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Pumpless arterio-venous extracorporeal lung assist compared with veno-venous extracorporeal membrane oxygenation during experimental lung injury

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Editor's key points

- Extracorporeal lung support is used to improve gas exchange in severe respiratory failure.
- Two novel devices were compared in a porcine model of acute lung injury.
- Both devices improved gas transfer and allowed lung-protective ventilation, but differed in their haemodynamic effects.

Background. Extracorporeal lung support is effective to prevent hypoxaemia and excessive hypercapnia with respiratory acidosis in acute respiratory distress syndrome. Miniaturized veno-venous extracorporeal membrane oxygenation (mECMO) and arterio-venous pumpless extracorporeal lung assist (pECLA) were compared for respiratory and haemodynamic response and extracorporeal gas exchange and device characteristics.

Methods. After induction of acute lung injury by repeated lung lavage, 16 anaesthetized and mechanically ventilated pigs were randomized to mECMO (Medos Hilite/Deltastream) or pECLA (iLA Novalung) for 24 h.

Results. Improved gas exchange allowed reduced ventilation and plateau pressure in both groups. An arterio-venous shunt flow of up to 30% of cardiac output resulted in a left cardiac work of 6.8 (2.0) kg m for pECLA compared with 5.0 (1.4) kg m for mECMO after 24 h ($P<0.05$). Both devices provided adequate oxygen delivery to organs. The oxygen transfer of pECLA was lower than mECMO due to inflow of arterial oxygenated blood [16 (5) compared with 64 (28) ml min^{-1} after 24 h, $P<0.05$]. Unexpectedly, the carbon dioxide transfer rate was also lower [58 (28) compared with 111 (42) ml min^{-1} after 24 h, $P<0.05$], probably caused by a Haldane effect preventing higher transfer rates in combination with lower extracorporeal blood flow.

Conclusions. Both devices have the potential to unload the lungs from gas transfer sufficiently to facilitate lung-protective ventilation. Although technically less complex, oxygen uptake and carbon dioxide removal are limited in pECLA, and cardiac work was increased. mECMO overcomes these limitations and might provide better cardiopulmonary protection.

Keywords: adult extracorporeal membrane oxygenation; animal; disease models; respiratory distress syndrome

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Extracorporeal lung support (ECLS) can provide sufficient gas exchange in severe acute respiratory distress syndrome (ARDS), when persistent hypoxaemia or excessive hypercapnia with severe respiratory acidosis despite optimized conservative therapy becomes life threatening.[1–3] The application of conventional extracorporeal membrane oxygenation (ECMO) with an oxygenator and a blood pump requires specifically trained staff to manage complex technical equipment and specific complications.

Various efforts have been made to simplify management and reduce the complication rate of ECLS. One strategy is the miniaturization of ECMO (mECMO) by use of highly integrated rotary blood pumps and optimized capillary membrane oxygenators with a polymethylpentene composite fibre avoiding plasma leakage. This results in reduced filling volumes and blood contacting surfaces.[4 5] Advanced monitoring of pump function (blood flow, rotational speed, arterial and venous circuit pressure, leak tightness, temperature) and bubble detection could also improve safety.[4]

Another approach is by pumpless extracorporeal lung assist (pECLA) that integrates an arterio-venous-driven oxygenator without a blood pump. Using this technique, the

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cardiac output drives extracorporeal blood circulation.[6 7] Such devices, that is, the interventional Lung Assist (iLA Membrane Ventilator®, Novalung, Hechingen, Germany), are characterized by minimized pressure decrease across the membrane and reduced extracorporeal surfaces. Only monitoring of extracorporeal blood flow, invasive mean arterial pressure, and observation of lower limb perfusion on the arterial cannulation site are required.

This study compared a compact veno-venous mECMO and an arterio-venous pECLA for haemodynamic response and respiratory effects, especially pulmonary gas transfer, to extracorporeal circulation. Secondary aims were to compare efficacy of extracorporeal gas exchange and device characteristics for 24 h after induction of experimental acute lung injury (ALI).

