Extracorporeal Life Support as Bridge to Lung Retransplantation: A Multicenter Pooled Data Analysis

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Background. Extracorporeal life support (ECLS) as a bridge to lung retransplantation has been reported only anecdotally. Thus, we analyzed combined data from our center with pooled data from published studies to identify selection criteria for this advanced therapy.

Methods. Four patients at our center were bridged on ECLS to lung retransplantation. Patient data were retrospectively retrieved from electronic records. The MEDLINE database was searched using the PubMed engine and yielded 13 relevant studies that included a minimum of 3 patients bridged to lung retransplantation, and four studies described detailed data on 17 patients. Patient data from our center (n = 4) were pooled with data from the MEDLINE database (n = 17) and analyzed.

Results. Of 21 patients, 3 (14%) died on ECLS awaiting retransplantation, and 18 (86%) underwent retransplantation after a median of 37 months (range, 0 to 168 months) after primary transplantation. Type of ECLS was extracorporeal carbon dioxide removal (ECCO2R)

in 4, venovenous extracorporeal membrane oxygenation (ECMO) in 7, venoarterial ECMO in 5, or was not mentioned in 2. The 90-day postoperative mortality was 28%. Overall 1-year survival was 48%. Patients bridged to retransplantation with ECCO2R/venovenous ECMO ($p = 0.05$) or on awake ECMO ($p = 0.06$) showed strong trends toward better survival in univariate analysis. Univariate and multivariate analysis identified a longer intertransplant interval as a statistically significant favorable prognostic factor. In a selected subgroup of patients (awake ECCO2R/venovenous ECMO support and intertransplant interval >2 years), 1-year survival reached 67%.

Conclusions. Despite limited overall 1-year survival for patients bridged with ECLS to lung retransplantation, careful patient selection may yield an acceptable 1-year survival of 67%.

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No randomized controlled trial to date has compared invasive mechanical ventilation (IMV) and extracorporeal membrane oxygenation (ECMO) strategies as a bridge to primary lung transplantation [1]. However, ECMO as a bridge is a promising strategy and its use has increased in recent years [2, 3]. In retrospective studies, it was associated with high perioperative morbidity and mortality but achieved acceptable 1-year survival, similar to patients bridged with IMV [4]. In a study that enrolled patients on ECMO as an alternative to IMV, outcome was even better for the ECMO group than for the IMV group, with 6-month survivals after primary lung transplantation of 80% and 50%, respectively [5].

The absolute number of lung retransplantations performed annually has been increasing for the last 2

decades, with a ratio to all adult lung transplantations being stable at approximately 5%, according to the International Society for Heart and Lung Transplantation Registry report [6]. Survival rates after lung retransplantation have improved over time, ranging from 60% to 78% at 1 year in recent reports [7], but have not yet fully reached the rates after primary lung transplantation [7].

Combining lung retransplantation and ECMO support as a bridging strategy is controversial and has only been reported anecdotally in the literature. In the current situation, where ECMO as a bridge becomes more accessible, the demand for lung retransplantation increases, and the donor pool is still scarce, it appears of paramount importance to investigate the outcome of these selected patients. Hence, we analyzed all patients bridged to lung retransplantation on ECLS at our center and combined their data with pooled patient data from the literature. We believe that identification of valuable clinical prognostic factors will assist in selecting patients who may benefit the most from this advanced therapy.

Abbreviations and Acronyms

AV	=	arteriovenous
BOS	=	bronchiolitis obliterans syndrome
CI	=	confidence interval
DLC	=	double-lumen cannula
ECLS	=	extracorporeal life support
ECMO	=	extracorporeal membrane oxygenation
ECCO2R	=	extracorporeal carbon dioxide removal
HR	=	hazard ratio
IMV	=	invasive mechanical ventilation
NA	=	not available
PGF	=	primary graft failure
VA	=	venoarterial
VV	=	venovenous
V-VA	=	veno-venoarterial

Material and Methods

From January 2009 to December 2014, 4 patients were bridged on ECLS to lung retransplantation at our center. Patient data were retrospectively retrieved from electronic records after the local ethical board (KEK-ZH-Nr: 2014-0385) approved the study.

