



# Minimal-flow ECCO<sub>2</sub>R in patients needing CRRT does not facilitate lung-protective ventilation

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## Abstract

Extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R) is intended to facilitate lung protective ventilation in patients with hypercarbia. The combination of continuous renal replacement therapy (CRRT) and minimal-flow ECCO<sub>2</sub>R offers a promising concept for patients in need of both. We hypothesized that this system is able to remove enough CO<sub>2</sub> to facilitate lung protective ventilation in mechanically ventilated patients. In 11 ventilated patients with acute renal failure who received either pre- or postdilution CRRT, minimal-flow ECCO<sub>2</sub>R was added to the circuit. During 6 h of combined therapy, CO<sub>2</sub> removal and its effect on facilitation of lung-protective mechanical ventilation were assessed. Ventilatory settings were kept in assisted or pressure-controlled mode allowing spontaneous breathing. With minimal-flow ECCO<sub>2</sub>R significant decreases in minute ventilation, tidal volume and paCO<sub>2</sub> were found after one and three but not after 6 h of therapy. Nevertheless, no significant reduction in applied force was found at any time during combined therapy. CO<sub>2</sub> removal was 20.73 ml CO<sub>2</sub>/min and comparable between pre- and postdilution CRRT. Minimal-flow ECCO<sub>2</sub>R in combination with CRRT is sufficient to reduce surrogates for lung-protective mechanical ventilation but was not sufficient to significantly reduce force applied to the lung. Causative might be the absolute amount of CO<sub>2</sub> removal of only about 10% of resting CO<sub>2</sub> production in an adult as we found. The benefit of applying minimal flow ECCO<sub>2</sub>R in an uncontrolled setting of mechanical ventilation might be limited.

**Keywords** ECCO<sub>2</sub>R · Interventional lung assist · ILA · ECLA · Protective ventilation

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## Introduction

Ventilation with low tidal volumes of 6–8 ml/kg ideal body weight (IBW) has become standard of care in ARDS patients [1]. This concept seemingly helps to decrease the risk of baro- and volutrauma on the affected lung and apparently even affects outcome favorably [2]. But today these

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principles are challenged: an IBW-based low  $V_T$ -strategy might not solely be sufficient to avoid tidal hyperinflation [3, 4]. Derived from these principles the concept of ultrapro-protective ventilation has been developed [5, 6]. However, a recently introduced concept stresses that no single variable (e.g. tidal volume or applied plateau- or delta pressure), but the mechanical energy inflicted on the lung corresponds to VILI (ventilator induced lung injury) [7]. The inevitable risk of consecutive hypercarbia might be accepted to a certain amount, but the effects of hypercarbia on whole-body physiology including the lung itself should not be neglected. Nevertheless, it has been shown that  $\text{CO}_2$  may also have a beneficial effect [8]. Side effects of hypercarbia include academia, increased shunt, shifted oxyhemoglobin dissociation curve [9], but also cardiac depression and impaired coronary artery perfusion [10]. As a consequence, further  $V_T$ -reduction might require additional extracorporeal support or dead space reductions to cope with these effects [4, 11–13].

The concept of extracorporeal  $\text{CO}_2$  removal was developed decades ago in the 1970s [14], but it required the growing knowledge on mechanisms of ventilator induced lung injury, recent technical developments and advanced options of dealing with complications [15, 16] to finally become clinically useful. Nowadays, different ECLA-devices (extracorporeal lung assist) are in clinical use. Other than active high-flow devices (extracorporeal membrane oxygenation, ECMO), mid-flow (about 1 l/min) and low-flow (about 500 ml/min) devices are readily used. Additionally, passive devices utilizing arteriovenous pressure difference are used.

In critically ill patients ARDS and renal failure (ARF) are commonly present simultaneously [17] and mortality remains unacceptably high [18]. Thus, both continuous renal replacement therapy (CRRT) and extracorporeal  $\text{CO}_2$ -elimination can be necessary. With a large bore catheter for CRRT in place, allowing for higher flow rates than regular multi-lumen catheters the mental leap to add  $\text{CO}_2$ -removal is obvious. Difficulties arise, because  $\text{CO}_2$ -removal is flow dependent. Different concepts have been strived to facilitate  $\text{CO}_2$  removal in low flow rates, some of them based on the Henderson–Hasselbalch-equation to convert  $\text{CO}_2/\text{H}^+$  to bicarbonate, which is then dialyzed [19–31], others on electrical dialysis [32]. But none of these concepts has made the transition to clinical usefulness.

In this light, a device integrating both processes into one single extracorporeal circuit (CRRT-ECCO<sub>2</sub>R) offers potential advantages. Although the low blood flow that is applied during CRRT cannot provide sufficient oxygenation and only limited  $\text{CO}_2$  elimination, it might be enough to facilitate lung protective mechanical ventilation [13]. Based on this rationale we aimed to test, whether minimal-flow CRRT-ECCO<sub>2</sub>R allows for a viable increase in lung protective ventilation without the undesirable side effects of hypercarbia or respiratory acidosis.