Methods

Animal preparation and instrumentation

Experiments were conducted according to ethical principles of laboratory animal care. After approval by the appropriate governmental animal care committee (Landesamt für Natur, Umwelt und Verbraucherschutz Nordrhein-Westfalen, Recklinghausen, Germany), in premedicated female pigs [bodyweight 45 (6) kg], anaesthesia was induced with 5 mg kg^{-1} thiopental and maintained with continuous infusion of 5–10 mg kg^{-1} h^{-1} thiopental and 8–12 μg kg^{-1} h^{-1} fentanyl. Animals were orotracheally intubated and mechanically ventilated in the supine position in a volume-controlled mode with a tidal volume (VT) of 10 ml kg^{-1} bodyweight, inspiratory to expiratory time ratio (*I:E*) 1:2, PEEP 5 cm H_2O, and inspiratory oxygen fraction ($F_{I_{O_2}}$) 1.0 (Servo 300A Ventilator, Siemens Elema, Lund, Sweden). Respiratory rate was adjusted to achieve normocapnia. Seldinger's technique was used to achieve vascular access using a 16 G arterial catheter (Vygon, Ecouen, France) and an 8.5 Fr venous sheath with a right heart catheter positioned in a pulmonary artery (Arrow, Erding, Germany) placed via the femoral artery and vein. Ringer's and hydroxyethylstarch (HES 200/0.5 10%) solutions were infused to maintain intravascular volume status. Urine output was measured via a transurethral bladder catheter. Body temperature was continuously measured using the thermistor of the right heart catheter and a convective air warming system (Warm Touch 5300A, Tyco Healthcare, Neustadt, Germany) was used to maintain normothermia. ALI was induced by repetitive lung lavages with 0.9% saline solution (40 ml kg^{-1} bodyweight) to wash out surfactant until the $Pa_{O_2}/F_{I_{O_2}}$ ratio was <13.3 kPa for at least 1 h.[8]

Arterial, central venous and pulmonary arterial pressures were directly transduced and recorded. Cardiac output was measured by intrapulmonary artery thermodilution and calculated by a standard monitor with an internal validation routine (AS/3 Compact, Datex-Ohmeda, Helsinki, Finland) from the mean of three validated bolus injections of 10 ml cool normal saline.

Extracorporeal circuit

Eight animals each were allocated to one of the investigational extracorporeal circulation circuits (ECC) by block randomization.

The *mECMO* circuit consisted of a HILITE® 7000 LT oxygenator with a polymethylpentene membrane of 1.9 m^2 (Medos AG, Stolberg, Germany) and a diagonal blood pump with control unit (Deltastream® DP1, Medos) as main components (Fig. 1). The femoral vein and the right external jugular vein were cannulated with 18 Fr cannulas. The device was placed close to the animals to allow shortened connecting tubes to reduce the filling volume (<500 ml). All blood contacting surfaces were heparin coated (Rheoparin®, Medos).

The *pECLA* consisted of a polymethylpentene oxygenator with heparin coating and a membrane surface area of 1.3 m^2 (iLA Membrane Lung®, Novalung). Filling volume was <250 ml (Fig. 1). The cannulas were inserted in the femoral artery (13 Fr) and in the femoral vein (15 Fr).

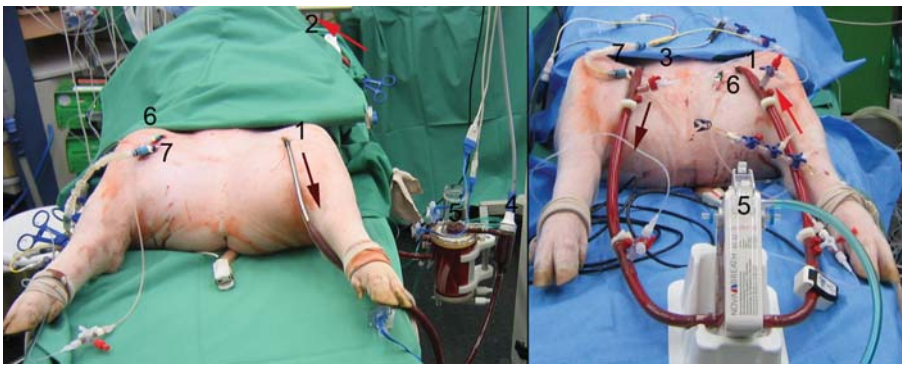

Fig 1 Photograph of mECMO (left) and pECLA (right). For veno-venous ECMO, circuit blood inflow was from the femoral vein (1) and return to the jugular vein (2) after passing blood pump (4) and oxygenator (5). In pumpless ECLA, blood from the femoral artery (3) flowed through the oxygenator (5) back into the femoral vein (1). Arterial (6) and right heart catheters (7) were placed in the contralateral femoral artery and vein, respectively.

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Both ECC were filled with HES solution. Circuit pressures were continuously monitored before and after the oxygenator and before the blood pump, where applicable. An ultrasonic flow meter (HT 110 Transonic Systems, Maastricht, The Netherlands) measured extracorporeal blood flow.

Experimental protocol

After induction of ALI, mechanical ventilation was changed to a pressure-controlled mode with plateau pressure (P_{Plat}) ≤30 cm H_2O, PEEP=8 cm H_2O, *I*:*E*=1:1, and VT=6–8 ml kg^{-1}; $F_{I_{O_2}}$ was regularly adjusted to maintain Pa_{O_2}=8.0–10.7 kPa. Respiratory rate was adapted to maintain normocapnia (Pa_{CO_2}=4.5–6.0 kPa). Plateau pressure was frequently adjusted to maintain target VT. An i.v. heparin bolus (5000 IU Heparin-Sodium, B.Braun, Melsungen, Germany) was given and continuous anticoagulation started to achieve an activated clotting time of 120–150 s. Animals were then connected to the respective ECC and blood flow was adjusted to 1–2 litre min^{-1} (~25–40% of cardiac output) and gas flow to 3 litre min^{-1} oxygen in veno-venous ECMO. In pECLA, gas flow through the membrane was stepwise increased to 6 litre min^{-1} and the mean arterial pressure was targeted to >75 mm Hg.

