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

Leiva-Juárez MM[1], Urso A[1], Arango Tomas E[1], Lederer D[1], Sanchez P[2], Griffith B[2], Davis RD[3], Daneshmand M[3], Hartwig M[3], Cantu E[4], Weyant MJ[5], Bermudez C[6], D'Cunha J[6], Machuca T[7], Wozniak T[8], Lynch W[9], Nemeh H[9], Mulligan M[10], Song T[11], Jessen M[12], Camp PC[13], Caldeira C[14] , Whitson B[15], Kreisel D[16], Ramzy D[17], **D'Ovidio F**[1].

[1]Columbia University Medical Center, [2]University of Maryland Medical Center, [3]Duke University, [4]University of Pennsylvania, [5]University of Colorado Denver, [6]University of Pittsburgh Medical Center, [7]University of Florida, [8]Indiana University, [9]University of Michigan, [10]University of Washington, [11]University of Chicago, [12]University of Texas Southwestern, [13]Brigham and Women's Hospital, [14]Largo Medical Center, [15]Ohio State University, [16]Barnes Jewish Hospital, [17]Cedars-Sinai Medical Center.

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There are no conflicts of interest or disclosures relevant to the development of this work by any of the authors

Background

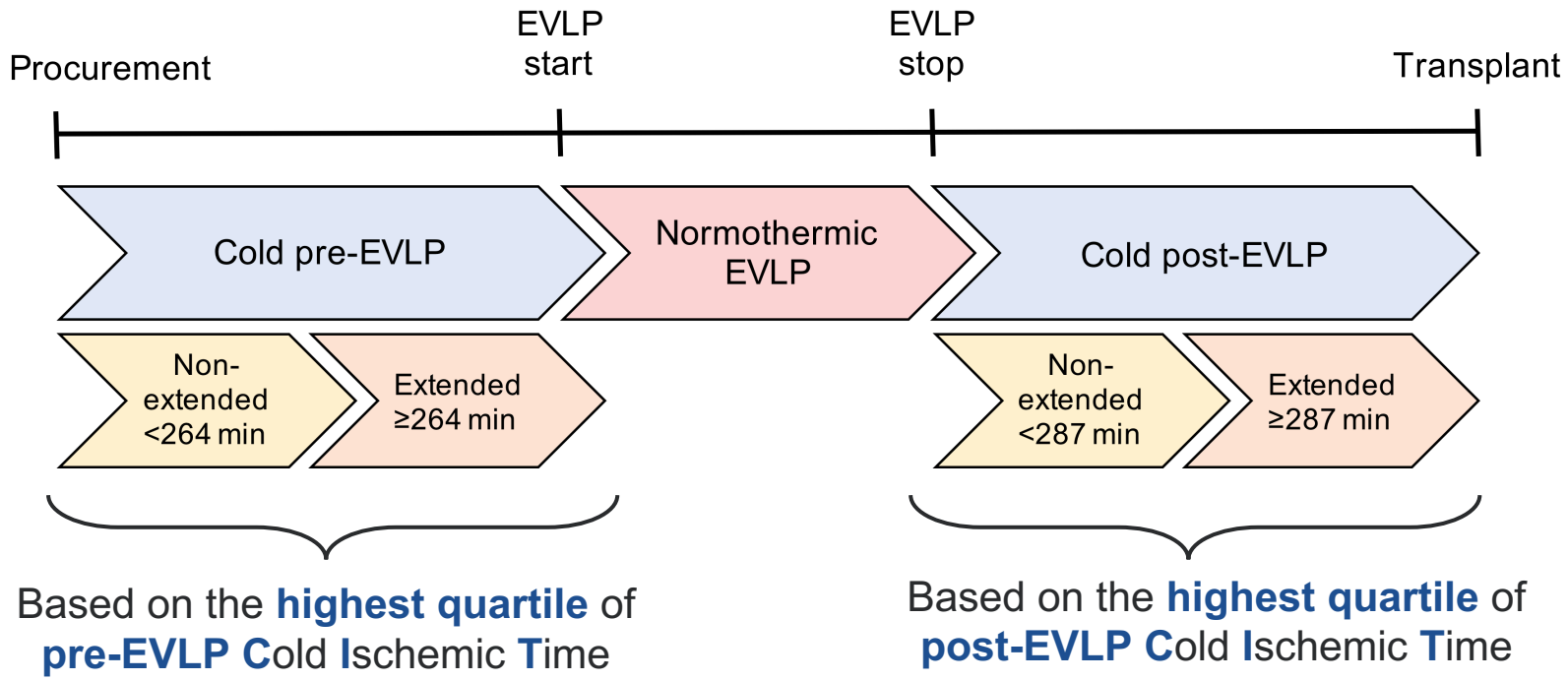
- A **minority** of donor lungs get transplanted
- **Ex-vivo lung perfusion** (EVLP) allows assessment and potential expansion of donor pool
- **Cold preservation** may be associated with adverse outcomes, such as **primary graft dysfunction** (PGD)
- EVLP involves **two sequences of cold preservation** which may prolong cumulative cold injury to the allograft

