Ex Vivo Lung Perfusion at St Joseph's Hospital Lung Transplant Program

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Lung Transplant Volume SJHMC



SJHMC Lung Transplant Program

Lung Waitlist Time (Months)



NORTON Thoracic Institute

SJHMC Lung Transplant Program



Source: SRTR Jan 2019



Challenges in Lung Transplantation

- Barriers to success
 - Lung donor shortage
 - Primary graft dysfunction
 - Long term survival





Lung Donor Shortage The need continues to grow...

~20% on waiting list do not get a transplant in time



Primary Graft Dysfunction Short & Long Term Impact

Severe PGD 3: 20-30% Incidence PGD 3 within the first 72hr correlates with both short and long term survival



n=450, ISHLT registry. Lee J., et al., Clin Chest Med 2011

Bryan A.Whitson et al. Primary Graft Dysfunction and long--term Pulmonary Function After Lung Transplantation. 26 J. HEART AND LUNG TRANSPLANTATION, 1004, 1004--1011 (2007).



STRATEGIES TO MAXIMIZE LUNG RECOVERY

- Extended criteria lungs
- DCD donors
- ECMO Bridge
- Ex Vivo Lung Perfusion





Extended Criteria Lungs Summary

- ECD Lungs help close the supply-demand gap
- Survival considerations
 - Age
 - Smoking hx
 - High LAS recipients
- Big picture
 - Survival without transplant is nil





STRATEGIES TO MAXIMIZE LUNG RECOVERY Donation After Circulatory Death

- Maastricht Categories
 - Uncontrolled-Uncommon
 - I. Found dead
 - II. Witnessed arrest unsuccessful resuscitation
 - IV. Cardiac arrest while brain dead
 - Controlled-Most Common
 - III. Awaiting cardiac death

Modified Maastricht - Paris DCD Work Group - 2013



First human lung transplant was DCD donor who died of myocardial infarction

Hardy et al. JAMA 1963;186:1065-74.



DCD Lung Expansion

Year Donor Recovered	Total Donors (includes DCDs)	Total DCDs	DCD Percent of Total	Number of OPO with at least one DCD
1995	5,363	64	1.2%	22
1996	5,418	70	1.3%	21
1997	5,479	78	1.4%	19
1998	5,793	75	1.4%	16
1999	5,824	87	1.7%	18
2000	5,985	118	1.9%	22
2001	6,080	167	2.7%	29
2002	6,190	190	3.1%	31
2003	6,457	270	4.1%	32
2004	7,150	393	5.4%	43
2005	7,593	564	7.4%	49
2006	8,017	642	8.0%	54
2007	8,085	791	9.8%	57
2008	7,989	849	10.6%	55
2009	8,022	920	11.5%	55
2010	7,943	941	11.8%	55
2011	8,126	1,057	12.9%	57
2012	8,143	1,107	13.6%	56
2013	8,268	1,206	14.6%	57
2014	8,596	1,292	15.0%	57
2015	9,080	1.494	16.5%	57

Source: Based on OPTN data through December 31, 2015.



DCD vs DBD Outcomes



Cypel et al. J Heart Lung Transplant 2015;34:1278–1282



DCD Challenges Dry Run

- Categories
 - Poor donor quality
 - Mainly in marginal donors on EVLP
 - Controlled DCD fails to expire
 - Common problem
 - Assess likelihood with clinical stability
 - Pressors/inotropes, spontaneous respiration, gag reflex, corneal reflex?
- Transplant Centers less likely to fly for DCD imports
 - \$\$\$\$
- Cost Burden- Who pays?
 - No operation for the recipient/insurance company
 - Transplant Center
 - OPO
 - Medicare cost report



STRATEGIES TO MAXIMIZE LUNG RECOVERY Buying Time with ECMO Bridge to Transplant

- Critical End Stage Lung Disease
 - Role of LAS
 - More rapid deterioration candidates
 - Conventional ventilation ineffective/harmful
 - ECMO Bridge to Transplant (BTT)
 - Pt selection is critical
 - Diminish/eliminate need for high vent settings
 - Requires specialized/dedicated ECMO team
 - Barriers to success
 - Myopathy
 - Delirium
 - Anticoagulation
 - Cannulation strategy
 - Waiting times





Lung Donor Shortage Buying Time with ECMO Bridge to Transplant

Extracorporeal membrane oxygenation as a bridge to lung transplantation: A single-center experience in the present era



Emily M. Todd, CCP,^a Sreeja Biswas Roy, MBBS,^b A. Samad Hashimi, MD,^c Rosemarie Serrone, MD,^d Roshan Panchanathan, BS,^c Paul Kang, MPH,^f Katherine E. Varsch, RN, MSN, CCTC,^g Barry E. Steinbock, BS,^a Jasmine Huang, MD,^c Ashraf Omar, MD,^b Vipul Patel, MD,^b Rajat Walia, MD,^b Michael A. Smith, MD,^c and Ross M. Bremner, MD, PhD^c

ABSTRACT

Objective: Extracorporeal membrane oxygenation has been used as a bridge to lung transplantation in patients with rapid pulmonary function deterioration. The reported success of this modality and perioperative and functional outcomes are varied.