Haemodynamic, ventilation, and gas exchange parameters were analysed before induction of ALI (pre-lung lavage), before starting the ECC with ALI, and after 1, 4, 8, 16, and 24 h. Pressure decrease across the oxygenator and blood flow in per cent of cardiac output was calculated. Partial pressures of oxygen and carbon dioxide, oxygen saturation, and haemoglobin concentration were measured in arterial blood, mixed venous blood, and in the ECC before entering and after exiting the oxygenator (ABL 510 and OSM 3, Radiometer, Copenhagen, Denmark). Oxygen and carbon dioxide transfer was calculated for oxygenator and animal lungs (see additional data file).[9] After 24 h of ECC, animals were killed by an anaesthesia overdose in combination with KCl bolus.

Statistical analysis

Data are presented as mean (SD). After confirmation of normal distribution with the Kolmogorov–Smirnov test, significance was tested within groups with repeated-measures ANOVA with post-test and between groups with unpaired *t*-test (InStat version 3.06, GraphPad, San Diego, CA, USA). A value of $P<0.05$ was considered statistically significant.

Results

After induction of ALI, $Pa_{O_2}/F_{I_{O_2}}$ decreased significantly to 9.2 (2.8) kPa in ECMO and 7.5 (2.5) kPa in pECLA from 70.4 (4.4) and 70.4 (7.6) pre-lung lavage. Venous admixture increased to 52 (14)% and 53 (8)%, respectively, compared with pre-lung lavage values of 15 (6)% and 15 (8)% ($P<0.05$ for pre-lung lavage *vs* after induction of ALI).

Gas exchange improved gradually in both groups, thus allowing a reduction in P_{Plat}, VT, and $F_{I_{O_2}}$ (Table 1). Oxygenation increased significantly after the start of ECLS in both groups and remained high for the whole study period. Pulmonary oxygen transfer decreased significantly with the start of mECMO, but not with pECLA.

Haemodynamic parameters remained within baseline values and no vasopressors were necessary to maintain target mean arterial pressure (Table 2). After the start of mECMO, cardiac output and stroke volume decreased, whereas cardiac output was maintained during pECLA. Despite a blood flow of 1.2 (0.2) litre min^{-1} through pECLA (representing arterio-venous shunt), oxygen delivery to the animal organs was not different between groups (Table 2) and no metabolic acidosis occurred to indicate tissue hypoxia (Table 1). Maintaining this cardiac output came at the cost of increased left and right ventricular work for pECLA [6.8 (2.0) and 1.6 (0.5) kg m, respectively] when compared with mECMO [5.0 (1.4) and 1.2 (0.4) kg m, respectively, $P<0.05$].

The extracorporeal blood flow was constant over time, but significantly lower with pECLA [1.2 (0.2) litre min^{-1}] than with mECMO [1.5 (0.2) litre min^{-1}, $P<0.05$]. For pECLA, this represented 25 (6)% of cardiac output, when compared with 34 (9)% in mECMO. The pressure decrease across the membrane was higher with mECMO due to the different fibre design, surface area, and the additional heat exchanger. Both oxygenators provided stable gas exchange until 24 h, as indicated by a high outflow P_{O_2} of 60 (16.3) kPa (mECMO) and 61.1 (17.3) kPa (pECLA), respectively. The oxygenator transfer rates of oxygen and carbon dioxide were higher for mECMO ($P<0.05$; Table 3 and Fig. 2).

We did not encounter technical failures (e.g. pump failure, rupture of pump or oxygenator housing, plasma leakage) or performance decline with either device. No bleeding complications or clinical signs of haemolysis occurred as indicated by the absence of mucosal bleeding, bleeding at catheter insertion sites, or haematuria. No thromboembolism was observed clinically or by macroscopic inspection of the oxygenator membrane post-experiment. The results of haemocompatibility testing have been reported elsewhere.[10]

Discussion

Both mECMO and pECLA demonstrated reliable performance over 24 h that improved gas exchange enough to unload the lungs and allow more lung-protective settings.

