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# Impact of sweep gas flow on extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R)



Stephan Strassmann<sup>1</sup>, Michaela Merten<sup>1</sup>, Simone Schäfer<sup>1</sup>, Jonas de Moll<sup>1</sup>, Daniel Brodie<sup>2</sup>, Anders Larsson<sup>3</sup>, Wolfram Windisch<sup>1</sup> and Christian Karagiannidis<sup>1\*</sup> 

\* Correspondence: [Christian.Karagiannidis@uni-wh.de](mailto:Christian.Karagiannidis@uni-wh.de)  
<sup>1</sup>Department of Pneumology and Critical Care Medicine, Cologne-Merheim Hospital, ARDS and ECMO Centre, Kliniken der Stadt Köln gGmbH, Witten/Herdecke University Hospital, Ostmerheimer Strasse 200, D-51109 Cologne, Germany  
Full list of author information is available at the end of the article

## Abstract

**Background:** Venovenous extracorporeal carbon dioxide (CO<sub>2</sub>) removal (vv-ECCO<sub>2</sub>R) is increasingly being used in the setting of acute respiratory failure. Blood flow rates range in clinical practice from 200 mL/min to more than 1500 mL/min, and sweep gas flow rates range from less than 1 to more than 10 L/min. The present porcine model study was aimed at determining the impact of varying sweep gas flow rates on CO<sub>2</sub> removal under different blood flow conditions and membrane lung surface areas.

**Methods:** Two different membrane lungs, with surface areas of 0.4 and 0.8 m<sup>2</sup>, were used in nine pigs with experimentally-induced hypercapnia. During each experiment, the blood flow was increased stepwise from 300 to 900 mL/min, with further increases up to 1800 mL/min with the larger membrane lung in steps of 300 mL/min. Sweep gas was titrated under each condition from 2 to 8 L/min in steps of 2 L/min. Extracorporeal CO<sub>2</sub> elimination was normalized to a PaCO<sub>2</sub> of 45 mmHg before the membrane lung.

**Results:** Reversal of hypercapnia was only feasible when blood flow rates above 900 mL/min were used with a membrane lung surface area of at least 0.8 m<sup>2</sup>. The membrane lung with a surface of 0.4 m<sup>2</sup> allowed a maximum normalized CO<sub>2</sub> elimination rate of 41 ± 6 mL/min with 8 L/min sweep gas flow and 900 mL blood flow/min. The increase in sweep gas flow from 2 to 8 L/min increased normalized CO<sub>2</sub> elimination from 35 ± 5 to 41 ± 6 with 900 mL blood flow/min, whereas with lower blood flow rates, any increase was less effective, levelling out at 4 L sweep gas flow/min. The membrane lung with a surface area of 0.8 m<sup>2</sup> allowed a maximum normalized CO<sub>2</sub> elimination rate of 101 ± 12 mL/min with increasing influence of sweep gas flow. The delta of normalized CO<sub>2</sub> elimination increased from 4 ± 2 to 26 ± 7 mL/min with blood flow rates being increased from 300 to 1800 mL/min, respectively.

**Conclusions:** The influence of sweep gas flow on the CO<sub>2</sub> removal capacity of ECCO<sub>2</sub>R systems depends predominantly on blood flow rate and membrane lung surface area. In this model, considerable CO<sub>2</sub> removal occurred only with the larger membrane lung surface of 0.8 m<sup>2</sup> and when blood flow rates of ≥ 900 mL/min were used.

**Keywords:** ARDS, Extracorporeal carbon dioxide removal, COPD, ECCO<sub>2</sub>R, ECMO

## Background

Veno-venous extracorporeal CO<sub>2</sub> removal (vv-ECCO<sub>2</sub>R) is increasingly being used in the setting of acute hypercapnic and hypoxemic respiratory failure to facilitate protective ventilation, allowing early extubation or even to avoid invasive mechanical ventilation [1–9]. In this context, ECCO<sub>2</sub>R blood flow rates range from 200 mL/min to more than 1500 mL/min [10–12], depending on the primary treatment aim [2]. Much effort has been spent in the last decade to increase CO<sub>2</sub> removal capacity by modifying the circuit and the system [13–15]. With respect to possible technical modifications, blood flow rates, sweep gas flow rates and membrane lung surface areas may be manipulated by the treating team at the bedside.

