Extending Cold Static Preservation at 10°C to Avoid Overnight Lung Transplantation: A Prospective Multi-Center Proof-of-Concept Clinical Trial

Objective: In preclinical studies, we have demonstrated that cold static preservation (CSP) at 10°C is an effective and reliable strategy for prolonged (>24h) preservation of pulmonary grafts, with underlying protective mechanisms related to the maintenance of mitochondrial health (Science Trans Med, 2021). Here, we report on a prospective multi-center clinical trial designed to investigate the feasibility of intentionally prolonging CSP at 10°C to avoid overnight (10pm - 6am) lung transplants.

Methods: To date, 40 consented patients have been enrolled in this prospective, non-randomized, single armed, multi-center study (n=63 target, NCT04616365). Donors with cross clamp times between 6pm and 4am were allowed to be enrolled in the study with the earliest allowed transplant starting time of 6am. Donor exclusion criteria included the need for ex vivo lung perfusion, while recipient exclusion criteria included re-transplantation and multi-organ transplantation. Lungs meeting study criteria were retrieved and transported in the usual fashion using a cooler with ice. Immediately upon arrival to the transplant hospital, lungs were transferred to a 10°C temperature-controlled refrigerator until implantation. The primary outcome of this study was incidence of ISHLT Primary Graft Dysfunction (PGD) Grade 3 at 72h, with secondary endpoints including: recipient time on the ventilator, ICU Length of Stay (LOS), hospital LOS, 30-day survival and lung function at 1-year. Outcomes were compared to a contemporaneous cohort of recipients at each center selected using propensity score matching for medical diagnosis, BMI, recipient status, and donor type at a 1:2 ratio.

Results: Currently, 37 patients have achieved at least 30 day follow up and were included in the analysis. The median recipient age was 65 years (55 - 74 years). Most patients (97%) received bilateral lung transplantation. Donor and recipient characteristics, and recipient outcomes are shown in Table 1. Mean CSP was significantly longer in the study group vs. matched controls for both the first (11h ± 2.6h vs. 6.1h ± 1.9h; $p<0.001$) and second implanted lung (13h ± 2.8h vs. 8.1h ± 2.1h, $p<0.001$). PGD 3 at 72h was 3% in the study group vs. 11% in matched controls ($p=0.27$). No differences were seen in the need for post-op ECMO (5 vs. 9%; $p=0.72$), patients extubated by 72h (76 vs. 70%; $p=0.66$), median ICU LOS (5 vs 5 days; $p=0.53$), and median hospital LOS (24 vs. 23 days; $p=0.33$). In a median follow up of 248 days, 2 study patients have died at days 136 and 370 from sepsis and lymphoma, respectively.

Conclusions: Intentional prolongation of donor lung CSP using 10°C storage appears to be clinically safe and feasible, with promising results. Avoidance of overnight transplants using this simple approach has the potential to improve transplantation logistics and performance, potentially significantly altering practice in clinical lung transplantation.

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Table 1. Study Characteristics and Outcomes

Donor				
		Study Cohort (n=37)	Matched Controls (n=74)	p-value
Donor Age				0.63
		52 years (Range 24 - 71)	56 years (Range 12 - 75)	
Lungs used				0.27
	Bilateral	36 (97%)	67 (91%)	
	Single	1 (3%)	7 (9%)	
Donation type				>0.99
	DBD	29 (78%)	58 (78%)	
	DCD	8 (22%)	16 (22%)	
Ex vivo lung perfusion				>0.99
		0 (0%)	0 (0%)	
Smoking History				0.19
	Yes	22 (59%)	34 (46%)	
	No	12 (32%)	37 (50%)	
	Unknown	3 (8%)	3 (4%)	
Donor P/F Ratio				0.078
		416 mmHg +/- 66 mmHg	445 mmHg +/- 84 mmHg	
Cold Ischemic Time				
	First Implanted Lung	11 h (Range 7.1–18 h)	6.1 h (Range 2.8 – 12 h)	**<0.01**
	Second Implanted Lung	13 h (Range 8.8 – 20 h)	8.1 (Range 4.1 – 13 h)	**<0.01**
Recipient				
Indication				>0.99
	ILD/IPF/Fibrosis	24 (65%)	48 (65%)	
	COPD/Emphysema	11 (30%)	22 (30%)	
	A1AT	2 (5%)	4 (5%)	
Post-Transplant Outcomes				
	Incidence of PGD3 at 72h	1 (3%)	8 (11%)	0.27
	Extubated by 72h	28 (76%)	52 (70%)	0.66
	ICU LOS	5 days (IQR 4 – 7 d)	5 days (IQR 2 – 9 d)	0.53
	Hospital LOS	24 days (IQR 20 – 28 d)	23 days (IQR 15 – 33 d)	0.33
	Post-LTx ECMO used	2 (5%)	7 (9%)	0.72
	30-day survival	37 (100%)	72 (97%)	0.55