Compared with other animal models without acute respiratory failure[11] or with ventilatory hypoxaemia and hypoventilation,[12] repeated lung lavage-induced lung injury has the advantage of simulating pulmonary and haemodynamic changes similar to clinical ALI. Although gas exchange improves over time with adequate ventilation alone, previous studies have demonstrated persistent mismatch of ventilation and perfusion and diffuse alveolar damage,[8 13] a clinical course not uncommon in humans with ALI. An increase in venous admixture after ALI and recovery to 13% and 17% after 24 h of ECLS are consistent with previous studies without ECLS (55% venous admixture after ALI and 13% after 24 h).[13] Of note, these historical controls have shown

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Table 1 Respiratory parameters and mechanical ventilation. Data presented as mean (SD) with $n=8$ for each group. *$P<0.05$ *vs* before ECC, #$P<0.05$ mECMO *vs* pECLA. ECC, extracorporeal circulation; SD, standard deviation

Time (h)	Pre-lung lavage	ALI before ECC	1	4	8	16	24
Respiratory rate (min^{-1})							
mECMO	24 (5)	26 (6)	22 (5)	19 (7)*	19 (9)*	19 (9)*	19 (9)*
pECLA	25 (1)	25 (2)	23 (4)	16 (5)*	16 (5)*	16 (5)*	16 (4)*
Tidal volume per body weight (ml kg^{-1})							
mECMO	9.8 (1.2)	9.2 (1.1)	8.5 (2.1)	6.9 (1.6)*	7.1 (1.1)*	7.2 (1.0)*	7.2 (1.2)*
pECLA	9.8 (0.4)	9.4 (0.9)	7.9 (1.2)	7.4 (1.1)*	7.7 (0.9)*	7.2 (1.5)*	6.8 (1.4)*
Plateau pressure (mbar)							
mECMO	21 (3)*	32 (3)	27 (4)*	24 (4)*	25 (6)	24 (5)*	24 (6)*
pECLA	20 (3)*	32 (5)	24 (3)*	22 (3)*	23 (2)*	22 (2)*	22 (2)*
PEEP (mbar)							
mECMO	5 (0)	5 (0)	8 (1)*	8 (1)*	8 (1)*	8 (1)*	8 (0)*
pECLA	5 (0)	5 (0)	8 (1)*	8 (0)*	8 (0)*	8 (0)*	8 (0)*
Inspired oxygen fraction							
mECMO	1.0 (0.0)	1.0 (0.0)	1.0 (0.1)	0.8 (0.2)*,#	0.6 (0.2)*	0.5 (0.2)*	0.5 (0.2)*
pECLA	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)	0.6 (0.2)*	0.5 (0.2)*	0.4 (0.1)*	0.4 (0.1)*
Pulmonary oxygen transfer (ml min^{-1})							
mECMO	115 (27)*	144 (48)	67 (43)*,#	67 (38)*,#	76 (41)*,#	72 (52)*,#	86 (45)#
pECLA	132 (46)	156 (60)	125 (48)	128 (46)	142 (32)	150 (29)	166 (41)
Pulmonary carbon dioxide transfer (ml min^{-1})							
mECMO	120 (72)#	144 (87)	78 (33)	77 (38)	83 (76)	100 (73)	75 (42)
pECLA	228 (73)	148 (86)	93 (46)	85 (61)	131 (73)	115 (75)	141 (76)
Total oxygen transfer (ml min^{-1})							
mECMO	115 (27)	144 (48)	120 (32)	131 (31)	155 (28)	150 (49)	149 (33)
pECLA	132 (46)	156 (60)	139 (54)	147 (49)	156 (34)	166 (29)	182 (43)
Total carbon dioxide transfer (ml min^{-1})							
mECMO	120 (72)#	144 (87)	207 (31)	159 (47)	200 (57)	209 (70)	187 (59)
pECLA	228 (73)	148 (86)	197 (48)	159 (49)	193 (51)	174 (74)	199 (74)
Pa_{O_2} (kPa)							
mECMO	70.4 (4.4)*	9.2 (2.8)	14.8 (7.1)#	22.8 (11.9)*	20.4 (6.7)*	17.5 (5.9)*	17.3 (4.8)*
pECLA	70.4 (7.7)*	7.5 (2.5)	27.2 (9.3)*	17.2 (7.3)*	17.6 (6.7)*	17.2 (4.8)*	16.3 (4.4)*
Pa_{CO_2} (kPa)							
mECMO	4.6 (1.9)*,#	7.1 (1.9)#	3.9 (1.1)*	5.1 (2.0)*	5.2 (1.6)*	4.4 (0.9)*,#	4.7 (0.9)*,#
pECLA	3.2 (0.4)*	5.3 (1.3)	3.6 (1.1)*	4.7 (0.8)	5.1 (0.8)	5.7 (1.1)	5.6 (0.8)
Arterial pH							
mECMO	7.54 (0.13)*,#	7.32 (0.08)#	7.55 (0.09)*	7.44 (0.11)*	7.41 (0.09)	7.44 (0.07)*	7.38 (0.11)
pECLA	7.67 (0.03)*	7.40 (0.08)	7.57 (0.08)*	7.47 (0.06)	7.42 (0.06)	7.38 (0.07)	7.38 (0.05)
Arterial base excess							
mECMO	4.77 (1.95)*,#	0.22 (1.73)	1.91 (1.67)*	0.54 (2.73)	−0.45 (2.38)	−2.08 (2.67)*	−2.57 (2.59)*
pECLA	6.96 (0.91)*	0.78 (4.39)	1.77 (1.78)	1.12 (1.72)	0.06 (1.24)	−0.92 (1.46)	−0.77 (1.55)
Pv_{O_2} (kPa)							
mECMO	8.2 (2.4)*	5.3 (1.2)	6.3 (1.7)	7.1 (1.7)*,#	7.2 (1.6)*,#	7.1 (2.4)*	7.2 (1.3)*,#
pECLA	6.7 (0.9)*	4.5 (0.8)	5.3 (1.3)	5.3 (2.7)*	5.6 (1.1)*	5.9 (1.5)*	5.9 (1.3)*

progressive recovery meaning that pECLA and mECMO both being imposed upon an identical background of spontaneous recovery.