Among these, blood flow rates were reported to have the strongest impact on CO<sub>2</sub> removal capacity [16, 17]. It was recently demonstrated that applying blood flow rates of 1000 mL/min with an appropriate membrane lung surface can remove about 50% of total CO<sub>2</sub> production and, therefore, can correct even severe respiratory acidosis [18]. Less is known about the influence of sweep gas flow in the setting of typical ECCO<sub>2</sub>R blood flow rates, especially in regard to different membrane lung surface areas. This is of particular importance since membrane lung surfaces from 0.4–1.3 m<sup>2</sup> also clearly impact on CO<sub>2</sub> removal capacities independent of the blood flow level [18].

Furthermore, CO<sub>2</sub> removal capacity is not only dependent on technical circumstances of the system, but also on the absolute CO<sub>2</sub> content of the blood. Most of the CO<sub>2</sub> of the body is stored as bicarbonate (HCO<sub>3</sub><sup>-</sup>) in slow reacting compartments such as bone [19, 20] and is, therefore, not directly accessible for CO<sub>2</sub> removal. Only 1–5% of the total CO<sub>2</sub> content is dissolved in the blood and can thus be extracorporeally removed. Importantly, the amount of soluble CO<sub>2</sub> is strongly correlated to the absolute CO<sub>2</sub> level in venous and arterial blood. Therefore, normalization of CO<sub>2</sub> removal to a PCO<sub>2</sub> of 45 mmHg before the membrane lung allows for the comparison of different settings independent of the amount of PCO<sub>2</sub> before the membrane lung [21].

The aim of the current study was, therefore, to determine the effect of varying degrees of sweep gas flow on normalized CO<sub>2</sub> removal using a clinically typical range of blood flows for ECCO<sub>2</sub>R via a porcine model of severe hypercapnic respiratory failure.

## Material and methods

### Veno-venous-extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R) techniques

For the vv-ECCO<sub>2</sub>R system, two different membrane lungs (Getinge, Maquet Cardiopulmonary Care, Rastatt, Germany) based on the Rotaflow® platform were used. The membrane lungs consisted of a polymethylpentene membrane with surface areas of 0.4 and 0.8 m<sup>2</sup>, respectively. These surface areas have been chosen due to the previous results [18] and current clinical practice in centres applying ECCO<sub>2</sub>R with different systems (0.4 and 0.8 m<sup>2</sup>). Both membrane lungs have a comparable rhomboid design. The systems were primed with normal saline solution. Heparin (5000 IE) was added to the running system, and bolus application of 5000 IE every 2–3 h was used during the running of the systems to avoid clotting.

For venous access, a 23 Fr Bicaval Avalon ELITE Dual Lumen Cannula® (Getinge Group, Maquet Cardiopulmonary Care, Rastatt, Germany) was inserted into the right jugular vein. Correct placement of the cannula was confirmed by echocardiography.

The membrane lung with 0.4 m<sup>2</sup> was measured with system blood flow rates of 300, 600 and 900 mL/min, whereas the membrane lung with 0.8 m<sup>2</sup> was measured with system blood flow rates from 300 to 1800 mL/min in increasing steps of 300 mL/min, respectively. For each single membrane lung surface area and blood flow rate, sweep gas flow was titrated in steps of 2 L/min increasing from 2 L/min to 8 L/min with a delivered oxygen fraction of 1.0.

