7.5	29.0 ± 17.7	0.428
Lung injury score on day 10	2.2 ± 0.6	2.1 ± 0.5	0.854	2.3 ± 0.8	2.2 ± 0.5	0.601
Length of stay in hospital (days)	46.7 ± 33	35.1 ± 17	0.113	42.0 ± 16.6	40.3 ± 15.7	0.815
Length of stay in ICU (days)	31.3 ± 23	22.9 ± 11	0.144	25.9 ± 13.1	31.0 ± 12.7	0.258
In-hospital mortality	7/40 (17.5 %)	6/39 (15.4 %)	1.000	1/21 (4.8 %)	1/10 (10 %)	0.563

**Fig. 2** Post-hoc analysis: probability of successful weaning in patients presenting with PaO₂/FIO₂ ≤150 versus >150 (only surviving patients)

incidence of avECCO₂-R-related adverse events was low (3 patients = 7.5 %): in one patient, transient ischemia of the lower limb was observed, while two patients developed a ‘false’ aneurysm as a result of arterial cannulation. The overall hospital mortality was low (16.5 %) and we found no significant difference between avECCO₂-R-group (17.5 %) and control (15.4 %).

Results of the cytokine assessments

TNF- α , IL-6, and IL-8 levels are presented in Table 4. Serum TNF- α levels remained unchanged during the early study period in both groups, while IL-6 levels decreased significantly in the avECCO₂-R-group, but not in the control group within 24 h after study initiation. IL-8

levels increased in the first few study days in the control group, but not in study patients.

Discussion

Lung protective ventilation using V_T's of 6 ml/kg/PBW and limiting P_{plat} to 30 cmH₂O improves outcomes in patients with acute lung injury [4]. However, the concept that this approach may not be sufficiently lung protective in all patients has been suggested by a post hoc analysis of the ARDSNet data [5], by animal investigations [21], human physiological studies [3], and by a clinical study [11]. We extended these findings in patients with severe established ARDS by performing a prospective