Another limitation to direct transfer of these results to clinical application is the lower body weight of our animal model compared with adult humans. However, both devices were developed for humans and have been in clinical use.[3 14] The characteristics of both devices allow increasing performance to match the higher demand for cardiac output and metabolism of an adult human, when larger cannulas and higher pump flow are used.

ECLS for ARDS is extremely complex and costly; it requires specific staffing and has a significant risk of potentially fatal complications.[1 15] The transport of patients on ECLS within and between hospitals becomes a regular necessity for access to specialized ARDS centres and therapeutic or

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Table 2 Haemodynamic values. Data presented as mean (SD) with $n=8$ for each group. *$P<0.05$ *vs* before ECC, #$P<0.05$ mECMO *vs* pECLA. ECC, extracorporeal circulation; SD, standard deviation

Time (h)	Pre-lung lavage	ALI before ECC	1	4	8	16	24
Heart rate (beats min^{-1})							
mECMO	88 (11)	89 (12)	86 (11)	68 (11)*,#	76 (18)	89 (17)	90 (21)
pECLA	91 (21)	89 (29)	89 (23)	85 (17)	88 (17)	95 (12)	105 (16)
Cardiac output (litre min^{-1})							
mECMO	5.5 (1.3)	5.7 (1.1)	6.1 (0.9)	4.6 (0.5)	4.0 (0.7)*	4.4 (1.3)*	4.7 (1.4)
pECLA	5.7 (1.6)	5.8 (3.0)	5.7 (2.9)	4.9 (1.7)	4.8 (1.4)	5.1 (1.2)	5.6 (0.9)
Stroke volume (ml)							
mECMO	62 (10)	65 (14)	72 (11)	69 (12)#	55 (13)	49 (12)*	53 (8)*
pECLA	62 (12)	64 (17)	63 (19)	57 (14)	55 (12)	54 (14)	54 (12)
Central venous pressure (mm Hg)							
mECMO	7 (3)	7 (3)	8 (4)	8 (2)	8 (2)	8 (2)	8 (3)
pECLA	8 (4)	8 (3)	8 (2)	8 (3)	8 (3)	8 (3)	8 (3)
Pulmonary capillary wedge pressure (mm Hg)							
mECMO	6 (2)#	7 (2)	8 (3)	8 (4)	8 (2)	9 (2)	8 (2)
pECLA	9 (3)	9 (3)	10 (2)	8 (3)	8 (3)	8 (3)	9 (2)
Mean arterial pressure (mm Hg)							
mECMO	101 (11)	91 (12)#	94 (15)	87 (6)#	86 (8)	80 (15)	83 (12)
pECLA	111 (11)	108 (13)	99 (11)	99 (16)	94 (16)*	92 (19)*	92 (17)*
Mean pulmonary arterial pressure *P* (mm Hg)							
mECMO	16 (5)*	22 (4)	21 (5)	29 (4)*	27 (6)*	26 (4)*	25 (4)
pECLA	19 (5)*	25 (4)	24 (4)	31 (6)*	30 (5)	29 (5)	29 (6)
Systemic vascular resistance (dyn s cm^{-5})							
mECMO	1423 (228)	1220 (261)	1167 (284)	1399 (132)	1599 (300)*	1437 (508)	1348 (378)
pECLA	1590 (638)	1645 (653)	1502 (621)	1627 (452)	1481 (273)	1375 (308)	1202 (228)
Pulmonary vascular resistance (dyn s cm^{-5})							
mECMO	147 (39)	209 (57)	177 (86)	363 (132)	378 (105)*	340 (82)	302 (86)
pECLA	168 (113)	270 (171)	235 (100)	431 (190)*	404 (196)*	354 (155)*	302 (142)
Left cardiac work (kg m)							
mECMO	7.6 (2.0)	6.9 (1.6)	7,4 (1.2)	5.2 (0.8)*	4.5 (1.0)*	4.4 (1.5)*,#	5.0 (1.4)*,#
pECLA	8.2 (2.0)	8.4 (5.2)	7,7 (4.8)	6.6 (3.2)	6.2 (2.6)	6.3 (2.4)	6.8 (2.0)
Right cardiac work (kg m)							
mECMO	0.7 (0.4)*	1.3 (0.6)	1.1 (0.3)	1.4 (0.3)	1.1 (0.4)	1.2 (0.5)	1.2 (0.4)#
pECLA	0.9 (0.2)	1.4 (0.9)	1.2 (0.6)	1.5 (0.4)	1.4 (0.4)	1.5 (0.4)	1.6 (0.5)
Total organ perfusion (litre min^{-1})							
mECMO	5.5 (1.3)	5.7 (1.1)	6.1 (0.9)	4.6 (0.5)#	4.0 (0.7)*	4.4 (1.3)*	4.7 (1.4)
pECLA	5.7 (1.6)	5.8 (3.0)	4.5 (2.7)	3.6 (1.5)*	3.6 (1.2)*	3.9 (1.1)*	4.4 (0.8)
Total oxygen delivery to organs (ml min^{-1})							
mECMO	577 (125)*	469 (121)	438 (129)	368 (92)	368 (108)	343 (103)*	394 (130)
pECLA	605 (151)*	432 (80)	421 (95)	396 (83)	371 (70)	380 (73)	348 (49)