During standardized conditions and application of volume-controlled mechanical ventilation the potential to reduce  $V_T$  by addition of ECCO<sub>2</sub>R has been shown [13]. The effect of ECCO<sub>2</sub>R during pressure controlled or pressure support ventilation, that allows or assists spontaneous breathing are less defined and might vary. We purposely did not control for the ventilator mode and settings applied, moreover treating physicians were blinded to whether  $\text{CO}_2$ -removal was active or not and ventilator settings were left to their judgment.

We hypothesized that a minimal-flow CRRT-ECCO<sub>2</sub>R is able to remove enough  $\text{CO}_2$  to facilitate lung protective ventilation in mechanically ventilated patients.

## Methods

The local ethics committee approved the study prior to patient enrollment. We included adult patients (age > 18 years) in need for mechanical ventilation and CRRT; hypercarbia was considered neither inclusion nor exclusion criterion. Patients were not eligible for the study if they were hemodynamically unstable (doses of norepinephrine or epinephrine  $\geq 0.1 \mu\text{g}/\text{kg}/\text{min}$ ), if they were in severe acute respiratory distress ( $\text{PaO}_2/\text{FiO}_2 < 100$ ), if they were thrombopenic (platelets  $< 50,000/\mu\text{l}$ ), if they had an acute bleeding ( $> 200 \text{ ml}/\text{h}$ ) or if further therapy was futile due to bad prognosis or patients will. Assessed patient characteristics consisted of age, sex, weight, height, diagnoses, SAPS II score, ICU-stay, ventilator times, and duration of renal replacement therapy.

For this trial we used a combined CRRT-ECCO<sub>2</sub>R device (EQUA-smart<sup>®</sup>, Hemodec (MEDIA), Modena; Italy), basic settings were employed following manufacturer guidelines.

Ventilation was conducted using conventional ICU ventilators (Evita 4, Dräger, Lübeck, Germany or Servo-i, Maquet Critical Care, Solna Sweden). Peak inspiratory pressure ( $P_{\text{insp}}$ ) was limited to 30 ccmH<sub>2</sub>O, ventilation modes used were either biphasic positive inspiratory airway pressure ventilation (Evita 4: BiPAP mode, Servo-i: BIVENT) or pressure support ventilation, depending on individual patient needs. ABGs were conducted frequently and used to modify ventilator settings aiming to keep  $\text{paCO}_2$  and pH as constant as possible during the preparatory phase of the trial.

CRRT was conducted using the CVVHDF mode, extraction dose 35 ml/kg, blood flow 300 ml/min,  $\text{O}_2$ -flow 10 l/min, and all parameters were kept constant throughout. Patients were randomized to receive either pre- or postdilution.

CRRT was started as indicated without  $\text{CO}_2$  elimination. Then  $\text{CO}_2$  elimination was added and closely monitored for 6 h keeping blood- and gas flow constant throughout the study period. After the course of 6 h of

CRRT plus ECCO<sub>2</sub>R we switched back to CRRT only. Treating physicians were blinded to the phase of the trial, i.e. if CO<sub>2</sub> removal was active or just CRRT. The following parameters were collected just before starting CO<sub>2</sub>-removal as well as 1, 3, and 6 h during ECCO<sub>2</sub>R: arterial blood pressure, heart rate, mode of ventilation, respiratory rate, tidal volume, FiO<sub>2</sub>, PEEP, peak inspiratory pressure ( $P_{\text{insp}}$ ), and ABG (paO<sub>2</sub>, paCO<sub>2</sub>, pH, SaO<sub>2</sub>). Data were collected using the standard PDMS system in the unit (ICCA<sup>®</sup>, Philipps) and the integrated data recorder of the EQUAsmart<sup>®</sup> device. Data were extracted from both sources and stored in a Microsoft<sup>®</sup> Excel<sup>®</sup> Worksheet.

We analyzed changes in minute ventilation, tidal volume, respiratory rate, power applied to the lung, and paCO<sub>2</sub> as well as CO<sub>2</sub> removal.

Furthermore, we compared CO<sub>2</sub> removal using pre- vs. postdilution. To quantify CO<sub>2</sub> removal, we calculated the difference in CO<sub>2</sub> contained in the afferent and efferent limb of the circuit. The calculation was performed using the equation described by Douglas et al. [33].

All parameters were tested for normal distribution using the Kolmogorov–Smirnov test, nevertheless due to small sample size we used statistical methods not reliant on normal distribution. Parameters were tested using the Kendall-test first and, if significance was found, additionally with the Wilcoxon-test for linked samples, we only report the Wilcoxon  $p$  value unless otherwise stated. CO<sub>2</sub> removal pre- vs. postdilution was tested using Mann–Whitney- $U$ -test for unrelated samples. Statistical calculations were done utilizing SPSS<sup>®</sup> Software Version 24, level of significance was assumed to be  $p < 0.05$ .

