TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Extracorporeal CO_2 removal as bridge to lung transplantation in life-threatening hypercapnia

Peter Schellongowski,[1] Katharina Riss,[1] Thomas Staudinger,[1] Roman Ullrich,[2] Claus G. Krenn,[2] Christian Sitzwohl,[2] Andja Bojic,[1] Philipp Wohlfarth,[1] Wolfgang R. Sperr,[1] Werner Rabitsch,[1] Clemens Aigner,[3] Shahrokh Taghavi,[3] Peter Jaksch,[3] Walter Klepetko[3] and György Lang[3]

1 Department of Medicine I, Intensive Care Unit 13i2, Medical University of Vienna, Vienna, Austria
2 Department of Anesthesiology, Medical University of Vienna, Vienna, Austria
3 Division of Thoracic Surgery, Department of Surgery, Medical University of Vienna, Vienna, Austria

Keywords
bridge, ECCO2-R, ECMO, interventional lung assist, lung transplantation.

Correspondence
Peter Schellongowski, Department of Medicine I, Medical, Intensive Care Unit 13i2, University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.
Tel.: +43 1 40400 44920;
fax: +43 1 40400 44980;
e-mail: peter.schellongowski@meduniwien.ac.at

Conflicts of interest
The authors have declared no conflicts of interest.

Received: 28 July 2014
Revision requested: 18 September 2014
Accepted: 6 November 2014
Published online: 5 December 2014

doi:10.1111/tri.12486

Summary

In patients awaiting lung transplantation (LTX), adequate gas exchange may not be sufficiently achieved by mechanical ventilation alone if acute respiratory decompensation arises. We report on 20 patients with life-threatening hypercapnia who received extracorporeal CO_2 removal (ECCO2-R) by means of the interventional lung assist (ILA®, Novalung) as bridge to LTX. The most common underlying diagnoses were bronchiolitis obliterans syndrome, cystic fibrosis, and idiopathic pulmonary fibrosis, respectively. The type of ILA was pumpless arteriovenous or pump-driven venovenous (ILA activve®, Novalung) in 10 patients each. ILA bridging was initiated in 15 invasively ventilated and five noninvasively ventilated patients, of whom one had to be intubated prior to LTX. Hypercapnia and acidosis were effectively corrected in all patients within the first 12 h of ILA therapy: $PaCO_2$ declined from 109 (70–146) to 57 (45–64) mmHg, $P < 0.0001$; pH increased from 7.20 (7.06–7.28) to 7.39 (7.35–7.49), $P < 0.0001$. Four patients were switched to extracorporeal membrane oxygenation due to progressive hypoxia or circulatory failure. Nineteen patients (95%) were successfully transplanted. Hospital and 1-year survival was 75 and 72%, respectively. Bridging to LTX with ECCO2-R delivered by arteriovenous pumpless or venovenous pump-driven ILA is feasible and associated with high transplantation and survival rates.

Introduction

The introduction of the lung allocation score has allowed for considering patients for lung transplantation (LTX) while being acutely decompensated [1]. In the sickest of these patients, mechanical ventilation alone may not guarantee adequate gas exchange. Thus, different modes of extracorporeal life support have come to the focus of interest in this setting. The use of extracorporeal membrane oxygenation (ECMO) with comparatively high blood flows has been described as bridging technique in patients with primarily hypoxic terminal respiratory failure by several centers [2–5]. In contrast, the reported number of patients with primarily hypercapnic terminal respiratory failure receiving extracorporeal CO_2 removal (ECCO2-R) with comparatively low blood flows is still limited in this setting [6–9].

In Austria, allocation of lungs is performed as 'center allocation', which means that the respective center decides which patient should receive the next organ. This practice favors patients with the highest urgency status and has allowed our center to gather considerable experience in bridging patients to LTX [4]. In this article, we summarize our 8-year experience with ECCO2-R as bridge to LTX, which includes the first use of a newly developed miniaturized pump-driven venovenous device.

Methods

We retrospectively analyzed all patients with hypercapnic respiratory failure who underwent arteriovenous (a/v) or venovenous (v/v) ECCO2-R by means of the interventional lung assist (ILA®, Novalung, Heilbronn, Germany) device as bridge to primary LTX or re-LTX at the Medical University of Vienna, General Hospital, between December 2005 and March 2014. More than 1500 LTX procedures have been performed in our center since 1998. Within the last 12 months of the observational period, 123 patients underwent LTX, of which 11 (8.9%) received bridging with different modes of extracorporeal gas exchange. Concerning the patients reported in this analysis, starting ECCO2-R, deciding on the respective device, and on the appropriate weaning strategy did not follow a predefined protocol and was at the discretion of the treating intensivist in cooperation with the responsible transplant pulmonologist and the lung transplant surgeon in charge. The analysis was conducted in accordance with the amended Declaration of Helsinki. The ethics committee of the Medical University of Vienna approved the protocol and waived the need for informed consent.

