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Low flow extracorporeal CO_2 removal in ARDS patients: a prospective short-term crossover pilot study

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Abstract

Background: Lung protective mechanical ventilation (MV) is the corner stone of therapy for ARDS. However, its use may be limited by respiratory acidosis.
This study explored feasibility of, effectiveness and safety of low flow extracorporeal CO_2 removal ($ECCO_2R$).

Methods: This was a prospective pilot study, using the Abylcap® (Bellco) $ECCO_2R$, with crossover off-on-off design (2-h blocks) under stable MV settings, and follow up till end of $ECCO_2R$. Primary endpoint for effectiveness was a 20% reduction of $PaCO_2$ after the first 2-h. Adverse events (AE) were recorded prospectively.
We included 10 ARDS patients on MV, with $PaO_2/FiO_2 < 150$ mmHg, tidal volume ≤ 8 mL/kg with positive end-expiratory pressure ≥ 5 cmH_2O, FiO_2 titrated to SaO_2 88–95%, plateau pressure ≥ 28 cmH_2O, and respiratory acidosis (pH <7.25).

Results: After 2-h of $ECCO_2R$, 6 patients had a ≥ 20% decrease in $PaCO_2$ (60%); $PaCO_2$ decreased 28.4% (from 58.4 to 48.7 mmHg, $p = 0.005$), and pH increased (1.59%, $p = 0.005$). $ECCO_2R$ was hemodynamically well tolerated. During the whole period of $ECCO_2R$, 6 patients had an AE (60%); bleeding occurred in 5 patients (50%) and circuit thrombosis in 3 patients (30%), these were judged not to be life threatening.

Conclusions: In ARDS patients, low flow $ECCO_2R$ significantly reduced $PaCO_2$ after 2 h, Follow up during the entire $ECCO_2R$ period revealed a high incidence of bleeding and circuit thrombosis.

Trial registration: https://clinicaltrials.gov identifier: NCT01911533, registered 23 July 2013.

Keywords: Acute respiratory distress syndrome, Lung protective mechanical ventilation, Extracorporeal carbon dioxide removal, Plateau pressure, Driving pressure

Background

Acute Respiratory Distress Syndrome (ARDS) is a frequently occurring disorder in critically ill patients, and is associated with poor short-term and long-term outcomes [1, 2]. Lung protective mechanical ventilation (MV), i.e. use of a tidal volume (V_T) of 6 mL/kg predicted body weight (PBW) and plateau pressure (P_{PLAT}) lower than 30 cmH_2O has been shown to lead to improved outcomes [3–5]. This is likely explained by decreasing overdistention and alveolar wall stress, and consequently decreased local and systematic inflammatory response [6]. Recent data suggest that reducing driving pressure (the difference between P_{PLAT} and positive end-expiratory pressure (PEEP) (P_{PLAT}-PEEP)), using MV with even lower V_T, and limiting respiratory rate may offer additional benefit [7–11].The use of lower V_T and lower respiratory rate may be limited by decreased elimination of CO_2 with resulting hypercapnia and respiratory acidosis. This may in turn lead to increased pulmonary shunt, elevated intracranial pressure, pulmonary hypertension, decreased myocardial contractility, decreased renal and splanchnic blood flow and the release of endogenous catecholamines [12, 13]. Moderate permissive hypercapnia is generally well tolerated when ventilating in a lung-protective manner. But the effect on survival of hypercapnic acidosis compared to low-tidal volume remains unclear [14]. In patients with normal kidney

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function, metabolic adaptation will compensate for respiratory acidosis, but this process takes some days.

In 1977 Kolobow et al. evaluated the use of extracorporeal CO_2 removal ($ECCO_2R$) in an animal model [15]; subsequently, Gattinoni et al. first used $ECCO_2R$ in patients with acute respiratory failure in 1986 [16]. $ECCO_2R$ can be performed using a blood flow (Qb) ranging from 300 to 1500 mL/min. Published experience with $ECCO_2R$ in ARDS patients consists mainly of cohort studies [17–21]. Some authors reported the use of $ECCO_2R$ in series with continuous renal replacement therapy (CRRT), offering an additional method of correcting acidosis. In these studies only patients who presented with acute kidney injury and ARDS were included [17–19].

