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ORIGINAL ARTICLE

Minimal invasive lung support via umbilical vein with a double-lumen cannula in a neonatal lamb model: a proof of principle

Florian Schmidt[1] · J. Kuebler[2] · M. Ganter[3] · T. Jack[1] · L. Meschenmoser[4] · M. Sasse[1] · M. Boehne[1] · H. Bertram[1] · P. Beerbaum[1] · H. Koeditz[1]

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Abstract
Purpose Acute respiratory distress syndrome, with the need for invasive mechanical ventilation (MV) remains a major cause of neonatal mortality and morbidity. Although venovenous extracorporeal lung support (VV-ECLS) has become a standard of care procedure in neonatal patients with acute pulmonary failure there are no reports regarding the use of a double-lumen cannula for extracorporeal minimal invasive lung support via the umbilical vein.
Methods A neonatal lamb model was used ($n = 3$). Umbilical vein was cannulated with a double-lumen catheter allowing venovenous extracorporeal gas exchange. Cannula was positioned with its tip in the right atrium. VV-ECLS was started and ventilation was stopped. Providing oxygenation and CO_2 removal solely through VV-ECLS hemodynamics, blood gases were measured.
Results Total VV-ECLS without MV was applied to all three neonatal lambs. Time on venovenous ECLS was 60, 120 and 120 min. Initial pCO_2 was 60, 56 and 65 mmHg compared to 31, 32 and 32 mmHg at the end of VV-ECLS. Initial pO_2 was 30, 27 and 26 mmHg compared to 22, 19 and 23 mmHg. Initial lactate was 5, 10 and 3.7 mmol/l compared to 13.3, 12.6 and 11.3 mmol/l at the end of VV-ECLS. MAP at baseline was 51, 52 and 65 mmHg compared to 36, 38 and 41 mmHg at the end of VV-ECLS. In all three lambs inotropes were admitted to maintain MAD >35 mmHg.
Conclusion Even without mechanical ventilation we were able to sufficiently remove pCO_2 with our new minimal invasive VV-ECLS using a double-lumen catheter via the umbilical vein, supporting the idea of a lung protective strategy in neonatal acute respiratory failure. pO_2 was measured 22, 19 and 23 mmHg, respectively, at the end of VV-ECLS, at least partially caused by recirculation phenomenon, which could possibly be improved by different cannula design. Inotropic support was necessary during VV-ECLS to achieve targeted MAD > 35 mmHg. While technically feasible, this new approach might allow further research in the field of extracorporeal lung support and therefore will follow the concept of a lung protective strategy in acute neonatal respiratory failure.

Keywords Venovenous extracorporeal lung support · Umbilical vein · Double-lumen cannula · Neonatal lamb model · Neonatal acute respiratory failure · Neonatal minimal invasive lung support

✉ Florian Schmidt
schmidt.florian@mh-hannover.de

[1] Department of Pediatric Cardiology and Intensive Care Medicine, Medical School Hannover, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany

[2] Department of Pediatric Surgery, Medical School Hannover, Hannover, Germany

[3] Clinic for Swine and Small Ruminants, University of Veterinary Medicine Hannover Foundation, Hannover, Germany

[4] Department of Cardiothoracic Surgery, Transplantation and Vascular Surgery, Medical School Hannover, Hannover, Germany

Introduction

Respiratory failure in term and preterm neonates is associated with significant mortality and morbidity. Although recent efforts had been made in the past to treat neonatal respiratory failure (e.g. prenatal glucocorticoid application, surfactant replacement therapy, low-pressure and low-tidal-volume mechanical ventilation strategies, inhaled nitric

oxide, nasal continuous positive airway pressure), invasive ventilation often is not dispensable. Unfortunately, in doing so, neonates are at a major risk to suffer from ventilator-associated lung injury [1–3]. To avoid ventilator-associated side effects, e.g. muscle atrophy due to analgosedation, pressure-related inflammation processes, which can cause additional lung damage (ventilator-induced lung injury = VILI) [4] new lung protective strategies have been introduced in the clinical management of adult respiratory failure recently [5] [6]. Nevertheless, there are no data in the neonatal population regarding a minimal invasive lung protective strategy including the umbilical vein for an extracorporeal gas exchange.