## Results

We enrolled 14 patients, 3 of them had to be excluded from analysis due to incomplete datasets, leaving 11 patients for further analysis. Pre- and postdilution was equally distributed between the groups; patient characteristics and initial ventilator settings are shown in Tables 1 and 2. Most of our patients were ventilated in assist-control mode (9 out of 11), two were ventilated in pressure support mode. All patients were ventilated in the spirit of a lung protective ventilation strategy using low tidal volumes; mean tidal volume at baseline was  $6.36 \pm 0.67$  ml/kg ideal bodyweight.

At baseline minute ventilation appeared to be 10.1 l/min (7.0–12.9 l/min), during CRRT-ECCO<sub>2</sub>R therapy a significant reduction in minute ventilation was observed to 9.2 l/min at 1 h (5.9–12.4 l/min,  $p < 0.05$ ), at 3 h there was still a reduction compared to baseline to 8.4 l/min (5.1–14.2 l/min), which was not significant ( $p = 0.052$ ), at 6 h there was still a reduction compared to baseline to 9.6 l/min (7.5–15.3 l/min), again not significant ( $p = 0.450$ ) (Fig. 1).

Respiratory rate was 23.6 bpm (18–39 bpm) at baseline. It was reduced to 21.1 bpm (15–26 bpm) at 1 h, to 23 bpm (17–34 bpm) at 3 h and increased slightly to 24.8 bpm (18–36 bpm) at 6 h into therapy, none of these changes reached significance (Kendall  $p = 0.127$ ).

Tidal volume was 425.5 ml (300–500 ml) at baseline. It increased to 440.6 ml (346–600 ml,  $p = 0.750$ ) after 1 h and decreased significantly to 364.1 ml (258–450 ml,  $p < 0.05$ ) after 3 h. After 6 h of therapy we found a decrease to 395 ml (305–550 ml) still, but this decrease was not statistically significant ( $p = 0.240$ ).

There was a statistically significant decrease in paCO<sub>2</sub> from 34.4 mmHg (29–49 mmHg) at baseline to 28.8 mmHg (20–40 mmHg,  $p < 0.05$ ) at 1 h, a statistically meaningful

**Table 1** Patient characteristics

Patient no.	Age	Sex	Height [cm]	Weight [kg]	IBW [kg]	Diagnosis	SAPS II	Dilution
1	62	F	162	100	54	Endocarditis	47	Post
2	61	M	185	105	80	Liver transplant	49	Pre
3	62	F	170	100	62	Sepsis/ARDS	55	Post
4	45	F	168	90	60	HOCM	43	Pre
5	66	M	172	91	68	Endocarditis	53	Pre
8	40	M	180	135	75	ARDS (H1N1)	56	Pre
10	63	M	176	96	71	Acute respiratory failure	48	Post
11	54	M	180	75	75	Pneumonia	22	Post
12	67	F	160	146	52	Sepsis	98	Post
13	70	M	172	75	68	Cardiogenic shock	49	Pre
14	77	M	180	90	75	Pneumonia	59	Post

IBW ideal bodyweight, SAPS Simplified Acute Physiology Score, ARDS adult respiratory distress syndrome, HOCM hypertrophic obstructive cardiomyopathy

**Table 2** Initial ventilator settings and oxygenation

Patient no.	Predicted tidal volume [6 ml/kg IBW]	Baseline						
		Tidal volume [ml]	Baseline ml/kg	paO <sub>2</sub> /F <sub>i</sub> O <sub>2</sub> ratio	PEEP [cmH <sub>2</sub> O]	P <sub>mean</sub> [cmH <sub>2</sub> O]	P <sub>insp</sub> [cmH <sub>2</sub> O]	Ventilation mode
1	325	330	6.11	269	8	14	21	Assist-control
2	475	470	5.88	260	6	12	19	Assist-control
3	369	350	5.65	130	12	20	28	Assist-control
4	358	380	6.33	113	12	18	24	Assist-control
5	407	440	6.47	204	7	12	17	Assist-control
8	451	470	6.27	140	19	24	30	Assist-control
10	430	410	5.77	208	12	16	21	Assist-control
11	451	450	6	289	5	12	20	Pressure support
12	314	420	8.08	220	10	14	23	Pressure support
13	407	460	6.76	215	5	9	16	Assist-control
14	451	500	6.67	268	8	14	20	Assist-control

IBW ideal bodyweight, paO<sub>2</sub> arterial partial pressure of oxygen, FiO<sub>2</sub> inspiratory oxygen fraction, PEEP positive end expiratory pressure, P<sub>mean</sub> mean airway pressure, P<sub>insp</sub> maximum inspiratory pressure

decrease to 31.7 mmHg (27–37 mmHg,  $p < 0.05$ ) was observed at 3 h, which kept constant to 31.6 mmHg (27–37 mmHg,  $p = 0.164$ ) at 6 h during CRRT-ECCO<sub>2</sub>R (Fig. 2).

We also calculated delta pressure, which was also not significantly different between data-acquisition-points (Kendall  $p = 0.143$ , data not shown).

