Increased Longevity of a Novel Gas Exchanger System for Low-Flow Veno-Venous Extracorporeal CO2 Removal in Acute Hypercapnic Respiratory Failure

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DOI: https://doi.org/10.1159/000526582

Blood Purification

Research Article

Blood Purif
DOI: 10.1159/000526582

Received: February 8, 2022
Accepted: July 15, 2022
Published online: November 2, 2022

Increased Longevity of a Novel Gas Exchanger System for Low-Flow Veno-Venous Extracorporeal CO_2 Removal in Acute Hypercapnic Respiratory Failure

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Keywords
Extracorporeal circulation · Extracorporeal CO_2 removal · Respiratory failure · Lung protective ventilation · Acute respiratory distress syndrome · Chronic obstructive pulmonary disease · Respiratory acidosis

Abstract

Introduction: Low-flow veno-venous extracorporeal CO_2 removal ($ECCO_2R$) is an adjunctive therapy to support lung protective ventilation or maintain spontaneous breathing in hypercapnic respiratory failure. Low-flow $ECCO_2R$ is less invasive compared to higher flow systems, while potentially compromising efficiency and membrane lifetime. To counteract this shortcoming, a high-longevity system has recently been developed. Our hypotheses were that the novel membrane system provides runtimes up to 120 h, and CO_2 removal remains constant throughout membrane system lifetime. ***Methods:*** Seventy patients with pH ≤ 7.25 and/or $PaCO_2$ ≥9 kPa exceeding lung protective ventilation limits, or experiencing respiratory exhaustion during spontaneous breathing, were treated with the high-longevity ProLUNG system or in a control group using the original gas exchanger. Treatment parameters, gas exchanger runtime, and sweep-gas VCO_2 were recorded across 9,806 treatment-hours and retrospectively analyzed. ***Results:*** 25/33 and 23/37 patients were mechanically ventilated as opposed to awake spontaneously breathing in both groups. The high-longevity system increased gas exchanger runtime from 29 ± 16 to 48 ± 36 h in ventilated and from 22 ± 14 to 31 ± 31 h in awake patients ($p < 0.0001$), with longer runtime in the former ($p < 0.01$). VCO_2 remained constant at 86 ± 34 mL/min ($p = 0.11$). Overall, $PaCO_2$ decreased from 9.1 ± 2.0 to 7.9 ± 1.9 kPa within 1 h ($p < 0.001$). Tidal volume could be maintained at 5.4 ± 1.8 versus 5.7 ± 2.2 mL/kg at 120 h ($p = 0.60$), and peak airway pressure could be reduced from 31.1 ± 5.1 to 27.5 ± 6.8 mbar ($p < 0.01$). ***Conclusion:*** Using a high-longevity gas exchanger system, membrane lifetime in low-flow $ECCO_2R$ could be extended in comparison to previous systems but remained below 120 h, especially in spontaneously breathing patients. Extracorporeal VCO_2 remained constant throughout gas exchanger system runtime and was consistent with removal of approximately 50% of expected CO_2 production, enabling lung protective ventilation despite hypercapnic respiratory failure.

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Introduction

Acute and acute-on-chronic hypercapnic respiratory failure in critically ill patients retains a high mortality [1, 2]. Depending on the cause and extent of hypercapnic respiratory failure, standard management includes noninvasive ventilation to maintain and support spontaneously breathing patients or intubation and mechanical ventilation. During mechanical ventilation, maintenance of lung protective ventilation with low tidal volume (V_T <6 mL/kg IBW) and limited inspiratory plateau pressure (P_{PLAT}) (P_{PLAT} ≤30 mbar) has been shown to decrease mortality in patients with acute respiratory distress syndrome (ARDS) [3]. More recently, the driving pressure (ΔP) as the difference between the P_{PLAT} and the positive end expiratory pressure (PEEP) has been postulated as an independent risk factor for mortality [4, 5]. To ensure lung protective ventilation despite progressive hypercapnic respiratory failure, as studied in patients with ARDS, the pulmonary gas exchange can be supported by extracorporeal CO_2 removal ($ECCO_2R$), reducing V_T, P_{PLAT}, and ΔP [6–9]. In patients mainly suffering from obstructive pulmonary disease such as chronic obstructive pulmonary disease (COPD), intubation, and mechanical ventilation may be avoided by reducing the work of breathing [9, 10]. As stated in a recent consensus statement [9], the challenge remains to balance the invasiveness of adjunctive procedures such as $ECCO_2R$ with the potential benefits. The application of low-flow $ECCO_2R$ reduces the invasiveness of the extracorporeal circuit as compared to higher flow systems due to the preclusion of large-bore catheters and high blood flow. However, low blood flow potentially affects the efficiency of the $ECCO_2R$ system [11] and the membrane lifetime mainly due to coagulation activation [12]. To counteract this shortcoming, a novel high-longevity low-flow $ECCO_2R$ system has recently been developed (ProLUNG high-longevity gas exchanger system, Estor, Milan, Italy), employing an improved geometric configuration, heparin-coated tubing, and a polymethylpentene-based membrane with phosphorylcholine coating as opposed to the conventional, polypropylene-based system. Our hypotheses were that (i) the novel gas exchanger system provides runtimes up to 120 h and (ii) CO_2 removal remains constant throughout membrane lifetime. The present study aimed to test our hypotheses by comparing treatment parameters, membrane runtime, and sweep gas outflow VCO_2 between patients treated with the ProLUNG $ECCO_2R$ system using the high-longevity versus the conventional gas exchanger system.

