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A novel pump-driven veno-venous gas exchange system during extracorporeal CO_2-removal

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Take-home message $ECCO_2$-R using iLA activve® in a setting of intermediate invasivity and mid-range blood flow can effectively remove CO_2. A clinically relevant oxygenation effect could be observed even at relatively low blood flow, which may help in designing an extracorporeal circuit tailored to a patient's individual needs.

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Abstract *Purpose:* Pump-driven veno-venous extracorporeal CO_2-removal ($ECCO_2$-R) increasingly takes root in hypercapnic lung failure to minimize ventilation invasiveness or to avoid intubation. A recently developed device (iLA activve®, Novalung, Germany) allows effective decarboxylation via a 22 French double lumen cannula. To assess determinants of gas exchange, we prospectively evaluated the performance of $ECCO_2$-R in ten patients receiving iLA activve® due to hypercapnic respiratory failure. *Methods:* Sweep gas flow was increased in steps from 1 to 14 L/min at constant blood flow (phase 1). Similarly, blood flow was gradually increased at constant sweep gas flow (phase 2). At each step gas transfer via the membrane as well as arterial blood gas samples were analyzed. *Results:* During phase 1, we observed a significant increase in CO_2 transfer together with a decrease in $PaCO_2$ levels from a median of 66 mmHg (range 46–85) to 49 (31–65) mmHg from 1 to 14 L/min sweep gas flow ($p < 0.0001$), while arterial oxygenation deteriorated with high sweep gas flow rates. During phase 2, oxygen transfer significantly increased leading to an increase in PaO_2 from 67 (49–87) at 0.5 L/min to 117 (66–305) mmHg at 2.0 L/min ($p < 0.0001$). Higher blood flows also significantly enhanced decarboxylation ($p < 0.0001$). *Conclusions:* Increasing sweep gas flow results in effective CO_2-removal, which can be further reinforced by raising blood flow. The clinically relevant oxygenation effect in this setting could broaden the range of indications of the system and help to set up an individually tailored configuration.

Keywords $ECCO_2$-R · iLA activve® · Hypercapnia · Decarboxylation · Extracorporeal circulation

Introduction

Extracorporeal gas exchange as supportive therapy in severe lung failure has become increasingly popular during the last years since technological progress has resulted in more biocompatible and effective systems. Replacement of failing lungs usually is achieved by veno-venous extracorporeal membrane oxygenation (ECMO) systems providing oxygenation as well as decarboxylation. The amount of CO_2-removal is mainly dependent on sweep gas flow and can be effectively achieved with blood flows through a gas exchange membrane from as low as 0.3–0.4 L/min to a maximum of about 1.0–1.5 L/min [1]. Oxygenation in contrast mainly depends on blood flow and usually requires flows of more than 60 % of cardiac output to achieve adequate oxygen delivery by

concomitantly reducing invasiveness of mechanical ventilation [2].

Extracorporeal CO_2-removal ($ECCO_2$-R) is used to enable tidal volume reduction even beyond standard of care lung-protective ventilation from the currently recommended 6 mL/kg IBW (ideal body weight) towards the range of 3–4 mL/kg. While this concept called "ultra-protective ventilation" has been shown to be feasible [3, 4], no definitive proof of beneficial effects on outcome in patients with severe respiratory failure exists to date. In isolated hypercapnic lung failure like in acute exacerbated COPD or in terminal chronic lung failure during bridging to lung transplantation, $ECCO_2$-R may effectively support non-invasive ventilation with the aim to avoid intubation or facilitate weaning from the ventilator [5–8].

