Partial Extracorporeal Carbon Dioxide Removal Using a Standard Continuous Renal Replacement Therapy Device: A Preliminary Study

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To test the feasibility, safety, and efficacy of partial extracorporeal CO_2 removal ($PECCO_2R$) using a standard continuous renal replacement (CRRT) device with a pediatric oxygenation membrane introduced into the circuit in a serial manner. In this retrospective single-center study, we have studied mechanically ventilated patients with persistent significant respiratory acidosis and acute renal failure requiring ongoing CRRT. Sixteen patients were treated with our $PECCO_2R$ device. $PaCO_2$ and arterial pH were measured before as well as at 6 and 12 hours after $PECCO_2R$ implementation. Hemodynamic parameters were continuously monitored. Our $PECCO_2R$ system was efficient to significantly reduce $PaCO_2$ and increase arterial pH. The median $PaCO_2$ before treatment was 77 mm Hg (59–112) with a median reduction of 24 mm Hg after 6 hours and 30 mm Hg after 12 hours (31% and 39%, respectively). The median pH increase was 0.16 at 6 hours and 0.23 at 12 hours. Partial extracorporeal CO_2 removal treatment had no effect on oxygenation. No complication was observed. Our $PECCO_2R$ approach based on the simple introduction of a pediatric extracorporeal membrane oxygenation membrane into the circuit of a standard CRRT device is easy to implement, safe, and efficient to improve respiratory acidosis. *ASAIO Journal* 2014; 60:564–569.

Key Words: extracorporeal carbon dioxide removal, respiratory failure, hypercapnia, acute respiratory distress syndrome, lung protective ventilation

Since the publication of the ARDSnet-trial,[1] protective ventilation has become standard treatment for patients with adult respiratory distress syndrome (ARDS) and acute lung injury (ALI).[2] However, owing to the limitation of plateau pressures and thus tidal volumes, clinicians have been increasingly confronted with hypercapnia and respiratory acidosis. In fact, the protocol of the ARDSnet-trial allowed the perfusion of sodium bicarbonate for compensation of pH values lower than 7.15 but repeated infusion rapidly leads to fluid overload and retention of sodium. In numerous studies,[3–8] further lowering of plateau pressures under the critical threshold of 28 cmH_2O has been shown to be related with a decreasing mortality, a finding that led to the concept of ultraprotective ventilation with tidal volumes of 4 ml/kg of predicted body weight (PBW) and even less. This tendency towards still smaller tidal volumes of course highlights the problem of ensuing hypercapnia.

As a result, alternative ways to compensate respiratory acidosis in patients with ARDS and ALI have been explored. Extracorporeal membrane oxygenation (ECMO) is a technique that allows efficient oxygenation and high flow extracorporeal CO_2 removal. In a recent study, ECMO has been shown to substantially reduce morbidity and mortality in ARDS, but the results of this single-center study may only be valid for few expert centers (Controlled Trial of Conventional Ventilatory Support vs Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure [CESAR]).[9] Several studies addressed the possibility of exclusive low flow extracorporeal CO_2 removal,[10–12] a strategy much less invasive and thus potentially accessible to many more intensive care units (ICUs), including community-based hospitals.[11,13–16]

About 20% of ICU patients have been reported to be treated for ARDS associated with acute renal failure and acute kidney injury (AKI)[17–19] and mortality rising up to 70–80% for these patients.[20–23] In fact, besides the systemic inflammatory response syndrome, which may lead to multiorgan failure involving lung and kidneys, there is a specific interaction between these two organ systems.[22–25]

In AKI with oliguria, respiratory distress may be because of volume overload but especially the activation of inflammatory pathways with massive liberation of cytokines and chemokines has been shown to induce apoptosis of pulmonary endothelial cells,[26–28] a feature well known in ALI as defined by the 1994 American-European Consensus Conference (AECCC) definition.[2]

On the other hand, ALI with hypoxia, hypercapnia, respiratory acidosis, and need for mechanical ventilation with high inspiratory and expiratory pressures may induce AKI. It is thus not surprising that limitation of plateau pressures in the ARDSnet-trial not only resulted in a reduction of mortality but also in a clear reduction of AKI.[1]

