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The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

Extended post-ex vivo lung perfusion cold preservation predicts primary graft dysfunction and mortality: Results from a multicentric study

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KEYWORDS:
ex vivo lung perfusion;
lung transplant;
primary graft dysfunction

BACKGROUND: Ex vivo lung perfusion (EVLP) allows for a reassessment of lung grafts initially deemed unsuitable for transplantation, increasing the available donor pool; however, this requires a pre- and post-EVLP period of cold ischemic time (CIT). Paucity of data exists on how the sequence of cold normothermic−cold preservations affect outcomes.

METHODS: A total of 110 patients were retrospectively analyzed. Duration of 3 preservation phases was measured: cold pre-EVLP, EVLP, and cold post-EVLP. The donor and recipient clinical data were collected. Primary graft dysfunction (PGD) and survival were monitored. Risk of mortality or PGD was calculated using Cox proportional hazards and logistic regression models to adjust for baseline characteristics.

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https://doi.org/10.1016/j.healun.2020.05.002

RESULTS: Using the highest quartile, patients were stratified into extended vs non-extended pre-EVLP (<264 vs ≥264 minutes) and post-EVLP (<287 vs ≥287 minutes) CIT. The rates of 1-year mortality (8.4% vs 29.6%, $p = 0.013$), PGD 2-3 (20.5% vs 52%, $p = 0.002$), and PGD 3 (8.4% vs 29.6%, $p = 0.005$) at 72 hours were increased in the extended post-EVLP CIT group. After adjusting for baseline risk factors, the extended group remained an independent predictor of PGD ≥2 (odd ratio: 6.18, 95% CI: 1.88−20.3, $p = 0.003$) and PGD 3 (odd ratio: 20.4, 95% CI: 2.56−161.9, $p = 0.004$) at 72 hours and 1-year mortality (hazard ratio: 17.9, 95% CI: 3.36−95.3, $p = 0.001$). Cold pre-EVLP was not a significant predictor of primary outcomes.

CONCLUSIONS: Extended cold post-EVLP preservation is associated with a risk for PGD and 1-year mortality. Pre-EVLP CIT does not increase mortality or high-grade PGD. These findings from a multicenter trial should caution on the implementation of extended cold preservation after EVLP.

J Heart Lung Transplant 2020;39:954−961

Lung transplantation is currently the only long-term treatment for patients with end-stage pulmonary disease. Organ shortage and a high rate of sub-optimal grafts during evaluation are the main limiting factors, with approximately 78% of organs rejected owing to poor donor lung function or high-risk donor comorbidities.[1] A strategy to increase the donor pool is through reassessment and treatment of initially rejected organs. The ex vivo lung perfusion (EVLP) platform allows near physiologic assessment of explanted lungs, which would otherwise be deemed unsuitable for transplantation. Long-term studies have shown that transplanted lungs evaluated by EVLP are not associated with increased mortality or chronic lung allograft dysfunction (CLAD) compared with standard transplanted lungs.[2]

As with other transplants, cold preservation is a fundamental part of procurement and transport of organs. To minimize catabolism, lungs are placed in cold static preservation (CSP) after explant. This involves topical and intravascular cooling using a low potassium dextran solution in the form of an antegrade flush through the pulmonary artery and a retrograde flush through the pulmonary veins in some centers. Cold preservation decreases the rate of production of oxygen radicals, cell death, and loss of epithelial barrier integrity.[3,4] In addition, the retrograde flush may expel any pulmonary artery thrombi and improve the overall distribution of the solution. This results in prevention of reperfusion injury and improved early graft oxygenation. Despite these beneficial properties, prolonged periods of CSP may be deleterious to graft function.