Systems for $ECCO_2$-R usually are designed to provide low blood flows as well as low invasivity and simple handling. The first device developed exclusively for $ECCO_2$-R comprises the iLA® system (Interventional Lung Assist, Novalung, Germany), a pumpless arterio–venous system with blood flowing from the femoral artery through a gas exchange membrane to a femoral vein passively driven by the pressure gradient. Due to the arteriovenous configuration and the low blood flows achievable, no clinically relevant effect on oxygenation occurs. As arterial cannulation is associated with risk of bleeding and limb ischemia [3], pump-driven veno-venous systems to provide CO_2-removal have been developed. All of these systems share the concept of low blood flows, miniaturized pumps, low volume tubing systems as well as special cannulas to guarantee low invasivity. A summary on role and potentials of low-flow CO_2 removal systems is given in a review by Terragni et al. [9]. Gas transfer in low-flow $ECCO_2$-R systems as well as in high-flow ECMO systems has been well described [2, 9], whereas data on gas exchange in the so called "mid-flow range" of blood flow from 1.0 up to 2.5 L/min are however lacking. The aim of our investigation was to gain insights into gas exchange with different settings of pump speed and sweep gas flow using the novel iLA activve® modular system in a setting of intermediate invasivity comprising a miniaturized centrifugal pump together with low volume tubing, a gas exchange membrane optimized for low to midrange blood flows as well as a jugular unicaval 22 F double lumen cannula.

Patients and methods

The study was conducted on a medical intensive care unit of a tertiary care university hospital. The protocol was approved by the local ethical review board. According to Austrian law, informed consent of unresponsive patients was obtained from themselves after regaining responsiveness.

Patients

We included ten critically ill patients undergoing extracorporeal gas exchange with the iLA activve® system in an $ECCO_2$-R setting matching the following criteria: pressure controlled mechanical ventilation, established sedation without spontaneous breathing, stable hemodynamic conditions and gas exchange at the time of study entry defined by FiO_2 $\leq$0.80, breathing rate $\leq$20/min, SaO_2 >92 %, pH-value between 7.35 and 7.45 and hemoglobin $\geq$8 g/dl. Exclusion criteria were age <18 or >89 years, pregnancy and participation in another experimental protocol, respectively. Patientś characteristics are shown in Table 1.

$ECCO_2$-R

iLA activve® is a compact extracorporeal pump-driven gas exchange system consisting of a miniaturized centrifugal pump and a polymethylpenthene gas exchange membrane (iLA membrane ventilator®, Novalung, Germany). In all patients a 22 F in diameter and 17 cm in length unicaval double lumen cannula (Novaport® twin, Novalung, Germany) was used to establish jugular venous access. The details of the system and its ability to effectively remove CO_2 are described elsewhere [10]. As tubing and cannula are heparin coated, no pre-heparinization was performed. Patients received a heparin bolus of 5000 units immediately after insertion of the cannula followed by continuous heparin infusion for systemic anticoagulation titrated to keep the activated partial thromboplastin time (aPTT) between 50 and 60 s.

Study protocol

The study was performed in two independent stages: During phase 1, sweep gas flow was increased stepwise from 1 L/min to a maximum of 14 L/min at a constant blood flow of 1.0 L/min. Fifteen minutes after setting each step, blood gas analyses were performed from the patient's arterial line, as well as from iLA tubing at the inlet and the outlet of the gas exchange membrane. At all steps, iLA settings (pump speed, blood flow) as well as pressures (venous suction pressure, intra-membraneous as well as arterial re-perfusion pressure) were recorded.

During phase 2, which was performed 60 min after phase 1, sweep gas flow was set to a constant level providing a pH within the normal range. Blood flow was increased stepwise from 0.5 to a maximum of 2.0 L/min by increasing pump speed. Fifteen minutes after each increase, the same measurements as during phase 1 were performed. Additionally, to assess hemolysis associated with higher pump speed and more negative suction