The effects of mechanical ventilation and ALI on renal function may be because of three distinct factors.[20] First, increasing positive end-expiratory pressure (PEEP) levels and plateau pressures decrease renal blood flow by directly reducing cardiac output[29] and by activating sympathic as well as renin–angiotensin systems. Furthermore, suppression of atrial natriuretic peptide release leads to oliguria and volume overload.[24,30,31] Second, hypoxia as well as hypercapnia have been reported to reduce renal blood flow[32] and thus to induce apoptosis of renal tubular cells.[33] Third, pressure- and volume-related damage of lung tissue induces release of high levels of proinflammatory cytokines that have been shown to directly cause renal injury.[34]

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In our secondary care community-based hospital with a multidisciplinary ICU of 24 beds, ARDS patients are treated with protective ventilation (Vt = 4–6 ml/kg of PBW, plateau pressure < 28–30 cmH_2O, PEEP > 5 cmH_2O) according to international recommendations. Patients with acute renal failure and ARDS or ALI are treated with complementary continuous renal replacement therapy (CRRT). If suitable, in patients with hypoxia and particularly severe disease ECMO may be used. However, in patients with a poor prognosis because of multiple comorbidities, poor quality of life before admission, high age, and multiorgan failure, aggressive treatment with ECMO may be withheld.

We selected patients with ARDS or ALI. All of these patients had respiratory acidosis and were treated with CRRT for associated renal failure; they all were considered not eligible for ECMO because of poor prognosis. These patients were treated in a compassionate fashion with partial extracorporeal CO_2 removal ($PECCO_2R$). Because all of these patients had an indication for CRRT, we decided to use this existing circuit rather than performing a second cannulation for a specific $PECCO_2R$ device. We therefore modified the standard CRRT system (Multifiltrate, Fresenius) by simply introducing a pediatric oxygenation membrane into the circuit. Using the database of these patients, we tested the feasibility and efficacy of this approach.

Material and Methods

Patient Population and Characteristics

We analyzed a database of 16 patients who were hospitalized in our 24-bed polyvalent ICU between August 2010 and June 2011. All of these patients were mechanically ventilated for acute respiratory failure because of ALI or ARDS or because of refractory hypercapnia because of chronic obstructive pulmonary disease (COPD) exacerbation, pneumonia, or acute asthma. At the same time, all patients were treated with CRRT for oliguric acute kidney injury.

All patients were ventilated according to a lung protective strategy with a tidal volume of 6 ml/kg of PBW or less and a plateau pressure of 30 mm Hg or less. PEEP values were set as high as possible with a minimum of 8 and a maximum of 16 cmH_2O, respecting the upper limit of 30 cmH_2O plateau pressure. Mean respiratory rate was 25.6 per minute,[23–28] except one patient treated for severe acute asthma (15 per minute). All patients had respiratory acidosis with pH < 7.33 and pCO_2 of 59 mm Hg or higher. Patient's age and characteristics are listed in **Tables 1** and **2**. Patients were not eligible for ECMO because of advanced lung fibrosis (one patients), congenital encephalopathy (one patient), advanced COPD with dyspnea stage 3 or 4 NYHA before ICU (eight patients), cirrhosis with hepatorenal syndrome (one patients), associated metastatic cancer (two patients), or advanced age (more than 70 years old) (three patients).

Treatment

Patients were treated with CRRT (continuous venovenous hemodialysis or continuous venovenous hemofiltration) using a standard device (Multifiltrate, Fresenius). An oxygenation membrane, originally designed for pediatric ECMO (HILITE 2400 LT, Medos), was introduced into the existing circuit in a serial manner, upstream from the hemofilter using special luer-lock connectors.

Membrane characteristics were as follows: surface 0.65 m^2, rheoparine-coated polypropylene, maximal blood flow 2400 ml/min, priming volume 95 ml, CO_2 transport capacity 30 ml/min for 500 ml/min of blood flow, and O_2 transport capacity 35 ml/min for 500 ml/min of blood flow. Anticoagulation was maintained as initiated for CRRT with nonfractionated heparin. All CRRT settings were left unchanged except blood flow, which was increased to a target of 500 ml/min. Blood flow of 400 ml/min was gradually achieved starting with 200 ml/min and then increased by steps of 100 ml/min. If CRRT pressures were within limits, blood flow was then increased to 450 and 500 ml/min. Oxygen flow for CO_2 washout was set at 10 l/min.