Using a previous generation of pumpless arterio-venous $ECCO_2R$, Bein et al. showed that this technique allowed protective MV with V_T of 3 mL/kg [22]. Fanelli et al. demonstrated that low-flow $ECCO_2R$ can safely be applied to facilitate ultra-protective MV with V_T of 4 mL/kg [23]. Since these effects were evaluated over several days, also metabolic adaption and improvement of gas exchange may have contributed to the pH, and the exact contribution of $ECCO_2R$ on pH control versus mechanical ventilation is uncertain.

The aim of our pilot study was to explore the short-term (2-h) effects of low-flow $ECCO_2R$ in steady state conditions in ARDS patients. In addition, we studied feasibility and adverse events of this treatment with special emphasis on bleeding and thrombosis.

Methods

Setting and patients

A prospective pilot study was conducted in the Intensive Care Unit of Ghent University Hospital, between December 2013 and May 2015. The ICU comprises a 14 beds medical, a 22 beds surgical and 10 beds cardiac surgical ICU. A convenience sample of 10 patients was included. Patients had to meet all of the following criteria for inclusion: 1. acute onset of moderate or severe ARDS, with a $PaO_2/FiO_2 < 150$ mmHg [24], 2. at least two hours of MV applying a V_T of 8 mL/kg PBW or less, with a positive end-expiratory pressure (PEEP) of 5 cmH_2O or more, and FiO_2 titrated to maintain an arterial oxygen saturation of 88–95% (PaO_2 55–80 mmHg), 3. P_{PLAT} of 28cmH_2O or higher, 4. respiratory acidosis with $pH < 7.25$, 5. informed consent obtained from the patient or the proxy. Exclusion criteria were: 1. age < 18 years, 2. pregnancy, 3. obesity with a body mass index higher than 30 kg/m^2, 4. contra-indication for anticoagulation with unfractionated heparin, 5. Underlying chronic restrictive cause of respiratory acidosis, such as severe chest wall abnormalities.

Inhaled nitric oxide, muscle relaxants, and prone positioning were administered according to the discretion of the attending physician. PBW was calculated based upon patients' length (measured with a measuring tape), for male patients: $50 + 0.91 \cdot$ (cm of height − 152.4) kg, and for female patients: $45.5 + 0.91 \cdot$ (cm of height − 152.4) kg [3]. Sedation was monitored at 8-h intervals, using the Richmond Agitation Sedation Score (RASS).

Study design

This paper discusses the results of a prospective single center pilot study with a crossover design.

To assess the immediate effects of $ECCO_2R$ on gas exchange, we used a crossover design alternating periods with ("on") and without ("off") $ECCO_2R$. The first 2-h study period without $ECCO_2R$ started as soon as the venous access for $ECCO_2R$ was in place. Following this, a first 2-h "on"-period was initiated with a Qb of 300 mL/min. The fraction of delivered oxygen via the oxygenator was kept at 1.0 with a gas flow of 7 L/min during "on"-periods. Hereafter followed the second 2-h "off"-period by setting the gas flow through the $ECCO_2R$ oxygenator at 0 L/min. Qb remained unchanged during this second "off"-period. During these 3 study periods, the settings for MV remained unchanged. After this second "off"-period, a second "on"- period was started, the gas flow was set again at 7 L/min and the Qb was increased to 400–500 mL/min. This "on"-period lasted as long as clinically indicated.

Extracorporeal CO_2 removal

Veno-venous $ECCO_2R$ was performed with the Abylcap® (Bellco®) device, mounted on a "Bellco" extracorporeal therapy machine. The Lynda® with a theoretical maximal Qb of 400 mL/min was used in the first 7 patients and the Amplya™ with a theoretical maximal Qb of 500 mL/min in the others.

A dedicated team of intensivists, dialysis nurses, ICU nurses, and perfusionists managed the extracorporeal therapy.