Table 1 Patient characteristics

Patients	Sex	Age (years)	Height (cm)	Weight (kg)	SAPS II	Diagnosis	CO (L/min)	Blood flow (L/min)	Sweep gas flow (L/min)
1	Female	67	166	80	38	AECOPD	4.2	0.9	2
2	Female	61	180	65	48	BOS, Re-LuTX	5.4	0.9	12
3	Male	45	175	60	59	COPD, LuTX	5.1	1.2	4
4	Female	31	160	45	35	BOS, Re-LuTX	5.1	1.4	10
5	Male	50	180	110	45	AECOPD	6.8	1.2	3
6	Male	25	175	70	57	Status asthmaticus	5.1	1.5	3
7	Male	41	180	120	70	ARDS	6.0	1.0	10
8	Female	26	160	49	42	CF, LuTX	6.9	1.7	4
9	Female	54	155	46	43	Pulmonary fibrosis, LuTX	4.7	1.4	3
10	Female	48	170	80	43	AECOPD	6.9	1.2	2
All (median, range)	Male/female 4/6	47	(25–67)	173		(155–180)	68	(45–120)	44 (35–70)
	5.3 (4.2–6.9)	1.2	(0.9–1.7)	4 (2–12)					

CO cardiac output, *AECOPD* acute exacerbated chronic obstructive pulmonary disease, *BOS* bronchiolitis obliterans syndrome, *Re-LuTX* lung re-transplantation, *ARDS* acute respiratory distress syndrome, *CF* cystic fibrosis, *LuTX* lung transplantation

pressures, free hemoglobin was measured 15 min after setting each step.

Blood gases and hemoglobin values were measured by a standard blood gas analyzer (Radiometer ABL 800 Flex), baseline cardiac output was estimated by pulse curve analysis (Vigileo®, Edwards Lifesciences, Irvine, USA). Ventilator settings were kept constant throughout the study period. In case of spontaneous breathing during the study period, sedation was increased to suppress breathing efforts. Oxygen and crude CO_2 transfer were calculated as difference between oxygen and CO_2 content prior to and after the gas exchange membrane according to standard equations [11]. Since variations in blood PCO_2 values would result in variable CO_2 removal rates, normalized CO_2 exchange rate was calculated based on a moving average of venous PCO_2 according to Wearden et al. [12]. The equations used to calculate gas transfer are given in the "Appendix".

During the study period all patients were monitored by an indwelling arterial line, ECG and pulse oximetry. The study was stopped if oxygen saturation declined to values below 88 %, if hemodynamic instability occurred, or if arterial pH was lower than 7.25 or higher than 7.55.

Statistical analysis

Non-parametric tests were chosen because of the small population studied. Continuous data are given as median and range, categorical variables as percentages. To compare the changes at different iLA settings, a non-parametric one-way ANOVA for repeated measures (Kruskal–Wallis Test) was used. Dunn's multiple comparison post test was used to compare pairs of time points. Calculations were performed by a statistic software package (GraphPad Prism®, GraphPad Software, San Diego, USA). Differences with a p-level less than 0.05 were considered as statistically significant.

Results

Ten patients on $ECCO_2$-R on the iLA activve® system were included into the study. Six patients were female, median age was 47 (range 25–67) years. Median hemoglobin level was 10.3 (8.3–12.4) g/dL, median cardiac output was 5.3 (4.2–6.9) L/min. Patients' characteristics and baseline data prior to study entry are given in Table 1. Ventilatory settings prior to start of $ECCO_2$-R as well as during $ECCO_2$-R immediately prior to study entry are shown in Table 2. During $ECCO_2$-R, $PaCO_2$ decreased significantly with concomitant reduction of ventilatory driving pressure and tidal volume. Two of the patients (20 %) had to be switched to full veno-venous ECMO during their further course, seven patients survived to hospital discharge (70 %). Seven patients remained without device associated complications, in two patients clotting of the gas exchange membrane occurred during $ECCO_2$-R, in one patient thrombosis of the right jugular vein after cannula removal was diagnosed.

Phase 1

Crude CO_2 transfer rate increased significantly with increasing sweep gas flow reaching a plateau from 8 to 14 L/min ($p < 0.0001$, supplemental figure S1a). This plateau was not observed when calculating normalized CO_2 transfer rate, which increased continuously with

increasing sweep gas flow ($p < 0.0001$, Fig. 1a). This was paralleled by continuously decreasing $PaCO_2$ from a median of 66 (range 46–85) mmHg at 1 L/min to 49 (31–65) mmHg at 14 L/min ($p < 0.0001$, Fig. 1b).