The power transmitted to the lungs owing to ventilator settings at each data-acquisition-point was calculated. We found the values to be 18.4 J/min (11.8–34 J/min) at baseline, 17.8 J/min (8.6–29.8 J/min,  $p = 0.695$ ) after 1 h, 15 J/min (6.2–32.8 J/min,  $p = 0.054$ ) after 3 h, and 16.3 J/min (8.0–23.5 J/min,  $p = 0.175$ ) after 6 h of therapy.

Total CO<sub>2</sub> removal of the tested device averaged over all recordings was 20.7 ml CO<sub>2</sub>/min (18.7–23.8 ml CO<sub>2</sub>/min) regardless of the mode of dilution applied.

Regarding the mode of dilution, we found no significant difference between predilution (CO<sub>2</sub> elimination 19.4 ml CO<sub>2</sub>/min, 15.0–26.1 ml CO<sub>2</sub>/min) and postdilution (CO<sub>2</sub> elimination 23.1 ml CO<sub>2</sub>/min, 17.5–28.7 ml CO<sub>2</sub>/min) ( $p = 0.26$ ) (Tables 3, 4).

No complications or adverse events occurred during conduction of the trial.

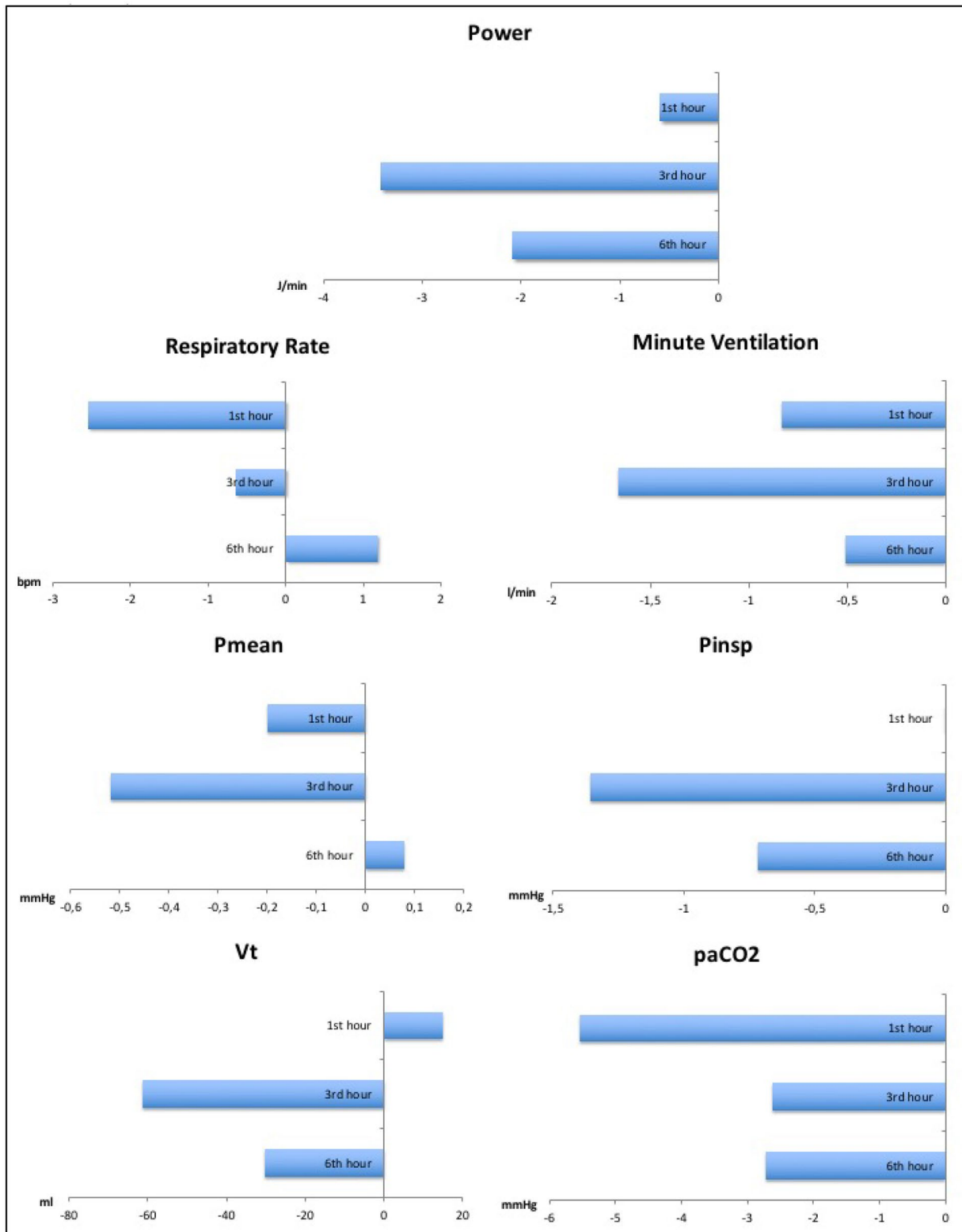
## Discussion

We used a combined approach that incorporates extracorporeal CO<sub>2</sub> removal in a system for hemodialysis (CRRT-ECCO<sub>2</sub>R). In patients with combined renal and respiratory failure this system was in our trial capable to safely reduce minute ventilation statistically significant in the first hour

of therapy. Nevertheless, it was not able to keep or even improve this result throughout the next hours of our trial. Furthermore, it is debatable if a mean reduction of 0.8 l/min although statistically significant is clinically meaningful. Especially because the statistically significant reduction in tidal volume appeared 2 h later at 3 h into therapy, when the decrease in minute ventilation was not statistically significant.