Data collection

The following parameters were extracted from the electronic patients′ records at baseline (= before the start of ILA therapy): gender, age, weight, underlying lung disease, arterial blood gas parameters (pH value, partial pressure of oxygen (PaO_2), carbon dioxide ($PaCO_2$), base excess, lactate), comorbidity assessed by the Charlson comorbidity index (CCI) [10], the simplified acute physiology score (SAPS II) [11], the sequential organ failure assessment (SOFA) score [12], mode of mechanical ventilation (invasive vs. noninvasive) and ventilator settings (positive end-expiratory pressure (PEEP), tidal volume, maximal inspiratory pressure), PaO_2/FiO_2 (P/F) ratio, as well as standard laboratory markers, respectively. Moreover, we recorded type of ILA (a/v or v/v), site and type of vascular cannulation, procedure-related complications (trauma or bleeding related to vascular cannulation, thrombosis), use of vasopressors and hemofiltration, course of respiratory failure (prevention of intubation, weaning from ventilation, ventilator settings, switch to full ECMO), LTX (yes/no) and LTX-related data, ICU and hospital survival, death date, if applicable, as well as the date of the last visit.

Extracorporeal CO_2 removal

For ECCO2-R, the ILA membrane ventilator was used allowing gas exchange by diffusion over a polymethyl penthene membrane with a surface area of 1.3 m^2. The device was operated in pumpless a/v or pump-driven v/v mode. In a/v ILA, arterial cannulation of the femoral artery was performed with a 13 or 15F cannula, and venous cannulation with a 15 or 17F cannula by employing ultrasound guided percutaneous Seldinger′s technique according to an established algorithm [13]. In v/v ILA, a double-lumen cannula (Novaport Twin, Novalung, Germany) was used for jugular (22F) or femoral (24F) venous access, accordingly. As the extracorporeal blood flow in a/v ILA is primarily determined by the systemic arteriovenous pressure gradient, we aimed to achieve mean arterial pressures above 80 mmHg [6]. For extracorporeal blood circulation in patients on v/v ILA, we employed a newly developed system platform which comprises of a pre-assembled closed tubing system incorporating the ILA gas exchanger, a centrifugal pump with diagonal flow and magnetic drive, and a control and information touch screen, all of which is mounted to a single trolley (ILA activve®, Novalung). The target blood flow in patients on ILA activve between 1000 and a maximum of 2000 ml/min was reached by titrating up pump speed. As sweep gas oxygen was used at gradually increased flow rates to achieve sufficient CO_2 elimination. A heparin bolus of 2000 IE was administered immediately after cannulation, and further anticoagulation was performed with continuous heparin to reach an activated partial thromboplastin time of 50–60 s. Functioning of the system regarding CO_2 removal was measured routinely in patients on controlled mechanical ventilation modes on a daily basis by reducing the sweep gas flow to zero. If the rise of $PaCO_2$ was less than 20%, and further increase of sweep gas flows was ineffective, the system was regarded inefficient and replaced, if ECCO2-R was still clinically indicated, respectively. Further details on our institutional standards are given elsewhere [14].

Statistical analysis

Continuous data are presented as median and interquartile ranges (25–75%) unless otherwise indicated. Dichotomous data are presented as number and percentage. Comparisons were performed using the Mann–Whitney U-test for continuous variables and the chi-square test for categorical variables. Differences were considered significant if $P < 0.05$. The product-limit method of Kaplan and Meier was used to analyze the probability of overall survival.

Results

Twenty patients received ILA support as bridging to planned primary LTX ($n = 13$) or re-LTx ($n = 7$) between 12/2005 and 03/2014. Table 1 gives an overview of the baseline characteristics.

Table 1. Baseline characteristics and underlying pulmonary diseases.

	All patients, $n = 20$
Characteristics at baseline	
Male/female ratio	8/12
Age	31 (24–47)
Planned primary LTX	13 (65)
Planned re-LTX	7 (35)
SAPS II	37 (31–42)
SOFA score	9 (7–10)
Invasive mechanical ventilation	15 (75)
Noninvasive mechanical ventilation	5 (25)
Pulmonary infection	16 (80)
Underlying pulmonary diseases	
Bronchiolitis obliterans syndrome III	7 (35)
Cystic fibrosis	5 (25)
Idiopathic pulmonary fibrosis	3 (15)
Emphysema	1 (5)
Chronic obstructive pulmonary disease	1 (5)
Hemosiderosis	1 (5)
Acute respiratory distress syndrome	1 (5)
Bronchopulmonary dysplasia	1 (5)

Data are given in numbers and percent *or* median (interquartile range).

