A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia*

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Objective: **Pump-driven extracorporeal gas exchange systems have been advocated in patients suffering from severe acute respiratory distress syndrome who are at risk for life-threatening hypoxemia and/or hypercapnia. This requires extended technical and staff support.**

Design: **We report retrospectively our experience with a new pumpless extracorporeal interventional lung assist (iLA) establishing an arteriovenous shunt as the driving pressure.**

Setting: **University hospital.**

Patients: **Ninety patients with acute respiratory distress syndrome.**

Interventions: **Interventional lung assist was inserted in 90 patients with acute respiratory distress syndrome.**

Measurements and Main Results: **Oxygenation improvement, carbon dioxide elimination, hemodynamic variables, and the amount of vasopressor substitution were reported before, 2 hrs after, and 24 hrs after implementation of the system. Interventional lung assist led to an acute and moderate increase in arterial oxygenation (Pao_2/Fio_2 ratio 2 hrs after initiation of iLA [median and interquartile range], 82 mm Hg [64–103]) compared with pre-iLA (58 mm Hg [47–78], $p < .05$). Oxygenation continued to improve for 24 hrs after implementation (101 mm Hg [74–142], $p < .05$). Hypercapnia was promptly and markedly reversed by iLA within 2 hrs ($Paco_2$, 36 mm Hg [30–44]) in comparison with before (60 mm Hg [48–80], $p < .05$), which allowed a less aggressive ventilation. For hemodynamic stability, all patients received continuous norepinephrine infusion. The incidence of complications was 24.4%, mostly due to ischemia in a lower limb. Thirty-seven of 90 patients survived, creating a lower mortality rate than expected from the Sequential Organ Failure Assessment score.**

Conclusions: **Interventional lung assist might provide a sufficient rescue measure with easy handling properties and low cost in patients with severe acute respiratory distress syndrome and persistent hypoxia/hypercapnia. (Crit Care Med 2006; 34:1372–1377)**

Acute respiratory distress syndrome (ARDS) is characterized by alveolar epithelial injury and—in consequence—by alveolar flooding, loss of surfactant, and destruction of alveolar architecture (1). The acute phase is manifested by the rapid onset of respiratory failure with severe hypoxemia refractory to supplemental oxygen and/or hypercapnia. Therapeutic strategies include artificial ventilation and the consideration of a "lung-protective strategy" (2) fluid management using extended hemodynamic monitoring, inhalation therapy of vasodilating drugs (3), and prone position (4). In situations of life-threatening forms of respiratory failure with persistent hypoxemia and/or hypercapnia unresponsive to conventional therapy, a pump-driven extracorporeal membrane oxygenation (ECMO) has been employed (5). Earlier randomized controlled studies, which may be considered "historical," failed to show an outcome benefit in adults for the ECMO technique (5, 6), and the authors did not advocate the use of ECMO in these patients, whereas improved outcome has been shown in children (7, 8). The application of such a technique is restricted for two reasons: a) side-effects and severe complications (bleeding, inflammation, surgical complications) remain an inherent problem of the method; and b) the ECMO technique requires extensive equipment with technical and support staff and it is an expensive treatment modality.

In experimental investigations (9–11), a pumpless extracorporeal interventional lung assist system (iLA) using the animals' arteriovenous pressure gradient has been described. Following this experimental experience, the clinical development of the iLA system has been performed in our hospital (12) and experience with the first 20 cases has been published (13). The system is characterized by a new membrane gas exchange system (lung assist device [LAD]) based on heparin-coated hollow fiber technology with optimized blood flow by reduction of resistance. The LAD is connected to the patient via arterial and venous cannulae inserted by Seldinger's technique. The system does not need extended technical and staff support, and the main advantage is easy handling. Furthermore, the system runs with a "low-dose" heparin infusion that does not exceed normal antithrombotic anticoagulation of the intensive care patient.

The aim of our retrospective analysis was to examine the effectiveness and the incidence of complications of iLA as a rescue measure in patients with severe ARDS and persistent hypoxemia/hypercapnia.