With outstanding evolutions in the field of extracorporeal life support (ECLS) (i.e. miniaturization, heparin-coated devices, double-lumen cannulas, specialized ECMO Teams) extracorporeal membrane oxygenation (ECMO) has evolved to the standard of care procedure in neonatal and pediatric patients with acute cardiopulmonary failure unresponsive to conventional therapy [7, 8]. Due to the risk of neurological complications associated with the cannulation and ligation of the right carotid artery, VA-ECMO has already been replaced by VV-ECMO cannulation in some tertiary ECMO centers [9, 10]. Routinely in the VV-ECMO setting there still is a need for a "two-vessel" access (one vessel for draining venous blood, the second to deliver oxygenated blood), which is sometimes difficult to realize due to limiting vessel sizes even in the neonatal population.

Recently, new double-lumen cannulas were successfully introduced [11, 12]. These double-lumen cannulas, routinely placed in the jugular or subclavian vein, offer new opportunities in the ECMO management of pediatric and adult patients. Procedural risks might be reduced and patient comfort can be improved, especially when being awake and mobilized under ECMO treatment [13–16]. Considering the optimal vessel access for ECMO cannulas only one clinical case report has demonstrated using the umbilical vein as a reinfusion route in neonatal VV-ECMO support [17]. Although the umbilical vein has also been used in animal artificial placenta models [18, 19] there are currently no data regarding the use of double-lumen cannulas via the umbilical vein for VV-ECLS in humans or animals.

The purpose of this proof of principle study therefore was to evaluate if a minimal invasive extracorporeal lung support is technically feasible using a double-lumen cannula via the umbilical vein in a neonatal lamp model for a short period of time (Figs. 1, 2). If so, and accompanied by ongoing miniaturization processes in the field of extracorporeal devices (e.g. cannulas), this new approach prospectively might bear the potential to be introduced in the treatment of acute neonatal respiratory failure (e.g. meconium aspiration, congenital diaphragmatic hernia) with the intention to allow a rapid and temporary lung assist, limiting morbidity due to surgical neck cannulation and aggressive mechanical ventilation in this vulnerable patient group.