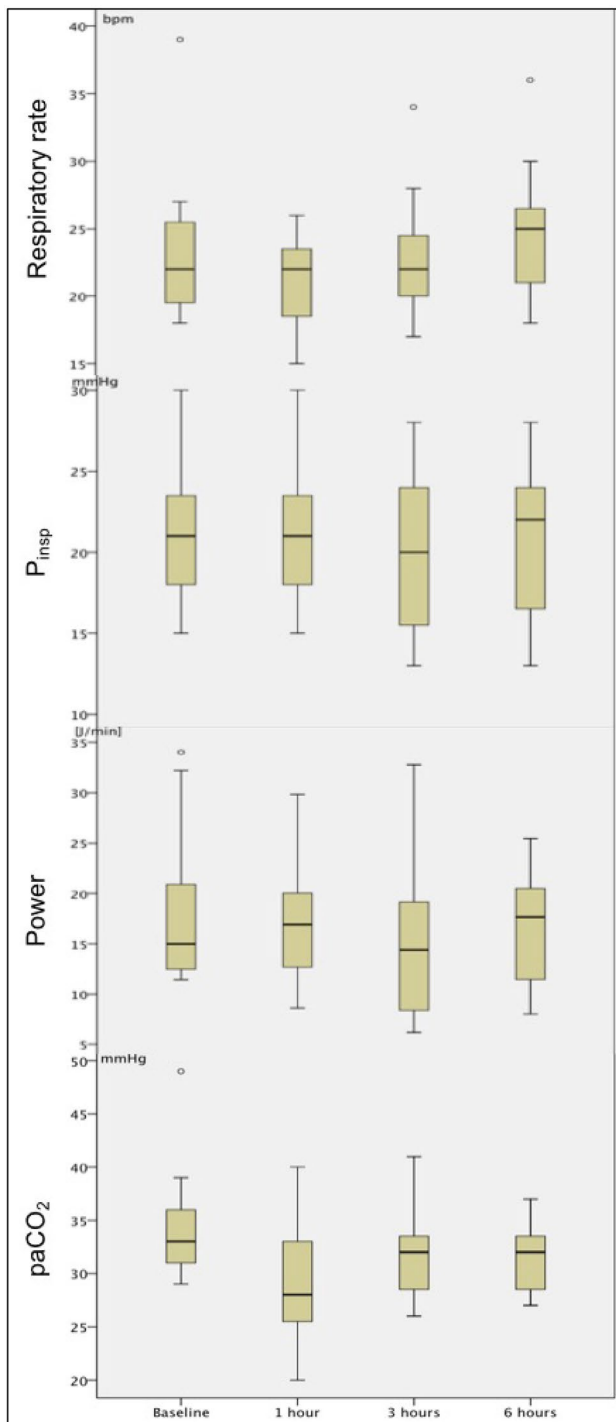
This argument gets even stronger when taking into account that CO<sub>2</sub> decreased significantly also at that exact point in time. But there is no significant corresponding decrease in respiratory rate. Calculating the power transmitted, although the formula has not been widely used yet, shows the same result; there is a non-significant decrease in power at this exact time.

Terragni et al. using the same device [13] found significant reductions in minute ventilation and concluded that CRRT-ECCO<sub>2</sub>R is sufficient to facilitate lung-protective ventilation. In their trial, a fixed tidal volume of 6 ml/kg was aimed and reached. After achieving this goal, the team removed CO<sub>2</sub> in the intervention group and found they were able to manage the increased CO<sub>2</sub> load produced by decreased tidal volumes. Looking at their data it becomes obvious that only a fixed amount of CO<sub>2</sub> was removed bringing CO<sub>2</sub> back to baseline before tidal volumes were reduced. Our approach was different. We adopted the ventilator settings as they stood and removed CO<sub>2</sub> first. Treating physicians were blinded to whether CO<sub>2</sub> removal was active or not. They were not briefed about the trial but kept going with routine practice to ventilate a patient according to the ALARA principle (as-low-as-reasonably-achievable) we use in our unit. We think our approach is much less



**Fig. 1** Composite figure of the analyzed parameters; each figure shows the evolution of the parameter displayed during the course of the trial relative compared to baseline. Parameters do not shape in any consistent manner but show a trend towards reductions after 3 h

of therapy. This is conclusive to the statistical measures performed.  $P_{mean}$  mean airway pressure,  $P_{insp}$  maximum inspiratory pressure,  $V_t$  tidal volume,  $paCO_2$  arterial partial pressure of carbon dioxide