DESCRIPTION OF THE SYSTEM AND APPLICATION TECHNIQUE

At the University Hospital of Regensburg, Germany, clinical development of a

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new iLA device was performed by an interdisciplinary working group consisting of perfusionists, cardiothoracic surgeons, internists, and anesthesiologists. The iLA is a single-use ultracompact extrapulmonary gas exchange system perfused by the heart. Apart from an oxygen supply (10–12 $L \cdot min^{-1}$), the system does not require additional energy or substrate sources. A passive femo-femoral shunt flow generated by the arterial blood pressure through a lung assist device (iLA, NovaLung GmbH, Hechingen, Germany) produces an effective CO_2 extraction and an improvement in arterial oxygenation at a blood flow rate of approximately 1.0–2.5 $L \cdot min^{-1}$. An average driving pressure difference of 60−80 mm Hg (femoral artery − femoral vein) is mandatory. To allow long-term function of the LAD, a new polymethylpentene diffusion membrane resistant to plasma leakage is used as a separation layer between phases (blood/gas). Due to the molecular structure of the separation layer, the passage of air bubbles from gas to the blood path in the event of negative pressure on the blood side is impossible. The entire effective gas exchange surface area amounts to 1.3 m^2. Integration of a heat exchanger is not necessary as temperature loss due to convection is negligible. To optimize hemocompatibility, the system is entirely (tip to tip) homogeneously treated with the coating method (Novalung Coating, NovaLung GmbH, Hechingen, Germany). This method consists of the application of high-molecular-weight heparin (Liquemin, Hoffmann LaRoche, Basel, Swisse) to a carrier layer of immobilized polypeptides. The iLA is suitable for patients with potentially reversible respiratory failure, for example, trauma, aspiration (14), pancreatitis, and sepsis. Contraindication for the application of the system is a hemodynamic depression of cardiac origin.

To connect the iLA to the patient, a special percutaneous cannulation system has to meet the following conditions: implantable with Seldinger technique, cannulae walls extremely thin to minimize resistance to flow, and availability in various diameters (13–21 Fr). In every individual case, the size of the cannula used (arterial, 13–21 Fr; venous, 19–21 Fr) is determined by the diameter of the vessel to be cannulated and the required shunt flow. Before puncture of the femoral artery, the diameter should be measured by ultrasound. After cannulation of the femoral artery and vein, a bolus of unfractionated heparin (5000 IU intravenously) is given, and the system is filled with hydroxyethyl starch or crystalloid solution such as normal saline (250 mL), independent from the size of the cannulae, and connected to the cannulae. Shunt flow is released slowly over 1–2 mins (Fig. 1). Functional control is achieved through a monitoring device (Blood Flow Monitor, NovaLung GmbH, Hechingen, Germany) that calculates blood flow through the system by transit time Doppler technology. A continuous infusion of heparin is given (200–600 IU/hr) into the arterial inflow cannula before the gas exchange system to achieve a mild prolongation of the activated partial thromboplastin time between 50 and 60 secs.

The weaning from iLA is typically performed as follows: After successful treatment of the underlying lung damage leading to a further reduction in invasive mechanical ventilation (positive end-expiratory pressure <10 cm H_2O, F_{IO_2} <0.6), a "cessation-trial" of iLA (reduction of gas supply to the system to approximately 1 L/min) is performed for 30 mins. In cases of no major deterioration of gas exchange variables during reduction of oxygen flow, the system is stopped and the cannulae are removed followed by extensive manual compression of the vessels for 30 mins. After that period a pressure banding is applied for 24 hrs.

Data Collection and Statistical Analysis. Pulmonary gas exchange (Pa_{O_2}/F_{IO_2} ratio, Pa_{CO_2}, pH), hemodynamics (mean arterial pressure), cardiac output, pharmacologic intervention (continuous norepinephrine infusion rate), and blood flow through the iLA system were retrospectively collected at three times: a) immediately before initiation of iLA; b) after 2 hrs on iLA; and c) after 24 hrs on iLA. The performance of the device in terms of CO_2 removal was evaluated as follows: The device inlet CO_2 content and outlet CO_2 content were calculated (derived from the Henderson-Hasselbalch equation) in all patients, and the amount of CO_2 removal was then assessed using the Fick equation (15).

Furthermore, patients were described by diagnosis, age, body mass index, gender, and the duration of mechanical ventilation before initiation of iLA. For subsequent analysis, patients were allocated to two groups, survivors and nonsurvivors. Our Institutional Review Board waived the need for approval due to the retrospective nature of this study.