Methods: We retrospectively reviewed all patients who underwent lung transplantation at our institution over 1 year (January 1, 2015, to December 31, 2015). Patients were divided into 2 groups depending on whether they required extracorporeal membrane oxygenation support as a bridge to transplant; preoperative characteristics, lung transplantation outcomes, and survival were compared between groups.

Results: Of the 93 patients, 12 (13%) received bridge to transplant, and 81 (87%) did not. Patients receiving bridge to transplant were younger, had higher lung allocation scores, had lower functional status, and were more often on mechanical ventilation at listing. Most patients who received bridge to transplant (n = 10, 83.3%) had pulmonary fibrosis. Mean pretransplant extracorporeal membrane oxygenation support was 103.6 hours in duration (range, 16-395 hours). All patients who received bridge to transplant extracorporeal membrane oxygenation support was 103.6 hours in duration (range, 16-395 hours). All patients who received bridge to transplant were decannulated immediately after lung transplantation but were more likely to return to the operating room for secondary chest closure or rethoracotomy. Grade 3 primary graft dysfunction within 72 hours was similar between groups. Lung transplantation success and hospital discharge were 100% in the bridge to transplant group; however, these patients experienced longer hospital stays and higher rates of discharge to acute rehabilitation. The 1-year survival was 100% in the bridge to transplant group and 91% in the non-bridge to transplant group (log-rank, P = .24). The 1-year functional status was excellent in both groups.

Conclusions: Extracorporeal membrane oxygenation can be used to safely bridge high-acuity patients with end-stage lung disease to lung transplantation with good 30-day, 90-day, and 1-year survival and excellent 1-year functional status. Longterm outcomes are being studied. (J Thorac Cardiovasc Surg 2017;154:1798-1809)



Artist's depiction of W ECMO dual-lumen Avalon cannula. Used with permission from Norton Thoracic Institute, Phoenix, Artzona.

Central Message

ECMO can be safely used as a bridge to LTx with high success rates and good short-term survival in select high-acuity patients with end-stage lung disease.

Perspective

ECMO can be used as bridge therapy in select critically ill patients who experience acute deterioration while awaiting LTx. Good shortterm outcomes regarding primary graft dysfunction rates, 1-year survival, and 1-year functional status can be achieved in select high-acuity patients.

See Editorial Commentary page 1810.

See Editorial page 1796.





Advances in Lung Transplantation

- Barriers to success
 - Lung donor shortage
 - Primary graft dysfunction
 - Long term survival



• What is the role of EVLP?



Advances in Lung Transplantation Donor Lung Preservation



VENTILATOR

• Ventilator

Rationale for EVLP

- Cold Static Storage
 - Slow metabolism
 - Decreases need for O2, nutrients, etc
 - Preservation by slowing organ deterioration for a short period
 - Unable to assess/recondition

- Normothermic EVLP
 - Tissue physiologically active
 - Allows for several hours:
 - Preservation
 - Assessment
 - Reconditioning



OCS System Designed to Address Limitations of Cold Ischemic Storage

Reduce Ischemic Injury (use of warm, oxygenated blood perfusion)

Optimization of Organ Condition

(Replenish depleted hormones and nutrients)

Ex-vivo Metabolic & Functional Assessment

(By maintaining the organ in physiologic state)









Advances in Lung Transplant Donor Lung Preservation

(Failed Resuscitation) Transplantation of lungs from a non-heart-beating donor Stig Steen^{(H), SE}, Trygve Sjöberg, Leif Pierre, Qiuming Liao, Leif Eriksson and Lars Algotsson Heart-Lung Donnon, University Hospital of Lund, S-22185 Lund, Sweden



S. Steen Lund, SE

THE LANCET Volume 307, Innue 2029, 17 March 2001, Pager 825-829 • First Clinical Application 2001

- 54 yo donor arrested due to MI
- Failed 190 min CPR (uDCD)
- Lung topically cooled and perfused
- Placed on EVLP for 65 min
- Successful R SLTx performed



Landmark Clinical Series from Toronto

- Extended criteria ٠ donor lungs underwent EVLP for 4 hours
- 20/23 EVLP lungs ٠ suitable for TX
- PGD 72 h similar to . control cohort

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation

Marcelo Cypel, M.D., Jonathan C. Yeung, M.D., Mingyao Liu, M.D., Masaki Anraku, M.D., Fengshi Chen, M.D., Ph.D., Wojtek Karolak, M.D., Masaaki Sato, M.D., Ph.D., Jane Laratta, R.N., Sassan Azad, C.R.A., Mindy Madonik, C.C.P., Chung-Wai Chow, M.D., Cecilia Chaparro, M.D., Michael Hutcheon, M.D., Lianne G. Singer, M.D., Arthur S. Slutsky, M.D., Kazuhiro Yasufuku, M.D., Ph.D., Marc de Perrot, M.D., Andrew F. Pierre, M.D., Thomas K. Waddell, M.D., Ph.D., and Shaf Keshavjee, M.D.