In current practice, we use a 13.5 F / 15 cm (jugular puncture) or a 13.5 F / 24 cm (femoral puncture) dual-lumen catheter (Niagara Slimcath, Bard) for standard CRRT. Because it turned out difficult to achieve target blood flow of 400–500 ml/min with these catheters, we adopted one of the following strategies:

When a femoral catheter was in use, it was switched for a 16 F / 27 cm catheter on the same site (HemoSplit XK, Bard) using a guide-wire, or the original catheter was left in place and a second dual-lumen catheter (13.5 F / 15 cm) was inserted in jugular position. When a jugular catheter was in use, a second dual-lumen catheter (13.5 F / 24 cm) was inserted in femoral position.

Thus, adequate blood flow was achieved either with one femoral 16 F / 27 cm dual-lumen catheter or with two 13.5 F double lumen catheters, one being in jugular position and femoral the other one. When two catheters were used, the aspiration line was connected to both femoral lumina using a Y-shaped luer-lock connector, reinjection in the same manner into the jugular catheter.

Anticoagulation was obtained as for standard CRRT by continuous infusion of heparin with a target PTT of 45–50 sec. Criteria for discontinuing $PECCO_2R$ was improvement of lung compliance, allowing a return to conventional ventilator settings.

Measurements

Blood gas analysis was performed before $PECCO_2R$, at 6 hours and at 12 hours. Systolic, diastolic, and mean arterial pressure as well as SaO_2 were continuously monitored. pCO_2, pH, pO_2/FiO_2, and mean arterial pressure were analyzed during treatment.

Ethical Considerations

Several of our patients presented severe hypoxia and therefore might have met criteria for ECMO. However, in a systematic discussion involving the staff of our unit and a member of the committee of ethics, these patients were considered not eligible for ECMO because of severe comorbidities with low quality of life before admission, high age, or poor prognosis because of multiorgan failure. Extracorporeal CO_2 removal was introduced in a compassionate fashion in these patients who presented with high plateau pressures and respiratory acidosis.

Table 1. Characteristics of Study Patients

Patients	Age	Gender	ICU Stay Before PECCO$_2$R	Ventilation Days Before PECCO$_2$R	Duration PECCO$_2$R	Ventilation Day After PECCO$_2$R	Total ICU Stay	Death
Patient 1	64	F	2	2	7	21	33	N
Patient 2	55	F	7	3	7	29	36	N
Patient 3	66	M	1	1	5	14	15	Y
Patient 4	49	M	6	4	2	14	20	N
Patient 5	70	F	3	3	3	3	6	Y
Patient 6	78	F	6	6	3	3	7	Y
Patient 7	68	F	1	1	5	12	15	N
Patient 8	24	F	0	0	7	21	21	Y
Patient 9	48	F	16	16	5	30	30	N
Patient 10	68	M	16	12	3	3	19	Y
Patient 11	62	M	2	2	12	14	16	Y
Patient 12	78	F	0	0	2.5	4	9	N
Patient 13	74	M	0	0	3	6	19	N
Patient 14	21	F	0	0	3	6	7	N
Patient 15	65	M	40	1	12	15	35	N
Patient 16	59	M	23	20	15	0	36	Y
Average	59.3		7.7	4.44	5.91	12.19	20.25	

ICU, intensive care unit; PECCO$_2$R, partial extracorporeal CO_2 removal.

At the time extracorporeal CO_2 removal was started, all patients were already under treatment with CRRT, and PECCO$_2$R was thus not an indication for an extracorporeal circulation by itself. Compassionate treatment with PECCO$_2$R was approved by the local committee of ethics. The patients being sedated, consent was obtained from patient's families after adequate information.

Results

From August 2010 to June 2011, 16 patients (seven males and nine females) were treated with our PECCO$_2$R technique. The median age was 64.5 (range 24–78 years). Nine patients were admitted for pneumonia (six community acquired and three hospital acquired), three patients had ARDS associated with septic shock, and one ARDS associated with acute pancreatitis. One was admitted for acute exacerbation of pulmonary fibrosis, one for severe acute asthma, and one for decompensation of alcoholic liver cirrhosis. Seven of these patients died; the other nine were discharged from the ICU (**Tables 1** and **2**).