Table 2. Gas exchange and ventilator settings prior and postextracorporeal carbon dioxide removal.

Characteristics	Before ILA	After ILA	*P*-value
All patients ($n = 20$)			
$PaCO_2$ (mmHg)	109 (70–146)	57 (45–64)	<0.0001
pH	7.20 (7.06–7.28)	7.39 (7.35–7.49)	<0.0001
PaO_2/FiO_2	142 (101–198)	160 (141–216)	0.32
Intubated patients ($n = 15$)			
$PaCO_2$	94 (70–146)	58 (47–61)	<0.001
pH	7.19 (7.03–7.28)	7.40 (7.34–7.48)	<0.0001
PaO_2/FiO_2	148 (91–207)	161 (140–215)	0.53
PEEP	9 (8–16)	8 (6–12)	0.08
Pmax	33 (29–36)	28 (25–30)	<0.01
Tidal volume	300 (208–385)	254 (184–308)	0.02
Tidal volume (ml/predicted body weight)	5.5 (2.7–6.4)	3.9 (2.9–5.3)	0.03
Minute volume	6.1 (4.5–7.5)	4.1 (2.6–4.5)	<0.01
Nonintubated patients ($n = 5$)			
$PaCO_2$	117 (84–183)	49 (40–87)	<0.01
pH	7.21 (7.07–7.30)	7.39 (7.37–7.51)	<0.01
PaO_2/FiO_2	142 (136–194)	160 (141–260)	0.29
Patients with a/v ILA ($n = 10$)			
$PaCO_2$	79 (73–144)	57 (41–70)	<0.01
pH	7.15 (7.00–7.24)	7.39 (7.34–7.39)	<0.01
PaO_2/FiO_2	174 (102–215)	148 (137–260)	0.92
Patients with ILA activve ($n = 10$)			
$PaCO_2$	113 (68–154)	58 (46–62)	<0.001
pH	7.23 (7.06–7.31)	7.44 (7.37–7.49)	<0.0001
PaO_2/FiO_2	139 (100–167)	163 (145–202)	0.29

ILA, interventional lung assist.
Data are presented as median (interquartile range).

At baseline, all patients presented with severe hypercapnia [$PaCO_2$: 109 (70–146)] and respiratory acidosis [pH: 7.20 (7.06–7.28)]. Five patients were noninvasively ventilated, while the remaining 15 patients were intubated and required high levels of sedation to allow for aggressive ventilator support in terms of controlled invasive mechanical ventilation (Table 2). Ten patients each received support with a/v ILA or ILA activve, whereas ILA activve was preferably used after its introduction to our institution in 2012, if available. There were no differences in baseline blood gas parameters between intubated and nonintubated patients, or between patients receiving support with a/v ILA and ILA activve, respectively (Table 3).

Bridge time period

Hypercapnia and acidosis were effectively corrected in all patients within the first 12 h of ILA therapy: $PaCO_2$ levels declined from 109 (70–146) to 57 (45–64) mmHg, $P < 0.0001$, and pH increased from 7.20 (7.06–7.28) to 7.39 (7.35–7.49), $P < 0.0001$, while the P/F ratio was not altered significantly. These findings applied to intubated and nonintubated patients as well as to patients with a/v ILA and ILA activve support, respectively (Table 2). The relative decline of $PaCO_2$ as well as the total increase in pH value and P/F ratio was not different between patients with a/v ILA and ILA activve (Table 3).

In intubated patients, ventilator settings (peak inspiratory pressure and tidal volumes) could be reduced markedly within the first 12 h of ILA therapy (Table 2). Three patients were extubated and remained on ILA until LTX, one patient was weaned from ILA and remained intubated until LTX, and one patient was extubated *and* weaned from ILA prior to LTX. In all but one intubated patients, sedation could be reduced to levels allowing for spontaneous breathing. In nine of the initially intubated patients (60%) and all of the initially nonintubated patients, active physical therapy was possible and performed at least once daily. In four of the five noninvasively ventilated patients, intubation could be prevented.

Four patients were switched from ILA to full extracorporeal membrane oxygenation (v/v ECMO: $n = 1$, v/a ECMO: $n = 3$) after 2 days on ILA support (range 1–5 days) due to progressive hypoxia and/or additional circulatory failure. Patients switched to pretransplant ECMO revealed a trend for lower P/F ratios at baseline (88 (range 67–174) vs. 157 (range 61–335), $P = 0.09$) with no differences regarding $PaCO_2$ or pH (data not shown).