ABSTRACT

BACKGROWND

More than 80% of donor lungs are potentially injured and therefore not considered From the Toronto Long Transplant Prosuitable for transplantation. With the use of normothermic ex vivo lung perfusion gum (M.C. J.C.Y. M.L. M.A. F.C. W.K. (EVLP), the retrieved donor lung can be perfused in an ex vivo circuit, providing an LGS, KY, M.P. AJP, T.KW, S.K.) and opportunity to reassess its function before transplantation. In this study, we exam- the interdepartmental Division of Critical ined the feasibility of transplanting high-risk donor lungs that have undergone EVLP.

METHODS

In this prospective, nonrandomized clinical trial, we subjected lungs considered to be high risk for transplantation to 4 hours of EVLP. High-risk donor lungs were defined by specific criteria, including pulmonary edema and a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PO, FIO,) less than 300 mm Hg. to General Huspital, 200 Elizabeth St., Lungs with acceptable function were subsequently transplanted. Lungs that were transplanted without EVLP during the same period were used as controls. The primary end point was primary graft dysfunction 72 hours after transplantation. Sec- N Engl Mod 2011;364:1431-46. ondary end points were 30-day mortality, bronchial complications, duration of mechanical ventilation, and length of stay in the intensive care unit and hospital.

U.S. IL, SA, MM, C.WC, CC, MH Care Medicine (#.S.S.). University of Toronto; the McEwen Centre for Regenerative Medicine, Toronto General Research institute (M.C., M.L., T.K.W., S.K.); and the Keanan Research Centre, Li Ka Shing Encwledge Institute, St. Michael's Hospi tal (A.S.S.) --- all in Toronto. Address reprint requests to Dr. Keshavjee at Toron-9N946, Toronto, ON MSG 2C4, Canada, or at shaf keshavjae@uhn.on.ca.



Clinical Trials-NOVEL

-Toronto Protocol

Prospective multicenter clinical trial (six U.S. centers)

- EVLP Group
 - P/F ratio < 300
 - Multiple blood transfusions
 - Pulmonary edema
 - DCD
 - Investigator deemed poor donor quality

The authors conclude that EVLP is a safe diagnostic tool to increase the percentage of tx lungs by screening the unused donor pool.

- Control Group
 - Historical
 - Standard criteria lungs

	EVLP (n=42)	Control (n=42)	р
Outcomes			
PGD 3 at any time point	9	4	0.2
MV days Median (Range)	1 (0-196)	1 (0-29)	0.4
ICU stay days Median (Range)	3 (1-197)	2.5 (1-144)	0.8
Hospital Stay days Median (Range)	13 (4-198)	11 (6-236)	1
30 day survival	41	42	1
1 year survival	38	40	0.7

Flavors of EVLP

Ingredients

- Perfusate
 - SteenTM Solution
 - Extracellular
 - Albumin
 - Dextran 40
 - +/- Red Blood Cells
 - OCS
 - SolutionTM/Perfadex
 - Low potassium dextran 40 based
 - No albumin
 - + Red Blood Cells

Recipes

- Lund
 - Static EVLP
 - Steen SolutionTM with RBC
- Toronto
 - Static EVLP
 - Steen SolutionTM alone
- Organ Care SystemTM
 - Portable EVLP
 - OCS Solution/Perfadex

with RBC

Several devices have been developed: OCS[™] Lung (Transmedics), Vivoline[®] LS1 (Vivoline Medical, Lund, Sweden), Lung Assist[®] (Organ Assist, Groningen, the Netherlands) and XPS[™] (XVIVO Perfusion AB)



Flavors of EVLP



Figure 3 Commercial devices for *ex vivo* lung perfusion. (A) OCS[™] Lung (Transmedics); source: www.transmedics.com. (B) Vivoline[®] LS1 (Vivoline Medical); source: www.vivoline.se. (C) Lung Assist[®] (Organ Assist); source: www.organ-assist.nl. (D) XPS[™] (XVIVO Perfusion AB); source: www.xvivoperfusion.com. Reprinted with permission from Van Raemdonck *et al.* [68].