diagnostic interventions.[16 17] To simplify the application and increase patient safety, different strategies have been pursued: miniaturization and simplification. Miniaturized *ECMO* is characterized by shortened tubing connections to oxygenators and a design change of rotational blood pumps, resulting in reduced priming volumes of <500 ml. The blood flow can be easily monitored and steered, simply by turning a knob.[4] New devices combining oxygenator and blood pump in the same housing are under development, which hold the potential for further miniaturization.[18] The abandonment of a blood pump simplifies and reduces the ECC by use of a low resistance oxygenator in *pECLA*.[7] The blood flow is driven by cardiac output, requiring arterial cannulation, which has raised some concerns about dependent limb ischaemia.[3] Further, extracorporeal flow runs in parallel to the systemic circulation and functions as a systemic left-to-right shunt.

Some limitations do apply. Although the reduction in the invasiveness of ventilation was not performed in a blinded fashion, the protocolized approach prevented large bias. As could be expected, the oxygen transfer rates were lower with pECLA, but both devices equally allowed reduction in

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Table 3 Extracorporeal circulation parameters. Data presented as mean (SD) with $n=8$ for each group.*$P<0.05$ *vs* 1 h, #$P<0.05$ mECMO *vs* pECLA. ECC, extracorporeal circulation; SD, standard deviation

Time (h)	1	4	8	16	24
Pressure decrease oxygenator (mm Hg)					
mECMO	23 (5)#	34 (21)#	35 (24)#	33 (20)#	33 (21)#
pECLA	5 (1)	6 (3)	9 (6)	9 (5)	9 (6)
Extracorporeal blood flow (litre min^{-1})					
mECMO	1.6 (0.2)#	1.6 (0.2)#	1.6 (0.1)#	1.5 (0.2)#	1.5 (0.2)#
pECLA	1.2 (0.2)	1.3 (0.2)	1.3 (0.2)	1.2 (0.2)	1.2 (0.2)
Gas flow (litre min^{-1})					
mECMO	3 (0)#	3 (0)#	3 (0)#	3 (1)#	3 (1)#
pECLA	6 (2)	6 (1)	6 (1)	6 (1)	6 (2)
Oxygen uptake of oxygenator (ml min^{-1})					
mECMO	53 (19)#	64 (25)#	79 (26)*,#	74 (33)*,#	64 (28)#
pECLA	14 (7)	19 (5)*	14 (5)	16 (6)	16 (5)
Carbon dioxide elimination of oxygenator (ml min^{-1})					
mECMO	130 (29)	105 (47)	118 (42)#	109 (39)#	111 (42)#
pECLA	104 (34)	74 (31)*	62 (36)*	59 (31)*	58 (28)*
Oxygen transfer rate of oxygenator per decilitre of blood (ml dl^{-1})					
mECMO	3.3 (0.8)#	3.9 (1.2)#	5.0 (1.3)*,#	4.8 (1.7)*,#	4.2 (1.3)*,#
pECLA	1.1 (0.4)	1.5 (0.3)*	1.1 (0.3)	1.3 (0.5)	1.3 (0.4)
Carbon dioxide transfer rate of oxygenator per decilitre of blood (ml dl^{-1})					
mECMO	8.4 (1.7)	6.4 (2.8)	7.6 (2.6)#	7.2 (2.5)#	7.6 (2.6)#
pECLA	8.4 (2.5)	5.8 (2.3)	4.8 (3.0)*	4.8 (2.6)*	4.8 (2.5)*