**Fig. 2** Combined whiskers-boxplots of studies parameters throughout the trial period. Differences in respiratory rates over time are marginal with no decrease found. Moreover, an increase is seen after 6 h. We do not have a conclusive explanation for this fact. In the first hour there was no difference in  $P_{insp}$ , after 3 h the median decreased but the values also spread wider, strangely enough  $P_{insp}$  increased after 6 h, we do not have an explanation for this. Counter intuitively the power applied did not decrease although  $CO_2$  was actually removed from the body, but it also did not increase. A clear decrease in arterial  $CO_2$  is seen after 1 h of therapy as expected due to extracorporeal  $CO_2$  removal. Nevertheless,  $CO_2$  is nearly back to baseline values at 3 h and stays at this level until 6 h of therapy. One explanation may be oxygenator exhaustion, but we did not have any hint towards this.  $paCO_2$  arterial partial pressure of carbon dioxide,  $P_{insp}$  maximum inspiratory pressure

**Table 3** Displayed are the measured or calculated values for each patient at each data acquisition point

Patient no.	Parameter	Baseline	1st hour	3rd hour	6th hour
1	$P_{insp}$ [cmH <sub>2</sub> O]	21	21	18	22
	$P_{mean}$ [cmH <sub>2</sub> O]	14	13	12	13
	PEEP [cmH <sub>2</sub> O]	8	8	8	8
	$V_t$ [ml]	330	400	258	382
	RR [bpm]	22	22	20	20
	MV [l/min]	8.8	8.6	5.1	7.5
	paCO <sub>2</sub> [mmHg]	39	28	35	32
	Power [J/min]	12.3	16.91	8.25	14.18
2	$P_{insp}$ [cmH <sub>2</sub> O]	19	19	16	16
	$P_{mean}$ [cmH <sub>2</sub> O]	12	12	11	n/a
	PEEP [cmH <sub>2</sub> O]	6	6	6	6
	$V_t$ [ml]	470	430	350	360
	RR [bpm]	20	20	20	20
	MV [l/min]	9.2	8.2	5.7	5.9
	paCO <sub>2</sub> [mmHg]	32	25	32	31
	Power [J/min]	14.99	20.14	9.82	8.0
3	$P_{insp}$ [cmH <sub>2</sub> O]	28	28	24	24
	$P_{mean}$ [cmH <sub>2</sub> O]	20	19	18	18
	PEEP [cmH <sub>2</sub> O]	12	12	12	12
	$V_t$ [ml]	350	450	300	305
	RR [bpm]	39	26	34	36
	MV [l/min]	12.9	11.7	9.8	10.4
	paCO <sub>2</sub> [mmHg]	29	22	30	28
	Power [J/min]	34.03	29.84	22.18	23.49
4	$P_{insp}$ [cmH <sub>2</sub> O]	24	24	20	22
	$P_{mean}$ [cmH <sub>2</sub> O]	18	18	16	16
	PEEP [cmH <sub>2</sub> O]	12	12	12	12
	$V_t$ [ml]	380	365	370	400
	RR [bpm]	22	22	22	22
	MV [l/min]	8.5	8.0	7.7	7.6
	paCO <sub>2</sub> [mmHg]	33	28	29	27
	Power [J/min]	16.8	16.8	14.4	18.28
5	$P_{insp}$ [cmH <sub>2</sub> O]	17	17	13	13
	$P_{mean}$ [cmH <sub>2</sub> O]	12	12	10	10
	PEEP [cmH <sub>2</sub> O]	7	7	7	7
	$V_t$ [ml]	440	497	330	345
	RR [bpm]	19	19	22	25
	MV [l/min]	9.1	9.2	6.5	7.8
	paCO <sub>2</sub> [mmHg]	32	20	28	29
	Power [J/min]	11.45	12.91	7.86	10.45
8	$P_{insp}$ [cmH <sub>2</sub> O]	30	30	28	28
	$P_{mean}$ [cmH <sub>2</sub> O]	24	24	24	24
	PEEP [cmH <sub>2</sub> O]	19	19	18	18
	$V_t$ [ml]	470	440	450	340
	RR [bpm]	25	25	28	28
	MV [l/min]	12.5	12.4	14.2	15.3
	paCO <sub>2</sub> [mmHg]	49	40	41	33
	power [J/min]	32.21	28.57	32.79	25.45
10	$P_{insp}$ [cmH <sub>2</sub> O]	21	21	26	25