The main cause of early post-operative death and an important prognostic factor in overall long-term outcomes is primary graft dysfunction (PGD).[5−7] Among interventions that have shown to decrease PGD are the use of CSP during transportation, slow reperfusion at low pulmonary artery pressures, and limiting the amount of cold ischemic time (CIT) before transplant.[3,6]

The standard protocol for EVLP involves a period of CSP during transport, followed by assessment at normothermic temperatures for 4 hours. After monitoring of oxygenation, dynamic compliance, pulmonary vascular pressures, and overall condition of the allograft, lungs are cooled to a temperature of 4˚C and transported to the operative suite for implantation. This sequence of CITs can be variable and depend on several recipient-, donor-, and logistics-related factors, which raise the concern for prolonged cumulative cold injury to the organ. It is currently unknown whether prolonged CIT before or after EVLP affects short- and long-term outcomes. The purpose of this study is to understand whether pre- and post-EVLP CSP are associated with adverse outcomes.

Methods

Population and treatment

Patients enrolled in the multicentric, non-randomized, open-labeled normothermic EVLP trial were retrospectively reviewed after recruitment was finalized. A total of 110 patients transplanted with lungs that had undergone EVLP were included in the study. Inclusion and exclusion criteria as well as the detailed trial protocol have been previously described.[7] In brief, after procurement, organs were placed in cold preservation solution and transported to the home institution. Grafts were incorporated into the EVLP circuit, perfused, and rewarmed in a step-wise fashion to a temperature of 32˚C within the first 30 minutes before restarting ventilation. Rewarming was then continued to a temperature of 37˚C, EVLP was maintained for a total time of approximately 4 hours, and the graft was serially assessed for physiologic parameters (oxygenation, dynamic compliance, pulmonary arterial resistance, and peak inspiratory airway pressures). Lungs considered suitable for transplantation were defined by partial pressure of alveolar oxygen (PaO_2)-to-fraction of inspired oxygen (FiO_2) ratio ≥350 mm Hg and pulmonary vascular resistance, dynamic compliance, and peak inspiratory pressure <15% of baseline and clinical judgment. All EVLP cases were done using the XVIVO Perfusion System platform (XVIVO perfusion, Göteborg, Sweden). Pre-EVLP cold time was defined by the interval between aortic cross clamp and the start of EVLP. Post-EVLP cold time was defined as the interval between cessation of EVLP and first transplanted lung.

Patients were stratified by extended vs non-extended pre- and post-EVLP CIT on the basis of the highest quartile.

Outcomes

Primary outcomes of interest were 1-year survival , rate of PGD Grades 2–3, and PGD Grade 3 at 72 hours after transplantation. Survival was followed up to 3 years as per trial protocol. PGD was diagnosed on the basis of PaO_2:FiO_2 ratios and allograft infiltrates on X-ray as per The International Society for Heart and Lung Transplant guidelines.[8] The cause of death was provided from mortality reports from each of the centers. These were established

clinically or by autopsy reports, if available. To understand the potential factors related to prolonged post-EVLP CIT, operative notes provided by each of the centers were analyzed for rates of intraoperative extracorporeal membrane oxygenation or cardiopulmonary bypass use, extensive lysis of adhesions, an unanticipated additional procedure, or a composite of these.

Statistical analysis

Differences in baseline characteristics were compared between groups using the Mann−Whitney test and chi-square test for continuous and categorical variables, respectively. Time-to-event rates were calculated using Kaplan−Meier curves, and the hypothesis was tested using the log-rank test. The effect of extended post-EVLP cold preservation on primary outcomes was adjusted to lung allocation score, pre-EVLP CIT, recipient age, donor smoking history, last donor PaO_2, type of transplant, and diagnosis based on historical predictors of adverse outcomes using multivariable analysis. In addition, several of the parameters of EVLP at the time of decision to transplant (pulmonary arterial pressure, the difference between venous and arterial PaO_2, static compliance, peak airway pressure), were added to the model to adjust for quantitative and qualitative differences in allograft function during EVLP. Covariates were regressed using a Cox proportional hazards model for time-to-event data. For rates of PGD Grades 2–3 and PGD Grade 3, a logistic regression model was used. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using Stata, version 14.0 (StataCorp, College Station, Texas).