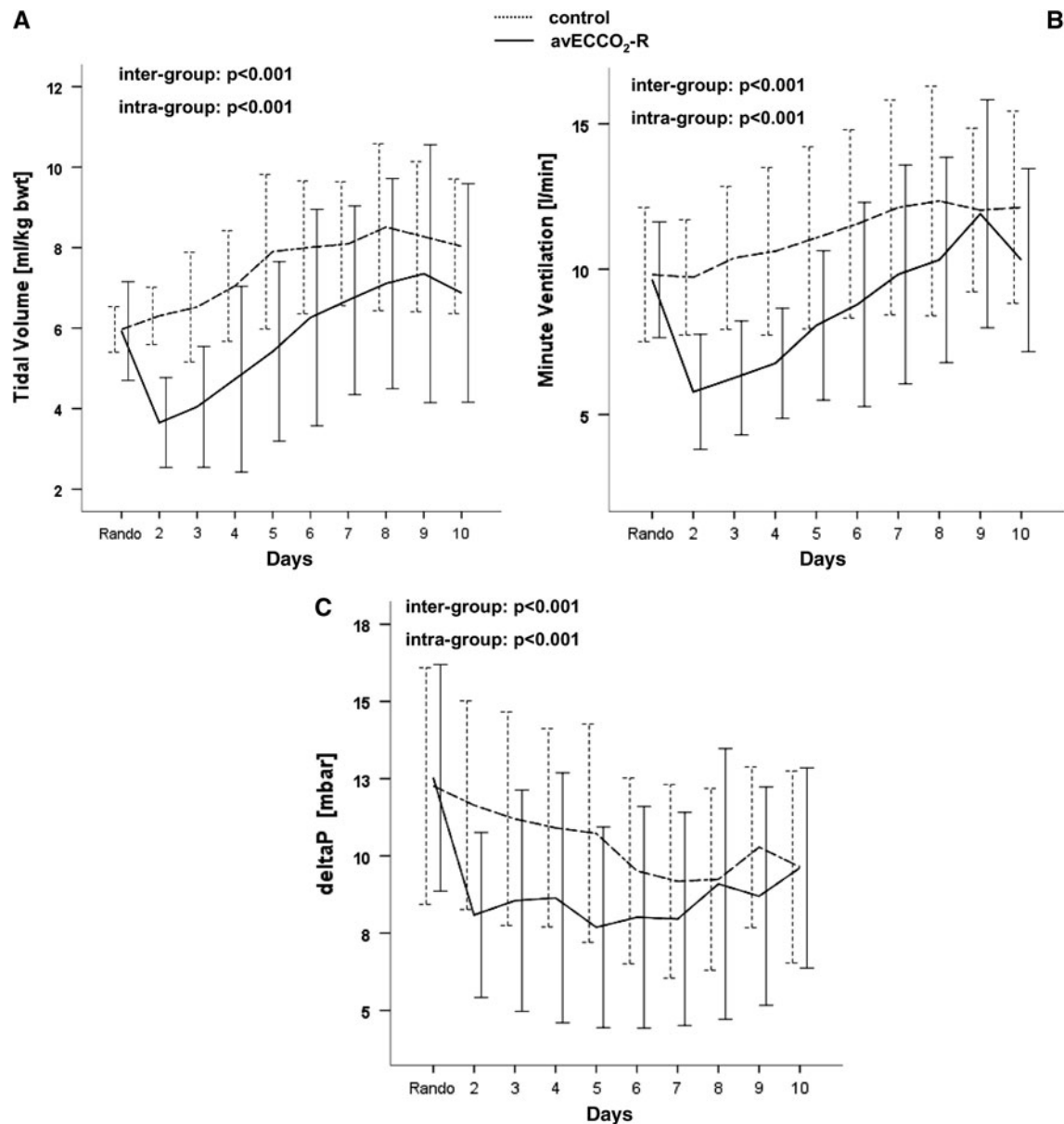


Fig. 3 Mean tidal volumes (ml per kg predicted body weight), minute ventilation and difference of plateau pressure and PEEP ($P_{\text{plat}} - \text{PEEP}$), in the treatment and control groups during the study period

randomized trial using a strategy of very low tidal volume ventilation (3 ml/kg) and an extracorporeal lung assist system providing CO₂-elimination.

The main findings of our study are: (1) Ventilation with ≈ 3 ml/kg PBW combined with avECCO₂-R was safe and feasible, and did not result in physiologically relevant hypercapnia/acidosis. (2) The use of extracorporeal CO₂-elimination was associated with a significant reduction in analgesic and sedative use, and resulted in an increased ratio of spontaneous breathing compared to control. (3) The serum levels of the pro-inflammatory cytokine IL-6 were significantly reduced in the early study period in

patients treated with very low V_T compared to control patients, and (4) Mechanical ventilation using lower tidal volumes (3 ml/kg) assisted by extracorporeal CO₂-removal was not associated with a significant reduction of the period of mechanical ventilation within 28 or 60 days or the intensive care and hospital stay, but a post hoc analysis demonstrated that ARDS patients who were more hypoxemic ($\text{PaO}_2/\text{FIO}_2 \leq 150$ at randomization) at baseline and who were treated with the low V_T strategy had a significantly shorter ventilation period.

The strength of this study is the evaluation of patients with 'established' ARDS: We only accepted patients for