In a second step, the PubMed search engine was used to search the MEDLINE database (keywords: extracorporeal membrane oxygenation, ECMO, extracorporeal life support, ECLS, bridge, lung transplantation, lung retransplantation, lung re-transplantation) to identify studies that included patients bridged with ECLS to lung retransplantation. Articles in English, French, and German, published between January 2000 and May 2015, were retrieved. Only relevant articles including detailed nonduplicative data on patients bridged to lung retransplantation with ECLS were selected. Articles were added after a manual search using the reference lists from selected papers. Finally, corresponding authors of the included articles were contacted to share missing data if needed. Case reports or case series comprising fewer than 3 patients bridged to lung retransplantation were excluded to minimize publication bias. Thereafter, data from our center were pooled with published patient data from the MEDLINE database.

In detail, ECLS included extracorporeal carbon dioxide removal (ECCO2R) devices and venovenous (VV) or venoarterial (VA) ECMO. The ECCO2R devices included the pumpless arteriovenous ILA (Novalung GmbH, Hechingen, Germany), the VV ProLung (Estor S.P.A., Pero, Italy), and the Decapsmart (Hemodec, Salerno, Italy) [8]. The ILA-activve (Novalung GmbH), used with a double-lumen cannula (DLC), was considered as VV ECMO [9]. If ECMO modes were switched during bridge to lung retransplantation, the most supportive mode of ECMO was used for statistical purposes, namely ECCO2R, followed by VV, and finally, VA. Awake ECMO patients were defined as patients without sedation, fully or partially weaned from IMV, allowing for mobilization, communication, and oral nutrition [9]. Primary graft failure included acute allograft rejection and primary graft dysfunction [10].

Statistical analysis was performed using IBM SPSS Statistics 20.0 software (IBM Corp, Armonk, NY). Overall survival was estimated from the date of retransplantation until death or the last follow-up using the Kaplan-Meier survival analysis method. The effect on survival of eight variables (age at transplantation, awake ECMO, ECMO mode, diagnosis and age at retransplantation, intertransplant interval, time on IMV or ECMO) was assessed by Cox regression for continuous variables and the log-rank test or Breslow test when necessary for discrete variables. Variables with strong trends or statistical significance were further analyzed in a multiple Cox regression model (backward). A p value of less than 0.05 was considered significant.

Results

The above-detailed search strategy yielded 175 published articles. After titles and abstracts were screened, 34 articles were retrieved in full and assessed. After further exclusion of articles lacking detailed data on patient outcome or comprising fewer than 3 patients bridged to lung retransplantation, three articles were eventually selected [9, 11, 12]. One patient underwent a second retransplantation and was excluded, for a total of 17 nonduplicative patients [12]. These 17 patients and their data were added to the 4 patients from our center, for a study cohort of 21 patients with intent to bridge to lung retransplantation with ECLS. Patient characteristics, details on bridge and retransplantation, and postoperative outcomes are reported in Table 1.

Of the 21 patients with intent to bridge to lung retransplantation, 3 died on ECLS before retransplantation, giving a waiting list mortality rate of 14%. Causes of death were not mentioned, but 1 patient (patient 3) suffered from respiratory failure and 1 patient (patient 7) from retroperitoneal hematoma, sepsis, and acute renal failure during the bridge period.

Eighteen patients (86%), who were a median age of 37 years (range, 17 to 63 years), were eventually bridged to lung retransplantation after a median of 11 days on ECMO (range, 2 to 86 days). Severe ECMO-related complications occurred in 3 patients (21%) during bridge; namely, bleeding (patients 11 and 21), acute renal failure (patients 19 and 21), sepsis (patient 19), and ventricular fibrillation (patient 21). A switch of ECMO mode was necessary in 3 patients (14%) due to development of hypoxic respiratory failure or hemodynamic instability. The 6 awake patients (33%) on ECMO were supported with ECCO2R devices (arteriovenous or VV) or VV-DLC ECMO.

The median interval between primary transplantation and retransplantation (intertransplant interval) was 37 months (range, 0 to 168 months). The diagnosis for retransplantation was mainly bronchiolitis obliterans syndrome (61%). Overall morbidity after retransplantation was 71%. One or more complications occurred in 10 patients, including acute renal failure in 6, neurologic

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