**Table 3** (continued)

Patient no.	Parameter	Baseline	1st hour	3rd hour	6th hour
11	$P_{\text{mean}}$ [cmH <sub>2</sub> O]	16	<i>16</i>	<b>19</b>	<b>19</b>
	PEEP [cmH <sub>2</sub> O]	12	<i>12</i>	<b>14</b>	<b>14</b>
	$V_t$ [ml]	410	<b>346</b>	<b>350</b>	<b>343</b>
	RR [bpm]	18	<i>18</i>	<b>25</b>	<b>25</b>
	MV [l/min]	7.0	<b>5.9</b>	<b>8.7</b>	<b>8.6</b>
	paCO <sub>2</sub> [mmHg]	30	<b>35</b>	<b>27</b>	33
	power [J/min]	14.21	<b>12.43</b>	<b>21.36</b>	<b>20.45</b>
	$P_{\text{insp}}$ [cmH <sub>2</sub> O]	15	<i>15</i>	<i>15</i>	<i>15</i>
	$P_{\text{mean}}$ [cmH <sub>2</sub> O]	n/a	n/a	n/a	n/a
	PEEP [cmH <sub>2</sub> O]	5	<i>5</i>	<i>5</i>	<i>5</i>
12	$V_t$ [ml]	450	<b>600</b>	<b>393</b>	<b>550</b>
	RR [bpm]	27	<b>15</b>	<b>17</b>	<b>24</b>
	MV [l/min]	11.5	<b>9.0</b>	<b>7.7</b>	<b>11.6</b>
	paCO <sub>2</sub> [mmHg]	37	<b>26</b>	<b>32</b>	<i>37</i>
	power [J/min]	12.65	<b>8.6</b>	<b>6.18</b>	<b>12.49</b>
	$P_{\text{insp}}$ [cmH <sub>2</sub> O]	23	<i>23</i>	<b>24</b>	<b>24</b>
	$P_{\text{mean}}$ [cmH <sub>2</sub> O]	14	<i>14</i>	n/a	n/a
	PEEP [cmH <sub>2</sub> O]	10	<i>10</i>	<i>10</i>	<b>9</b>
	$V_t$ [ml]	420	<b>414</b>	<b>401</b>	<b>445</b>
	RR [bpm]	26	<b>22</b>	<b>23</b>	<b>30</b>
13	MV [l/min]	10.7	<b>9.4</b>	<b>9.5</b>	<b>12.5</b>
	paCO <sub>2</sub> [mmHg]	29	<b>27</b>	<b>26</b>	<b>27</b>
	power [J/min]	22.69	<b>19.2</b>	<b>16.25</b>	<b>20.57</b>
	$P_{\text{insp}}$ [cmH <sub>2</sub> O]	16	<i>16</i>	<b>15</b>	<b>17</b>
	$P_{\text{mean}}$ [cmH <sub>2</sub> O]	9	<i>9</i>	<i>9</i>	<i>9</i>
	PEEP [cmH <sub>2</sub> O]	5	<i>5</i>	<i>5</i>	<i>5</i>
	$V_t$ [ml]	460	<b>434</b>	<b>374</b>	<b>447</b>
	RR [bpm]	18	<i>18</i>	<i>18</i>	<i>18</i>
	MV [l/min]	8.3	<b>7.8</b>	<b>6.9</b>	<b>8.1</b>
	paCO <sub>2</sub> [mmHg]	35	<b>33</b>	<b>37</b>	<b>37</b>
14	Power [J/min]	11.8	<b>10.47</b>	<b>8.51</b>	<b>8.23</b>
	$P_{\text{insp}}$ [cmH <sub>2</sub> O]	20	<i>20</i>	<i>20</i>	<i>20</i>
	$P_{\text{mean}}$ [cmH <sub>2</sub> O]	14	<i>14</i>	<i>14</i>	<i>14</i>
	PEEP [cmH <sub>2</sub> O]	8	<i>8</i>	<i>8</i>	<i>8</i>
	$V_t$ [ml]	500	<b>470</b>	<b>429</b>	<b>429</b>
	RR [bpm]	24	<b>25</b>	<i>24</i>	<b>25</b>
	MV [l/min]	12.2	<b>11.3</b>	<b>10.6</b>	<b>9.7</b>
	paCO <sub>2</sub> [mmHg]	33	<i>33</i>	<b>32</b>	<b>34</b>
	Power [J/min]	19.11	<b>19.91</b>	<b>16.95</b>	<b>17.66</b>

Bold suggests improvement, italic suggests status-idem, italicized bold suggest deterioration

$P_{\text{insp}}$  maximum inspiratory pressure,  $P_{\text{mean}}$  mean airway pressure, PEEP positive end expiratory pressure,  $V_t$  tidal volume, RR respiratory rate, MV minute ventilation, paCO<sub>2</sub> arterial partial pressure of carbon dioxide

of a laboratory situation but reflects everyday life closer than the approach Terragni et al. used. The authors were able to show, that in a controlled environment, CRRT-ECCO<sub>2</sub>R enables treating physicians to decrease tidal

volume and control for increased carbon dioxide via the extracorporeal circuit. In our uncontrolled situation CO<sub>2</sub> was removed first and we observed, if lung protective ventilation resulted. In this setting, we were not able to show statistical significance, although absolute trends towards protective ventilation could be found. Data provided in the aforementioned article do not allow for calculation of applied power retrospectively.

We were able to confirm the findings of Terragni et al. in that both studies show a constant portion of CO<sub>2</sub> being removed by this system. As expected by the minimal-flow, the amount of CO<sub>2</sub> elimination is limited. The capacity to remove CO<sub>2</sub> we found is likely to be insufficient in some cases. Since there is only very little experience with this system and technique, further evidence must be generated. Another drawback is the very limited amount of oxygenation at these flow rates making it feasible for patients with partial respiratory insufficiency only.