Statistical analyses were performed using SigmaStat, version 3.0 (Systat Software GmbH, Erkrath, Germany). As revealed by the Kolmogorov-Smirnov method, most datasets significantly varied from the pattern expected if they were drawn from a population with a normal distribution. Nonparametric procedures were therefore applied for intergroup (Mann-Whitney rank sum test, Kruskal-Wallis analysis of variance on ranks) and intragroup analysis (Wilcoxon signed rank test, Friedman repeated-measures analysis of variance on ranks). In case of significant differences, especially in additional *post hoc* analysis, all pairwise multiple comparison procedures (Dunn's method) are warranted. Results were considered significant at $p < .05$. Data are presented as median and interquartile range unless specified otherwise.

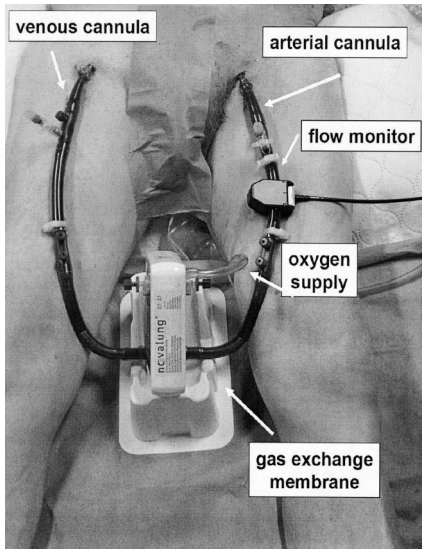

Figure 1. Schema of the interventional lung assist system. A passive femo-femoral shunt flow generated by the arterial blood pressure passes a gas exchange membrane (in the box), in which an oxygen flow is inserted.

RESULTS

Between November 1996 and September 2004, a total of 90 patients were treated with iLA for ≥24 hrs. The clinical algorithm for the beginning of iLA treatment followed the recommendations given by Lewandowski and colleagues (16). Patients suffering from severe respiratory failure who were at risk for acute life-threatening hypoxemia and/or excessive hypercapnia were assigned to iLA when the combined use of advanced optimized therapeutic strategies had failed: ventilation in a pressure-controlled mode (target respiratory setting: peak inspiratory pressure <35 cm H_2O, respiratory rate <20 breaths/min, in-

spiration/expiration ratio = 1:1), optimization of positive end-expiratory pressure to achieve a maximal gas exchange improvement without compromising cardiac output, in combination with other measures to reduce pulmonary edema (continuous administration of furosemide and/or continuous pump-driven venovenous hemodiafiltration). Additional supportive measures consisted of analgosedation, administration of vasoactive agents (norepinephrine, dobutamine), and parenteral or enteral nutrition. Positional maneuvers (prone position) were only performed under hemodynamically stable conditions. A failure of these strategies was stated when sufficient oxygenation was not achieved (Pa_{O_2} <55 mm Hg at F_{IO_2} = 1) and/or when hypercapnia had induced arterial acidosis with a concomitant increase in hemodynamic instability within 2 hrs after initiation of optimization or when a distinct tendency toward deterioration was observed.

The diagnoses leading to respiratory failure and other characteristic data are demonstrated in Table 1. Thirty-seven patients survived hospital treatment, whereas the hospital mortality rate was 58.8% (53 nonsurvivors). Survivors were significantly younger than nonsurvivors, had significantly lower body mass index, and had a significantly shorter duration of mechanical ventilation before initiation of iLA.

Box and whisker plots (95th, 75th, 50th, 25th, and 5th percentiles) and individual patient data of the variables Pa_{O_2}/F_{IO_2} ratio and Pa_{CO_2} before initiation of iLA and after 2 hrs and 24 hrs on iLA are given in Figure 2. The iLA induced a significant and prompt carbon dioxide removal that resulted in a reduction of hypercapnia and consequently in the possibility of less "aggressive" ventilation. Furthermore, iLA led to an acute and moderate increase in arterial oxygenation in most patients. Between survivors and nonsurvivors, we found no difference in the amount of carbon dioxide removal or additional arterial oxygenation.