The Abylcap® device contains the Lilliput 2 (LivaNova) oxygenator; this is a polymethylpentene hollow fiber oxygenator, phosphorylcholine coated, with a surface of $0.67m^2$ and a priming volume of 90 mL. The priming volume of the entire heparin-coated set without oxygenator is 109 mL. Venous access was obtained preferentially via the femoral vein with a 24 cm, 13.5 French double lumen catheter (Niagara™, Bard). Blood was pumped through the oxygenator via a non-occlusive roller pump.

Anticoagulation was performed with unfractionated heparin (UFH). After an initial bolus dose of 10 IU UFH/kg, heparin infusion was titrated to achieve an activated clotting time (ACT) of 180–220 s. ACT was measured every 30 to 60 min and once heparin titration was stable, every 4 h. ACT was monitored with the Medtronic ACT plus® system or the Hemochron ® signature elite.

Mechanical ventilation

During the first six hours of the study period, the treating physicians were advised not to change the MV settings. This allowed evaluating the effects of $ECCO_2R$ alone during this initial study period. From the start of the second "on"-period, MV was left at the discretion of the treating physician; with the only recommendation that of ventilating the patient as lung-protective as possible. Practically, MV settings were aimed toward $P_{PLAT} < 25cmH2O$ and $V_T < 6$ mL/PBW. The "higher FiO_2 and lower PEEP" protocol of the ALVEOLI study was proposed [25]. We recommended setting of respiratory rate lower than 30/min. Inversed ratio was not allowed.

Data management & analysis

During the first 6-h study period, MV parameters, arterial blood gas analysis and $ECCO_2R$ parameters were collected every two hours. Hereafter, data were recorded per 8 h. In addition, all adverse events, with special emphasis on bleeding events, thrombosis, and transfusion requirements were prospectively recorded.

The Murray score was calculated using the calculator on the "Cesar-trial" website http://cesar.lshtm.ac.uk/murrayscorecalculator.htm.

In order to have an objective judgment for bleeding, this was scored according the Bleeding Academic Research Consortium (BARC), and the Global Utilization of Streptokinase and Tpa for Occluded arteries (GUSTO) definitions for bleeding [26]. For a detailed description of the BARC and GUSTO definitions, please find an additional file as an online supplement (Additional file 1).

The primary endpoint was a reduction of 20% in arterial carbon dioxide pressure ($PaCO_2$) after the two hours of $ECCO_2R$ therapy. Secondary endpoints were the short-term effect of $ECCO_2R$ on pH, feasibility of performing the technique, and bleeding and circuit thrombosis during $ECCO_2R$ treatment. In addition, we report the ventilation parameters and blood gasses after 5-d of $ECCO_2R$.

A statistical package (SPSS Statistics version 22 (IBM®) was used to perform statistical analysis. Since the small number of patients included, data were considered not normally distributed. Variables were reported as median [inter quartile range] or number (proportion). Comparison of related variables was tested with the Wilcoxon Signed Rank test. A *p*-value of 0.05 was considered significant.

Results

The baseline characteristics of the included patients are presented in Table 1. The median duration of $ECCO_2R$ therapy was 6 days [5; 12]. Four patients were initiated on CRRT during the study. CRRT was started at earliest after 10 h of $ECCO_2R$ therapy, so after the initial "off-on-off" evaluation. When CRRT was used, this was with separate vascular access. The maximum Qb during the second on-period of $ECCO_2R$ was 400 mL/min [399; 410]. At day 1 median heparin dosage was 19.5 IU/kg/h [11.0; 25.4] with an ACT of 211 s [186; 225].