### Animal model

The study was approved by the Animal Research Committee of Uppsala University/Sweden (ethical approval number C77/16). Pigs (body weight = 39 ± 2 kg) were anaesthetized with IV ketamine 25–50 mg/kg/h, midazolam 90–80 µg/kg/h, fentanyl 3–6 µg/kg/h, and rocuronium 2.5–5.0 mg/kg/h was added when adequate anaesthesia was ascertained by lack of response of painful stimulation between the front hooves. The trachea was intubated with a cuffed endotracheal tube (inner diameter, 7 mm). The pigs were ventilated with a Servo-i ventilator (Maquet Critical Care, Solna, Sweden). Body temperature was kept at 38 °C throughout the study period by use of a heater cooling unit (Maquet Critical Care, Solna, Sweden). Arterial blood was sampled from the left carotid artery. The estimated CO<sub>2</sub> production in this setting is about 200–280 mL/min in pigs [22, 23], which is comparable to a resting adult human.

### Study design

V<sub>v</sub>-ECCO<sub>2</sub>R was performed in nine pigs following endotracheal intubation, mechanical ventilation and induction of hypercapnia by increased dead space ventilation, as described previously [16, 18]. Anatomical dead space was increased by adding an additional tube between the endotracheal tube and the “Y” piece of the ventilator circuit. The length of the additional tube was titrated until hypercapnia was induced with a target PaCO<sub>2</sub> value ranging between 90 and 110 mmHg. The animals were ventilated in a volume-controlled mode with a tidal volume of 220–250 mL, a positive end-expiratory pressure of 5 cmH<sub>2</sub>O and a breathing frequency of 14–16/min. The dead space fraction and minute ventilation were subsequently maintained for the entire duration of the experimental period after having reached equilibrium with the target PaCO<sub>2</sub> of 90 to 110 mmHg.

The experiments were performed in each pig in a standardized fashion. PaCO<sub>2</sub> was equilibrated between every system for at least 30 min. When PaCO<sub>2</sub> was stable at the target, blood flow was increased stepwise from 300 mL/min to 1800 mL/min. At each blood flow level, sweep gas flow was titrated from 2 to 8 L/min in steps of 2 L/min.

### CO<sub>2</sub> and blood gas measurement

Blood gas analysis was performed with an ABL 800, Radiometer, (Copenhagen, Denmark) with separate measurement for haemoglobin. Extracorporeal CO<sub>2</sub> removal was calculated as reported in detail in previous studies [18, 24, 25]. Of note, to compare the amount of CO<sub>2</sub> removal at different pre-membrane PCO<sub>2</sub> levels, the extracorporeal CO<sub>2</sub> removal was normalized to a PCO<sub>2</sub> of 45 mmHg. This normalization allowed comparison of CO<sub>2</sub> removal rates at different PCO<sub>2</sub> levels, since CO<sub>2</sub> removal in general is markedly dependent on the amount of soluble CO<sub>2</sub> (and thus of PCO<sub>2</sub>) in the blood [26].

In more detail, the authors are aware that it is difficult to normalize CO<sub>2</sub> removal to a specific PaCO<sub>2</sub> precisely, since CO<sub>2</sub> can also be dissolved from bicarbonate. However,

the carbon dioxide dissociation curve is quite linear in the  $PCO_2$ -interval in our study, i.e. when  $PCO_2$  is reduced (in our study by the ECCO<sub>2</sub>R system), this will reduce the blood content of carbon dioxide according to the slope of the curve. Another factor that affects the  $CO_2$  removal is the Haldane effect; since blood  $PO_2$  increases in the ECCO<sub>2</sub>R-membrane, the Haldane effect will cause a parallel shift downwards of the  $CO_2$  dissociation curve, and thus the difference between two  $PCO_2$  levels will be more pronounced [27–29].