Results

A total of 110 patients enrolled in the trial were transplanted with grafts subjected to EVLP. Pre- and post-EVLP CIT were divided into quartiles, and those within the fourth quartile were defined as extended. Pre-EVLP–extended CIT (>264 minutes, $n = 28$, median: 339 minutes, actual range: 264−649 minutes) was compared with non-extended (≤264 minutes, $n = 82$, median: 173 minutes, actual range: 66−259 minutes) (refer to Supplementary Figure S1a and b available online at www.jhltonline.org). In a similar fashion, outcomes were compared for extended (>287 minutes, $n = 27$, median: 347 minutes, actual range: 289−492 minutes) and non-extended (≤287 minutes, $n = 83$, median: 183 minutes, actual range: 10−287 minutes) post-EVLP CIT (Figure 1). The cumulative CIT ranged from 141 to 760 minutes.

Table 1 shows the donor baseline characteristics between non-extended and extended cold pre- and post-EVLP times. The recipient baseline demographics are shown in Table 2.

Overall survival

Overall survival was similar between those with extended and those with non-extended pre-EVLP CIT (Figure 2a). Overall survival was significantly decreased in those with an extended post-EVLP CIT (Figure 2b). The difference in conditional survival for patients that survived >1 year was not significant (Supplementary Figure S2 online). On the basis of this, a cutoff of 1-year survival was chosen as a primary survival outcome. There was no clear predilection toward specific causes of death between extended and non-extended post-EVLP CIT (Supplementary Table S1 online).

Primary outcomes

The rates of 1-year mortality (14.6% vs 10.7%, $p = 0.562$) and PGD Grades 2–3 (31.7% vs 17.9%, $p = 0.16$) were similar between non-extended and extended pre-EVLP CIT (Supplementary Table S2 online). The rates of PGD Grade 3 at 72 hours were increased in patients with non-extended pre-EVLP CIT (15% vs 0%, $p = 0.015$). There was no significant difference in the rates of 30-day (0% vs 2.4%, $p = 0.404$) and 90-day mortality (0% vs 4.9%, $p = 0.234$) between these groups.

Extended post-EVLP CIT was associated with increased rates of 1-year mortality (8.4% vs 29.6%, $p = 0.013$) and PGD Grades 2–3 (20.5% vs 51.9%, $p = 0.002$) and PGD Grade 3 (8.4% vs 29.6%, $p = 0.005$) at 72 hours after transplantation. Both 30-day (0% vs 7.4%, $p = 0.012$) and 90-day mortality (1.2% vs 11.1%, $p = 0.017$) were significantly increased in the extended post-EVLP CIT group. Observations were adjusted for lung allocation score, cold pre-EVLP time, recipient age, donor smoking history, donor PaO_2, type of transplant, EVLP parameters at the time of decision to transplant, and underlying diagnosis using multivariable analysis. Extended post-EVLP CIT remained an independent predictor of 1-year mortality (hazard ratio: 17.9, 95% CI: 3.36−95.3, $p = 0.001$), PGD Grades 2–3 (odd ratio [OR]: 6.18, 95% CI: 1.88−20.3, $p = 0.003$), and PGD Grade 3 (OR: 20.4, 95% CI: 2.56−161.9, $p = 0.004$) (Table 3). The effect was significant after adjusting by number of cases performed by each center: 1-year mortality

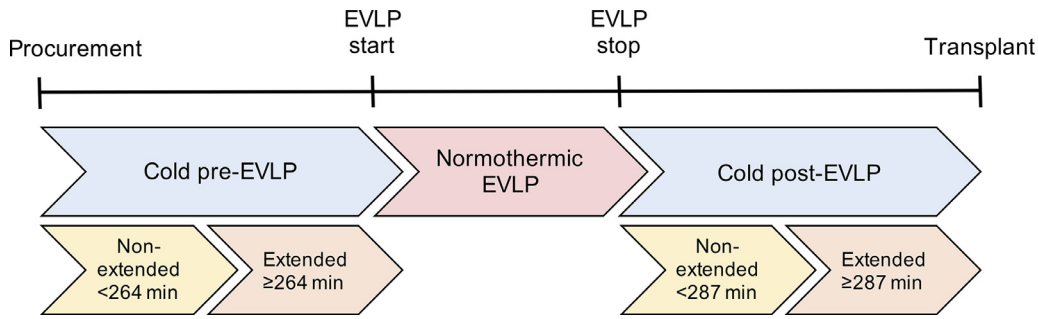

Figure 1 EVLP protocol and experimental design. EVLP, ex vivo lung perfusion.