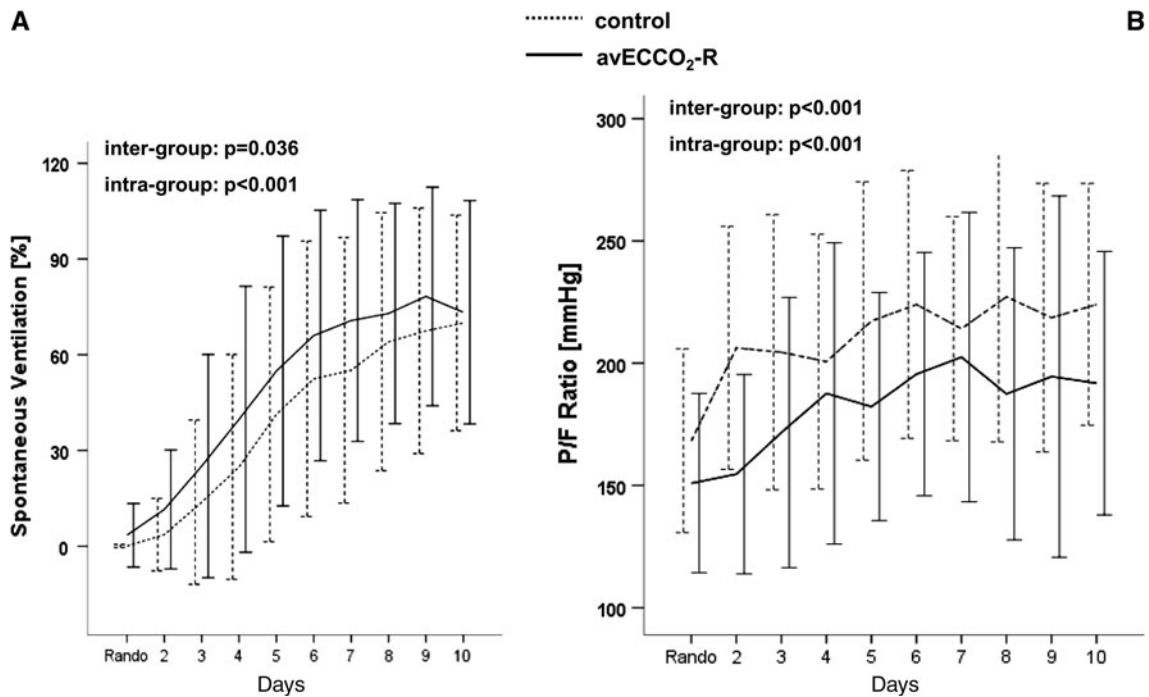


Fig. 4 Percent of spontaneous ventilation on minute ventilation and oxygenation ($\text{PaO}_2/\text{FIO}_2$) in the treatment and control groups during the study period

Table 4 The serum level of tumor necrosis factor (TNF), interleukin 6 (IL-6), and interleukin 8 (IL-8) in treatment and control patients (median values and 25/75 percentiles)

TNF (pg/ml)	Before begin of the study	24 h	48 h	72 h
avECCO ₂ -R ($n = 20$)	19.8 (13.8–23)	20 (13.2–23.6)	15.3 (13.7–21.4)	22.5 (12.8–33.2)
Control ($n = 15$)	20.5 (14.2–26.8)	21 (13.9–48.6)	15.9 (13.6–28)	15.2 (12.7–25)
IL-6 (pg/ml)				
avECCO ₂ -R ($n = 20$)	163 (86–419)	85 (50–193) ^{\$}	53 (20–109) ^{\$\$}	60 (35–155) ^{\$}
Control ($n = 15$)	97 (84–214)	111 (52–171)	102 (58–166)	64 (18–90)
IL-8 (ng/l)				
avECCO ₂ -R ($n = 20$)	72 (23–98)	65 (30–100)	71 (28–94)	81 (43–120)
Control ($n = 15$)	34 (23–49)	36 (24–126)	45 (29–529)	25 (17–191)

^{\$} $p < 0.05$ in comparison with before

^{\$\$} $p < 0.01$ in comparison with before

randomization who passed a ‘stabilization period’ (24-h ventilation period with high PEEP) and other measures of optimization and who continued to have persistent impairment of oxygenation ($\text{PaO}_2/\text{FIO}_2 \leq 200$). In a recent analysis [13] this patient group was identified as having a high mortality compared to patients with $\text{PaO}_2/\text{FIO}_2 > 200$. However, our study has limitations. Due to a restriction of the enrolment period to 3 years and a ‘strict’ recruitment protocol we did not reach the pre-specified sample size. Another limitation is the fact that we only enrolled patients with stable hemodynamics, since severe cardiovascular instability was an exclusion criterion for the pumpless circuit. This exclusion criterion might explain the very low mortality rate in the overall study population.