### Statistics

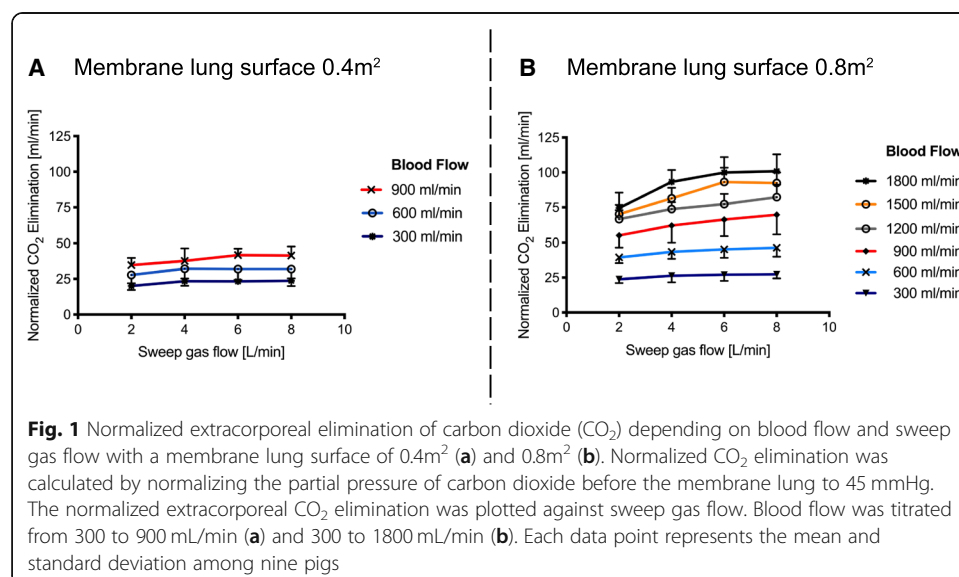
For statistical analysis, GraphPad Prism 7 for Macintosh computer (La Jolla, CA 92037, USA) was used. Data were tested for normality using the Kolmogorov-Smirnov test. All data are given as mean with standard deviation.

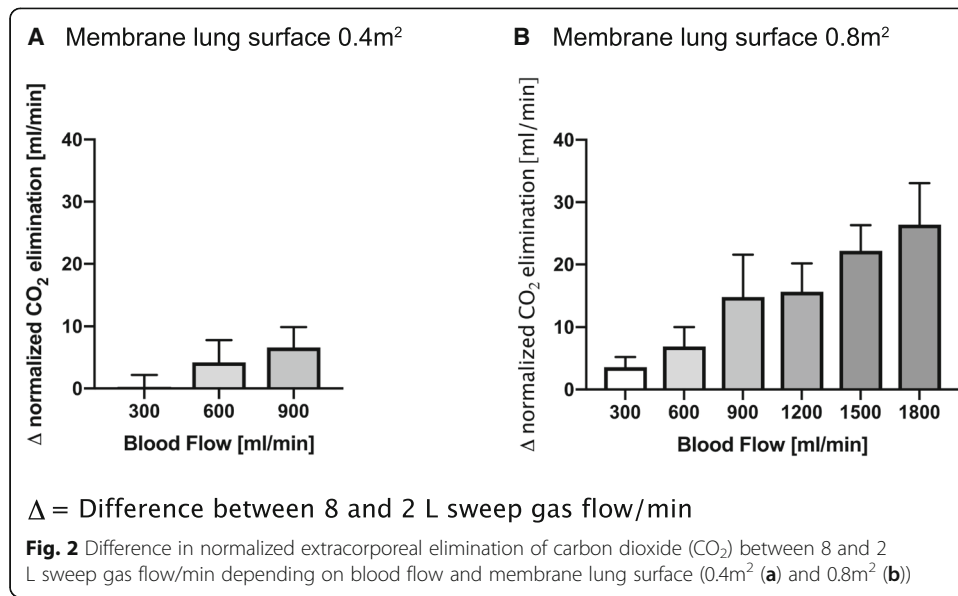
### Results

For independent comparison, normalized  $CO_2$  elimination (Figs. 1 and 2 and Table 1) was calculated by normalizing the partial pressure of  $CO_2$  before the membrane lung to 45 mmHg to compensate for different  $PCO_2$  levels pre-membrane lung as previously described [18, 21]. Non-normalized extracorporeal  $CO_2$  removal (Fig. 3) with different  $CO_2$  levels pre-membrane lung are presented in Fig. 4, demonstrating a blood flow-, sweep gas flow- and membrane lung-dependent  $CO_2$  removal capacity.