Purpose

Elucidate the effect of **pre- vs post-EVLP** cold ischemic time on lung transplant outcomes

Study design

NOVEL trial: 110 patients transplanted with EVLP reassessed donor allografts



Based on the **highest quartile** of **pre-EVLP Cold Ischemic Time**

Based on the **highest quartile** of **post-EVLP Cold Ischemic Time**

Primary outcomes:

- ✓ 1-year mortality
- ✓ PGD grade 2-3 at 72 hours post-transplant
- ✓ PGD grade 3 at 72 hours post-transplant

Donor demographics

		Pre-EVLP CIT			Post-EVLP CIT		
	Overall	Non-Extended (n=83)	Extended (n=27)		Non-Extended (n=83)	Extended (n=27)	
	n(%)	n(%)	n(%)	*P* value	n(%)	n(%)	*P* value
Age	33.5 [24-46]	33 [24-45]	38 [23.5-50]	0.184	33 [23-45]	34 [36-48]	0.445
Donor PaO2	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

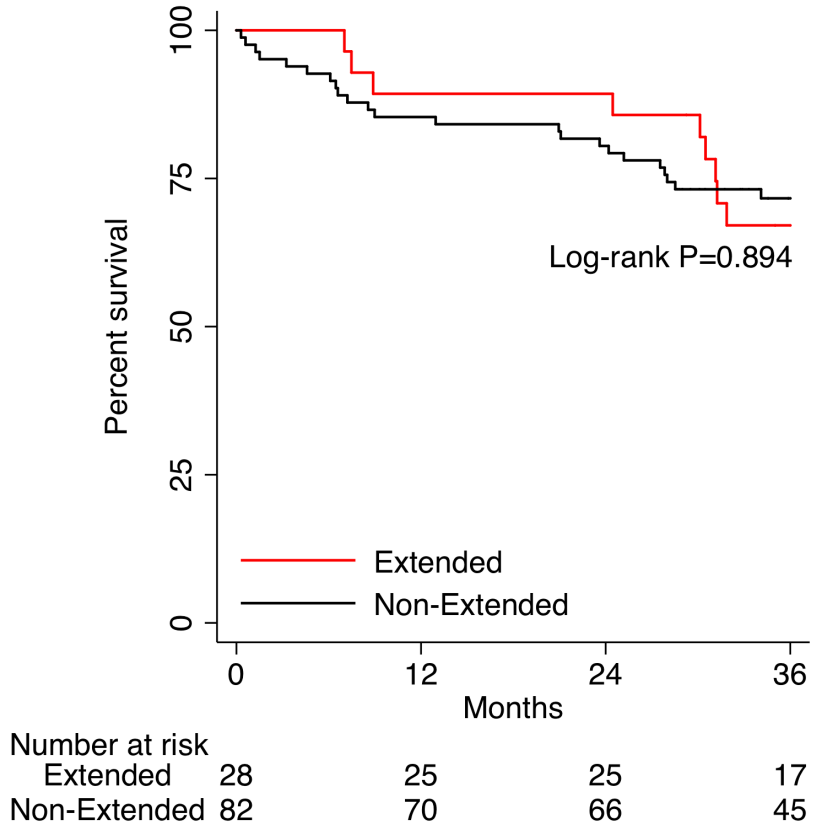
CIT: cold ischemic time, DBD: declared brain dead, DCD: declared cardiac dead, CMV: cytomegalovirus, CVA: cerebrovascular accident

Recipient Demographics

		Pre-EVLP CIT			Post-EVLP CIT		
	Overall	**Non-Extended (n=83)**	**Extended (n=27)**		**Non-Extended (n=83)**	**Extended (n=27)**	
	n(%)	**n(%)**	**n(%)**	***P* value**	**n(%)**	**n(%)**	***P* value**
Age	62 [56-66]	62 [46-65]	62.5 [56.5-67.5]	0.333	62 [53-65]	63 [60-68]	0.067
LAS	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	208.5 [140-264]	173 [131-220]	300 [279-348]	<0.001	208 [139-259]	215 [141-270]	0.492
EVLP time	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	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)	