Table 1 Donor Demographic Characteristics

Characteristic	Overall, *n* (%)	Pre-EVLP CIT			Post-EVLP CIT		
		non-extended (*n* = 83), *n* (%)	extended (*n* = 27), *n* (%)	*p*-value	non-extended (*n* = 83), *n* (%)	extended (*n* = 27), *n* (%)	*p*-value
Age, years (range)	33.5 (24–46)	33 (24–45)	38 (23.5–50)	0.184	33 (23–45)	34 (36–48)	0.445
Donor PaO_2, mm Hg (range)	341 (275–419	336 (275–404)	379 (279–438.5)	0.233	337 (267–392)	378 (289–462)	0.066
Female gender	28 (25.5)	19 (23.2)	8 (28.6)	0.347	21 (25.3)	7 (25.9)	0.948
Type of donor							
DBD	82 (74.5)	56 (68.3)	26 (92.9)	0.01	64 (77.1)	18 (66.7)	0.279
DCD	28 (25.5)	26 (31.7)	2 (7.1)		19 (22.9)	9 (33.3)	
CMV-positive	53 (48.2)	41 (50)	16 (57.1)	0.514	45 (54.2)	12 (44.4)	0.377
Positive sputum stain	48 (43.6)	38 (46.3)	10 (35.7)	0.311	37 (44.6)	11 (40.7)	0.636
Cause of death							
CVA	25 (22.7)	16 (19.5)	9 (32.1)	0.067	16 (19.3)	0 (0)	0.203
Hypoxia	38 (34.5)	34 (41.5)	4 (14.3)		27 (32.5)	11 (40.7)	
Trauma	42 (38.2)	29 (35.4)	13 (46.4)		36 (43.4)	6 (22.2)	
Other	5 (4.5)	3 (3.7)	2 (7.1)		4 (4.8)	1 (3.7)	
Smoking status							
Current	45 (40.9)	32 (39)	13 (46.4)	0.728	33 (39.8)	12 (44.4)	0.264
Former	14 (12.7)	12 (14.6)	2 (7.1)		10 (12)	4 (14.8)	
Never	48 (43.6)	36 (43.9)	12 (42.9)		39 (47)	9 (33.3)	
Pulmonary edema	39 (35.5)	30 (36.6)	9 (32.1)	0.671	30 (36.1)	9 (33.3)	0.791
>10 U transfusion	13 (11.8)	8 (9.8)	5 (17.9)	0.252	10 (12)	3 (11.1)	0.896

Abbreviations: CIT, cold ischemic time; CMV, cytomegalovirus; CVA, cerebrovascular accident; DBD, declared brain dead; DCD, declared cardiac dead; EVLP, ex vivo lung perfusion; PaO_2, partial pressure of alveolar oxygen; U, units.

Values are given in *n* (%) unless indicated otherwise.

(hazard ratio: 19.5, 95% CI: 3.47–109.6, $p = 0.001$), PGD Grades 2–3 (OR: 6.94, 95% CI: 1.98–24.4, $p = 0.003$), and PGD Grade 3 (OR: 34.2, 95% CI: 2.78–420.7, $p = 0.006$). Pre-EVLP CIT was not a significant predictor of any of the primary outcomes. The median time to extubation after transplant was 1 day (25^{th}–75^{th} percentile range: 1–3) for non-extended and 2 days (25^{th}–75^{th} percentile range: 1–12) for extended post-EVLP CIT ($p = 0.012$).