Materials and methods

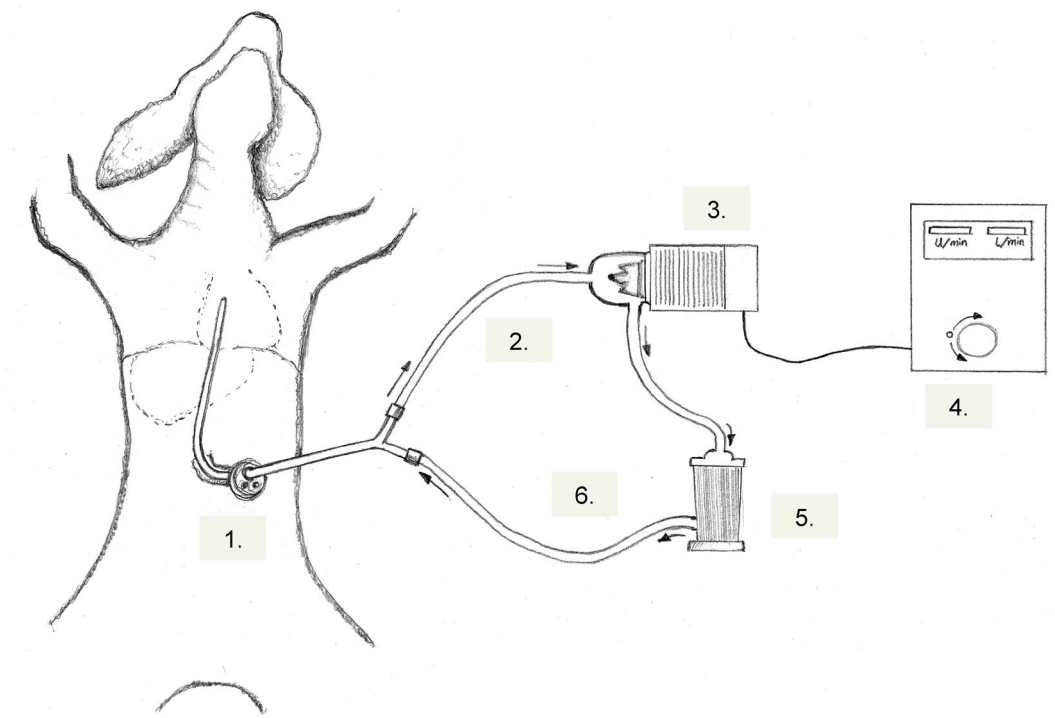
Study design and animal model

After approval by the local animal authorities and in accordance with National Institute of Health Guidelines, three pregnant ewes of German Blackheaded Mutton were used with an average gestation of 139–143 days (term = 150 days). All invasive procedures were conducted using standard sterile technique. Ewes were anesthetized with ketamine–HCl (10 mg/kg/KG) and epidural anesthesia while Cesarean section was done surgically using a midline laparotomy to expose the uterus. Hysterotomy was performed to deliver the three neonatal lambs. After delivery anesthesia of the ewe was acheived by xylazine (0.5 mg/kg/KG) and isoflurane. After delivery and cardiopulmonary adaptation, the neonatal lambs were then anesthetized with intravenous propofol (2–3 mg/kg/KG) and fentanyl (5 µg/kg/KG) whereas continuous relaxation was induced with pancuronium (1–2 mg/kg/KG/h). Intubation was performed using an endotracheal tube with low-pressure cuff (4.0, VYGON) and mechanically ventilated with 2.5 % isoflurane in oxygen-air (FiO_2 0.21). Anesthesia and relaxation were maintained throughout the preparation process with isoflurane, fentanyl (5–10 µg/kg/KG/h) and pancuronium (1–2 mg/kg/KG/h). Body temperature was maintained using an infrared lamp (LP1, Lister, Germany) and a circulating water mattress (HICO Aquatherm 650, Hirtz, Cologne, Germany). Heart rate, invasive blood pressure and body temperature were measured using a patient monitoring system.

Designed as a proof of principle case series, experiments were designed only for a short period of time with a defined maximum of 120 min. After the last measurements, lambs were euthanized by intravenous injection of pentobarbital.

Catheter placement

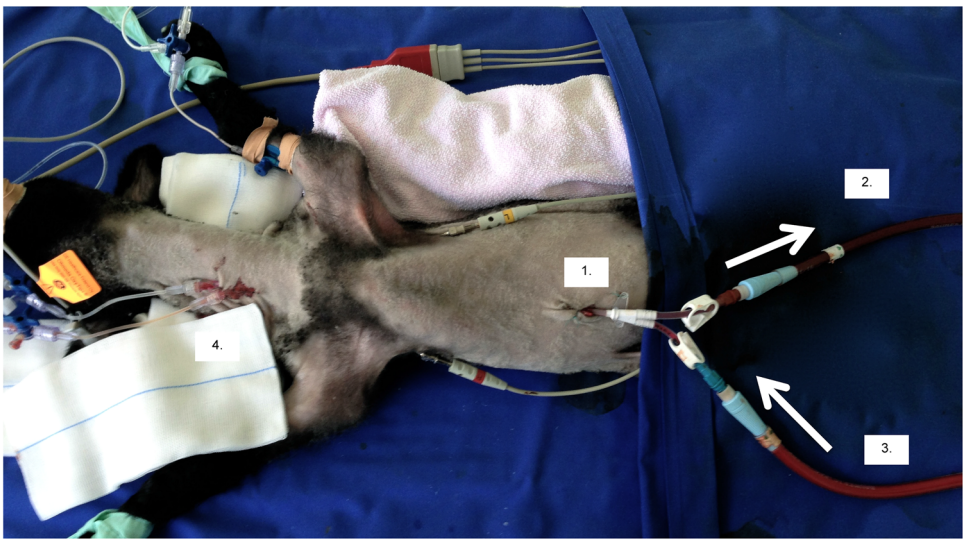
Central monitoring line was placed in the lamb's right carotid artery and a catheter was inserted in the right/left V. saphena lateralis for maintenance IV fluids, fluid boluses, and medications. Arterial pressure was recorded from a calibrated pressure transducer. After the neonatal lambs were instrumented and stable under mechanical ventilation, a bolus of 100 IU/kg heparin was injected intravenously into the lamb and activated clotting time (ACT) was