The membrane lung with a surface of  $0.4\text{ m}^2$  allowed a maximum normalized  $CO_2$  elimination rate of  $41 \pm 6\text{ mL/min}$  with 8 L/min sweep gas flow and 900 mL blood flow/min (Fig. 1 and Table 1). Increase of a sweep gas flow from 2 to 8 L/min, at its maximal effect, increased the normalized  $CO_2$  elimination from  $35 \pm 5$  to  $41 \pm 6\text{ mL/min}$  at 900 mL blood flow/min, whereas at lower blood flow rates, any increase was less effective, levelling out early on at 4 L sweep gas flow/min.

The membrane lung with a surface area of  $0.8\text{ m}^2$  showed comparable results within blood flow rates from 300 to 600 mL/min, although the absolute amount of  $CO_2$

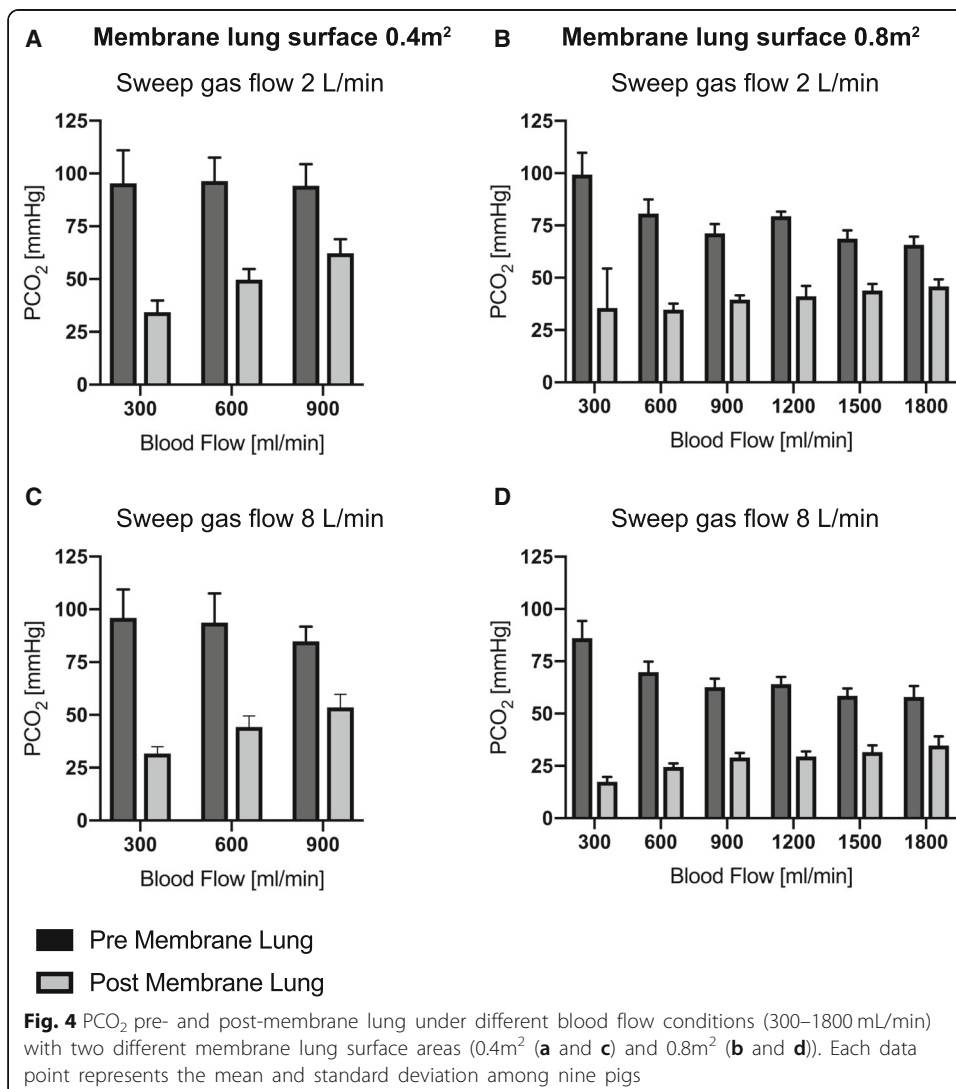
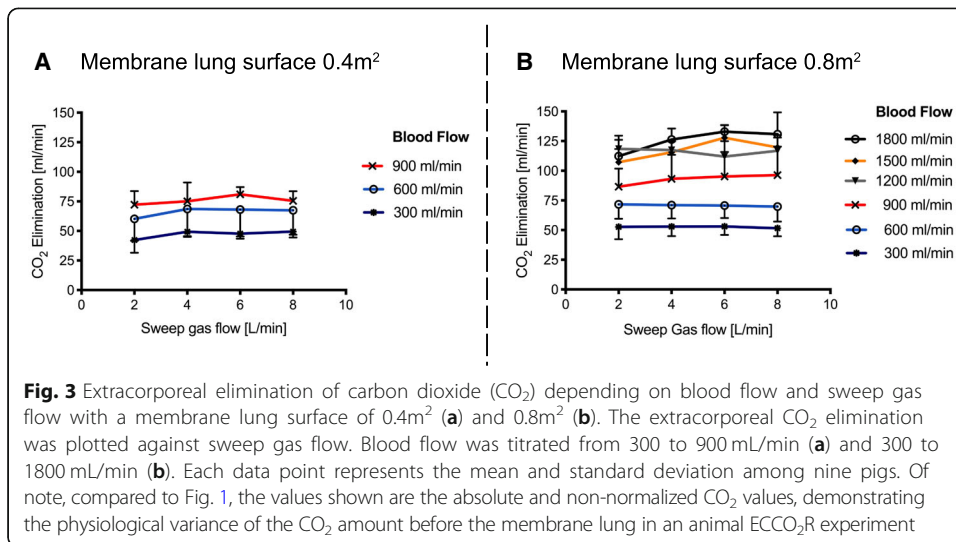