In Table 2, Pa_{O_2}/F_{IO_2} ratio, Pa_{CO_2}, pH, mean arterial pressure, cardiac output, mixed venous oxygen saturation, continuous norepinephrine infusion rate, and iLA flow at different times (before initiation of iLA and after 2 hrs and 24 hrs on iLA treatment) in survivors, nonsurvivors, and all patients are presented. Due to reversal of hypercapnia, pH was normalized rapidly and norepinephrine infusion could be reduced markedly in surviving patients within 24 hrs, whereas in nonsurviving patients the amount of hemodynamic support persisted. Under these measures, mean arterial pressure remained stable in all patients and a successful arteriovenous shunt of about 2 $L \cdot min^{-1}$ was established. Mixed venous oxygen saturation was increased significantly immediately after initiation of iLA. The mean duration of iLA treatment was 5 ± 5 days (not different between survivors and nonsurvivors).

Initiation of iLA resulted in a significant decrease in F_{IO_2}, minute ventilation, and tidal volume within 2 hrs (Table 3), whereas respiratory frequency and peak inspiratory pressure could be reduced markedly after 24 hrs. The level of positive end-expiratory pressure was not affected during the first period of interventional lung assist. The amount of CO_2 removal calculated 2 hrs after initiation of iLA was 141 $mL \cdot min^{-1}$ (interquartile range, 85–211). Laboratory variables are presented in Table 4. During iLA treatment, we observed a moderate prolongation of partial thromboplastin time whereas platelet count remained stable. The serum level of creatine kinase showed a trend toward elevation.

The frequency of complications is reviewed in Table 5. In 22 patients (24.4%), serious complications were observed. Episodes of ischemia of a lower limb after arterial cannulation were major problems and led to amputation in one patient. In all other cases of ischemia, the cannulae were removed and normal perfusion of the limb was restored. Since those episodes usually happened a few days after initiation of iLA, the cessation of the system did not result in a severe deterioration of gas exchange in most cases and weaning was continued successfully. Cannula thrombosis was only observed in the early period without specially designed cannulae before 2001, but altogether the mortality rate or the frequency of complications did not change

Table 1. Patient data and characteristics

Diagnosis Leading to Acute Respiratory Distress Syndrome	No. of Patients (%)
Pneumonia	30 (33)
Multiple trauma	15 (17)
Pancreatitis, peritonitis	11 (12)
Sepsis	11 (12)
Postoperative	10 (11)
Brain injury	8 (9)
Aspiration, near-drowning	5 (6)
Total	90 (100)

Parameter	Survivors (S)	Nonsurvivors (NS)	All Patients	*p* (S vs. NS)
Patients	37	53	90	
Age, yrs	32 (22–49)	49 (33–60)	44 (26–59)	.009
Female/male ratio	8/29	13/40	21/69	NS
Body mass index	24.1 (22.5–26.6)	27.7 (24.0–30.8)	25.4 (23.4–29.7)	.001
Days on ventilator before ILA	1 (1–8)	4 (1–14)	3 (1–10)	.034
SOFA score	10 (7–11)	11 (8–14)	11 (8–13)	.016
Lung injury score	3.7 (3.3–3.8)	3.5 (3.3–3.8)	3.5 (3.5–3.8)	NS

Data are presented as median (interquartile range), except female/male ratio.

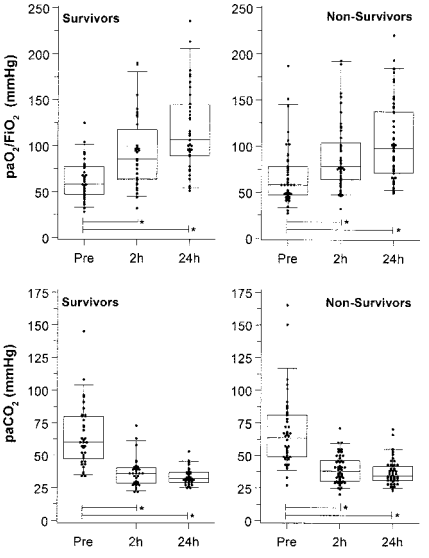

Figure 2. Individual patient data of variables Pa_{O_2}/F_{IO_2} ratio and Pa_{CO_2} before initiation of interventional lung assist (*Pre*) and after 2 hrs and 24 hrs on interventional lung assist (*2h* and *24h*). Box and whisker plots (95th, 75th, 50th, 25th, and 5th percentiles). *$p < .05$, Friedman repeated-measures analysis of variance on ranks with all pairwise multiple comparison procedures by Dunn's method.