1. Double-lumen catheter entering the umbilical vein for extracorporeal support; 2. Venous drainage of desoxygenated blood from the right heart; 3. Centrifugal pump; 4. ECMO console; 5. Oxygenator; 6. Oxygenated blood returning through the arterial line of the double-lumen catheter to the right heart;

Fig. 1 Schema of the used VV-ECMO circuit in our near-term lamb model

Fig. 2 In vivo demonstration of the VV-ECMO circuit in our near-term lamb model



1. Double-lumen catheter in the umbilical vein for extracorporeal support; 2. Venous drainage of desoxygenated blood from the right heart to the ECMO circuit; 3. Oxygenated blood returning through the arterial line of the double-lumen catheter to the right heart; 4. Arterial and venous line for invasive monitoring

monitored with a Hemachron machine [Hemochron® Jr. International Technidyne Corporation (ITC), NJ]. Goal ACT was >300 s. The umbilical vessel was then exposed and the umbilical vein was cannulated with the double-lumen catheter (10–11.5 Fr., 120–135 mm, MAHURKAR™, Dialysis Catheter, Covidien, Mansfield, USA). Tip of the double-lumen catheter was placed under radiological control passing the ductus venosus into the right atrium (Fig. 1). The lambs were then attached to the veno-ovenous ECLS circuit (see below). Once extracorporeal circuit was started and clinical situation remained stable, mechanical ventilation was stopped and the endotracheal

tube was clamped while analgosedation and relaxation were maintained using propofol (2–3 mg/kg/h), fentanyl (10–20 μg/kg/h) and pancuronium (1–2 mg/kg/h).

Extracorporeal circuit and settings

For VV-ECLS a Deltastream DP 3, Medos, Medizintechnik AG, Germany centrifugal pump was used in combination with rheoparine coated ¼ in. tubing, Medos Medizintechnik AG, Germany and Hilite 800 LT membrane oxygenator, Medos Medizintechnik AG, Germany for all lambs (Table 1). The sweep gas was of 100 % O_2 throughout the whole experiment. The circuit was primed with 120 ml of isotonic saline solution. Extracorporeal gas exchange was commenced with deoxygenated blood draining from the umbilical vein and the venous side of the double-lumen whereas oxygenated blood was reinfused through the arterial side of the double-lumen catheter to the right atrium.

Data collection and analysis

Fetal blood gases were analyzed (ABL 800, Radiometer, Germany) from the carotid artery. Basic physiologic parameters, hemodynamics and ACT's were recorded in short intervals during extracorporeal support. Complete blood count and a metabolic panel including liver enzymes were sampled at the beginning and end of each experiment. Mean values were calculated using Excel version 14.4.9 software package (Microsoft).

Results

Technical feasibility of VV-ECLS via umbilical vein and clinical annotations

In all three neonatal lambs minimal invasive venovenous extracorporeal lung support (VV-ECLS) could be initiated successfully using a double-lumen cannula via the umbilical vein. Time on VV-ECLS was 60, 120 and 120 min. Circuit flow ranged between 0.22 and 0.55 l/min with associated blood flow levels of 60–170 ml/kg/min (Table 1).

No complications occurred during cannulation and transition to VV-ECLS in all of our three lambs. In lamb No. 1, in which a 10 Fr. double-lumen cannula was used, the targeted extracorporeal support time of 120 min (120′) was not achieved due to hemodynamic instability (Table 1). Although this lamb received intermittent fluid boluses under inotropic support, blood pressure decreased significantly. In this case, time on support was 60 min

Table 1 Animal data, VV-ECMO devices, settings, time supported on VV-ECMO and complications