Table 3. Gas exchange, therapy settings, and outcomes depending on the mode of therapy.

Characteristics	a/v ILA (n = 10)	ILA activve (n = 10)	P-value
Baseline			
$PaCO_2$ (mmHg)	79 (73–144)	113 (68–154)	0.51
pH	7.15 (7.0–7.24)	7.23 (7.06–7.31)	0.36
PaO_2/FiO_2	174 (102–215)	139 (100–167)	0.49
Therapy characteristics			
ILA blood flow (L/min)	1.0 (0.95–1.75)	1.35 (1.1–1.53)	0.38
ILA sweep gas flow (L/min)	3.0 (2.0–6.5)	2.0 (1.0–5.8)	0.58
Invasive mechanical ventilation	8 (80)	7 (70)	1.00
Vasopressors at any dose	7 (70)	7 (70)	1.00
Therapy-associated complications			
Severe bleeding	0 (0)	2 (20)	1.00
Thrombosis after removal of cannula	1 (10)	2 (20)	
Heparin-induced thrombocytopenia	1 (10)	0 (0)	
Change of the membrane	3 (30)	0 (0)	
Outcomes			
Change in $PaCO_2$ (mmHg)	−49 (−55-(−35))	−52 (−61-(−29))	0.78
Change in pH	0.15 (0.14–0.32)	0.25 (0.14–0.33)	0.76
Change in PaO_2/FiO_2	6 (−7-21)	20 (1–70)	0.23
Upgrade to ECMO	1 (10)	3 (30)	0.58
Successful LTX	10 (100)	9 (90)	1.00
Time from start of iLA to LTX	10.5 (5–22)	4 (2–10)	0.14
ICU length of stay (days)	40 (35–50)	38 (16–56)	0.83
Hospital survival	9 (90)	6 (60)	0.30

ILA, interventional lung assist; LTX, lung transplantation; ECMO, extracorporeal membrane oxygenation.
Data are presented as numbers (percent) *or* median (interquartile range).

Transplantation

After a median bridging time of 8 (4–11) days, 19 patients (95%) were transplanted successfully. The type of transplantation was bilateral LTX (n = 8), size-reduced bilateral LTX (n = 5), lobar bilateral LTX (n = 5), and one single LTX with contralateral pneumonectomy (n = 1), respectively. Intra-operative support was employed in 18 patients and consisted of v/a ECMO with central (n = 16) or femoral cannulation (n = 2), as well as ILA activve (n = 1). Support with v/a ECMO was prolonged into the postoperative period in eight patients (42%) and lasted 3 (2–3) days. Patients receiving induction therapy with alemtuzumab (n = 14) underwent immunosuppression with tacrolimus and corticosteroids. The remaining patients received either antithymocyte globuline (n = 1) or no induction (n = 4) and underwent immunosuppression with a triple therapy consisting of tacrolimus, corticosteroids, and mycophenolate mofetil.

Morbidity and complications

Therapy-associated complications were encountered in six patients, comprising of asymptomatic thrombosis diagnosed after removal of the venous cannula in three patients (jugular: n = 2; femoral: n = 1), bleeding associated with the femoral venous cannula in two patients, both of which required surgical intervention, and suspected heparin-induced thrombocytopenia with clotting of the membrane in one patient, respectively. Repeated elective changes of the ILA membrane due to decreased CO_2 removal capacity were documented in three patients (Table 3). None of these complications were associated with lasting organ dysfunction, impairment, or death.

Other complications in the postoperative period included acute renal failure requiring hemofiltration (n = 6), need for hematothorax evacuation (n = 3), reperfusion edema with primary graft dysfunction grade 3 (n = 2), perforation of the colon (n = 1), as well as several neurological complications including postoperative delirium (n = 5), posterior reversible encephalopathy syndrome (n = 3), grand mal epilepsy (n = 3), critical illness polyneuropathy (n = 2), and recurrent laryngeal nerve paralysis (n = 1), respectively.

Early outcome and survival

The majority of patients (n = 13) were weaned from mechanical ventilation over a tracheostomy. Time on mechanical ventilation after LTX was 10 (6–25) days. ICU and hospital length of stay was 38 (21–50) and 62 (34–79) days, respectively. Five patients (25%) died during the ICU stay, one of them prior to LTX and four in the postoperative period, all due to septic multiorgan failure. All other patients survived to hospital discharge. Two patients died 10 and 11 months after LTX due to ongoing rejection (Table 4). Thirteen patients were alive after a median follow-up of 28 (range 3–103) months, and 1-year survival was 72% (the 1-year follow-up was not yet reached in two patients). Of the seven retransplanted patients, five survived to hospital discharge. All but one patient of those switched to

Table 4. Transplantation, extracorporeal therapy, and outcomes.