Table 1 Baseline characteristics

Baseline characteristics	N (%) or median [IQR]
Number of patients included	10 (100%)
Age (y)	50.5 [34.8; 63.3]
Gender	Male 6 (60%)/female 4 (40%)
SAPS 3 score	72.5 [61.0; 79.3]
Characteristics at inclusion	
Length of ICU stay before inclusion (h)	26 [20.5; 67.5]
Days with ARDS criteria on CT scan or chest radiography on the day of inclusion	2 [1; 3.25]
SAPS 3 score	69.5 [57.75; 79.25]
Vasopressor use	10 (100%)
RRT use	0
PaCO2 (mmHg)	68.3 [57.7; 86.2]
pH	7.21 [7.11; 7.23]
PaO2/FiO2 (mmHg)	83 [67.6; 121.1]
Murray score	3.5 [3.2; 3.5]
Moderate ARDS (PaO_2/FiO_2: 100–200 mmHg)	4 (40%)
Severe ARDS (PaO_2/FiO_2 < 100 mmHg)	6 (60%)
Nitric Oxide inhalation	6 (60%)
Neuromuscular blockers	10 (100%)
Prone ventilation	2 (20%)
P_{PLAT} (cmH2O)	31.5 [28.8; 35.5]
Driving pressure (P_{PLAT} –PEEP) (cmH_2O)	19.0 [17.5; 24.0]
V_T/PBW (mL/kg)	6.9 [6.31; 7.48]

y Years, *SAPS 3* simplified acute physiology score 3, *RRT* Renal replacement therapy, *$PaCO_2$* Partial pressure of arterial carbon dioxide, *PaO_2/FiO_2* the ration of partial pressure of arterial oxygen and fraction of inspired oxygen, *P_{PLAT}* Plateau pressure, *V_T* tidal volume, *PBW* Predicted body weight

The protocol required settings of the MV to be unaltered during the 6-h crossover, in order to be able to

ICU survival was 70%, hospital survival was 60%, and survival at day 28, and 90 was respectively 60% and 60%. In 4 patients, $ECCO_2R$ was the upper limit of life support, as after team discussions, these patients were not deemed to be candidates for extracorporeal membrane oxygenation (ECMO) therapy. Three patients died in the ICU because of limitations in therapy unrelated to $ECCO_2R$.

Short term effects of $ECCO_2R$

study the short-term effects of $ECCO_2R$ in steady state conditions. In one patient the treating physician modified MV settings during the first off period, with resulting decrease of $PaCO_2$ (132 to 58 mmHg). In order to secure the detection of the effect of $ECCO_2R$, ventilation conditions remained unchanged for the next four hours. PCO_2 values of this patient have been withdrawn from analysis of the first "off" -period (fig. 1a). Median $PaCO_2$ remained stable during the first 2-h "off"-period (delta change −8.6% [−11.4; 3.0], $p = 0.441$), decreased during the "on"-period (−28.4% [−12.2; −34.3], $p = 0.005$), and subsequently increased during the second "off"-period (32.6% [18.5; 36.8], p = 0.005). During the 2-h on period 6 patients (60%) had a decrease in $PaCO_2$ of 20% or greater (fig. 1b).

Median pH remained stable during the first 2-h "off"-period (delta change 0.28% [−0.07; 0.76], $p = 0.078$) (figure1d), increased during the first "on"-period (1.59% [0.49; 2.02], p = 0.005) (fig. 1e), and decreased again during the second "off"-period (−1.28% [−1.50; −0.77], p = 0.005) (fig. 1f).

Feasibility and adverse events

Insertion of the double lumen catheter was troublesome in 2 patients (20%). One patient (10%) had transfusion of 1 unit of RBCs after insertion of the catheter. One patient (10%) had premature cessation after 6-h of $ECCO_2R$ for presumed hemorrhagic pericardial effusion. This finding was not confirmed after cessation of therapy.

During $ECCO_2R$, bleeding was observed in 5 patients (Table 2). Patient 3 had a nosebleed and was bleeding at the insertion points of the $ECCO_2R$ catheter and the central venous catheter. Patient 4 was bleeding at the insertion point of the $ECCO_2R$ catheter, had a pharyngeal bleeding and hematuria. Patient 5 was bleeding during insertion of the catheter. Patient 7 had minor bleeding during tracheal and pharyngeal aspirations. Patient 9 was bleeding at the insertion point of the $ECCO_2R$ catheter. According to the GUSTO criteria and BARC definitions, bleeding was scored in 4 patients (40%) as moderate or 3a, and in 1 patient (10%) as mild or 2 [26]. Five patients (50%) received transfusion of red blood