Oxygen transfer tended to increase at 10 and 14 L/min ($p = 0.06$, Fig. 1c). PaO_2 however, remained stable until increasing sweep gas flow to 10 and 14 L/min which led to a significant decrease during these two steps from 80 (58–103) mmHg at 1 L/min to 65 (36–95) mmHg at 14 L/min ($p < 0.0001$, Fig. 1d).

Phase 2

Sweep gas flow was set to a median of 4 L/min (range 2–12 L/min). Together with an increasing crude as well as normalized CO_2 transfer rate ($p < 0.0001$, Fig. 2a; supplemental figure S1b), $PaCO_2$ decreased continuously from a median of 60 (39–72) mmHg at 0.5 L/min to 48 (38–62) mmHg at 2.0 L/min with increasing blood flow ($p < 0.0001$, Fig. 2b).

Oxygen transfer increased significantly with higher blood flow ($p < 0.0001$, Fig. 2c). Concomitantly, PaO_2 increased significantly from 67 (49–87) mmHg at 0.5 L/min to 117 (66–305) mmHg at 2.0 L/min ($p < 0.0001$, Fig. 2d), resembling a significant and clinically relevant increase in PaO_2/FiO_2 from 107 (76–218) to 206 (89–508), $p < 0.0001$.

To achieve the desired steps of blood flow, pump speed had to be increased from 2500 (2100–2800) rpm for a blood flow of 0.5 L/min to 6600 (5600–7300) rpm for 2.0 L/min. Venous suction pressure decreased from −6 (−2 to −14) mmHg at 0.5 L/min to −122 (−88 to −185) mmHg at 2.0 L/min (Fig. 3a). Intramembraneous and arterial pressures increased significantly with higher blood flows ($p < 0.0001$, data not shown), while transmembraneous pressure increased only slightly from 4 (1–24) mmHg at 0.5 L/min to 12 (3–22) mmHg at 2.0 L/min ($p = 0.007$). At a blood flow of 2.0 L/min free hemoglobin measured 15 min after adjustment of pump speed rose significantly ($p = 0.03$, Fig. 3b).

Discussion

In the particular setting of extracorporeal gas exchange described herein, effective removal of CO_2 with increasing sweep gas flow could be demonstrated. By using the same gas exchange membrane as in our study (iLA, Novalung, Germany) in a pumpless arterio–venous configuration, comparable results have been generated in a sheep model [13] as well as in patients with acute lung failure [3]. Zhou and co-workers demonstrated increasing CO_2 removal with increasing sweep gas flow up to 10 L/min, while a further increase was associated with only minimally higher rate of CO_2 removal [13]. The same was true in our study with respect to crude CO_2 transfer, which reached a maximum at 8 L/min. $PaCO_2$ however, decreased continuously up to a sweep gas flow of 14 L/min. Patients were sedated to suppress spontaneous breathing for the study period, thus ventilation was kept unchanged throughout the study. As variations in CO_2 production within the short study period under unchanged conditions seems unlikely, this phenomenon most likely reflects the influence of blood CO_2 values on elimination rate. Indeed, when calculating normalized CO_2 elimination rate, a continuous increase in CO_2 transfer could be observed. Moreover, a time dependent effect leading to further decrease of arterial CO_2 could account for this finding. CO_2 elimination seems to undergo a biphasic elimination during $ECCO_2$-R with rapid removal of physically dissolved CO_2 during the first 2 h followed by a smaller reduction in $PaCO_2$ afterwards due to the delayed

Table 2 Mechanical ventilation settings prior to $ECCO_2$-R as well as during $ECCO_2$-R at study baseline