Table 2. Variables in survivors, nonsurvivors, and all patients (median values and interquartile ranges)

	Survivors			Nonsurvivors		
	Pre	2 Hrs	24 Hrs	Pre	2 Hrs	24 Hrs
Pao_2/Fio_2 ratio, mm Hg	58 (48–77)	87 (64–112)[a]	109 (89–143)[b]	58 (47–78)	78 (64–103)[a]	97 (71–137)[b]
$Paco_2$, mm Hg	60 (47–80)	36 (29–41)[a]	32 (29–37)[b]	64 (49–81)	38 (30–46)[a]	35 (31–42)[b]
pH	7.27 (7.17–7.37)	7.44 (7.37–7.54)[c,a]	7.46 (7.43–7.49)[b]	7.28 (7.18–7.36)	7.41 (7.31–7.50)[c,a]	7.45 (7.38–7.50)[b]
MAP, mm Hg	79 (70–85)	90 (79–100)[a]	85 (81–100)[b]	75 (64–80)	86 (78–98)[a]	87 (80–97)[b]
CO, $L \cdot min^{-1}$	8.6 (6.6–9.9)	9.9 (9.0–11.0)[a]	9.4 (7.7–10.9)	9.0 (6.9–10.6)	9.9 (7.6–11.8)	9.8 (7.6–10.8)
Norepinephrine, $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.30 (0.13–0.47)	0.29 (0.12–0.52)	0.10 (0.03–0.23)[c]	0.18 (0.02–0.49)	0.30 (0.11–0.55)	0.27 (0.14–0.55)[c]
iLA flow, $L \cdot min^{-1}$	—	2.3 (2.0–2.6)[c]	2.3 (2.1–2.6)	—	2.0 (1.8–2.3)[c]	2.2 (1.8–2.5)

	All Patients		
	Pre	2 Hrs	24 Hrs
Pao_2/Fio_2 ratio, mm Hg	58 (47–78)	82 (64–103)[a,d]	101 (74–142)[b]
$Paco_2$, mm Hg	60 (48–80)	36 (30–44)[a]	34 (30–39)[b]
pH	7.27 (7.18–7.36)	7.42 (7.35–7.52)[a]	7.45 (7.41–7.50)[b]
MAP, mm Hg	76 (66–81)	86 (78–99)[a]	86 (81–100)[b]
CO, $L \cdot min^{-1}$	9.0 (6.8–10.2)	9.9 (7.9–11.4)[a]	9.7 (7.6–10.9)[b]
Svo_2, %	65 (58–68)	75 (62–80)[b]	75 (63–80)[b]
Norepinephrine, $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.27 (0.04–0.48)	0.29 (0.12–0.54)	0.21 (0.09–0.51)
iLA flow, $L \cdot min^{-1}$	—	2.2 (1.9–2.5)	2.2 (1.9–2.5)
CO_2 removal, $mL \cdot min^{-1}$	—	141 (85–211)	136 (100–169)

[a] $p < .05$ 2 hrs vs. pre; [b] $p < .05$ 24 hrs vs. pre; [c] $p < .05$ survivors vs. nonsurvivors; [d] $p < .05$ 2 hrs vs. 24 hrs.

over the 8-yr observational period. The main causes of death were septic shock or persistent systemic inflammatory response syndrome and multiple organ failure (Table 6).

DISCUSSION

Recently it has been shown by the results of the ARDS network study (2) that in patients suffering from severe acute lung injury or ARDS, the mode of ventilation strategy affects outcome. Meanwhile, it is accepted that the concept of a "lung-protective strategy" reduces ventilator-induced lung injury by avoidance of high inspiratory pressure and large tidal volume. Pulmonary gas exchange in patients with ARDS is characterized by hypoxemia and/or hypercapnia. Although hypercapnia might be accepted under certain conditions as "permissive" (17), a negative influence on the integrity of the lung (18) and on other organ systems (acidosis, renal impairment, hypotension) can often be observed, predominantly in hemodynamically unstable patients. Furthermore, in patients with severe damage of the lung of primary origin (chest trauma, aspiration of gastric contents, pneumonia) or of nonpulmonary origin (pancreatitis, peritonitis, massive transfusion) (19), it is often impossible to maintain "acceptable" gas exchange despite optimization of the ventilation mode.