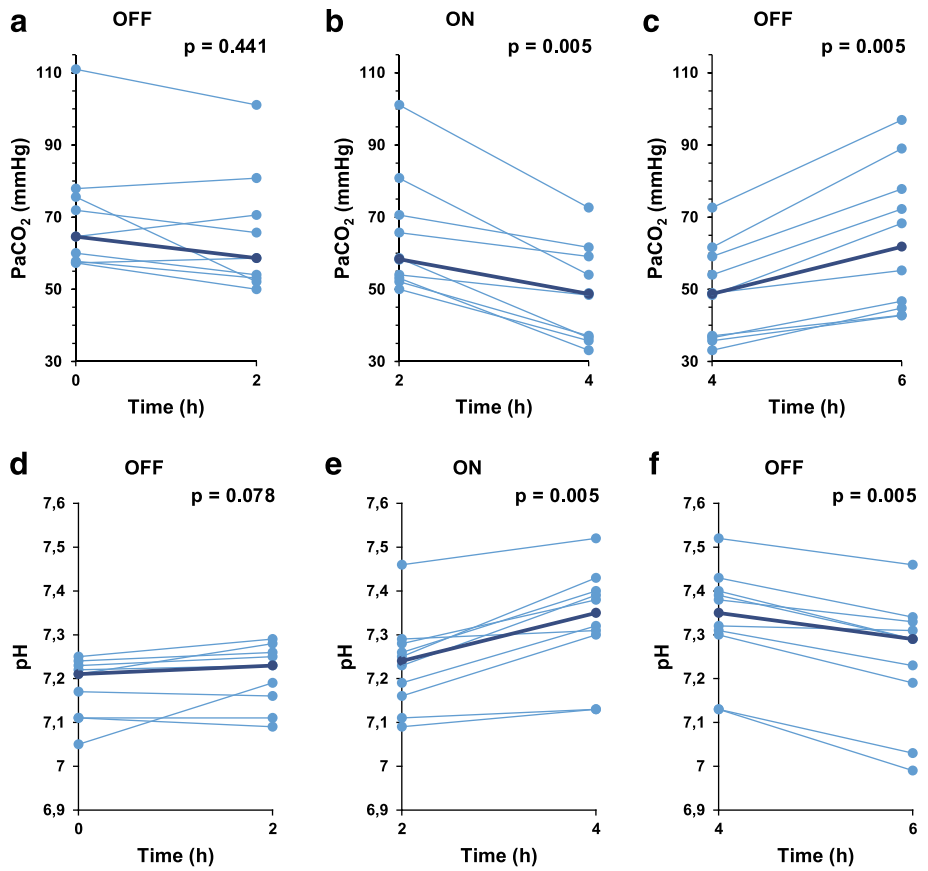

Fig. 1 Evolution of PaCO2 during the 6-h off-on-off period. **a**: Evolution of PaCO2 during the first 2-h off period. **b**: Evolution of PaCO2 during the first 2-h on period. **c**: Evolution of PaCO2 during the second 2-h off period. **d**: Evolution of pH during the first 2-h off period. **e**: Evolution of pH during the first 2-h on period. **f**: Evolution of pH during the second 2-h off period. This figure was created with Excel (Office)

Table 2 Bleeding, clotting in circuit and transfusion needs

Patient no	Clotting in circuit	Bleeding	Transfusion	Cumulative Units of PC during $ECCO_2R$	GUSTO bleeding criteria	BARC type
1				0		0
2				0		0
3		Y	Y	4	moderate	3a
4	Y	Y	Y	4	moderate	3a
5	Y	Y	Y	3	moderate	3a
6				1		0
7		Y		0	mild	2
8				1		0
9		Y	Y	3	moderate	3a
10	Y		Y	2		0
total	3/10	5/10	5/10	1.5 [0; 3.25]		

"*Y*" yes, an empty box means no, *PC* Packed Cells, *GUSTO* Global Utilization of Streptokinase and Tpa for Occluded arteries definition of bleeding, *BARC* Bleeding Academic Research Consortium definition for bleeding

cells. In none of the patients, bleeding resulted in hemodynamic instability.