Patients	Vt (mL)		RR (/min)		PEEP (mbar)		PaO_2/FiO_2		$PaCO_2$ (mmHg)	
	Prior to $ECCO_2$-R	Study baseline	Prior to $ECCO_2$-R	Study baseline	Prior to $ECCO_2$-R	Study baseline	Prior to $ECCO_2$-R	Study baseline	Prior to $ECCO_2$-R	Study baseline
1	213	350	25	12	6	8	187	189	87	40
2	354	250	29	15	6	7	142	171	117	75
3	455	300	20	14	6	5	140	82	70	54
4	264	115	10	10	12	8	270	84	61	42
5	443	290	22	14	14	12	102	84	57	40
6	258	300	18	12	5	7	84	180	137	36
7	534	330	25	15	12	16	76	75	52	53
8	130	220	35	11	11	8	101	72	145	64
9	390	270	25	13	4	4	110	169	67	57
10	313	260	14	12	3	6	131	118	75	70
Median	334	280	24	13	6	8	121	101	72	54
Range	(130–534)	(115–350)	(10–35)	(10–15)	(3–14)	(4–16)	(76–270)	(72–189)	(52–145)	(36–75)

Vt tidal volume, *RR* respiratory rate

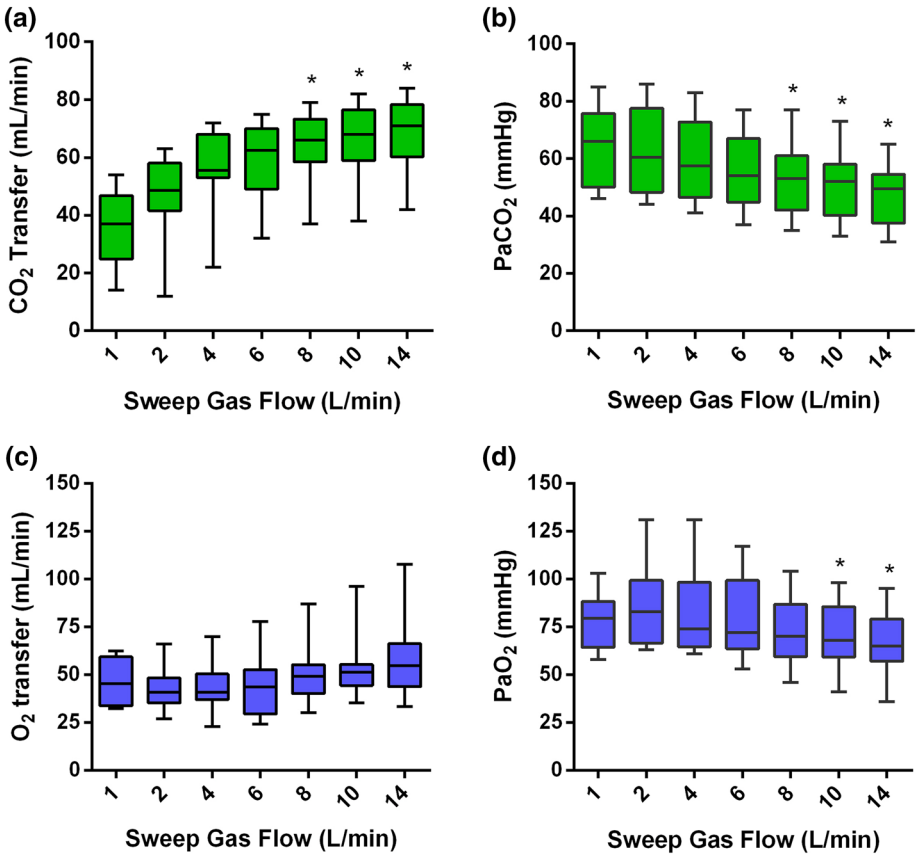

Fig. 1 Normalized CO_2 transfer and $PaCO_2$ (**a**, **b**) as well as oxygen transfer and PaO_2 (**c**, **d**) during stepwise increase of sweep gas flow (study phase 1). *Asterisks* denote statistically significant changes compared to baseline ($p < 0.0001$)

liberation of bicarbonate from slow compartments [14]. The intervals of 15 min between each step were chosen arbitrarily based on clinical experience. The study period for titrating sweep gas flow thus resulted in 105 min, which could be too short a time for carbon dioxide levels to reach a stable equilibrium. This limitation has to be taken into account when interpreting our findings.