Materials and Methods

The study protocol was reviewed and approved by the Ethics Committee at the University of Zurich, approval number KEK 2018-00973. Written informed consent for subsequent use of health-related data was obtained from patients and/or relatives as required.

Study Design and Patient Population

All patients treated for hypercapnic respiratory failure with a ProLUNG $ECCO_2R$ system at the Medical Intensive care Unit at the University Hospital of Zurich between October 2009 and January 2017 were included in this single-center, retrospective analysis of prospectively collected data. An initial description of the first 20 patients in this cohort, using the conventional gas exchanger system, was previously reported [12]. Inclusion criteria for $ECCO_2R$ treatment were patients older than 18 years with hypercapnic respiratory failure (pH ≤ 7.25 and/or $PaCO_2$ ≥9 kPa) [9] and exceeding the limits of lung protective ventilation as defined by peak airway pressure (P_{PEAK}) ≤30 mbar, V_T <6 mL kg^{-1} IBW, ΔP <15 mbar [3, 5], and respiratory rate (RR) <25 min^{-1} in mechanically ventilated patients [13] or spontaneously breathing patients at risk for respiratory exhaustion. Exclusion criteria for $ECCO_2R$ treatment were indication for high blood flow extracorporeal membrane oxygenation (ECMO) according to the clinician's application of the ELSO-guidelines [14], contraindications to full systemic anticoagulation, and treatment futility as perceived by the treating physician. The data on treatment parameters, membrane system runtime, and VCO_2 were compared between the ProLUNG $ECCO_2R$ system with a conventional gas exchanger system with 24 h of expected runtime employed from January 2009 to December 2014, and a novel high-longevity gas exchanger system with 120 h of expected runtime used from January 2015 to January 2017.

$ECCO_2R$ Treatment Protocol

Upon the decision by the treating physician to initiate $ECCO_2R$ treatment, a 13F double-lumen dialysis catheter (High Flow Dolphin, Gambro, Lund, Sweden) with a length of either 200 or 250 mm chosen depending on patient size and catheter position was introduced via the right internal jugular vein into the right atrium via ultrasound-guided vessel puncture using the Seldinger technique and digital fluoroscopy or via the femoral vein into the inferior vena cava. A bolus of unfractionated Heparin of 2,500 I.E. followed by a continuous infusion was initiated per protocol before initiation of the $ECCO_2R$ treatment and monitored via anti-FXa activity once per day and 6 h after each dose adjustment, with a goal of 0.3–0.5 I.E. mL^{-1}. $ECCO_2R$ was initiated according to current recommendations [9] with a blood flow target of 400 mL min^{-1}. Sweep gas flow was initially applied at 10 L min^{-1} and titrated according to treatment targets, at a fraction of oxygen (FiO_2) of 0.21. The inlet and pre- and post-membrane pressure (P_{INLET}, P_{PRE}, P_{POST}) were measured using three fluid-filled pressure transducers. The ProLUNG $ECCO_2R$ system employs a peristaltic roller pump to apply volume-controlled blood flow in the range of 100–450 mL/min across a phosphorylcholine-coated polymethylpentene membrane at a membrane surface area of 1.81 m^2 (high-longevity system) or previously a phosphorylcholine-coated polypropylene membrane at a membrane surface area of 1.35 m^2 (conventional system), which is positioned in series after the pump

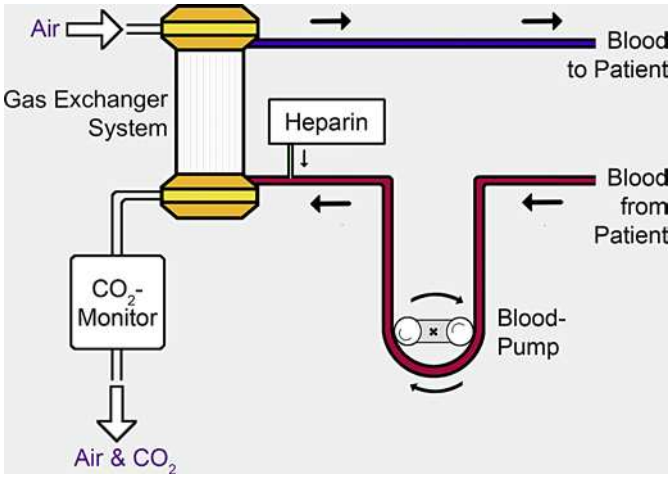

Fig. 1. Schematic illustration of the low-flow veno-venous ECCO$_2$R hemoperfusion system used in the present study.