In 3 patients (30%), clots were observed in the circuit. In 2 patients (20%), clotting of the circuit occurred after temporary stop of the heparin infusion because of increased ACT results.

We observed transient and short-lasting alkalemia (defined as pH > 7.45) in 8 patients (80%).

Evolution of ventilation and blood gasses after 5-d $ECCO_2R$

Plateau pressure, P_{PLAT}-PEEP and V_T/PBW were significantly reduced after 5 days of therapy (Table 3). This was accompanied with a steady increase of bicarbonate and pH. Median pH at the moment of decision of weaning from $ECCO_2R$ was 7.42 [7.39; 7.44].

A significant increase in PaO_2/FiO_2 was noted, indicating amelioration of ARDS.

Discussion

In this prospective crossover pilot study in patients with moderate or severe ARDS, we found that with stable MV settings, low flow $ECCO_2R$ resulted in a rapid decrease of $PaCO_2$ with almost one-third. During the whole treatment period, we observed a high incidence of bleeding and thrombosis.

In our study, we evaluated the short-term effects of $ECCO_2R$ in steady state MV conditions, using study periods of 2-h. It is therefore reasonable to presume that changes in $PaCO_2$ can be attributed to the effects of $ECCO_2R$ only, and were not obscured by an improvement of respiratory function, metabolic compensation, or change in settings of the mechanical ventilator. This is an important aspect that was not studied before. Several other studies have reported the beneficial effects of $ECCO_2R$ on $PaCO_2$ in ARDS patients. However these differed from our study in study design, the non-reporting of short-term effects, combined use with CRRT, and the use of other devices such as pumpless arterio-venous devices [17, 19, 21–23, 27]. An important advantage of this low flow veno-venous $ECCO_2R$ treatment is that Qb up to 500 mL/min can be achieved by using a catheter that is also used for CRRT, making it a less invasive technique compared with others that are using an arterial catheter or large bore wire-reinforced ECMO cannulas [22, 23, 27–30]. However, it should be noted that despite our use of relatively small-bore catheters of 13.5F, catheter insertion was difficult in two patients.

We observed some variability in response to $ECCO_2R$. A possible explanation for this may be a difference in volume of distribution of CO_2. Two main components that determine CO_2 removal are Qb and sweep gas flow. Here we used a Qb of 300 mL/min during the first "on"-period of our study, in which we demonstrated an almost 30% decrease of CO2. In the second "on"-period, a median Qb of 400 mL/min allowed adequate removal of CO2. Our findings are in contrast to others who have reported higher Qb. For instance, Karagiannidis et al. suggested in their study in pigs a Q_B of 750 to 1000 mL/min for efficient CO2 removal [31], and Bein et al. used in vivo a Qb of 2.2 L/min for the A-V iLA device [27, 32]. An explanation for the efficacious CO_2 removal despite low Qb in our study may be the deep sedation used in our patients, limiting CO_2 production. Another determinant for CO_2 removal is sweep gas flow. In this study the sweep gas flow was kept at 7 L/min, with a FiO_2 of 1.0, since we found in a previous study that CO_2 removal rate only marginally improved above gas flows of 6 L/min [33].

After 5 days of $ECCO_2R$ we observed a marked decrease in P_{PLAT}, P_{PLAT}-PEEP and V_T. This resulted in a more lung protective strategy of MV with ventilation settings of V_T, P_{PLAT} and driving pressure below the