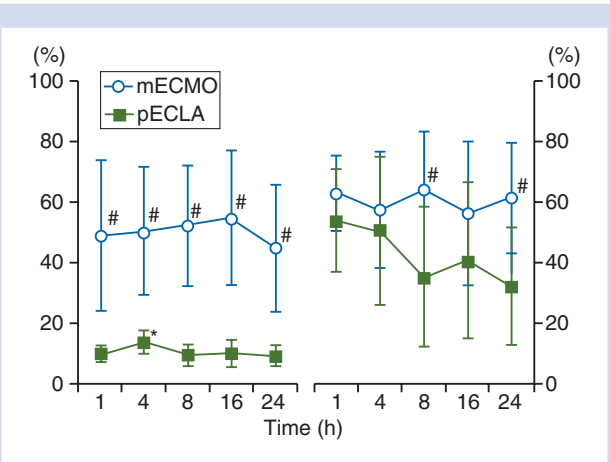

Fig 2 Extracorporeal oxygen uptake (left panel) and carbon dioxide transfer rate (right panel). Extracorporeal gas transfer of mECMO and pECLA is presented in per cent of total oxygen consumption and carbon dioxide production. Data are displayed as mean and SD with $n=8$ for each group ($P<0.05$: * *vs* 1 h; # mECMO *vs* pECLA).

F_{IO_2}, tidal volumes, and plateau pressure. Hyperdistension can occur even during low tidal volume ventilation with a plateau pressure of 28–30 cm H_2O.[19] The potential to reduce injurious ventilation settings might be the greatest benefit from ECLS, which is addressed in several clinical studies.[20–22] However, in contrast to low flow extracorporeal carbon dioxide removal,[22 23] veno-venous ECMO is effective in improving outcome in cases of severe ARDS with ongoing hypoxaemia[1] and for severe respiratory failure due to novel H1N1(2009).[24 25]

Haemodynamic effects

Cardiac output decreased after the start of mECMO, the anticipated physiological reaction to enhanced oxygen supply,[26] and haemodynamic parameters were not impaired. The implications of pECLA are not so clear. There was no change in cardiac output, although oxygen supply was equally enhanced. The extracorporeal flow is a functional shunt, thus reducing theoretical systemic and organ perfusion (not measured). This came at the cost of increased cardiac workload in pECLA. However, oxygen delivery was maintained and not different from mECMO, and no metabolic acidosis occurred to indicate anaerobic metabolism. Interestingly, oxygen delivery did not improve after the start of either device, again pointing at a reduction in ventilation invasiveness as the most important mechanism for benefit. It is hard to imagine that any device or treatment that increases cardiac afterload and stroke work could be beneficial in a patient population with significant pre-existing co-morbidities. The protection of the lung ('putting the lung at rest') and the heart is worthwhile in a situation where both are at stress. The company has recently presented further development of their product with pump support (iLA Active®), which might be attributed to these considerations.

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Oxygenator effects

According to Fick's principle, gas exchange across semi-permeable membranes correlates with the partial pressure difference as driving force. This pressure difference is smaller for arterial blood passing the pECLA membrane compared with the low saturated venous blood in veno-venous ECMO. Severe hypoxaemia was reversed, although the oxygen transfer rate was limited to 10% of total body oxygen consumption in this study, but has been reported to reach 16–17% in previous studies.[27 28] We speculate that the Bohr effect contributes to effects seen in pECLA. By reduction in blood and alveolar P_{CO_2}, alveolar P_{O_2} increases despite constant $F_{I_{O_2}}$, and combined with reversal of respiratory acidosis facilitates oxygen uptake by haemoglobin by a leftward shift of the oxygen-binding curve.

Opposite to blood flow-limited oxygen uptake, carbon dioxide transfer capacity is limited mainly by gas flow. Thereby, carbon dioxide elimination should be equal in pECLA and mECMO. *In vitro* testing of carbon dioxide transfer standardized to ISO 7199[29] demonstrated comparable elimination rates of ~85–90 ml min^{-1} for both devices at a blood flow rate of 1.5 litre min^{-1}, despite a smaller membrane surface of pECLA.[30 31] However, *in vivo* carbon dioxide transfer per millilitre of blood was inferior for pECLA, although the P_{CO_2} decrease was not significantly different between devices. The Haldane effect oxygenation of venous blood in the ECMO oxygenator reduces the binding capacity for carbon dioxide, which increases P_{CO_2} and facilitates carbon dioxide transfer according to Fick's principle. With the inflow of oxygenated blood into the membrane lung, the Haldane effect is negligible for pECLA. A higher gas-to-blood flow ratio during pECLA was more than counterbalanced by higher blood flow during mECMO, whereby carbon dioxide elimination was potentiated by the logarithmic correlation of blood flow and carbon dioxide transfer.

mECMO and pECLA were efficient, safe, and easy to use and allowed for improved lung-protective ventilation settings. Even though appealing by technical simplicity, the pECLA has significant disadvantages: limited blood flow increased cardiac workload, the need to maintain high systemic vascular resistance, and the potential to cause limb ischaemia at the femoral arterial cannulation site. So far, there has not been a clinical heads-on comparison between pump-driven and pumpless ECLS. However, since the main benefit of ECLS in ventilated patients with severe ARDS might not be to maintain gas exchange, but to protect the lungs, a device that allows protective ventilation and reduces demand on the heart might be advantageous. mECMO has overcome some of the limitations of conventional veno-venous ECMO. It therefore holds a theoretical superiority to pECLA, which remains to be proven in future clinical trials.