	All patients, n = 20
Type of transplantation	
Bilateral LTX	8 (40)
Size-reduced bilateral LTX	5 (25)
Lobar bilateral LTX	5 (25)
Right single LTX with contralateral pneumonectomy	1 (5)
Characteristics of extracorporeal therapy	
Arteriovenous iLA	10 (50)
Venovenous iLA	10 (50)
Successful transplantation	19 (95)
Bridging failure	1 (5)
Time from start of iLA to LTX	8 (4–11)
Upgrade to high-flow ECMO	4 (20)
Outcome	
ICU length of stay, days	38 (21–50)
Hospital length of stay, days	62 (34–79)
ICU and hospital survival	15 (75)
1-year survival	13/18* (72)
Follow-up of hospital survivors, months	28 (range 3–103)

Data are given as numbers (percent) *or* median (interquartile range), unless otherwise stated.
*1-year follow-up not reached in two patients.

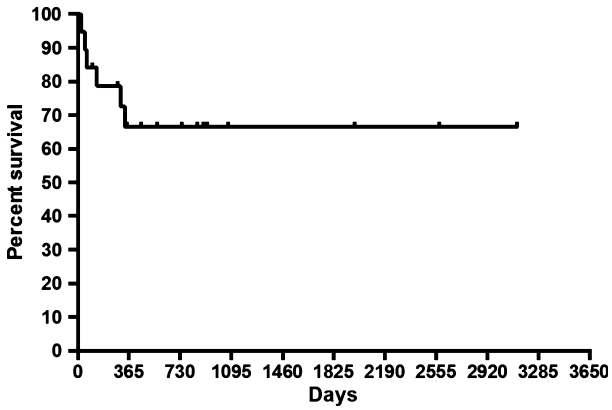

Figure 1 Long-term survival of patients receiving extracorporeal CO_2 removal as bridge to lung transplantation as analyzed by the method of Kaplan and Meier. Survival was 79% after 6 months and 67% after 12 and 24 months, respectively.

pretransplant ECMO survived to hospital discharge and became long-term survivors. The probability of survival as estimated by the method of Kaplan and Meier is given in Fig. 1.

Discussion

The herein presented data represent the so far largest series of ECCO2-R as bridge to LTX with respect to efficacy and outcome. Ten patients were supported with the pumpless a/v ILA membrane ventilator, while the other 10 were treated with the novel pump-driven v/v ILA activve® system. $PaCO_2$ levels and acidosis were effectively corrected in all patients, independent from the mode employed. Subsequently, invasiveness of ventilation and sedation levels could be reduced in intubated patients, which allowed for spontaneous breathing and—in some patients—active participation in physical therapy or even extubation prior to LTX. Likewise, intubation was prevented in all but one noninvasively ventilated patient. Twenty percent of patients developed progressive hypoxia and/or severe circulatory failure while awaiting LTX and thus had to be switched to full v/v or v/a ECMO. The overall rate of successful LTX was 95%.

In recent years, several centers have reported on the successful use of ECMO as bridge to LTX in patients with *hypoxic* respiratory failure refractory to aggressive invasive ventilation [2–5]. While v/v ECMO is commonly used in such patients with *hypoxic* lung failure alone, v/a ECMO might be necessary in additional cardiovascular failure and depicts the exclusive standard of care in patients with significant pulmonary hypertension in our center. Transplant rates in patients bridged with ECMO are reported to be around 80%, and long-term survival ranges from 50 to 74% [2–5,15]. Importantly, pre-LTX ECMO status may not negatively influence long-term survival and graft function [3,4,16]. Full ECMO is capable of providing total extracorporeal support in terms of oxygenation, decarboxylation, and—in case of v/a cannulation—circulation. To ensure proper oxygenation, high blood flows of at least 2–5 l per minute are required [17]. For this purpose, high diameter cannulation is required, which can be achieved by v/v femoro-jugular access, or insertion of a bicaval dual-lumen cannula access, alternatively. Either way depicts a rather intricate procedure, which is to be performed by at least two experienced interventionists, while the latter access additionally bears the risk of right ventricular malposition or even rupture [18,19]. Furthermore, ECMO systems require relatively large priming volumes and high doses of heparin, all of which result in considerable rates of complications, comprising mainly of hemorrhagic, thrombotic, as well as mechanical obstacles [20,21].