In our study, increasing blood flow at constant sweep gas flow led to a less pronounced, but significant increase in CO_2 transfer together with a decrease in $PaCO_2$. These findings are in line with the iLA sheep models of Jayroe et al. and Zhou et al. [1, 13], who both demonstrated increasing CO_2 removal by raising blood flow up to 1.4 and 1.6 L/min, respectively. Our data suggest an increase in CO_2 elimination up to even 2.0 mL/min of blood flow. Recently, a study in patients on veno-venous ECMO did not reveal any effect on CO_2 by raising blood flow from more than 2 L/min to higher levels [2]. Summing up these data, an increase in blood flow up to about 2 L/min might add to CO_2 elimination while at higher levels CO_2 removal seems to be dependent on sweep gas flow only. In clinical practice however, arterio–venous iLA as well as the setting described in our study using the pump driven iLA system, have been shown to effectively eliminate CO_2 at blood flow rates between 1.0 and 1.5 mL/min [10, 15].

In veno-venous extracorporeal gas exchange, oxygenation depends mainly on blood flow. In a study on patients suffering from severe ARDS undergoing veno-venous ECMO therapy, increasing blood flow to 60 % of cardiac output was necessary to adequately supply oxygen and concomitantly enable reduction of invasiveness of ventilation [2]. In our study, increasing blood flow to more than 1.0 L/min led to a clinically significant increase in oxygen transfer and PaO_2. A concomitant beneficial effect on oxygenation could be due to reduction of alveolar pCO_2 and a concomitant increase in alveolar pO_2, according to Dalton's Law. This effect however could not be observed during increasing sweep gas flow with even more pronounced reduction in PCO_2. Although a blood flow of 1.5 and 2.0 L/min resembled only 28 and 38 % of the cohort's median cardiac output, respectively, the increase in PaO_2/FiO_2 would have enabled a less invasive ventilatory support in most patients. It has to be taken into account, however, that suction pressures at a blood flow of 2 L/min in many patients approached negative values associated with possible shear stress to blood cells and ensuing hemolysis [16]. Rising levels of free haemoglobin underline this hypothesis and it may be speculated that keeping patients for longer than 15 min at these negative suction pressures would have led to pronounced damage of blood