Declaration of interest

R. Kuhlen received consultancies, honoraria, and grants from Nova lung related to this study.

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Appendix

Formulas used for analysis of study results

Pressure decrease in oxygenator (ΔP_{oxy}) (mm Hg):

$$\Delta P_{oxy} = \text{mean blood pressure}_{\text{after oxygenator}} - \text{mean blood pressure}_{\text{before oxygenator}}$$

Oxygen content (CO_2) (ml dl^{-1}):

$$CO_2 = (SO_2\,\text{Hb}\,1.36 \times 100^{-1}) + (P_{O_2}\,0.0031)$$

Carbon dioxide content of total blood (CCO_2) (ml dl^{-1}) adapted from Douglas and colleagues.[9]

$$CCO_2 = C_{\text{plasma}}CO_2\{1 - 0.0289\text{Hb}[(3.352 - 0.456SO_2)(8.142 - \text{pH})]^{-1}\}$$

$$s = 0.0307 + [0.00057(37 - T)] + [0.00002 - (37 - T)^2]$$

$$\text{p}K' = 6.086 + [0.042(7.4 - \text{pH})] + (\{38 - T\}\{0.00472 + [0.00139(7.4 - \text{pH})]\})$$

$$C_{\text{plasma}}CO_2 = 2.226sP_{CO_2}[1 + 10^{(\text{pH}-\text{p}K')}]$$

Transfer rate of oxygen per decilitre of blood of oxygenator ($T_{oxy}O_2$) (ml dl^{-1})

$$T_{oxy}O_2 = C_{\text{after oxy}}O_2 - C_{\text{before oxy}}O_2$$

Transfer rate of carbon dioxide per decilitre of blood of oxygenator ($T_{oxy}CO_2$) (ml dl^{-1})

$$T_{oxy}CO_2 = C_{\text{before oxy}}CO_2 - C_{\text{after oxy}}CO_2$$

Oxygen uptake of oxygenator ($V_{oxy}O_2$) (ml min^{-1})

$$V_{oxy}O_2 = T_{oxy}O_2\text{BF}$$

Carbon dioxide elimination of oxygenator ($V_{oxy}CO_2$) (ml min^{-1})

$$V_{oxy}CO_2 = T_{oxy}CO_2\text{BF}$$

Oxygen uptake of lung ($V_{lung}O_2$) (ml min^{-1})

$$V_{lung}O_2 = (C_{\text{arterial}}O_2 - C_{\text{mixed-venous}}O_2)\text{CO}$$

Carbon dioxide elimination of lung ($V_{lung}CO_2$) (ml min^{-1})

$$V_{lung}CO_2 = (C_{\text{arterial}}CO_2 - C_{\text{mixed-venous}}CO_2)\text{CO}$$

Total oxygen uptake ($V_{total}O_2$) (ml min^{-1})

$$V_{total}O_2 = V_{oxy}O_2 + V_{lung}O_2$$

Total carbon dioxide elimination ($V_{total}CO_2$) (ml min^{-1})

$$V_{total}CO_2 = V_{oxy}CO_2 + V_{lung}CO_2$$

Systemic vascular resistance (SVR) (dyn s cm^{-5})

$$\text{SVR} = (\text{MAP} - \text{ZVP})80\text{CO}^{-1}$$

Left cardiac work (LCW) (kg m)

$$\text{LCW} = \text{CO}(\text{MAP} - \text{PCWP})\,0.0144$$

Pulmonary vascular resistance (PVR) (dyn s cm^{-5})

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$$PVR = (MPAP - PCWP)80CO^{-1}$$

Right cardiac work (RCW) (kg m)

$$RCW = CO(MPAP - CVP)0.0144$$

Venous admixture (Q_S/Q_T) (%)

$$\frac{Q_S}{Q_T} = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2}$$

$$CcO_2 = (Hb\,1.36(1 - MetHb - CoHb)) + (F_{IO_2}(P_{baro} - 47) - Pa_{CO_2}\,1.25)0.0031$$

Total organ perfusion (Q) (litre min^{-1})

$$Q = CO - BF$$

Total oxygen delivery to organs (DO_2) (ml min^{-1})

$$DO_2 = C_{arterial}O_2Q$$

Abbreviations: SO_2, oxygen saturation; Hb, haemoglobin concentration; P_{O_2}, partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide; pH, pH value of blood; T, blood temperature; BF, extracorporeal blood flow; CO, cardiac output; MAP, mean arterial pressure; CVP, central venous pressure; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CcO_2, pulmonary capillary oxygen content; MetHb, methaemoglobin; CoHb, carbon monoxide haemoglobin; F_{IO_2}, inspired oxygen fraction; P_{baro}, atmospheric pressure.

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