(Fig. 1). Two separate technical iterations as described elsewhere [12] are combined in the conventional gas exchanger system group in the present study. Quantitative VCO_2 monitoring was provided via volumetric side-streaming infrared CO_2 measurement in the sweep gas outflow (ProLUNG Meter; Estor, Milan, Italy). Membrane systems were exchanged in case of premature clotting as indicated by a rapid increase in the transmembrane pressure gradient or unrecoverable system failure or after a maximum of 120 h of runtime regardless of CO_2 removal efficiency. ECCO$_2$R treatment was weaned and discontinued upon resolution of hypercapnic respiratory failure defined by pH > 7.25 and/or $PaCO_2$ <9 kPa and lung protective ventilation or compensated spontaneous breathing [9], when patients awaiting lung transplantation were transferred to the operation room, when an upgrade to high-flow veno-venous ECMO due to progressive hypoxic respiratory failure was initiated according to the treating physician or in case of decision for treatment withdrawal.

Respiratory Support Treatment Protocol

In mechanically ventilated patients, mechanical ventilation was applied using the Dräger Evita XL ventilator (Dräger Medical, Lübeck, Germany) or the Hamilton S1 ventilator (Hamilton medical, Bonaduz, Switzerland; used in all patients after December 2013), respectively, using Bilevel Positive Airway Pressure or IntelliVent-Adaptive Support Ventilation® modes. Mechanical ventilation in ARDS patients targeted V_T <6 mL kg^{-1} IBW, P_{PEAK} ≤30 mbar, ΔP <15 mbar, and RR <25 min^{-1} regardless of concurrent ECCO2R therapy or not. V_T, RR, respiratory minute volume, P_{PEAK}, PEEP, and FiO_2 were recorded. P_{PEAK} during pressure-controlled ventilation was used as surrogate parameter for P_{PLAT} [15]. Non-intubated, spontaneously breathing patients were supported by noninvasive ventilation, nasal high-flow oxygen therapy, or oxygen supplementation via nasal cannula. FiO_2, support mode, PEEP, and RR were recorded. Escalation of respiratory support with veno-venous ECMO or mechanical ventilation was considered by the treating physician in case of systemic arterial hemoglobin oxygen saturation <90% despite FiO_2 >90% or respiratory exhaustion.

Data Collection and Statistical Analysis

ECCO$_2$R blood flow, sweep gas flow, VCO_2, P_{INLET}, P_{PRE}, and P_{POST} were recorded alongside arterial and pre- and post-membrane blood gas analysis results every 24 h throughout treatment up to 120 h after treatment start to assess ECCO$_2$R treatment effect. Arterial blood gas analysis was additionally recorded 30 min before treatment start to serve as baseline. The same set of parameters was recorded in 12-h intervals starting at gas exchanger system change to assess efficiency throughout gas exchanger system runtime. Anti-FXa activity was monitored every 24 h in steady-state and 6 h after change of the heparin dose. Platelet count, plasma fibrinogen concentration, and international normalized ratio were measured every 24 h. Mechanical and noninvasive ventilation parameters were noted 30 min before and 1, 24, 48, 72, and 120 h after ECCO$_2$R treatment start. Patient characteristics, respiratory parameters, and blood gas measurements were compared between different time points and between the high-longevity and conventional gas exchanger system using one- or two-way linear mixed-effect model analysis [16] with the effect in question entered as fixed effects and intercepts for subjects and per-subject random slopes representing the effect on the dependent variables entered as random effects. For comparison between the longevity and conventional gas exchanger system and the mechanically ventilated versus spontaneously breathing patients, a two-way mixed linear model was used, with both groups entered as fixed effects. p values were calculated using a likelihood ratio test of the full model with the effect in question against a "null model" that lacks the effect in question [17]. p values for individual fixed effects were obtained via the Satterthwaite approximation [18]. A two-sided $p < 0.05$ was considered statistically significant. For all statistical analyses, a fully scripted and reproducible data management pathway was created within the R environment for statistical computing, version 3.4.1 [19]. Linear mixed-effects modeling was performed using the R library lme4, version 1.1.13 [16]. The graphical output was generated using the R library ggplot2, version 2.2.1 [20]. Values are specified as the mean ± standard deviation.

Results

Patient Characteristics and Outcome

Overall, 70 patients (age 56 ± 16 years, BMI 24.5 ± 7.5 kg m^{-2}, 64% male) underwent ECCO$_2$R treatment during the study period. Of those, 33 were treated with the high-longevity and 37 with the conventional gas exchanger system. The most prevalent underlying pathologies were ARDS in mechanically ventilated patients and chronic obstructive pulmonary disease in awake spontaneously breathing patients. Patient characteristics were evenly distributed among both treatment groups. 69% (48/70) of patients were mechanically ventilated at initiation of ECCO$_2$R treatment as opposed to the use of ECCO$_2$R to support awake spontaneous breathing. Weaning of the ECCO$_2$R system was achieved in 70% (49/70) of patients, and 49% (24/49) of these patients were discharged from the hospital after successful weaning of ECCO$_2$R treat-

Table 1. Patient characteristics, etiology of acute respiratory failure, and outcome in patients treated with $ECCO_2R$ using the high-longevity versus conventional gas exchanger system