Mean length of ICU stay was 20.25 days (range 6–36), mean of ICU days before PECCO$_2$R was 7.7 days (0–40), and the mean duration of mechanical ventilation before PECCO$_2$R was 4.4 days (0–20). The mean duration of PECCO$_2$R treatment was 5.9 days (2–15). Target blood flow of 400–500 ml/min was achieved in all our patients. In four patients, a 16Fr catheter was inserted at concomitant start of CRRT and PECCO$_2$R, in three of the remaining 12 patients a second 13.5Fr catheter was needed to obtain target blood flow.

Table 2. Effect of Partial Extracorporeal CO_2 Removal on Gas Exchange

	MAP (mm Hg)			PaO_2/FiO_2			pCO_2 (mm Hg)			pH		
Patients	Before Device	At 6 hours	At 12 hours	Before Device	At 6 hours	At 12 hours	Before Device	At 6 hours	At 12 hours	Before Device	At 6 hours	At 12 hours
Patient 1	70	100	85	69	100	155	59	55	45	7.28	7.30	7.42
Patient 2	85	85	74	136	133	101	67	62	54	7.33	7.37	7.41
Patient 3	61	68	74	70	58	100	112	73	62	7.10	7.19	7.33
Patient 4	80	78	82	85	100	80	75	47	32	7.15	7.35	7.41
Patient 5	83	104	109	110	62	70	73	54	44	7.06	7.29	7.43
Patient 6	86	70	80	137	98	98	69	52	45	7.04	7.28	7.37
Patient 7	73	91	90	137		168	60	40	31	7.16	7.35	7.53
Patient 8	70	68	70	320	312	160	73	57	60	7.28	7.28	7.32
Patient 9	67	75	70	200	213	197	65	49	44	7.19	7.28	7.39
Patient 10	68	84	73	80	63	84	83	63	58	7.13	7.29	7.34
Patient 11	73	76	80	152	128	140	78	48	47	7.15	7.33	7.35
Patient 12	99	71	62	140	177	185	82	28	30	7.12	7.47	7.53
Patient 13	60	68	65									
Patient 14	75	65	83	70	92	194	88	51	52	7.16	7.38	7.30
Patient 15	80	107	75	226	173	131	99	63	50	7.16	7.37	7.46
Patient 16	80	86	72	68	97	146	80	52	58	7.30	7.48	7.48
Median	74	77	74.5	136	100	140	75	52	47	7.16	7.33	7.41
Average	75.63	81.00	77.75	133.75	132.40	138.06	77.31	52.94	47.31	7.17	7.33	7.40

MAP, mean arterial pressure; PaO2, partial pressure of O2 in arterial blood; FiO2, fraction of inspired oxygen; pCO2, partial pressure of carbon dioxide.

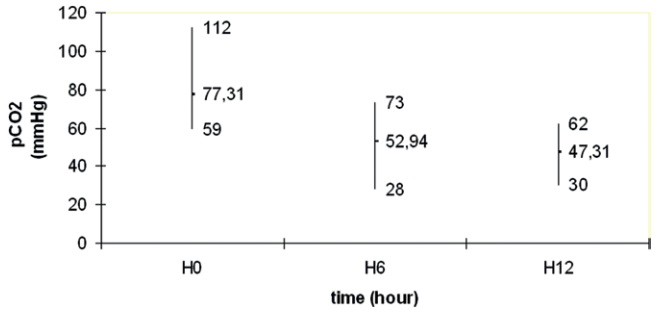

Figure 1. pCO_2 (partial pressure of CO_2) reduction under partial extracorporeal CO_2 removal.

The mean pCO_2 value before treatment was 77.3 mm Hg (59–112). Mean pCO_2 reduction was 24.4 mm Hg after 6 hours and 30 mm Hg after 12 hours (31% and 39%, respectively) (**Figure 1**). Mean pH increase was 0.16 at 6 hours and 0.23 at 12 hours (**Figure 2**). Partial extracorporeal CO_2 removal treatment had no effect on oxygenation, the mean pO_2/FiO_2 ratio being 133 (68–320) before treatment and 138 (70–197) at 12 hours.