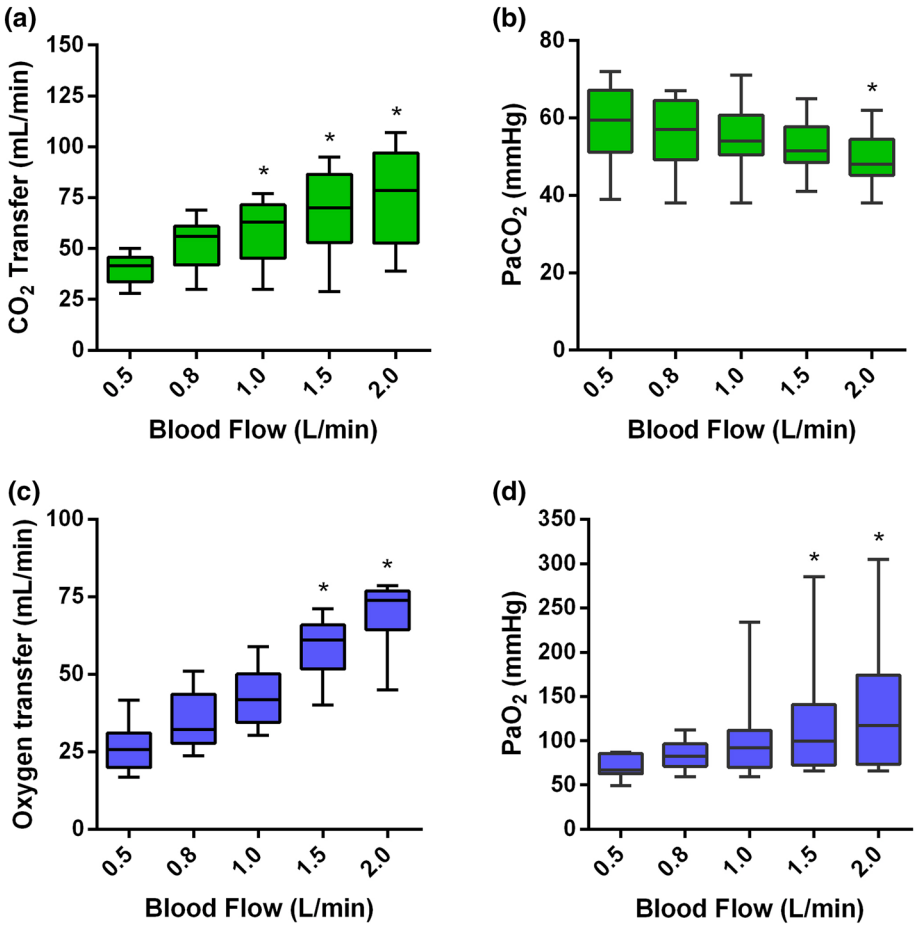

Fig. 2 Normalized CO_2 transfer and $PaCO_2$ (**a**, **b**) as well as oxygen transfer and PaO_2 (**c**, **d**) during stepwise increase of blood flow (study phase 2). *Asterisks* denote statistically significant changes compared to baseline ($p < 0.0001$)

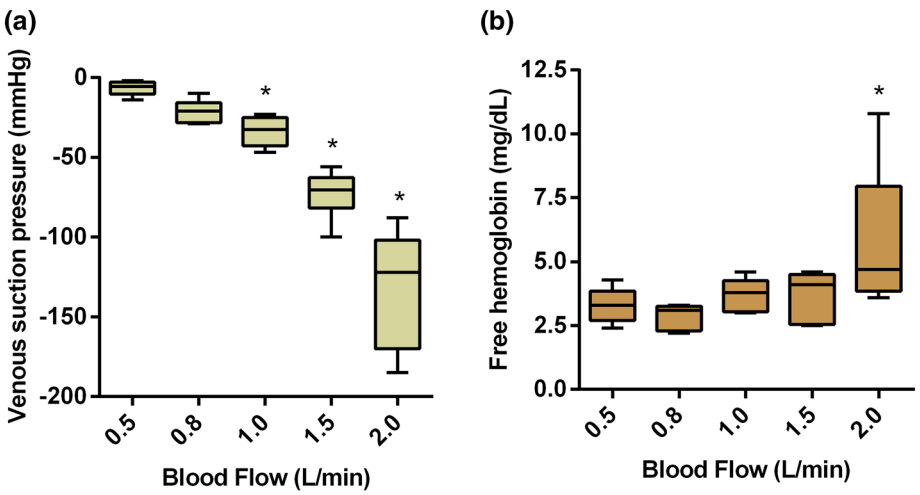

Fig. 3 Suction pressures (**a**) and free hemoglobin levels (**b**) during stepwise increase of blood flow (study phase 2). *Asterisks* denote statistically significant changes compared to baseline ($p < 0.0001$ in **a** and $p < 0.05$ in **b**)

cells. Suction pressures at 1.5 L/min could be kept below −100 mmHg and can be regarded as safe [16]. The interpretation of the relation of extracorporeal blood flow to cardiac output has to be regarded with caution. It has to be emphasized that in our study cardiac output was measured by pulse wave analysis via a Vigileo® monitor (Edwards Lifesciences, Irvine, USA). Referring to Slagt et al. an inherent shortcoming of this technique using uncalibrated arterial pressure waveform analysis is a reduced ability of exact measurement of cardiac output [17]. Additionally, transient vasopressor therapy could have led to further errors in cardiac output estimation [18].