Operative risk factors for the extended cold post-EVLP time

Operative notes were individually evaluated for risk factors of prolonged explant. Risk factors considered were the need for cardiopulmonary bypass, extracorporeal membrane oxygenation, an additional unplanned procedure, extensive adhesions, or a composite of these. There were no significant differences in the rates of reported risk factors for prolonged explant (Supplementary Table S3 online).

Discussion

This study reports outcomes related to prolonged pre- and post-EVLP CIT on the basis of multicentric data. In our cohort, patients with a post-EVLP CIT over 287 minutes had significantly increased rates of high-grade PGD at 72 hours after transplantation and decreased overall survival in addition to more days on mechanical ventilation. Prolonged pre-EVLP CIT was not associated with any of these adverse outcomes. Prolonged post-EVLP CIT remained an independent predictor of PGD Grades 2–3 and 1-year mortality after adjusting for purposeful donor- and patient-related risk factors.

EVLP allows for the reassessment and potential treatment at normothermic temperatures of lungs that would have otherwise been unsuitable for transplant. Clinical outcomes using EVLP have shown no significant difference in the rate of PGD or mortality in comparison with standard lung transplantation.[7,9] Lungs rejected on the basis of clinical or physiologic parameters are procured in the standard fashion and transported in CSP to the home institution. Grafts are then connected to the EVLP circuit and assessed for 4–6 hours.[10] After monitoring physiologic parameters (dynamic compliance, oxygenation, vascular resistance), a decision can be made as to the adequacy of the lung for transplantation. The graft is then cooled and stored in ice until transplantation. This sequence of CITs raises the concern as to whether the total cumulative CIT could be associated with adverse outcomes.

The effect of CSP on allograft function and long-term outcomes is a controversial topic. Early reports have associated CIT with increased rates of mortality and reperfusion injury after 5–6 hours of cold ischemia.[11–13] However, more recent studies have challenged this notion, showing that CIT is not independently associated with adverse outcomes.[14–16] There is an increase in the overall CIT as centers become more aggressive with transplantation.[17] A recent report of 15,784 patients by The International Society for Heart and Lung Transplant showed that overall and bronchiolitis obliterans syndrome–free survival did not

Table 2 Recipient Demographic Characteristics

Characteristics	Overall, *n* (%)	Pre-EVLP CIT		*p*-value	Post-EVLP CIT		*p*-value
		Non-extended (*n* = 83), *n* (%)	Extended (*n* = 27), *n* (%)		Non-extended (*n* = 83), *n* (%)	Extended (*n* = 27), *n* (%)	
Age, years (range)	62 (56–66)	62 (46–65)	62.5 (56.5–67.5)	0.333	62 (53–65)	63 (60–68)	0.067
LAS, **score (range)**	36.9 (33.4–44.5)	36.4 (33.3–44.7)	38.7 (33.6–43.5)	0.939	36 (33.3–44.7)	39.5 (34.6–43.4)	0.398
Pre-EVLP CIT, **minute (range)**	208.5 (140–264)	173 (131–220)	300 (279–348)	<0.001	208 (139–259)	215 (141–270)	0.492
EVLP time, minute (range)	233.5 (210–263)	231.5 (207–269)	243.5 (210.5–259.5)	0.708	230 (201–263)	240 (220–267)	0.378
Post-EVLP CIT, minute (range)	200.5 (144–287)	193.5 (145–277)	206 (143–625)	0.808	183 (134–233)	347 (304–409)	<0.001
Double lung transplant	63 (57.3)	48 (58.5)	15 (53.6)	0.647	51 (61.4)	12 (44.4)	0.236
Female gender	41 (37.3)	32 (39)	9 (32.1)	0.516	35 (42.2)	6 (22.2)	0.063
Diagnosis							
CF	7 (6.4)	5 (6.1)	2 (7.1)	0.791	6 (7.2)	1 (3.7)	0.217
COPD	48 (43.6)	38 (46.3)	10 (35.7)		41 (49.4)	7 (25.9)	
ILD	55 (50)	33 (40.2)	14 (50)		29 (34.9)	18 (66.7)	
Other	1 (0.9)	6 (7.3)	2 (7.1)		7 (8.4)	1 (3.7)	