	Conventional gas exchanger system group	High-longevity gas exchanger system group	*p* value
Patients, *n*	37	33	
Patient characteristics			
Age, years	55±15	58±18	0.41
Weight, kg	73±26	69±21	0.48
Height, cm	168±9	170±8	0.41
Body mass index, kg/m^2	25.5±8.6	23.5±6.1	0.28
Sex (male), *n* (%)	23 (62)	22 (67)	0.89
Etiology of acute respiratory failure, *n* (%)			
ARDS	14 (38)	13 (39)	0.71
COPD	6 (16)	6 (18)	
Cystic fibrosis	5 (14)	5 (15)	
Chronic transplant rejection	5 (14)	4 (12)	
Pulmonary fibrosis	6 (16)	2 (6)	
Other	1 (3)	3 (9)	
Treatment protocol, *n* (%)			
Extended lung protective ventilation	23 (62)	25 (76)	0.33
Awake, spontaneously breathing	14 (38)	8 (24)	
Outcome, *n* (%)			
Treatment withdrawal on $ECCO_2R$	9 (24)	12 (36)	0.24
In-hospital mortality after $ECCO_2R$ weaning	12 (33)	13 (39)	

Values are given as mean±standard deviation for continuous variables and absolute number and relative percentage over all patients for categorical variables. Percentages were calculated within the respective gas exchanger system group.

ment. No differences between both treatment groups were observed for treatment mode and outcome (shown in Table 1).

$ECCO_2R$ System Runtime and Efficiency

135 and 211 of the high-longevity and conventional gas exchanger sets were used for a total treatment time of 4,853 and 4,952 h, respectively (shown in online suppl. Fig. 1; see www.karger.com/doi/10.1159/000526582 for all online suppl. material). The runtime of individual sets was 45 ± 36 and 27 ± 16 h ($p < 0.001$). Fifteen percentage of the high-longevity gas exchanger sets reached a runtime of more than 96 h with 4% reaching the intended lifetime of 120 h, while 38% did not reach a runtime over 24 h (shown in Fig. 2a). For both sets, a longer runtime was observed in mechanically ventilated patients compared to awake spontaneously breathing patients (48 ± 36 vs. 31 ± 31 h for the high-longevity and 29 ± 16 vs. 22 ± 14 h for the conventional gas exchanger set, $p < 0.01$ for ventilation and $p < 0.0001$ for gas exchanger type).

CO_2 removal efficiency, as estimated by the pre-to-post-membrane blood CO_2 partial pressure difference, decreased slightly from 0 to 48 h of individual gas exchanger system runtime in both groups (from 6.3 ± 1.3 to 5.8 ± 1.4 kPa and from 7.1 ± 2.2 to 4.6 ± 1.4 kPa with the high-longevity and conventional gas exchanger system, $p < 0.0001$ for gas exchanger runtime and $p = 0.81$ for gas exchanger type, online suppl. Table 1). However, VCO_2 as measured in the sweep gas remained similar throughout gas exchanger system runtime and did not differ between both groups (from 80.2 ± 29.9 to 76.0 ± 34.6 mL min^{-1} and from 98.0 ± 28.6 to 86.2 ± 30.1 mL min^{-1}, $p = 0.11$ for gas exchanger runtime and $p = 0.93$ for gas exchanger type, shown in Fig. 2b and online suppl. Table 1). Across all measurement points, 86.3 ± 34.2 mL min^{-1} of CO_2 were removed by the extracorporeal circuit.

Consistently, the high-longevity gas exchanger permitted to achieve higher blood flow rates closer to the target of 400 mL min^{-1}, at 359 ± 72 versus 325 ± 86 mL min^{-1} ($p < 0.01$), with an increase in blood flow throughout gas exchanger system runtime (302 ± 97 starting blood flow vs. 382 ± 55 mL min^{-1}, $p < 0.001$, online suppl. Table 1). Catheter inlet negative pressure was similar in both groups ($p = 0.95$), while the transmembrane pressure gradient was found to be consistently lower in the high-longevity gas exchanger group ($p = 0.02$) and remained constant