Lamb no.	Weight (kg)	Gestational age (days)	Pump	Oxygenator	Tubes	Catheter placement/location	ECMO blood flow (l/min)	ECMO gas flow (l/min)	Mean ACT (s)	VV-ECLS support (min)	Clinical annotations
1	3.4	139	Deltastream DP 3, Medos	Hilite 800 LT, Medos	univers.LSM-ECMO-Set 1/4″	10 Fr. Mahurka, 135 mm, double-lumen catheter Umbilical vein	0.2–0.25 (= 60–75 ml/kg/min)	1.0–3-0	>300	60	Hemodynamic instability[a]
2	3.2	140	Deltastream DP 3, Medos	Hilite 800 LT, Medos	univers.LSM-ECMO-Set 1/4″	11.5 Fr. Mahurka, 135 mm, double-lumen Catheter Umbilical vein	0.35–0.55 (= 110–170 ml/kg/min)	1.0–3.0	>300	120	None
3	3.5	143	Deltastream DP 3, Medos	Hilite 800 LT, Medos	univers.LSM-ECMO-Set 1/4″	11.5 Fr. Mahurka, 135 mm, double-lumen catheter Umbilical vein	0.35–0.45 (= 100–130 ml/kg/min)	1.0–3.0	>300	120	None

[a] After 60 min of VV-ECLS decrease of blood pressure and bradycardia of unknown origin

(60′), whereas in the other lambs support could successfully be established for the defined time of 120 min.

VV-ECLS and blood gases, SaO_2 and pH

Initial pCO_2 was 60, 55 and 65 mmHg compared to 31, 32 and 32 mmHg at the end (60/120″) of VV-ECLS demonstrating sufficient CO_2-elemination using the minimal invasive VV-ECLS. Initial pO_2 was 30, 27 and 26 mmHg compared to 22, 19 and 23 mmHg at the end (60/120″) of VV-ECLS. Baseline SaO_2 was 83, 77 and 74 % at initiation of VV-ECLS compared to 57, 49 and 65 % at the end (60/120″) of extracorporeal support. Arterial pH at baseline was 7.22, 7.32 and 7.17 compared to 7.21, 7.19 and 7.17 at the end (60/120″) of VV-ECLS (Table 2).

Lamb hemodynamics and lactate during VV-ECLS

Baseline heart rate under VV-ECLS was 155, 160 and 170/min vs. 155, 100 and 136/min at the end (60/120″) of the experiment. Mean arterial pressure (MAP) at baseline was 51, 55 and 65 mmHg compared to 36.38 and 41 mmHg at the end (60/120″) of VV-ECLS. Inotropes (norepinephrine) initially were started with a continuous infusion of 0.02 µg/kg/min and had to be increased (max. 1.0 µg/kg/min in lamb No. 1) throughout the extracorporeal support in all three lambs to maintain a targeted MAP >35 mmHg. Lactate increased from a baseline level of 5, 10 and 3.7 to 13.3, 12.6 and 11.3 mmol/l at the end (60/120″) of the experiment (Table 3).

Blood count and laboratory values

Laboratory values were collected at baseline and at the end of the experiment in all three lambs. White blood cells count (2.8, 3.2 and 2.0 vs. 1.0, 0.6 and 0.2K/µL), hemoglobin (13.8, 13.5 and 12.6 vs. 7.8, 7.5 and 6.0 g/dL) and platelet count (178, 188 and 169 vs. 123, 126 and 71K/µL) decreased in all three lambs throughout the extracorporeal lung support. Intraabdominal organ parameters including AST (30, 93 and 28 vs. 31, 65 and 12 U/L) and lipase (8, 9 and 6 vs. 10, 6 and 5 U/L) remained stable under extracorporeal support. LDH remained stable throughout the VV-ECLS without signs of hemolysis (Table 4).

Table 2 Respiratory parameters and pH under veno-venous extracorporeal lung support

Clinical parameters	Lamb no. 1	Lamb no. 2	Lamb no. 3
pCO_2 (mmHg)			
Baseline	60	56	65
30 min	35	26	43
60 min	31	28	39
120 min	[a]	32	32
pO_2 (mmHg)			
Baseline	30	27	26
30 min	24	34	17
60 min	22	20	17
120 min	[a]	19	23
SaO_2 (%)			
Baseline	83	77	74
30 min	67	88	40
60 min	57	51	44
120 min	[a]	49	65
pH			
Baseline	7.22	7.32	7.17
30 min	7.26	7.36	7.15
60 min	7.21	7.2	7.18
120 min	[a]	7.19	7.17

pCO_2 arterial partial carbon dioxide, *pO_2* arterial partial oxygen, *SaO_2* arterial oxygen saturation