removal was higher than with a surface area of 0.4 m<sup>2</sup> (Fig. 1 and Table 1). However, the effect of increased sweep gas flow from 2 to 8 L/min was comparable to the smaller membrane lung. When progressing from 900 mL/min up to 1800 mL/min, there was an increasing effect of increasing sweep gas flow on extracorporeal CO<sub>2</sub> elimination (Table 1). Blood flow rates of 900 mL/min showed an increase in normalized CO<sub>2</sub> elimination from 55 ± 9 to 70 ± 14 mL/min (delta normalized CO<sub>2</sub> elimination of 15 mL/min) by increasing the sweep gas flow from 2 to 8 L/min. With each step of increase in blood flow (steps of 300 mL/min), the influence of increased sweep gas flow also increased. Accordingly, the maximum delta between 2 and 8 L sweep gas flow/min (26 ± 7 mL/min) occurred with 1800 mL blood flow/min.

**Table 1** Normalized extracorporeal CO<sub>2</sub> elimination (absolute values are given in millilitre per minute). Normalized CO<sub>2</sub> elimination was calculated by normalizing the partial pressure of carbon dioxide before the membrane lung to 45 mmHg. Values are given as mean with standard deviation

	Sweep gas flow 2 L/min	Sweep gas flow 4 L/min	Sweep gas flow 6 L/min	Sweep gas flow 8 L/min
ML surface 0.4m <sup>2</sup>				
BF 300 mL/min	20.1 ± 2.9	23.3 ± 3.2	23.2 ± 2.3	23.7 ± 3.7
BF 600 mL/min	27.8 ± 5.8	32.2 ± 6.9	32.0 ± 7.6	32.0 ± 6.6
BF 900 mL/min	34.8 ± 4.9	37.7 ± 8.7	41.7 ± 4.5	41.4 ± 6.3
ML surface 0.8m <sup>2</sup>				
BF 300 mL/min	23.8 ± 2.8	26.3 ± 4.7	27.0 ± 4.3	27.4 ± 3.0
BF 600 mL/min	39.4 ± 4.1	43.4 ± 5.0	45.2 ± 6.1	46.3 ± 6.4
BF 900 mL/min	54.9 ± 8.5	62.1 ± 12.1	66.3 ± 11.9	69.8 ± 14.1
BF 1200 mL/min	66.6 ± 6.4	73.8 ± 4.9	77.4 ± 7.2	82.3 ± 9.0
BF 1500 mL/min	70.2 ± 6.6	81.5 ± 7.5	93.2 ± 10.2	92.4 ± 7.6
BF 1800 mL/min	74.5 ± 11.0	93.3 ± 8.4	100.0 ± 11.0	100.9 ± 12.0