Table 3. Changes in respiratory variables before and during interventional lung assist in all patients

	Pre	2 Hrs	24 Hrs
Fio_2	1.0 (1.0–1.0)	0.9 (0.8–1.0)[a,b]	0.8 (0.69–0.9)[c]
Minute ventilation, $L \cdot min^{-1}$	13.0 (10.0–16.4)	11.0 (8.0–14.1)[a]	9.9 (8.0–14.8)[c]
Tidal volume, mL	430 (360–540)	410 (330–480)[a]	380 (320–470)[c]
Respiratory frequency, breaths/min	27 (21–43)	25 (20–40)	23 (17–39)[c]
Peak inspiratory pressure, cm H_2O	38 (35–40)	36 (32–39)	35 (31–39)[c]
PEEP, cm H_2O	15 (12–17)	15 (13–18)	14 (12–18)

[a] $p < .05$ 2 hrs vs. pre; [b] $p < .05$ 2 hrs vs. 24 hrs; [c] $p < .05$ 24 hrs vs. pre.

The concept of an extracorporeal gas exchange (ECMO) has been developed and integrated in critical care successfully through past decades (5, 11, 20, 21). The technique of ECMO establishes a venovenous shunt consisting of a pump, a membrane lung, and a heat exchanger. Despite technical advances of those systems (heparin-coated systems, refinements in membrane oxygenator technology), the technique of a pump-driven extracorporeal lung assist is associated with a marked incidence of complications (50%: coagulation disorders, bleeding) (21) and it might induce an inflammatory response. Moreover, the therapeutic procedure of ECMO requires a high level of technical and staff support and is costly.

In conjunction with a group of engineers (Novalung GmbH, Hechingen, Germany), we developed a new system using an arteriovenous shunt and a membrane lung that is characterized by an extremely low flow resistance. The system allows the avoidance of a pump by using the patient's arteriovenous pressure gradient as the driving force. After sampling experience on small databases of critically ill patients (12, 13), we now present a retrospective analysis of the acute effects of iLA in 90 patients. After implementation of the system, we observed a rapid and dramatic increase in carbon dioxide removal and a moderate improvement in oxygenation in most patients, allowing a significant reduction of ventilatory "aggression" within hours. Carbon dioxide removal in extracorporeal circulation is a function of the membrane lung geometry, material, surface area, $Paco_2$, and, to

Table 4. Laboratory variables before and during interventional lung assist treatment

	Pre	2 Hrs	24 Hrs
Hemoglobin, g/dL	9.8 (4.6–13.4)	10.0 (8.1–13.4)	10.4 (9.2–12.8)
Partial thromboplastin time, secs	42.5 (29–108)	58.0 (39–122)[a]	48.0 (41–102)
Platelet count/μL	143,000 (22,000–430,000)	111,000 (31,000–278,000)	115,000 (31,000–286,000)
Creatine kinase, IU/L	114 (24–2880)	142 (31–2260)	181 (29–14,260)

[a] $p < .05$ vs. pre.
Values are median (interquartile range).

Table 5. Frequency of complications and side effects

Complication/Side Effect	No. of Patients
Ischemia of a lower limb after cannulation	9
Cannula thrombosis	4
Compartmental syndrome in a lower limb	4
Hematoma/aneurysm at cannulation site	2
Hemolysis	1
Intracerebral hemorrhage	1
Diffuse bleeding/shock syndrome during cannulation	1
All	22 (24.4%)

Table 6. Causes of death in 53 patients during/after interventional lung assist treatment