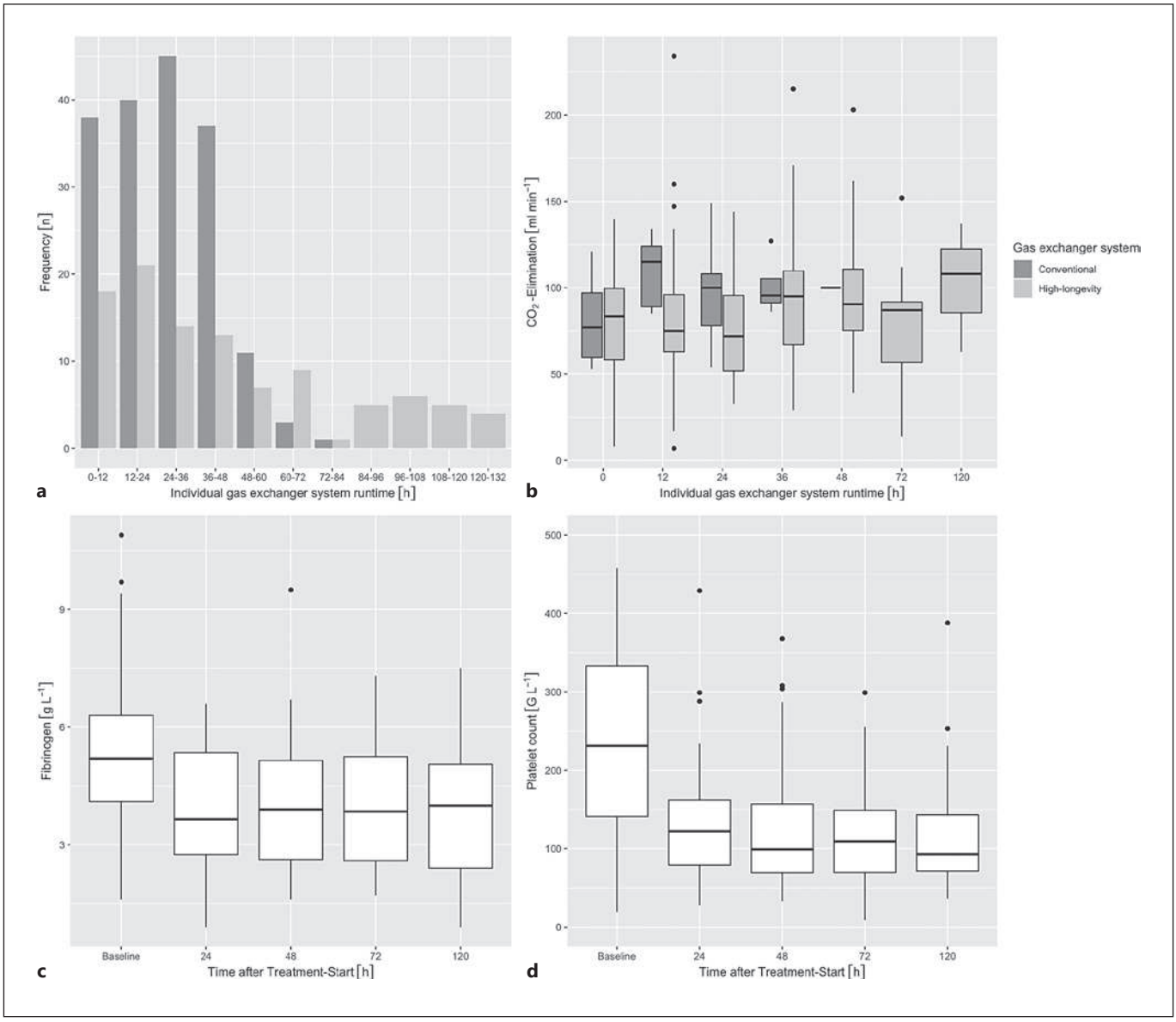

Fig. 2. Frequency of gas exchanger system change is higher in the conventional gas exchanger system (**a**). Quantitative CO_2 elimination was similar in both systems and remained constant throughout the runtime of individual gas exchanger systems (**b**). A decrease in fibrinogen and platelet count was observed throughout treatment in both the high-longevity and conventional gas exchanger systems (**c**, **d**).

throughout gas exchanger system runtime in both groups (p = 0.16, online suppl. Table 1). A trend toward lower catheter inlet negative pressure was observed in awake spontaneously breathing versus mechanically ventilated patients (−102.9 ± 40.2 vs. −75.62 ± 37.83, p = 0.07).

Coagulation Parameters and Adverse Events

Overall, the targeted anti-FXa activity of 0.3–0.4 I.E. mL^{-1} was reached within 1 h of treatment initiation and thereafter remained constant throughout the treatment time (p = 0.82, online suppl. Table 2). Regardless of the gas exchanger system, fibrinogen and platelet count decreased by 11 and 39% within the first 24 h ($p < 0.01$ and $p < 0.0001$, shown in Fig. 2c, d; online suppl. Table 2); the former remained constant throughout treatment (p = 0.51), while the latter further decreased by 5% at 120 h of treatment ($p < 0.0001$). One patient suffered a catheter-related thrombosis and 1 patient non-catheter-related