Ventilator settings were volume control; mean tidal volume was 5.9 ml/kg of PBW before treatment, 5.9 ml/kg at 6 hours, and 5.56 ml/kg at 12 hours. Mean plateau pressures before treatment were 27.7 cmH_2O before treatment (21–32), 27.13 cmH_2O at 6 hours, and 25.6 cmH_2O at 12 hours.

Hemodynamic tolerance of $PECCO_2R$ was comparable to standard CRRT. Mean arterial pressure before treatment was 75.6 mm Hg, 81 mm Hg at 6 hours, and 78 mm Hg at 12 hours without any significant changes in the needs of vasopressor support. No complication linked to $PECCO_2R$ treatment was noted. Results are shown in **Table 2** and **Figures 1** and **2**.

Discussion

The aim of our study was to analyze whether our very simple approach of partial extracorporeal CO_2 removal was easy to use, economic, effective, and safe. In fact, we found that our staff, used to installation, handling, and supervision of CRRT, had virtually no problem with supplementary $PECCO_2R$ introduced into the same circuit. Installation of the oxygenation membrane using the dedicated luer-connectors is easy, and priming of the circuit is identical to usual CRRT. All staff used to the installation of CRRT was able to connect the $PECCO_2R$ membrane after a single verbal instruction. Time needed for new nurses to install CRRT with a $PECCO_2R$ membrane was the same as for a standard CRRT circuit without $PECCO_2R$. Supervision of CRRT with $PECCO_2R$ was identical to standard CRRT supervision because the renal replacement therapy device (Multifiltrate, Fresenius) and the pressure alarms were used without any modification.

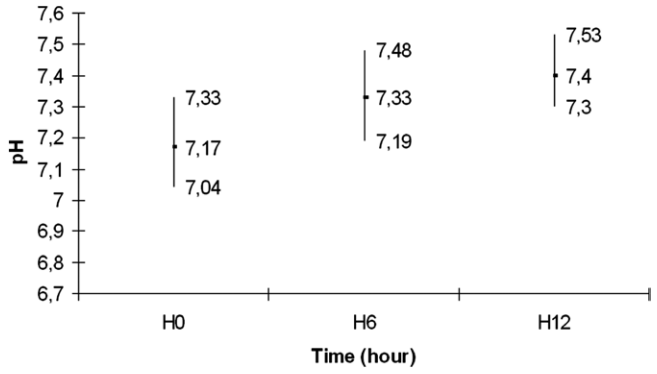

Figure 2. pH increase under partial extracorporeal CO_2 removal.

Patients with acute respiratory failure and acute kidney injury frequently have concomitant[35] failure of other organ systems and therefore prolonged ICU stays. In this population, the need of several central venous catheters may rapidly become critical and the possibility to perform CRRT and $PECCO_2R$ using a single femoral dual-lumen catheter may therefore be a supplementary advantage of our approach. Using our system, partial CO_2 removal could be performed at a comparatively low cost.

In pediatric clinical practice, the HILITE 2400 LT membrane is commonly used for up to 21 days. Mean treatment in our observational study was 6 days, and a single membrane per patient was thus sufficient. Because the CRRT circuit is limited to a 72 hour use, the $PECCO_2R$ membrane was disconnected, rinsed with saline in a sterile manner, and reconnected to the new circuit every 72 hours. The HILITE 2400 LT membrane with the dedicated luer-locks was purchased at 480 euros per unit. Because all other devices and consumables were exclusively those of the CRRT already under way, no further costs applied.

In comparison, all other available techniques use dedicated in general expensive devices and consumables, which in certain cases have to be changed frequently during therapy. Thus, compared with all other commercialized $PECCO_2R$ systems, our approach was very cost-effective.

We performed $PECCO_2R$ on Fresenius Multifiltrate. These machines are currently used in our ICU for CRRT. To introduce the oxygenation membrane into the circuit, we used specially designed luer-lock connectors adapting the original 3/8 inflow of the HILITE to the 3/4 caliber of the CRRT circuit. Theoretically, this type of oxygenation membrane may be introduced into the circuit of any other commercially available CRRT system, using adequate connectors and respecting an installation upstream from the hemofilter in order not to interfere with the security systems of the machine. However, in practice, $PECCO_2R$ should not be performed on standard CRRT machines without consulting the manufacturer.