A lack of reliability should therefore be considered regarding the accuracy of values.

Surprisingly, despite a tendency for increasing oxygen transfer with increasing sweep gas flow, systemic oxygenation worsened. Taken into account that iLA blood flow, ventilation settings as well as hemodynamics including cardiac output also remained unchanged throughout the titration of sweep gas flow, an effect on pulmonary gas exchanged must be assumed. Schmidt et al. demonstrated a decrease in arterial pulmonary pressures with increasing sweep gas flow, indicating pulmonary vasodilatation [2]. Better oxygenation in the pulmonary artery due to higher oxygen transfer could have led to abolition of physiologic hypoxic vasoconstriction and consequently to an increase of pulmonary shunt fraction, thus resembling administration of a systemic vasodilator. It has been shown that unselective vasodilation leads to increase of shunt fraction as well as deterioration of systemic oxygenation [19]. However, in phase 2, while oxygen transfer did increase with higher blood flows, arterial oxygenation improved significantly. We hypothesize that the more pronounced effect on oxygen transfer observed during phase 2 might have outweighed the possible negative effect on pulmonary shunt fraction. Our data, however, are not sufficient to prove this hypothesis.

In summary, our results prove that decarboxylation with iLA activve® efficiently takes place with increasing sweep gas flow up to 10 L/min. Higher sweep gas flow rates yield impaired oxygenation and should therefore be avoided. Increasing blood flow to more than 1 L/min seems to amplify the decarboxylation effect and should be considered in severe hypercapnic conditions. Increasing blood flow to $\geq$1.5 L/min leads to a relevant oxygenation effect. The role of extracorporeal gas exchange systems able to provide blood flows in the so called "mid range" has not yet been defined. Although these systems appear to offer lower invasivity by single venous access, smaller then bicaval ECMO single vessel cannulas as well as smaller extracorporeal blood volumes, it remains to be elucidated if they may be advantageous with respect to complications and outcome. Our data show however, that modern systems of extracorporeal gas exchange offer high flexibility and a wide range of respiratory support, which should enable intensivists to tailor the setting to the individual need of a patient. This may offer the possibility of broaden indications from isolated hypercapnia towards additional oxygen supply in patients with mild to moderate hypoxic respiratory failure. Individualizing extracorporeal gas exchange to a specific clinical scenario may well help to enable avoidance of invasive mechanical ventilation in selected groups of high risk patients like those suffering from acute exacerbated COPD, severe asthma or immunosuppression. The findings presented in here may contribute to prepare clinical trials focusing on outcome of acute respiratory failure in these particular groups of patients, if extracorporeal gas exchange with the goal of maintaining spontaneous ventilation is established early.

Compliance with Ethical Standards

Conflicts of interest Two of the authors (Thomas Staudinger, Peter Schellongowski) received speaker fees from Novalung.

Appendix

Calculation of O_2 content, CO_2 content, O_2 transfer and CO_2 transfer.

- O_2 content (mL O_2/dL blood) = 1.34 × (Hb) × SaO_2 + 0.0031 × PO_2. The factor 1.34 is specified in mL × g^{-1} and the factor 0.0031 is specified in mL × dL^{-1} × $mmHg^{-1}$.
- CO_2 content (mL CO_2/dL blood) = 22.4 × (HCO_3^-) + 0.030 × PCO_2. The factor 22.4 (molecular volume of a gas) is specified in L × Mol^{-1}, and the factor 0.030 is specified in mMol × $mmHg^{-1}$.
- O_2 transfer (mL/min) = [(O_2 content)$_{out}$ − (O_2 content)$_{in}$] × blood flow × 10;
- CO_2 transfer (mL/min) = [(CO_2 content)$_{in}$ − (CO_2 content)$_{out}$] × blood flow × 10.

Normalized CO_2 transfer rate.

- VCO_2(norm) = VCO_2(actual) x (45 mmHg/PCO_{2in}).

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