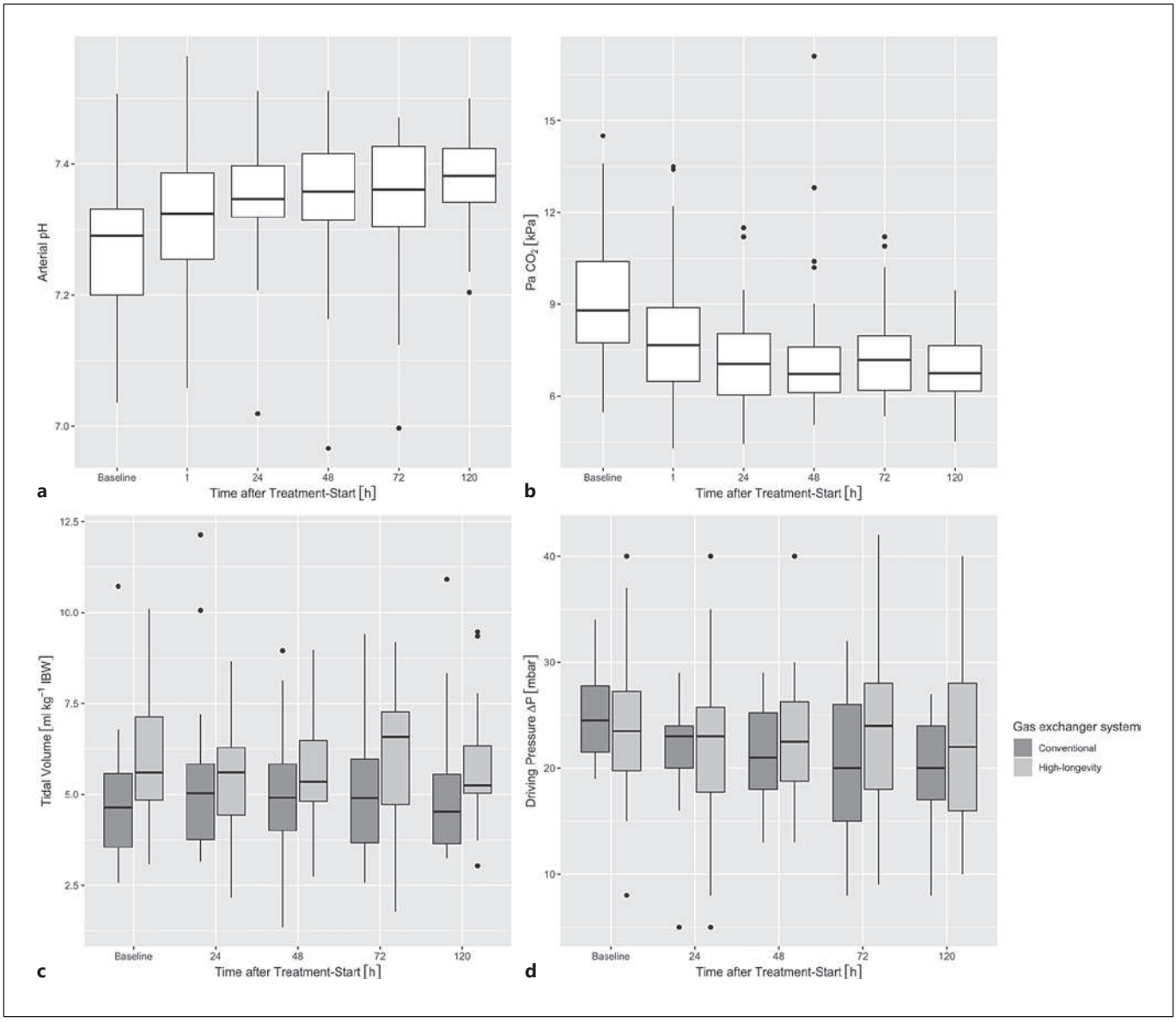

Fig. 3. Normalization of arterial pH (**a**) and $PaCO_2$ (**b**) was observed throughout 120 h after treatment start. In both gas exchanger groups, tidal volumes were kept below 6 mL kg^{-1} throughout treatment (**c**), while pulmonary ΔP could be decreased (**d**). Baseline denotes measurements taken before $ECCO_2R$ treatment initiation per patient treated. IBW, Ideal Body Weight.

bleeding. In another patient, heparin-induced thrombocytopenia was diagnosed, whereas $ECCO_2R$ treatment was continued under anticoagulation with bivalirudin (Angiox®). No catheter-related injuries were recorded. The three observed adverse events occurred in the high-longevity gas exchanger system group.

Impact of $ECCO_2R$ on Respiratory Mechanics

Overall, $PaCO_2$ decreased from 9.1 ± 2.0 kPa to 7.9 ± 1.9 kPa within the first hour of treatment ($p < 0.0001$) and further to 6.9 ± 1.2 kPa at 120 h of treatment ($p = 0.01$, shown in Fig. 3b). pH increased from 7.27 ± 0.10 to 7.32 ± 0.10 kPa within the first hour ($p < 0.0001$) and to 7.38 ± 0.07 at 120 h ($p < 0.01$, shown in Fig. 3a). In 48 mechanically ventilated patients, P_{PEAK} and ΔP decreased within 120 h of treatment from 31.1 ± 5.1 to 27.5 ± 6.8 mbar and

from 24.4 ± 5.6 to 21.5 ± 7.9 mbar ($p < 0.01$ and $p < 0.001$, Fig. 3d) alongside V_T that remained below 6 mL kg^{-1} at 5.4 ± 1.8 and 5.7 ± 2.2 mL kg^{-1} at initiation and 120 h of treatment ($p = 0.61$, shown in Fig. 3c). In 14 of 22 spontaneously breathing patients, intubation and mechanical ventilation were prevented throughout the ICU stay, while 10 of those patients were upgraded to veno-venous ECMO therapy. The need for upgrade to veno-venous ECMO was exclusively observed in patients treated with the intention of bridge to lung transplantation who were suffering from cystic fibrosis ($n = 7$), chronic transplant rejection ($n = 2$), and pulmonary fibrosis ($n = 1$) which experienced secondary severe hypoxic respiratory failure. None of the patients suffering from exacerbated COPD who were treated with the intention to bridge to recovery received secondary ECMO treatment. No differences were found in the effect of $ECCO_2R$ treatment on arterial blood gases and respiratory mechanics using both gas exchanger systems.