Table 3 Evolution in ventilatory measurements

	Inclusion	Day 2	Day 3	Day4	Day 5	Difference	% change	p
P_{PLAT} (cmH_2O)	31.5 [28.8; 35.5]	25.0 [22.5; 30.5]	26.0 [22.0; 29.5]	25.0 [22.0; 27.0]	24.0 [21.0; 26.0]	10.0 [4.5; 12.5]	−31.4 [−36.2; −15.4]	0.008
V_T (mL)	334 [317; 469]	300 [270; 353]	318 [270; 390]	300 [251; 344]	308 [243; 347]	69.0 [20.0; 90.0]	−20.9 [−26.3; −5.17]	0.008
V_T/PBW (mL/kg)	6.85 [6.31; 7.48]	5.60 [4.90; 6.05]	5.80 [4.75; 6.45]	5.30 [4.55; 6.20]	5.00 [4.55; 5.95]	1.6 [0.8; 2.15]	−23.7 [−31.3; −13.9]	0.008
Driving Pressure: P_{PLAT} –PEEP (cmH_2O)	19.0 [17.5; 24.0]	14.0 [11.0; 18.5]	15.0 [11.0; 19.0]	15.0 [11.0; 17.0]	14.0 [10.0; 16.5]	9.0 [3.5; 12]	−39.1 [−52.2; −21.7]	0.012
PEEP (cmH_2O)	12.0 [9.0; 12.75]	11.0 [8.5; 14.5]	11.0 [8.0; 13,5]	10.0 [8.0; 11.50]	10.0 [8.0; 10.0]	2.0 [−1.0; 2.0]	16.7 [−16.7; 16.7]	0.305
Respiratory Rate	32.0 [27.8; 33.0]	30.0 [27.5; 31.5]	30.0 [27.0; 31.5]	30.0 [27.0; 33.5]	30.0 [26.0; 33.5]	3.0 [−1.0; 6.0]	9.1 [−3.0; 20.0]	0.235
pH	7.21 [7.11; 7.23]	7.33 [7.29; 7.38]	7.38 [7.31; 7.42]	7.39 [7.34; 7.44]	7.43 [7.40; 7.44]	0.23 [0.20; 0.26]	3.19 [2.77; 3.63]	0.008
PaO_2/FiO_2 (mmHg)	83.0 [67.6; 105.4]	131.4 [90.2; 212.7]	137.2 [118.9; 223.8]	142.0 [116.1; 245.5]	233.6 [135.7; 320.1]	91.9 [29.9; 213.8]	144.0 [30.8; 232.2]	0.011
$PaCO_2$ (mmHg)	68.3 [57.3; 86.2]	50.3 [42.9; 63.9]	51.5 [48.2; 62.2]	56.8 [46.6; 63.1]	59.3 [48.2; 60.9]	14.6 [4.0; 35.8]	22.2 [6.9; 38.0]	0.021
$HCO3^-$	22.6 [22.1; 29.6]	25.7 [20.3; 34.1]	25.7 [25.3; 30.0]	29.1 [27.9; 39.3]	35.3 [29.4; 41.9]	−7.6 [−12.1; −3.2]	−34.2 [−51.2; −14.8]	0.021
FiO_2	0.83 [0.68; 1.00]	0.55 [0.40; 0.75	0.55 [0.35; 0.73]	0.60 [0.35; 0.73]	0.50 [0.35; 0.73]	0.25 [0.05; 0.5]	45.5 [5.9; 50.0]	0.017

Data are expressed as median [IQ25; IQ75]. Difference: the median of the difference between the data at time of inclusion and at day 5

currently recommended [7–10]. Decreased V_T, P_{PLAT} and P_{PLAT}-PEEP without an increase in $PaCO_2$ may offer benefits for ARDS patients, since it may lead to a further decrease of inflammatory mediators in broncho-alveolar fluid and systemic circulation, which in turn may contribute to less lung damage and improved outcomes [17, 23]. Since pH was still 7.43 at day 5, it might have been feasible to achieve even more pronounced decreases of mechanical ventilation settings.

Adequate anticoagulation remains challenging in the management of $ECCO_2R$-patients. In our study, 30% of all patients experienced some form of circuit thrombosis. This was accompanied with a temporal increase in $PaCO_2$ and consequent change of the ventilator to less lung protective settings. We also observed bleeding and need for transfusion of red blood cells in 50% of patients. Others have also reported bleeding and blood loss as an important complication of $ECCO_2R$ [22, 27, 34]. This complication seems to occur more frequently in $ECCO_2R$ compared to CRRT (16%), a well-established extracorporeal therapy for AKI [35]. We can only speculate on the etiology of bleeding in these patients. Potential causes could be the poor correlation of both ACT and aPTT with the heparin concentration [36, 37], and the activation of platelets and induction of other coagulation abnormalities by unfractionated heparin and/or the $ECCO_2R$ circuit [38].The use of visco-elastic monitoring such as TEG, RoTEM or Sonoclot, preferable in combination with a platelet function test may allow better monitoring of coagulation in these patients.