Partial extracorporeal CO_2 removal using a pediatric ECMO membrane introduced into a standard CRRT circuit was efficient in terms of reducing pCO_2 levels and increasing pH. Mean pCO_2 reduction was 30.07 mm Hg at H12 (38%) and mean pH increase was 0.22 at H12 with a rising relative efficiency for higher pCO_2 level / lower pH values. Because we achieved for all our patients a blood flow between 400 and 500 ml/min and thus a quite comparable blood flow, we were not able to study the relationship between the efficiency of CO_2 removal and blood flow. However, manufacturer's indications about the carbon dioxide transfer capacity of the HILITE membrane show a linear relation between blood flow and CO_2 extraction. Still higher CO_2 extraction might thus be achieved with a further increase of blood flow.

The potential of our approach in reducing tidal volumes and plateau pressures according to the strategy of ultraprotective ventilation was not addressed in our study. Terragni *et al*.[3,11,13] showed that a reduction of tidal volumes from 6 to 4 ml/kg of PBW with stable pH and pCO_2 levels was possible

using the Decapsmart device.[16] Because pCO_2 reduction and pH improvement with our approach were comparable to those reported for treatment with Decapsmart, a similar potential of reducing tidal volumes seems reasonable. However, only a prospective study will be able to test this hypothesis.

Partial extracorporeal CO_2 removal using a pediatric ECMO membrane introduced into a standard CRRT circuit was safe. The priming volume of the HILITE 2400 LT membrane being very small (95 ml), we did not observe any impact on patient's hemodynamics. As in standard CRRT, we observed some cases of transient hypotension starting treatment with CRRT associated to PECCO$_2$R, which easily could be corrected by infusion of 250 cc of saline. The progressive increase of blood flow to a minimum of 400 and a maximum of 500 ml/min did not cause any complementary hypotension. In the population studied, we did not observe any case of hemorrhage, gas embolism, or thrombosis. In fact, by introducing the oxygenation membrane upstream from the hemofilter, all security systems of the Multifiltrate CRRT system (bubble catcher and pressure sensors) were left intact without any modification.

Veno-venous ECMO is an efficient treatment for hypoxic and hypercapnic acute respiratory failure. A recent single-center study by CESAR[9] showed an improvement of survival in ARDS patients treated with ECMO. Another international prospective multicenter study is under way (Combes: NCT 01470703). Because of restricted blood flow, PECCO$_2$R has but very little effects on blood oxygenation and indications for ECMO and PECCO$_2$R are thus very distinct. Different systems for partial extracorporeal CO_2 removal are actually available.

A pumpless, arterio-venous device (Novalung, Novalung GmbH, Hechingen, Germany) has been shown to be effective in lowering pCO_2 and improving pH levels,[36–39] but the need for arterial catheterization makes its use difficult in arteritic and obese patients. Complications with ischemia have been reported in up to 25% after cannulation of the femoral artery. Furthermore, bloodflow is driven by the arterio-venous gradient, and its use is thus restricted in patients with shock, hypotension, and unstable hemodynamics. High cost of the device further restricts its use mainly to expert centers.

Decapsmart (Hemodec Hemodec S.r.l. - Via T. Caruto, 9-84131 Salerno, Italy)[16,40] and Hemolung (Alung Technologies Pittsburgh, PA)[15] are pump-driven veno-venous systems for PECCO$_2$R. Numerous studies showed their effectiveness in reducing CO_2 levels and correcting respiratory acidosis. However, both systems require dedicated material, which for the moment remains expensive limiting its widespread use. Furthermore, the need of a dedicated central venous access may be critical in these complex patients with frequent multiorgan failure.

Conclusion

In conclusion, our approach with PECCO$_2$R by simple introduction of a pediatric ECMO membrane into the circuit of a standard CRRT device was easy to implement and to use, safe and inexpensive in particular when compared with other systems. It allowed concomitant PECCO$_2$R and CRRT using a single circuit for extracorporeal circulation. Even with a relatively low blood flow of 400–500 ml/min, significant reduction of pCO_2 and improvement of pH levels could be achieved. Effectiveness in CO_2 reduction was comparable to the one observed using established systems for PECCO$_2$R. This system is potentially suitable for all ICUs using CRRT, with no need for supplementary specific devices or training. However, effectiveness, impact on ultraprotective ventilation, safety, and cost-effectiveness should be assessed in a large, prospective trial.

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