Abbreviations: CF, cystic fibrosis; CIT, cold ischemic time; COPD, chronic obstructive pulmonary disease; EVLP, ex vivo lung perfusion; ILD, interstitial lung disease; LAS, lung allocation score.
Values are given in *n* (%) unless indicated otherwise.

correlate with CIT, albeit a significant increase in 30-day mortality and rate of acute rejection within the first year after transplantation. The discrepancy in the literature suggests that the adverse effects of CSP are likely multifactorial and not individually related to ischemic time. For instance, Hayes et al.[18] analyzed the United Network for Organ Sharing registry and found that centers with a decreased volume of lung transplant (<150 in their 10-year follow-up) had decreased survival with CIT > 6 hours, whereas there was no statistical difference in centers with increased volume. Another study suggests the interaction of age and CIT as an independent predictor of 1-month and 1-year mortality.[19] Furthermore, on the basis of the period of normothermic perfusion, the effect of pre- and post-EVLP cold ischemic events may be fundamentally different. This further complicates the extrapolation of available data on CIT to lung transplants that underwent EVLP.

Whether EVLP restores baseline lung homeostasis and halts cold ischemic injury is debatable and a topic of active research. During EVLP, lungs are perfused with a solution that contains albumin, dextrans, glucose, and an intracellular formulation of electrolytes primarily to maintain osmotic balance. There are scant data on the metabolic profile of lungs during EVLP; however, pre-clinical data show that lactate tends to build up in the perfusate with time, and glucose tends to decrease, with a variable relationship with early graft dysfunction and pulmonary edema.[20,21] The role of glucose metabolism in the identification of high-risk grafts requires further study to draw any meaningful conclusions. Nevertheless, on the basis of the above data, it seems that lungs are metabolically active while on EVLP and tend to shift to anaerobic metabolism with glucose consumption and lactate production. This suggests that the baseline metabolic characteristics at the initiation of the pre- and post-EVLP CIT may be different.

Until now, the independent effects of pre- and post-EVLP CSP on post-transplant outcomes have been limited to preclinical studies. In a porcine model, Hsin et al.[22] procured lungs with an initial CIT of 10 hours followed by EVLP for 6 hours. Pigs were then stratified to a short (2 hours) vs a long (10 hours) post-EVLP CIT. Lungs were then transplanted and perfused for 4 hours and found similar markers of cell death and inflammation in the short vs long post-EVLP CIT groups. Another study compared porcine lungs transplanted immediately after EVLP vs those transplanted 6 hours after EVLP CSP.[23] After transplantation and 2 hours of reperfusion, those transplanted immediately after EVLP vs 6 hours post-EVLP CSP had similar reported lung injury scores and PaO_2-to-FiO_2 ratios. Both studies failed to show a difference in immediate markers of tissue injury after reperfusion; however, the functional status of the transplant beyond the initial hours of reperfusion was not studied. Moreover, these were done in healthy pig recipients with a normal cardiopulmonary reserve, which may further confound the effect of prolonged post-EVLP CIT.

Yeung et al.[24] analyzed the overall ischemic time in a pooled retrospective cohort of patients that underwent lung transplantation with or without EVLP. As expected, patients with EVLP accounted for the vast majority of