Furthermore, we evaluated the effect of pre- versus postdilution on CO<sub>2</sub>-removal. By theory, predilution would be more efficient in terms of CO<sub>2</sub>-removal than postdilution because higher efflux rates can be achieved. In spite of this theory we did not find any significant difference in CO<sub>2</sub>-removal between the two modes. One possible explanation could be a suboptimal membrane lung, so that pre- vs. postdilution should be tested using another membrane lung to verify or falsify this possibility.

There are limitations to our study. First, our sample size was small; we might have missed statistical significance for this reason, although this seems unlikely by looking at our data. Second, this was a feasibility study; we did not have a control group. Third, inclusion criteria were kept very broad so that we included only due to the need of CRRT and mechanical ventilation. All patients included were not in need for ECCO<sub>2</sub>R, they did find without it before and after. We, therefore, do not know if the system works for patients with a heavy CO<sub>2</sub> load. On the other hand, this is strength as well, because we can largely exclude recruiting bias. From our results one can see that CO<sub>2</sub> removal consistently was 21 ml CO<sub>2</sub>/min. This is only about one-tenth of the normal resting CO<sub>2</sub> production in an adult. Taking this into account it is very unlikely that a significant amount of CO<sub>2</sub> can be removed using this system in a severely hypercarbic patient who would need it the most.

After all, experience is limited with these jack-of-all-trades devices, making it hard to draw general conclusions on their effectiveness. Further research needs to be conducted with those systems to find the right patients benefiting from it, since from our results shown here one cannot conclude that hypercarbic patients will benefit from the small amount of CO<sub>2</sub> removal we found.

**Table 4** Displayed are the mean and standard deviation for all measured patients at the data acquisition points

Parameter	Baseline	1st hour	3rd hour	6th hour
Respiratory rate [bpm]	23.64 ± 5.71	21.09 ± 3.29	23.00 ± 4.59	24.82 ± 4.90
Minute ventilation [l/min]	10.06 ± 1.89	9.23 ± 1.82*	8.40 ± 2.46	9.55 ± 2.60
PEEP [cmH <sub>2</sub> O]	9.45 ± 3.96	9.45 ± 3.96	9.55 ± 3.92	9.45 ± 3.92
$P_{insp}$ [cmH <sub>2</sub> O]	21.27 ± 4.51	21.27 ± 4.51	19.91 ± 4.78	20.55 ± 4.52
$P_{mean}$ [cmH <sub>2</sub> O]	15.30 ± 4.15	15.10 ± 4.09	14.78 ± 4.64	15.38 ± 4.64
Tidal volume [ml]	425.45 ± 51.05	440.55 ± 65.17	364.09 ± 52.96*	395.05 ± 66.15
paCO <sub>2</sub> [mmHg]	34.36 ± 5.51	28.82 ± 5.64*	31.73 ± 4.31*	31.64 ± 3.44
Power [J/min]	18.39 ± 7.67	17.80 ± 6.51	14.96 ± 7.73	16.30 ± 6.43

Statistical significance as found by the Wilcoxon test is marked by a star, statistical significance was assumed to be at  $p < 0.05$ , we compared the measured values at the data acquisition points referenced to baseline

PEEP positive end expiratory pressure,  $P_{insp}$  maximum inspiratory pressure,  $P_{mean}$  mean airway pressure, paCO<sub>2</sub> arterial partial pressure of carbon dioxide

## Conclusion

Based on our current knowledge the least harmful approach to mechanical ventilation should be chosen to avoid ventilator-induced injury. Although extracorporeal CO<sub>2</sub> removal using minimal-flow systems suffers from a limited efficiency, the concept of reduced invasiveness, which is enabled by vascular access with smaller cannulas, is appealing. This is especially true since fusing CRRT and ECCO<sub>2</sub>R in patients that require both treatments might enhance the benefit.

With our study we were able to find detached statistically significant reductions in minute ventilation, tidal volume, and paCO<sub>2</sub>. In our study, we found no significant decrease in applied power besides aforementioned statistically significant reductions in surrogates for lung protection during mechanical ventilation. From our trial, we need to draw the conclusion that ECCO<sub>2</sub>R using minimal flow rates with that merely small amount of CO<sub>2</sub> removal we found is most likely not sufficient to benefit patients with heavy CO<sub>2</sub> load.

**Author Contributions** OM initiated, designed and helped conducting the study, was involved in statistical analysis and interpreting the data, wrote and revised the manuscript. LOH condensed and analyzed the data and drafted and revised the manuscript. JB performed data acquisition and analysis and revised the manuscript. DH helped interpreting and analyzing the data. JH helped acquiring and analyzing data and revised the manuscript. MQ initiated and designed the study and was involved in data analysis and revising the manuscript. All authors agree to be accountable for all aspects of the work and have read and approved the final manuscript.

## Compliance with ethical standards

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