[a] 60 min of VV-ECLS support due to hemodynamic instability

Table 3 Hemodynamic parameters and lacate under veno-venous extracorporeal lung support

Clinical parameters	Lamb no. 1	Lamb no. 2	Lamb no. 3
HR (/min)			
Baseline	155	160	170
30 min	132	140	152
60 min	155	147	150
120 min	[a]	100	136
BP (mmHg)			
Baseline	75/40 (51)	78/43 (52)	80/50 (65)
30 min	65/32 (43)	68/30 (42)	66/36 (47)
60 min	58/25 (36)	53/34 (33)	55/29 (37)
120 min	[a]	56/29 (38)	57/31 (41)
Lactate (mmol/l)			
Baseline	5	10	3.7
30 min	8.9	12	9.6
60 min	13.3	12.7	11.7
120 min	[a]	12.6	11.3
NA (µg/kg/min)			
Baseline	0.02	0.02	0.02
30 min	0.05	0.04	0.04
60 min	1.0	0.25	0.3
120 min	[a]	0.3	0.35

HR heart rate, *BP* blood pressure, *NA* norepinephrine

[a] 60 min of VV-ECLS support due to hemodynamic instability

Table 4 Laboratory values under veno-venous extracorporeal lung support

Clinical parameters	Lamb no. 1	Lamb no. 2	Lamb no. 3
WBC (K/μL)			
Baseline	2.8	3.2	2.0
End	1.0	0.6	0.2
Hb (g/dL)			
Baseline	13.8	13.5	12.6
End	7.8	7.5	6.0
PC (K/μL)			
Baseline	178	188	169
End	123	126	71
AST (U/L)			
Baseline	30	93	28
End	31	65	12
LDH (U/L)			
Baseline	–	766	411
End	360	439	170
Lipase (U/L)			
Baseline	8	9	6
End	10	6	5

WBC white body cell count, *Hb* hemoglobin, *PC* platelet count, *AST* aspartate aminotransferase, *LDH* lactate dehydrogenase

Discussion

Although mechanical ventilation is a life-saving need in acute respiratory failure the ventilator inherent induced barotrauma is associated with crucial side effects including VILI, and muscle atrophy. While trying to avoid ventilator-associated side effects lung protective strategies including low tidal volume ventilation, e.g. have been developed with the intention to reduce the strains on the lungs during mechanical ventilation to a minimum [20]. As ongoing research demonstrated that that even low tidal volumes can potentially harm the lungs, extracorporeal membrane ventilators recently have been introduced as a in the clinical management of adult respiratory failure [6].

While there are lack of data in the neonatal population, the purpose of this proof of principle pilot study was to evaluate the technical feasibility for a new approach of minimal invasive venovenous ECLS in a neonatal lamb model. Although recent advances had been made in the field of VV-ECLS, this is the first report demonstrating partial extracorporeal lung support without mechanical ventilation using a double-lumen cannula via the umbilical vein.

Contributing to the literature [21] while including our own clinical experiences in VV-ECMO we initially calculated that blood flow levels of 130 ml/kg/min might have the potential to generate gas exchange without additional mechanical ventilation. As we choose a near-term neonatal lamb model (139–143 vs. 145 days = term) we suspected that a total lung support via a double-lumen cannula might be critical without additional mechanical ventilation.

Once on VV-ECLS sufficient CO_2 elimination using our new approach could be achieved without additional mechanical ventilation in all three lambs. Nevertheless there was progressive lactate accumulation with sub-physiologic pO_2 values demonstrating inadequate end-organ perfusion. As our primary intention was to demonstrate technical feasibility we decided to accept lower pO_2 with inadequate oxygen delivery.