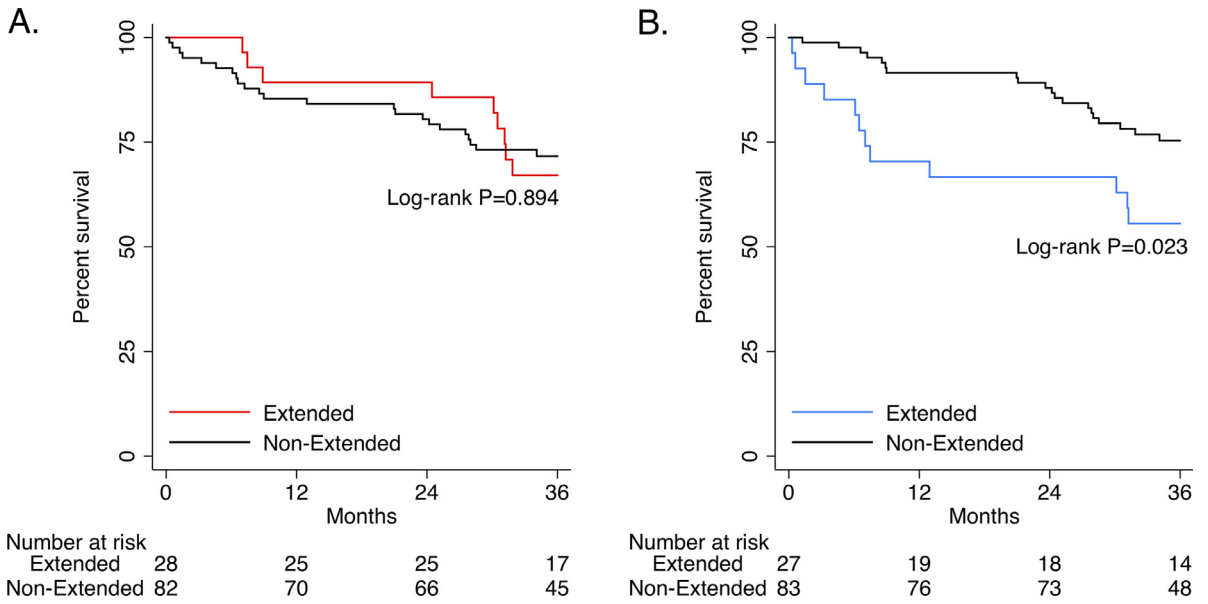

Figure 2 Role of pre- and post-EVLP CITs on overall survival. The patient with non-adjusted lung transplant actual survival curves of recipients grouped according to extended (a) pre-EVLP and (b) post-EVLP CITs. CIT, cold ischemic time; EVLP, ex vivo lung perfusion.

Table 3 Multivariable Analyses for 1-Year Survival, PGD Grades 2–3, and PGD Grade 3

1-year mortality	HR	95% CI	*p*-value
Extended post- EVLP CIT	17.88	3.36–95.29	0.001
LAS	1.06	1.00–1.13	0.053
Extended pre-EVLP CIT	1.00	0.99–1.01	0.711
Recipient age	1.06	0.96–1.18	0.249
Donor smoking history	3.24	0.77–13.71	0.11
Donor PaO_2	0.99	0.99–1.00	0.066
Bilateral transplantation	3.50	0.64–18.99	0.147
Diagnosis			
COPD	1.00	—	—
ILD	0.13	0.02–0.80	0.028
Both lungs perfused en bloc	0.35	0.06–1.87	0.217
Last ΔPaO_2	1.01	0.81–1.27	0.919
Last PAP	1.00	0.99–1.01	0.592
Last CStat	1.00	0.98–1.02	0.701
Last PAWP	0.95	0.79–1.15	0.61
PGD 2–3 at 72 hours	**OR**	**95% CI**	
Extended post- EVLP CIT	6.18	1.88–20.31	0.003
LAS	1.01	0.97–1.06	0.643
Extended pre-EVLP CIT	1.00	1.00–1.01	0.803
Recipient age	0.96	0.89–1.04	0.316
Donor smoking history	1.25	0.44–3.54	0.672
Donor PaO_2	1.00	0.99–1.00	0.061
Bilateral transplantation	0.65	0.17–2.43	0.52
Diagnosis			
COPD	1.00	—	—
ILD	0.90	0.26–3.07	0.862
Other	1.08	0.12–9.44	0.943
Both lungs perfused en bloc	1.51	0.29–7.80	0.62
Last ΔPaO_2	1.00	0.99–1.01	0.692
Last PAP	0.97	0.83–1.13	0.68

(*continued on next page*)

Table 3 (*Continued*)