Of note, Fig. 4 demonstrates a linearly decreasing CO<sub>2</sub> pre-membrane lung with increasing blood flow rates (Figs. 4a and b) with a more pronounced effect with higher sweep gas flow rates (Figs. 4c and d).

## Discussion

The present study provides the most comprehensive overview to date of the influence of sweep gas flow on the CO<sub>2</sub> removal capacity of ECCO<sub>2</sub>R systems with varying blood flow rates and membrane lung surface areas as used in this model. It adds to previous animal studies on technical determinants of successful vv-ECCO<sub>2</sub>R. While two former studies using a comparable study design have primarily focused on the impact of the blood flow rate [16] and the membrane lung surface area [18], respectively, on the capability of the system to remove CO<sub>2</sub>, the present study aimed to determine the role of the sweep gas flow in the intersection of these three key components of vv-ECCO<sub>2</sub>R. The main finding is that the impact of the sweep gas flow varies depending on the size of the membrane lung and the chosen blood flow rate. Thus, the impact of the sweep gas flow rate is clinically negligible when using a small membrane lung surface area of 0.4 m<sup>2</sup> in addition to blood flow rates of up to 900 mL/min.

In contrast, the impact of the sweep gas flow rate appears to be clinically more critical when using a larger membrane lung surface of 0.8 m<sup>2</sup>. In this case, the difference of the CO<sub>2</sub> elimination, following mathematical normalization to 45 mmHg when comparing 8 and 2 L sweep gas flow per minute, is at least 10 mL/min or even higher at a blood flow rate of 900 mL/min, and this difference appears to gradually increase when using even higher blood flow rates. Eventually, this difference reached approximately 25 mL/min at a blood flow rate of 1800 mL/min, taking into account that normalized CO<sub>2</sub> elimination is calculated, thus the real CO<sub>2</sub> removal capacity might be even higher if CO<sub>2</sub> before the membrane lung is above 45 mmHg.

The present findings confirm one of the previous porcine studies on pathophysiological and technical considerations of ECCO<sub>2</sub>R [16]. This study had already signified that the capability of extracorporeal CO<sub>2</sub> removal rises with increasing sweep gas flow rates. However, the experiments of increasing sweep gas flow rates in this former study were performed with a fixed blood flow rate of 1000 mL/min. Therefore, the current study adds to the existing knowledge in so far as the increased capability to extra-corporally remove CO<sub>2</sub> at higher sweep gas flow rates is substantially greater with higher blood flow rates, but negligible with a blood flow below 600 mL/min.

However, in view of the current and the previous findings, the amount of blood flow still appears to play the most important role for the success of vv-ECCO<sub>2</sub>R. Nevertheless, current evidence, including the present trial, now suggests that there is a complex interplay between the three major selectable regulating variables, i.e. blood flow rate, sweep gas flow rate and the membrane lung surface area.

The present study has some important clinical implications: First, severe hypercapnia is most sufficiently handled by ECCO<sub>2</sub>R with a large enough membrane lung surface area ( $\geq 0.8$  m<sup>2</sup>) using higher blood flow as well as sweep gas flow rates. Second, to achieve the desired results for vv-ECCO<sub>2</sub>R, the main technical determinants of vv-ECCO<sub>2</sub>R (membrane lung surface area, blood flow rate and sweep gas flow rate) should be assessed before starting up the procedure. In addition, in order to adequately compare different methods, these technical conditions have to



be determined in advance and reported in clinical studies. This may be most relevant in future clinical trials with adaptive designs which are dependent on the CO<sub>2</sub> removal capacity.