Planning our experiment, including literature research, we found out that a 10 Fr. catheter seems the best for our minimal invasive approach. Although our purpose was to use the newly introduced double-lumen Avalon®-Cannula's which were found to be used safely in the management of acute respiratory failure, we realized that sizes smaller <13 Fr. actually were not available at the market (personal contact). Therefore, we decided to use an available 10 Fr. double-lumen dialysis catheter being aware that this catheter might be suboptimal for sufficient VV-ECLS support. While this catheter could be placed without complications no sufficient blood flow could be generated in our first lamb with only 60–75 ml/kg/min (Table 1). Hemodynamic instability was observed and the defined time of 120 min ECLS was not reached. Realizing that cannulation was atraumatic and in order to generate higher blood flows we changed to the 11.5 Fr. double-lumen dialysis catheter in lambs 2 and 3. This catheter could generate targeted blood-flow levels (110–170 ml/kg/min) and demonstrated sufficient CO_2 elimination over the defined 120 min. Nonetheless although blood flow levels seem adequate, oxygenation was severely compromised with rising lactate levels demonstrating insufficient end-organ perfusion, reduced O_2 delivery, and increased oxygen consumption, despite 100 % FiO_2 of the sweep gas.

As recirculation phenomenon is exclusive to venovenous ECMO support, it is standard of care to monitor the amount of recirculating blood in the clinical routine [22]. The Extracorporeal Life Support Organization (ELSO) currently published guidelines at their homepage for the identification and management of recirculation in venovenous ECMO [23]. Although we effectively did not monitor recirculation we would postulate that inadequate oxygen delivery that we measured in all three lambs could be avoided while using a cannula constructed for venovenous gas exchange (e.g. Avalon®-Cannula).

To guarantee hemodynamic stability during VV-ECLS inotropic support increasing concentrations of norepinephrine were necessary in all three lambs. Comparable to the clinical setting of acute respiratory failure where

catecholamines are routinely necessary during ECMO initiation, we were not able to reduce inotropic support throughout the experiment. The need for arising inotropic support with arising lactate levels contributes to the already described insufficient pO_2 delivery without additional mechanical ventilation in our setting with supposed recirculation phenomenon.

Regarding our laboratory values we demonstrated a decrease in white blood cells, platelet counts and hemoglobin during extracorporeal lung support. These findings are well known and can be addressed to hemodilution and surface activation process induced by the extracorporeal components including oxygenator, cannula and tubing systems [24–26]. Although only for a short period of time and therefore without definitive conclusion no laboratory signs of liver damage or hemolysis were seen throughout the experiment with stable AST and LDH levels demonstrating atraumatic position of the cannula.

Although technically feasible, some points have to be addressed prior to applying our new approach of umbilical vein VV-ECLS in a clinical setting:

1. Sample size and bypass time were chosen to provide proof of principle but larger groups and longer observation periods are needed.
2. No pre- and post umbilical vein cannula pressures to assess any kind of cannula trouble (e.g. cannula suction).
3. Detection of recirculation phenomenon which is crucial in the management of venovenous ECMO to guarantee sufficient systemic oxygen delivery [23].

Nevertheless this concept of a minimal invasive lung support, which follows the idea of a lung protective strategy, might have the potential to augment therapeutic strategies in neonatal refractory respiratory failure, e.g. in neonatal patients suffering from meconium aspiration or in the setting of congenital diaphragm hernia.

Conclusion

In summary, our data are demonstrating that minimal invasive extracorporeal lung support with a double-lumen catheter via the umbilical vein is technically feasible. While on VV-ECLS sufficient CO_2 elimination could be achieved without additional mechanical ventilation supporting the idea of a lung protective strategy in acute respiratory failure. Nevertheless, there was progressive lactate accumulation with sub-physiologic pO_2 values demonstrating inadequate end-organ perfusion. While recirculation phenomenon through the double-lumen cannula was not excluded throughout the experiment we would hypothesize that inadequate oxygen delivery will be improved by different cannula design. In its current status this new approach is yet not ready for application in the clinical routine. However, with the ongoing developments in the field of extracorporeal devices these data might allow further research in the field of extracorporeal lung support and therefore will follow the concept of a lung protective strategy in acute neonatal respiratory failure.

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Compliance with ethical standards

Conflict of interest This study was partially funded by Medos Medizintechnik AG, Germany. Dr. Schmidt and Dr. Koeditz report that they have been paid lecture and travel fees from Medos Medizintechnik AG. No other potential conflict of interest relevant to this article was reported. We would like to thank Medos Medizintechnik AG for their technical support (Deltastream DP 3 centrifugal pump and circuit).

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