Discussion

The present study demonstrates that a novel, high-longevity gas exchanger system for low-flow $ECCO_2R$ provided increased gas exchanger runtime. However, despite the increased longevity demonstrated for the new system compared to the conventional system, the anticipated runtime of 120 h was reached in 4% of applications and overwent 96 h in 15% of applications. Our data confirmed the safety and efficiency of $ECCO_2R$ in a large single-center cohort of patients treated with low-flow $ECCO_2R$ and in a broad range of etiologies and demonstrated the constant removal of approximately 50% of the expected systemic VCO_2.

Improved Gas Exchanger System Permitted Extended Runtime

Gas exchanger runtimes around 17 h were reported for first-generation low-flow $ECCO_2R$ systems [12], alongside relevant coagulatory activation most likely associated the low blood flow rates combined with the large total membrane surface area necessary for efficient CO_2 removal [12, 21]. Coagulation activation during $ECCO_2R$ has been shown to be associated with increased incidence of bleeding complications [21]. The frequency of clotting of the gas exchanger systems translate to accumulated blood loss throughout the treatment. From a technical perspective, the selection of membrane composition, surface area, and properties of the tubing allows to optimize the balance between coagulatory activation and efficiency [22]. In the present study, a modified gas exchanger system equipped with a polymethylpentene-based membrane with phosphorylcholine coating and larger membrane surface area showed an increased runtime of the gas exchanger system of 67% reaching in average 45 h, in comparison to the conventional configuration employing a polypropylene-based, phosphorylcholine-coated membrane. The choice of a comparatively large membrane surface area in the high-longevity system, alongside the former material's lower potential for coagulatory activation but also reduced CO_2 permeability as compared to the latter [22], may explain the relatively high CO_2 removal efficiency that remained similar to the conventional system, while avoiding an increased clotting risk that would otherwise be associated with a larger membrane [21, 23]. Differences in membrane coating in the present system further supported the use of a large membrane surface area of up to 1.8 m^2 [24], whereas in a previous animal model with conventional membranes, the efficiency did not further increase above 1.0 m^2 [11]. Our data show that even though higher blood flow was achieved alongside a lower transmembrane pressure gradient with the new systems, the coagulation activation in the high-longevity system was comparable to the conventional system, as shown by a decrease in fibrinogen and platelets of 11% and 44% during the first 72 h of treatment despite monitored therapeutic anticoagulation. Nevertheless, the observed rate of bleeding complications was low in both groups. Overall, the risk-/benefit ratio and feasibility of low-flow $ECCO_2R$, alongside extended applications for low-flow $ECCO_2R$ such as the combination with renal replacement therapy as previously described [25], could potentially benefit from the increase in runtime demonstrated in the present study, with further technological improvements remaining desirable.

Quantitative Extracorporeal VCO_2 Measurement Revealed Consistent Elimination of CO_2 throughout Gas Exchanger System Runtime

Previous studies have reported $ECCO_2R$ efficiency expressed as the difference in pre-to-post-membrane CO_2 partial pressure to range between 5 and 7 kPa [12, 21]. A moderate decline efficacy throughout the gas exchanger system runtime was observed in these studies, in consistence with our present findings. However, this surrogate parameter is limited by omitting the nonlinear relationship between CO_2 partial pressure and total CO_2 content of the blood. In the present study, we performed quantitative extracorporeal VCO_2 measurements taken

during $ECCO_2R$ therapy and report a removal of approximately 90 mL min^{-1} of CO_2. This finding in a clinical setting is in accordance to the reported quantification of the interrelation between blood flow rate and CO_2 elimination in experimental bench [11] and in animal studies [26]. Our data show that CO_2 removal efficiency by low-flow $ECCO_2R$ remains constant during gas exchanger system runtime when directly measured. One possible explanation for this finding may be the dependency of the pre-to-post-membrane CO_2 partial pressure difference on pre-membrane PCO_2, which could act as a confounding factor in longitudinal measurements due to its decrease over time. Thus, from a clinical perspective, it is noteworthy that despite coagulatory activation and premature clotting in some cases, CO_2 removal remains unaffected throughout gas exchanger system runtime.