Strengths of our study are the prospective crossover design with detailed short-term evaluation of the effects of $ECCO_2R$. This allowed us to evaluate the effects of $ECCO_2R$ with the patient serving as its own control. In addition, we reported the adverse events, more in particular bleeding, meticulously and in a structured way according to the validated GUSTO and BARC scales. As until now, no RCT's have proven advantage over permissive hypercapnia, it is important to quote the principle 'primum non nocere' to guide clinicians considering $ECCO_2R$. Finally, this study evaluated $ECCO_2R$ in moderate ($n = 4$) and severe ARDS patients ($n = 6$), and as such reflects the recommended cohort of ARDS patients that may benefit of $ECCO_2R$ [24]. We want to discuss the following limitations of this pilot study. We report data on a small number of patients in a single center setting. Second, we may have underestimated the short-term effects of $ECCO_2R$ during the first six hours of our study period as we only used a Qb of 300 mL/min. Third, reduction of V_T, P_{PLAT} and driving pressure were the main goals of management of MV in this study. Recently, the large epidemiologic LUNG SAFE study showed that a lower respiratory rate is also associated with better patient outcomes [39]. These results were not available at time of the initiation of the study, and decreasing respiratory rate was therefore not set as a goal for MV here. Finally, we can only speculate on the efficacy of $ECCO_2R$ using low Qb in patients who are more awake.

Conclusions

We showed the feasibility of CO2 removal with a low flow $ECCO_2R$ device in patients with moderate and severe ARDS. Crossover design allowed us to evaluate the short-term effects of $ECCO_2R$ in steady state conditions, with the patient serving as his own control, and demonstrated an almost one-third decrease of $PaCO_2$ within a 2-h study period. However, $ECCO_2R$ treatment was associated with bleeding in half of the patients and circuit thrombosis in one third. These complications should be explored in greater detail and may be a major barrier for larger studies on efficacy of $ECCO_2R$.

Additional file

Additional file 1: In this Word file the "Bleeding Academic Research Consortium Definition for Bleeding" and the "Global Utilization of Streptokinase and Tpa for Occluded arteries definition of bleeding" are described. (DOC 36 kb)

Abbreviations

ACT: activated clotting time; AE: adverse events; aPTT: activated partial tromboplastin time; ARDS: acute respiratory distress syndrome; BARC: Bleeding Academic Research Consortium; COPD: chronic obstructive pulmonary disease; CRRT: continuous renal replacement therapy; $ECCO_2R$: extracorporeal CO_2 removal; GUSTO: Global Utilization of Streptokinase and Tpa for Occluded arteries; MV: mechanical ventilation; $PaCO_2$: arterial carbon dioxide pressure; PaO_2/ FiO_2: the ratio of the arterial oxygen partial pressure to fractional inspired oxygen; PBW: predicted body weight; PC: packed cells; PEEP: positive end-expiratory pressure; P_{PLAT}: plateau pressure; Qb: blood flow; RBC: Red blood cells; RRT: renal replacement therapy; SAPS 3: simplified acute physiology score 3; V_T: tidal volume

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Study concept and design: HP, EH, PD, FDS, SE, CR: Acquisition of data: HP, Analysis and interpretation of data: HP, SE, EH: Drafting the manuscript: HP,

EH: Critical revision of the manuscript for important intellectual content: EH, SE, FDS, PD: Supervision: EH: All authors read and approved the final manuscript.

Ethics approval and consent to participate
This study was conducted in agreement with the declaration of Helsinki and approved by the Ethics Committee of the Ghent University Hospital (EC 2013/505). Inclusion was only possible after obtaining written informed consent from the patient or the proxy.

Consent for publication
Not applicable.

Competing interests
H. Peperstraete: speaker honoraria for an educational program of Bellco.

Publisher's Note

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