In contrast, ECCO2-R can be achieved by systems with lower priming volumes, relatively small diameter a/v cannulation in pumpless ECCO2-R, or easy going double-lumen cannulas without the need for complex insertion techniques in miniaturized pump-driven v/v systems, all with lower heparin requirements, respectively [17]. In fact, some v/v ECCO2-R devices may be operated at low blood flows of 0.3–0.5 l/min. Such devices have been described in several case series on patients with chronic obstructive pulmonary disease [22,23] and acute respiratory distress

Table 5. Reported bridge cases with the interventional lung assist and outcomes (2006–2014).

Author	Year published	Center	Bridging modality	Attempted	Successful LTX	Hospital survival	1-year survival
Fischer *et al.*	2006	Hannover [6]	a/v	12	10 (83)	8 (67)	8 (67)
Ricci *et al.*	2010	Torino [7]	a/v	6	2 (33)		
Haneya *et al.*	2011	Regensburg [30]	a/v	5	4 (80)	4 (80)	
Bartosik *et al.*	2011	Dublin [8]	a/v	2	2 (100)		
Gottlieb *et al.*	2012	Hannover [9]	a/v	29			
Kim *et al.*	2012	Seoul [31]	a/v	1	1 (100)	1 (100)	1 (100)
Schellongowski *et al.*	2014	Vienna	a/v = 10 v/v = 10	20	19 (95)	15 (75)	13* (72)

Data are given as numbers (percent); a/v = arteriovenous; v/v = venovenous.
Blank fields refer to nonreported data. Three patients on a/v ILA had already been reported in an earlier report of our group, which has not been listed above to prevent duplication [4].
*1-year follow-up not reached in two patients.

syndrome (ARDS) [24–26]. However, the amount of CO_2 elimination at these very low blood flows is limited [17]. Furthermore, reliable data on the efficacy of these systems are lacking, and bridge to LTX has been successful in only one of six reported cases [7]. On the contrary, the ILA membrane ventilator is capable of eliminating up to 50% of CO_2 production at intermediate blood flows of 1–2 l/min in a/v mode. Oxygenation, however, is far less affected [17,20,27]. Arteriovenous ILA treatment has been used in ARDS allowing for a reduction of invasiveness of ventilation and a higher proportion of successful weaning [28]. Moreover, in patients with acute hypercapnic exacerbation of chronic pulmonary disease and failure of noninvasive ventilation, a matched pair analysis by Kluge *et al.* suggests that a/v ILA therapy may be capable of avoiding intubation [29].

Fischer *et al.* were the first to report on the use of a/v ILA as bridge to LTX in a total of 12 hypercapnic patients, of which 10 were successfully transplanted, and 8 (66%) were alive at 1-year follow-up. The authors found similar effects of ILA therapy on CO_2 removal, correction of acidosis, and the resulting reduction of ventilator settings, when compared to our data [6]. In the meantime, several centers have reported on a total of 55 hypercapnic patients who underwent ECCO2-R by a/v ILA as attempted bridge to LTX [6–9,30,31]. However, unfortunately important outcomes including rate of successful LTX, short- and long-term survival have not been indicated in several of these reports (Table 5).

The main purpose of ILA therapy in all of our patients was to overcome life-threatening hypercapnia to survive to LTX. This goal was achieved in all but one patient. Moreover, ILA was initiated with two different short-term goals depending on the respective clinical setting: (i) In all invasively ventilated patients, a reduction of ventilatory support could be achieved enabling less sedation and allowing for spontaneous breathing and early mobilization in most patients. (ii) Intubation could be prevented in all but one noninvasively ventilated patient. This finding suggests that the 'awake ECMO' concept by Fuehner *et al.* (=ECMO as bridge to LTX in nonintubated patients) [32] can be successfully translated into an 'awake ILA' concept in patients with hypercapnic respiratory failure.

We are the first center to report on the use of the newly developed pump-driven v/v ILA activve system [14]. No significant differences regarding the reduction of arterial $PaCO_2$, as well as increase of pH and P/F ratio were found compared to a/v ILA. However, advantages of the ILA activve system may be (i) its independence from hemodynamics, as its performance does not depend on cardiac output; (ii) extended monitoring measuring pressures in the extracorporeal circuit in addition to blood flow allowing for early detection of possible mechanical problems; (iii) in case of progressive hypoxia or additional cardiovascular failure the same platform may be used for high-flow ECMO, as the ILA membrane is approved for blood flows up to 4.5 l/min, and the centrifugal pump may be run at flows of up to 8 l/min. However, this is not possible with the herein used cannulation techniques, and adequate access needs to be established.