Low-Flow $ECCO_2R$ Supported Respiratory Mechanics in Mechanically Ventilated and Spontaneously Breathing Patients with Acute Hypercapnic Respiratory Failure

In accordance with previous studies [8, 27], the present study shows a high success rate in enabling lung protective ventilation in mechanically ventilated patients with hypercapnic respiratory failure, even with worsening lung function. While previous studies have used varying blood flow rates and cannulation sizes to achieve $ECCO_2R$ [8], the present study represents to our knowledge the largest cohort of patients treated with low-flow $ECCO_2R$ using a single 13F double-lumen vascular access technique, demonstrating that pulmonary ΔP during mechanical ventilation could be reduced over time while maintaining tidal volume below 6 mL kg^{-1}. Together, these changes in pulmonary mechanics indicated an improvement of lung compliance, which is a requirement for a successful bridge-to-recovery strategy supported by $ECCO_2R$. Overall, however, the patients included in the present study have a higher mortality as compared to some previous studies [6, 21]. The difference in observed mortality may be mainly explained by differences in underlying disease conditions and severity of disease among studies. Nevertheless, like for all invasive techniques, careful patient selection for $ECCO_2R$ taking prognosis and potential for recovery into account should be prioritized as previously stated [28] and deserves further investigation. In spontaneously breathing patients, our data confirm previous findings [29], supporting the utility of $ECCO_2R$ to avoid intubation in patients suffering from COPD. The 36% lower catheter inlet pressure observed in spontaneously breathing patients as compared to mechanically ventilated patients suggests that further advances in catheter technology may mitigate the interaction between high negative inspiratory forces and extracorporeal blood flow to increase the gas exchanger longevity of $ECCO_2R$ in spontaneously breathing patients. In patients with hypercapnic respiratory failure due to cystic fibrosis and chronic transplant rejection, where $ECCO_2R$ was initiated with the intention of bridge to transplantation, $ECCO_2R$ served to reduce the total time of awake ECMO therapy, which had to be initiated during disease course due to a subsequent decline in oxygenation capacity. In these cases, current $ECCO_2R$ systems may hold an economic disadvantage in exchange for a temporary reduction in invasiveness. These findings are consistent with previous studies using high-flow $ECCO_2R$ patients [30]. Further, even considering recent studies, it remains to be answered if lung protective or ultra-protective ventilation strategies supported by $ECCO_2R$ may have a positive impact on outcome [31].

Limitations

Due to the retrospective, non-randomized study design, limitations include a possible gain of treatment experience during the observation period of 7 years. Consistent with the ongoing discussion in the current literature, we believe that the main changes could pertain to the decision when to initiate $ECCO_2R$ treatment [28], which would only have a minor influence on the comparison between both gas exchanger systems. Further, as a prospectively collected but retrospectively analyzed study, a selection bias cannot be excluded. However, patient characteristics were comparable between groups. Even though the proportion of spontaneously breathing patients as opposed to mechanically ventilated patients included in the conventional system group was 38% versus 24% in the high-longevity system group, and more membrane system clotting has been observed in spontaneously breathing versus mechanically ventilated patients; the absence of a statistically significant difference in these proportions in both groups deprioritizes this factor as a major source of bias. The use of 13F double-lumen catheters may have contributed to a higher pre-membrane pressure and/or lower blood flow rate as compared to slightly larger catheters, such as 14 or 15F, which could further increase the membrane system runtime. This does not influence the comparison between both groups since the employed catheters remained the same. For analysis of gas exchanger efficiency through-

out the treatment, later time points per definition only include the analysis of still intact sets, thus leading to a possible selection bias. Nevertheless, even in case of early clotting and need for replacement of a gas exchanger set, efficiency remained constant throughout the entire lifetime of a gas exchanger set.

Conclusions

Using a high-longevity gas exchanger, membrane lifetime in low-flow $ECCO_2R$ could be extended in comparison to previous systems. However, the targeted lifetime of 120 h was achieved in 4% and a runtime of 96 h in 15% of gas exchanger systems. Especially runtimes in spontaneously breathing patients were decreased. $ECCO_2R$ remained constant throughout membrane runtime and was consistent with removal of approximately 50% of expected systemic CO_2 production measured by VCO_2. Hypercapnia was reduced in spontaneously breathing patients as well as in invasive mechanically ventilated patients, and ventilation invasiveness could be reduced after initiation of $ECCO_2R$ treatment. $ECCO_2R$ remains a resource-demanding treatment, and patient selection remains a key issue in order to avoid futile treatment.

Acknowledgments

The authors wish to thank Eva-Maria Kleinert for her support during treatment and data collection.

Statement of Ethics

The study protocol was reviewed and approved by the Ethics Committee at the University of Zurich, approval number KEK 2018-00973. Written informed consent for subsequent use of health-related data was obtained from patients and/or relatives as required.

Conflict of Interest Statement

Matthias Peter Hilty has received financial compensation for travel and accommodation from Baxter Inc. in the past. The other co-authors state no conflicts of interest.

Funding Sources

This research did not receive any funding from agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

Shalimar Mila Konopasek collected data, analyzed data, drafted the manuscript; Stefanie Klinzing analyzed data, and edited the manuscript; Pedro David Wendel Garcia analyzed data and edited the manuscript; Matthias Peter Hilty designed the study, treated patients, collected data, analyzed data, and drafted the manuscript; Marco Maggiorini designed the study, treated patients, and edited the manuscript.

Data Availability Statement

Data supporting the conclusions of the present study are included in this article or its online supplementary material files. Further inquiries can be directed to the corresponding author.

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