Cause of Death	No. of Patients (%)
Septic shock, persistent systemic inflammatory response syndrome	26 (49)
Multiple organ failure	13 (25)
Cardiac failure	10 (19)
Cerebral injury	4 (7)
All	53 (100)

a lesser extent, blood and gas flow through the membrane. For a typical membrane lung, Bartlett (22) reported a CO_2 clearance of 60 mL·min^{-1} per one square meter surface area at a blood flow rate between 1 and 2 L·min^{-1}. In the present study, a median CO_2 removal rate of 140 mL·min^{-1} using a surface area of 1.3 m^2 was observed. Although in experimental animal studies (10, 11), a total arteriovenous CO_2 removal was found resulting in the possibility of "apneic ventilation," we were not able to confirm these findings in patients suffering from severe ARDS due to trauma, sepsis, or inflammation syndrome. Using a "medium-sized" gas exchange surface area adapted to reduced blood flow resistance, we hypothesize that a complete CO_2 removal in our patients allowing "apneic ventilation" is not possible predominantly due to an increase in CO_2 production in these severely ill patients.

To establish an adequate arteriovenous shunt (≥1.5 L/min), the continuous infusion of vasopressors was necessary in all patients, since a mean arterial pressure of ≥70 mm Hg was required. After implementation of the iLA system and after de-escalation of invasive ventilatory variables (frequency, tidal volume, F_{IO_2}), the aim of our therapeutic strategy was to treat the underlying pathophysiologic conditions of lung damage and then—after improvement of lung function—to wean the patients from iLA.

However, the hospital mortality rate was high in our retrospective analysis. Our assessment of the severity of illness by Sequential Organ Failure Assessment score (median score = 11) indicates that we used our system in most severe critically ill patients suffering from multiple organ dysfunction or failure. Antonelli and coworkers (23) assessed the Sequential Organ Failure Assessment score in trauma patients and found a global score of 8 ± 4 in nonsurvivors and a score of 4 ± 3 in survivors. Our results indicate that some of our patients were too ill and their hemodynamic situation was too unstable to tolerate an interventional system and to benefit from extracorporeal lung assist. Furthermore, 12 of the patients in which we used our system suffered from cancer and in these patients the mortality rate was extremely high (nine of 12 = 75%). In our analysis, nonsurvivors had received markedly higher doses of vasopressors, and they were significantly older and more obese. Meanwhile, we have drawn consequences from these findings and we accept limitations and restrictions for indication of iLA implementation in patients with cancer or refractory shock, in geriatric patients, in patients suffering from *adipositas per magna*, or in those developing multiple organ dysfunction syndrome. Another important consequence is the insertion of smaller arterial cannulae that allow improved distal perfusion while maintaining adequate blood flow through iLA. Finally, the absence of an "inflammatory response syndrome" when using iLA in comparison with ECMO has not yet been proven and needs to be investigated.

A most interesting result from our data is the fact that a timely initiation of iLA seemed to positively influence the outcome, since mortality rate was lower in those patients who had a shorter period of artificial ventilation before initiation of iLA. Similar findings were observed for the application of other adjunctive therapeutic measures in ARDS patients, such as the technique of high-frequency oscillatory ventilation (24) or ventilation in prone position (25). Those observations underline the importance of strict algorithms for timely intervention in patients with acute ARDS, since an early de-escalation of invasive ventilation mode may improve outcome.

Nevertheless, the blood gas exchange capacity, predominantly the oxygenation capacity, of iLA is limited in comparison with pump-driven ECMO for two reasons: First, the flow through the artificial lung membrane is restricted. Because with ECMO flow rates of 4–6 L·min^{-1} can be achieved, physically iLA *per se* will never be equally effective. Second, the establishment of an arteriovenous shunt limits the oxygen transfer capacity, since preoxygenated blood passes the artificial membrane. On the other hand, we can show with our analysis that iLA exerts a most effective carbon dioxide removal and a moderate increase in oxygenation in severe ARDS. The most evident advantages of the system are the handling properties, a relatively low incidence of severe complications in comparison with pump-driven ECMO, and low cost. Although protective ventilation is a scientifically well-based treatment necessity (2), its clinical implementation in severely injured lungs is restricted by the

need to provide adequate gas exchange. The limitation of our study is that it is based on retrospective data, but we hypothesize that the concept of iLA might allow clinicians to prioritize lung protection over "aggressive" ventilation by providing extrapulmonary gas exchange. Further prospective investigations will be needed to prove the value of the pumpless extracorporeal interventional lung assist both in the "rescue" or "life support" scenario described in the current study and in clinical situations where lung protection to improve long term pulmonary function can be enabled by iLA.

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