Switch to full ECMO (v/a or v/v) became necessary in 20% of our patients. Those affected revealed a trend for worse oxygenation at baseline. Decision for upgrade to full ECMO support depended, however, on the further clinical course rather than on baseline oxygenation. We, therefore, cannot derive a definitive P/F cutoff value for preferring full ECMO to ECCO2-R. Individual considerations, such as the invasiveness of ventilation and the anticipated course of the respiratory failure will have to be taken into account when choosing the mode of extracorporeal therapy.

When compared to the data of Fischer *et al.* [6] rate of bridging failure and hospital mortality was lower in our cohort (5 vs. 17% and 25 vs. 33%), which may, of course,

be chance findings in the context of fairly small cohorts. However, differences could also be due to unequal case mixes, general improvements in ICU management over time, and importantly, shorter bridging time intervals in our patients, alternatively. We believe that preventing complications and anew deterioration by doing everything possible to minimize waiting times on extracorporeal support is of utmost importance. The existing system of center allocation is supportive when considering patients on bridge to LTX by any extracorporeal mode. Furthermore, aggressive handling of available organs with regard to size matching, use of marginal donors, and LTX over the blood group is performed in our center whenever possible.

Similar to prior reports, the use of a/v ILA and ECMO therapy, thirty percent of our patients experienced procedure-related complications, mainly comprising of thrombosis and bleedings [17,21,27]. None of these events resulted in lasting organ dysfunction, impairment, or death. Supposed that none of our patients were likely to survive to LTX, it seems reasonable to implement rescue therapies with potentially serious side effects. To minimize possible risks, we propose to establish local protocols concerning the following questions: What are the clinical criteria to use extracorporeal gas exchange as bridge to LTX? Which device and which cannulation strategy should be used for which patient? What is the optimal anticoagulation management? Furthermore, even though cannulation in a/v ILA and ILA activve can be performed by intensivists themselves, support by surgeons and perfusionists should be available on short notice in case of cannula-associated complications or the necessity for switch to full ECMO.

The formal limitations of our report are the ones typically associated with a retrospective analysis. Most importantly, our findings reflect the experience of a single center with > 100 LTX procedures per year *and* a focus on extracorporeal life support. Thus, it may be difficult to generalize our findings to other centers. Moreover, we did not measure CO_2 removal, amount of oxygen delivery, and recirculation values, which limits our findings concerning the gas exchange performance of the systems employed.

In conclusion, ECCO2-R using a/v ILA or ILA activve is a feasible and efficient method to bridge invasively and noninvasively ventilated patients with life-threatening hypercapnia to LTX. However, some patients will progress to severe hypoxic respiratory and/or cardiovascular failure. Thus, providing high-flow v/v or v/a ECMO must be possible on short notice.

Authorship

PS, KR, TS and GL: participated in research design. PS, KR, RU, CGK, CS, PJ and GL: participated in collection of the data. PS: performed the statistical analysis. PS, TS and GL: participated in writing of the manuscript. AB, PW, WRS, WR, CA, ST and WK: participated in reviewing and correcting the manuscript. PS, KR, TS and GL: participated in manuscript preparation and submission.

Funding

Self funded. PS and TS have received lecture fees from Novalung Corp. and Maquet Corp. The remaining authors have no conflicts of interest to disclose.

Acknowledgements

None.

References

1. Egan TM, Murray S, Bustami RT, *et al.* Development of the new lung allocation system in the United States. *Am J Transplant* 2006; **6**: 1212.
2. Hammainen P, Schersten H, Lemstrom K, *et al.* Usefulness of extracorporeal membrane oxygenation as a bridge to lung transplantation: a descriptive study. *J Heart Lung Transplant* 2011; **30**: 103.
3. Bermudez CA, Rocha RV, Zaldonis D, *et al.* Extracorporeal membrane oxygenation as a bridge to lung transplant: midterm outcomes. *Ann Thorac Surg* 2011; **92**: 1226; discussion 31-2.
4. Lang G, Taghavi S, Aigner C, *et al.* Primary lung transplantation after bridge with extracorporeal membrane oxygenation: a plea for a shift in our paradigms for indications. *Transplantation* 2012; **93**: 729.
5. Lafarge M, Mordant P, Thabut G, *et al.* Experience of extracorporeal membrane oxygenation as a bridge to lung transplantation in France. *J Heart Lung Transplant* 2013; **32**: 905.
6. Fischer S, Simon AR, Welte T, *et al.* Bridge to lung transplantation with the novel pumpless interventional lung assist device NovaLung. *J Thorac Cardiovasc Surg* 2006; **131**: 719.
7. Ricci D, Boffini M, Del Sorbo L, *et al.* The use of CO_2 removal devices in patients awaiting lung transplantation: an initial experience. *Transplant Proc* 2010; **42**: 1255.
8. Bartosik W, Egan JJ, Wood AE. The Novalung interventional lung assist as bridge to lung transplantation for self-ventilating patients - initial experience. *Interact Cardiovasc Thorac Surg* 2011; **13**: 198.
9. Gottlieb J, Warnecke G, Hadem J, *et al.* Outcome of critically ill lung transplant candidates on invasive respiratory support. *Intensive Care Med* 2012; **38**: 968.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987; **40**: 373.

11. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; **270**: 2957.
12. Vincent JL, Moreno R, Takala J, *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707.
13. Zimmermann M, Bein T, Arlt M, *et al.* Pumpless extracorporeal interventional lung assist in patients with acute respiratory distress syndrome: a prospective pilot study. *Crit Care* 2009; **13**: R10.
14. Hermann A, Staudinger T, Bojic A, *et al.* First experience with a new miniaturized pump-driven veno-venous extracorporeal CO_2-removal system (iLA-Activve(R)): A retrospective data analysis. *ASAIO J* 2014; **60**: 342.
15. Boffini M, Venuta F, Rea F, *et al.* Urgent lung transplant programme in Italy: analysis of the first 14 months. *Interact Cardiovasc Thorac Surg* 2014; **19**(5): 795.
16. Toyoda Y, Bhama JK, Shigemura N, *et al.* Efficacy of extracorporeal membrane oxygenation as a bridge to lung transplantation. *J Thorac Cardiovasc Surg* 2013; **145**: 1065; discussion 70-1.
17. Terragni P, Maiolo G, Ranieri VM. Role and potentials of low-flow CO(2) removal system in mechanical ventilation. *Curr Opin Crit Care* 2012; **18**: 93.
18. Chimot L, Marque S, Gros A, *et al.* Avalon(c) bicaval dual-lumen cannula for venovenous extracorporeal membrane oxygenation: survey of cannula use in France. *ASAIO J* 2013; **59**: 157.
19. Hirose H, Yamane K, Marhefka G, Cavarocchi N. Right ventricular rupture and tamponade caused by malposition of the Avalon cannula for venovenous extracorporeal membrane oxygenation. *J Cardiothorac Surg* 2012; **7**: 36.
20. Muller T, Philipp A, Luchner A, *et al.* A new miniaturized system for extracorporeal membrane oxygenation in adult respiratory failure. *Crit Care* 2009; **13**: R205.
21. Lewandowski K. Extracorporeal membrane oxygenation for severe acute respiratory failure. *Crit Care* 2000; **4**: 156.
22. Abrams DC, Brenner K, Burkart KM, *et al.* Pilot study of extracorporeal carbon dioxide removal to facilitate extubation and ambulation in exacerbations of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2013; **10**: 307.
23. Burki NK, Mani RK, Herth FJ, *et al.* A novel extracorporeal CO(2) removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. *Chest* 2013; **143**: 678.
24. Gattinoni L, Pesenti A, Mascheroni D, *et al.* Low-frequency positive-pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. *JAMA* 1986; **256**: 881.
25. Terragni PP, Del Sorbo L, Mascia L, *et al.* Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology* 2009; **111**: 826.
26. Forster C, Schriewer J, John S, Eckardt KU, Willam C. Low-flow CO_2 removal integrated into a renal-replacement circuit can reduce acidosis and decrease vasopressor requirements. *Crit Care* 2013; **17**: R154.
27. Bein T, Weber F, Philipp A, *et al.* A new pumpless extracor poreal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med* 2006; **34**: 1372.
28. Bein T, Weber-Carstens S, Goldmann A, *et al.* Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO_2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med* 2013; **39**: 847.
29. Kluge S, Braune SA, Engel M, *et al.* Avoiding invasive mechanical ventilation by extracorporeal carbon dioxide removal in patients failing noninvasive ventilation. *Intensive Care Med* 2012; **38**: 1632.
30. Haneya A, Philipp A, Mueller T, *et al.* Extracorporeal circulatory systems as a bridge to lung transplantation at remote transplant centers. *Ann Thorac Surg* 2011; **91**: 250.
31. Kim YR, Haam SJ, Park YG, Lim BJ, Park YM, Paik HC. Lung transplantation for bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation. *Yonsei Med J* 2012; **53**: 1054.
32. Fuehner T, Kuehn C, Hadem J, *et al.* Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. *Am J Respir Crit Care Med* 2012; **185**: 763.