EVLP: ex-vivo lung perfusion, LAS: lung allocation score, CIT: cold ischemic time, COPD: chronic obstructive pulmonary disease, ILD: interstitial lung disease

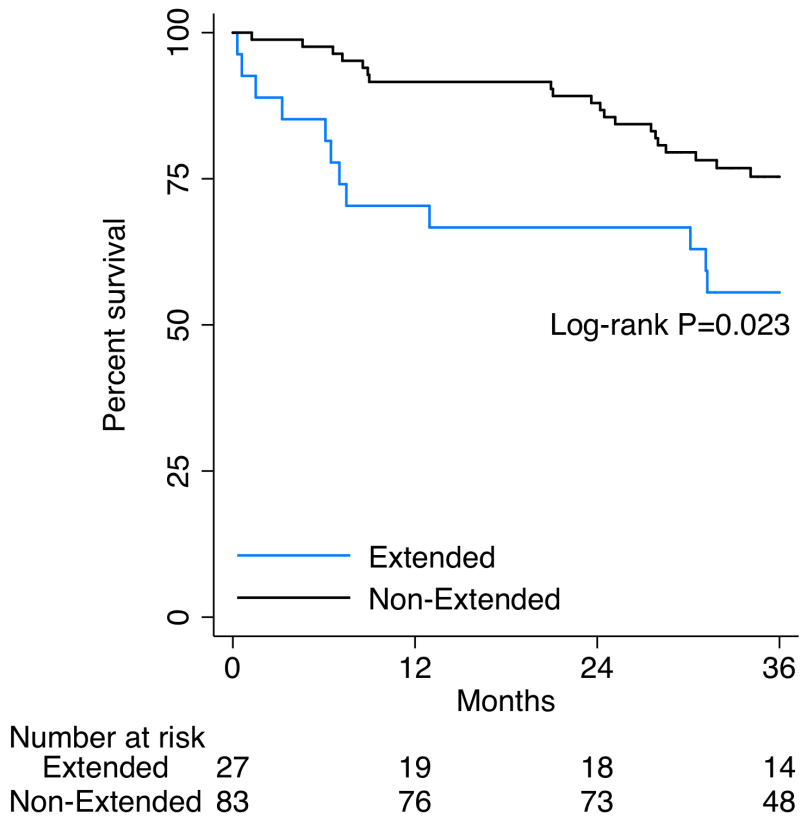
Pre-EVLP **C**old **I**schemic **T**ime does not influence primary outcomes



	Non-Extended (n=82) n(%)	Extended (n=28) n(%)	p-value
1-year mortality	12 (14.6)	3 (10.7)	0.562
PGD 2-3 at 72h	26 (31.7)	5 (17.9)	0.16
PGD 3 at 72h	15 (18.3)	0 (0)	0.015

PGD: primary graft dysfunction.

Extended **post**-EVLP **C**old **I**schemic **T**ime is associated with increased PGD and mortality



	Non-Extended (n=83) n(%)	Extended (n=27) n(%)	P value
1-year mortality	7 (8.4)	8 (29.6)	0.013
PGD 2-3 at 72h	17 (20.5)	14 (51.9)	0.002
PGD 3 at 72h	7 (8.4)	8 (29.6)	0.005

PGD: primary graft dysfunction.

Post-EVLP CIT is an independent predictor of one-year mortality

1-year mortality

	HR	95% Confidence Interval		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 PaO2	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 ΔPaO2	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

Post-EVLP CIT is an independent predictor of PGD 2-3 at 72h

PGD 2-3 at 72 hours

	OR	95% Confidence Interval		P value
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 PaO2	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 ΔPaO2	1.00	0.99	1.01	0.692
Last PAP	0.97	0.83	1.13	0.68
Last Cstat	1.01	0.99	1.02	0.588
Last Pawp	1.02	0.89	1.16	0.785

Post-EVLP CIT is an independent predictor of PGD 3 at 72 hrs

PGD 3 at 72 hours

	OR	95% Confidence Interval		P value
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 PaO2	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 ΔPaO2	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

Conclusions

- ✓ **Pre-EVLP** cold ischemic time is **not associated** with high grade PGD or mortality
- ✓ **Post-EVLP** cold ischemic time is an **independent predictor** of high-grade **PGD** at 72 hours post-transplant and **mortality**
- ✓ These findings from a multicenter trial should caution on implementation of extended post-EVLP cold preservation, particularly when difficult surgeries are expected