Tidal hyperinflation [3, 4, 22], and cyclic recruitment/derecruitment [23, 24] are important mechanisms leading to ventilator-induced lung injury in patients with ARDS, but sufficient clinical data are lacking indicating that a reduction of these phenomena is beneficial. The inhomogeneously injured lung leads to heterogeneous distribution of airway pressure and V_T , resulting in partial hyperinflation, cyclic opening and closing of moderate injured lung regions, and no ventilation in atelectatic regions, making it difficult to choose a single V_T that completely limits ‘global’ stress/strain injury [25]. Since it is not possible to adopt ventilation to the protective ‘demands’ of different lung regions, we hypothesized that even a small V_T of 6 ml/kg might aggravate VILI, and therefore we carried out the first reported randomized

controlled study using a very low tidal volume lung strategy.

Our data demonstrate the integration of augmented spontaneous breathing in the ventilation management of severe ARDS patients [26, 27] without a consequent increase in tidal volume or in the demand for sedative agents. We hypothesize that avECCO₂-R might allow an easy ‘switch’ from controlled low V_T -ventilation to augmented spontaneous breathing with minimal patient-ventilator asynchrony. Although we did not formally assess ineffective breathing or other signs of asynchrony, we demonstrated that the respiratory rate was not different between the groups, whereas the demand for sedation was significantly lower in the avECCO₂-R group. A reduction of the hypercapnia likely resulted in decreased respiratory drive as shown by Karagiannidis and coworkers [28] using neurally adjusted ventilatory assist (NAVA).

In the present study, avECCO₂-R required higher fractional inspiratory oxygen concentration to maintain adequate oxygenation, while both patient groups were treated with the same high PEEP management. There are two possible mechanisms to explain this finding. The first is a decrease in alveolar ventilation due to the removal of CO₂ by the extracorporeal circuit [19], and the second mechanism relates to potential de-recruitment of the lung as demonstrated by Dembinski et al. [29] in a lung lavage animal model (V_T 3 ml/kg and avECCO₂-R). However, in this study the authors used a relatively low PEEP level (5 cmH₂O), where we used a ‘high PEEP strategy’. Such a finding is of clinical relevance when considering extracorporeal CO₂-elimination as an adjunct measure for lung protective ventilation [30] with very low V_T [31]. A ‘safe border’ of V_T to derecruitment is not known.

On the other hand use of very small V_T 's might reduce VILI. Using an experimental model, Frank et al. [21] demonstrated that a reduction in V_T from 6 to 3 ml/kg led to a further reduction of epithelial and endothelial injury (extravascular lung water, alveolar epithelial type I cell antigen [RT 140]) in acid-injured rat lungs. In line with

these experimental findings we found that ventilation with very low V_T reduced serum levels of the proinflammatory cytokine IL-6 compared with ‘normal’ protective V_T .

In recent years, techniques of extracorporeal lung support have become easier to use, with smaller devices and greater efficacy. There is evidence that this has led to a reduction in the rate of severe complications [32]. In the present study only moderate complications attributable to avECCO₂-R occurred in three patients (7.5 %), and none led to permanent impairment. This complication rate is down from 24 and 12 % [10, 15], likely related to the use of a screening algorithm, careful evaluation, new material and a modified insertion technique [15].

In summary, we demonstrate that the use of very low tidal volume (\approx 3 ml/kg PBW) combined with extracorporeal elimination of carbon dioxide is feasible without major side effects and might be beneficial in the treatment of patients with severe ARDS. The integration of augmented spontaneous breathing might be easier and more comfortable with extracorporeal CO₂-removal, and a reduced demand for sedative and analgesic medication could be advantageous. Future studies are required to determine whether ‘ultraprotective’ ventilation will improve survival in patients suffering from severe ARDS.

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Conflicts of interest T. Bein and A. Slutsky are consultants for Novalung and received honoraria. A. Slutsky is also a consultant to Maquet Medical. The other authors declare no conflicts of interest.

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