The present study has some limitations related to the porcine model used and the calculated CO<sub>2</sub> removal. These limitations have been extensively discussed in the previous publications on vv-ECCO<sub>2</sub>R using a very similar setting for the animal experiments and are, therefore, with reference to the previous studies only briefly addressed [16, 18]. First, data acquired in pigs cannot automatically be transferred into the clinical scenario; however, it has been shown that CO<sub>2</sub> production in pigs is comparable to CO<sub>2</sub> production observed in adult humans requiring mechanical ventilation [23], likely allowing comparison. Second, the typical clinical scenario of exacerbated chronic obstructive pulmonary disease (COPD) with severe airflow limitation was not simulated. Therefore, the interaction between vv-ECCO<sub>2</sub>R and mechanical ventilation could not be investigated. Third, the animals were not critically ill and had a normal CO<sub>2</sub> production in contrast to patients with an acute exacerbation of COPD or with sepsis, who usually have higher CO<sub>2</sub> production. Therefore, the conclusions regarding the clinical effectiveness of different systems used for vv-ECCO<sub>2</sub>R in the clinical setting must be tempered.

## Conclusions

The influence of sweep gas flow on the CO<sub>2</sub> removal capacity of ECCO<sub>2</sub>R systems depends predominantly on blood flow rate and membrane lung surface area. In this model, considerable CO<sub>2</sub> removal occurred only with the larger membrane lung surface of 0.8m<sup>2</sup> and when blood flow rates of ≥ 900 mL/min were used. Furthermore, it can be emphasized that sweep gas flow has a significant impact on CO<sub>2</sub> removal capacity in ECCO<sub>2</sub>R, but only if blood flow rates of 900 mL/min and above are applied. Finally, in regard to future ECCO<sub>2</sub>R clinical trials, especially those with adaptive designs, it will be important to understand the influence of sweep gas flow in the intersection of blood flow, membrane lung surface area and sweep gas flow.

## Abbreviations

ML: Membrane lung; vv-ECCO<sub>2</sub>R: Veno-venous extracorporeal CO<sub>2</sub> removal

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## Availability of data and materials

All data generated or analysed during this study are included in this published article.

## Authors' contributions

CK designed the study (together with StSt, SiSc, JdM and MM). CK, StSt, JdM, SiSc and MM performed the experiments and data acquisition and analyzed the physiological data together with all co-authors. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The study was approved by the Animal Research Committee of Uppsala University/ Sweden (ethical approval number: C77/16).

## Consent for publication

Not applicable.



### Competing interests

CK received travel grants and lecture fees from Maquet, Rastatt, Germany; StSt received travel grants and lecture fees from Maquet Cardiopulmonary, Rastatt, Germany; and WW received fees for advisory board meetings and lectures from Maquet Cardiopulmonary, Rastatt, Germany. CK and WW received an open research grant for the hospital from Maquet Cardiopulmonary, Rastatt, Germany. A.L, JdM, MM and SiSc reported no conflicts of interest. DB reports serving as the cochair of the trial steering committee for the VENT-AVOID trial sponsored by ALung Technologies; serving on the medical advisory board for Baxter; and previously serving on the medical advisory boards of ALung Technologies and Kadence (Johnson & Johnson), with all compensation for these activities paid to Columbia University.

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### Author details

<sup>1</sup>Department of Pneumology and Critical Care Medicine, Cologne-Merheim Hospital, ARDS and ECMO Centre, Kliniken der Stadt Köln gGmbH, Witten/Herdecke University Hospital, Ostmerheimer Strasse 200, D-51109 Cologne, Germany.

<sup>2</sup>Division of Pulmonary, Allergy and Critical Care, Columbia University College of Physicians and Surgeons/New York-Presbyterian Hospital, New York, NY, USA. <sup>3</sup>Hedenstierna Laboratory, Anesthesiology and Intensive Care, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden.

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