PGD 2–3 at 72 hours	**OR**	95% CI	
Last CStat	1.01	0.99–1.02	0.588
Last PAWP	1.02	0.89–1.16	0.785
PGD 3 at 72 hours	OR	95% CI	
Extended post- EVLP CIT	20.37	2.56–161.93	0.004
LAS	1.02	0.94–1.10	0.652
Extended pre-EVLP CIT	1.00	0.99–1.01	0.717
Recipient age	0.92	0.81–1.04	0.187
Donor smoking history	6.01	0.79–45.45	0.082
Donor PaO_2	0.99	0.98–1.00	0.048
Bilateral transplantation	0.55	0.05–5.66	0.616
Diagnosis			
COPD	1.00	—	—
ILD	0.44	0.06–3.07	0.406
Other	3.50	0.14–85.31	0.443
Both lungs perfused en bloc	2.12	0.16–28.76	0.571
Last ΔPaO_2	0.99	0.97–1.00	0.047
Last PAP	0.80	0.57–1.14	0.216
Last CStat	1.02	1.00–1.05	0.076
Last PAWP	1.07	0.90–1.28	0.459

Abbreviations: CIT, cold ischemic time; COPD, chronic obstructive pulmonary disease; Cstat, static compliance; EVLP, ex vivo lung perfusion; HR, hazard ratio; ILD, interstitial lung disease; OR, odds ratio; PaO_2, partial pressure of alveolar oxygen; PAP, pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; **PGD**, Primary graft dysfunction; LAS, lung allocation score.

those with ischemic times >12 hours (95%). However, they failed to see a change in the rate of mortality or PGD at 72 hours between those with prolonged overall ischemic times. In addition, neither pre-EVLP, post-EVLP, or EVLP times were significant predictors of mortality in a univariate analysis. This was concordant with the univariate analysis in our study, which failed to find an association with overall mortality (data not shown but available). Nevertheless, further analysis showed a significant relationship between extended post-EVLP CIT and the chosen primary outcomes. Although the study by Yeung et al.[24] was not designed to analyze patients within their EVLP group, there was a trend toward a greater proportion of patients that died at 1 year in the upper half of their prolonged ischemic group. The number of consecutive EVLP cases done by an institution may also play a role in outcomes in the setting of prolonged CIT.

Our multicentric study reports the independent effect of pre- and post-EVLP on PGD and survival after lung transplantation. Post-EVLP CIT is an independent predictor of high-grade PGD at 72 hours and early mortality. Pre-EVLP CIT did not correlate with adverse outcomes, despite adjusting for individual patient risk factors and functional allograft parameters. Although there were no clear differences in the reported causes of death, mortality correlated closely with high-grade PGD. Among other factors, reperfusion injury due to PGD is a known consequence of prolonged ischemic time.[25,26] This causes diffuse alveolar damage and correlates with acute rejection, CLAD, and overall mortality.[5] Although the study failed to identify risk factors for prolonged post-EVLP CIT, these results should caution clinicians on the effect of prolonged ischemic times and advocate expeditious lung implantation after EVLP.

Limitations

There are several limitations to this study intrinsic to its retrospective nature. Little information is available from the review of operative notes as to the cause of prolonged post-EVLP time. There are several factors that can prolong post-EVLP, which include difficult explant surgery, individual institution logistics, concomitant procedures, among others. We were not able to conclude on the factors associated with an increased cold post-EVLP time. This study also followed patients up to 3 years after surgery, which allows for the comparison of early outcomes only. This may select for patients with early mortality and does not allow for assessment of CLAD. Longer follow-up may elucidate long-term mortality and graft survival in this population.

Conclusions

In conclusion, this is the first multicenter study comparing the effect of CIT on post-transplant mortality and PGD. Extended cold post-EVLP time was associated with a greater incidence of severe PGD, more days on mechanical ventilation, and increased mortality. The overall pre-EVLP cold time was not associated with adverse outcomes. These findings from a multicenter trial should caution on the implementation of extended post-EVLP cold preservation, especially when difficult surgeries are expected as per redo transplants or hostile pleural spaces.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

Supplementary data

Supplementary data associated with this article can be found in the online version at www.jhltonline.org/.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2020.05.002.

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