EVLP Timing

- Location
 - Delayed-Toronto and Lund protocols
 - Lungs transported on ice to home institution
 - Then instrumented onto the EVLP machine
 - Then placed on ice again prior to implantation
 - Immediate-OCSTM
 - Lungs placed immediately on device at donor site
 - Then placed on ice prior to implantation
 - Data?



Best Timing for EVLP?









The OCSTM Lung System





ICU for the Donor Lungs Monitored Parameters





Designed for Maximum Portability







- Detachable wheels allow it to fit in all standard modes of transportation for organ retrieval
- Lightweight carbon-fiber construction, weighs ~38 kg, and can be easily lifted by two adults
- Three on-board batteries
- Easy rolling between destinations







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Bronchoscopy Assessment Capability





OCS Lung Clinical Data Highlights

THE LANCET

bemothermic perfusion of donor lungs for preservation

and assessment with the Organ Care System Long before Infatteral transplantation: a pilot study of 12 patients

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American Journal of Transplantation

Combined Liver and Lung Transplantation Wi Extended Normothermic Lung Preservation in Patient With End-Stage Emphysems Complic Drug-Induced Acute Liver Failure

Received in March 1814

Perfusion

Utilization of the Organ Care System Long for the assessment of longs from a donor after cardiac death (DCD) before bilateral

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REVUE CANADIENNE DE PNEUMOLOG Lung transplantation from donors after circulatory

death using portable ex vivo lung perfusion tion duration," token in

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The Journal of

Heart and Lung Transplantation

First Lung Tramplants Using Controlled and Uncontrolled DCD Lungs Evaluated with OCS-Long Partable Enviro Perfusion System E.Maradelles, / M. Ciroloha, / P. Meda, 7 R. Junon, 7 G. Ding, 7 C. Gorcia-Collo,¹ A. Morda,¹ / Theorem Surgery Department, Hospital Universitation Paerts de Hierry, Matrid Spain, 'Anesthesiology Department, Hospital Parriera de mierro, Balaria, Apaño, "Anestineranargo Departmente, Insepteur Daiversidario Paerta de Hierro, Madrid, Speac, "Porumology Department,

Hospital Universitario Paerte de Hierro, Medrid, Spain.

Purpose: We are reporting on the first global experience using the movel penalse QCS Lang exviso perfinion system to proserve, recent and asses studie GCS Lang extrict performant system to preserve, sector and assess studied and incontrolled DCD doner lungs for long transplantation. DCS lang is designed to reduce cold techemia injury on donor langs while allowang to prokenged manifering and normalization physical give preservation. Methods: Longs from uncontrolled DCDs (sDCDs) were obtained after jedicial & family concert, retrieved using our previously described protototation as survey controlled denses (zDCDs) were retrieved and preserved following standard procedures. Grains were instrumented and perfected on the OCS Lang using high streets OCS has relation supplemented with pRBCs to achieve circulating bemanocrit - 20% and ventilated at 20cC and transported in this factors to the transplant center. Monitoring was cent during transportation and objective evaluation to us were performed at different taxes points to assess the on-yperation capacity of the langs. A matterial the association of an end of the state of th bilateral transplantation to matching recipients. Residue Sis DCD lange were retrieved and assessed on OC3-Lang (5

behaviors for LOCD range were retrieved and assessment in Oc.5-Ling C. accountilled DCDs, I controlled). Donor data are shown in attached table. These long grafts were considered valid and transplanted (2 eDCD longs, 1 (DCD). Our recipient was on the high approxy to and out procedures were COLLEG CARE REQUEST WITH the test regression of the matching procession with performed under extracorporate citeralation. All struct recipients are alive (Structural as 11/11/2013). 34 months, 2 months and 1 months and free from BOS. PGD at 72h for each recipient was 0, 1 and 0. Conclusion: Normathermal enviro perfession with OC'S 4 ang of uncontrolled

DCDs decreases the long cold inchemic times inherent to these denses. It the advectory for using over researce times mercure to inser donors. It also allows for unstanded comprehensive evaluation of both (DCD and s(DCD have a preventing transplantation of anderperforming grafts and avoiding uncertainty, with promising early choical results.





THE LANCET Respiratory Medicine

Articles

Normothermic ex-vivo preservation with the portable Organ \mathcal{P} (\mathbb{P}) Care System Lung device for bilateral lung transplantation (INSPIRE): a randomised, open-label, non-inferiority, phase 3 study

Gregor Warnecke, Dirk Van Raemdonck, Michael A Smith, Gilbert Massard, Jasleen Kukreja, Federico Rea, Gabriel Loor, Fabio De Robertis, Jayan Nagendran, Kumud K Dhital, Francisco Javier Moradiellos Díez, Christoph Knosalla, Christian A Bermudez, Steven Tsui, Kenneth McCurry, I-Wen Wang, Tobias Deuse, Guy Lesèche, Pascal Thomas, Igor Tudorache, Christian Kühn, Murat Avsar, Bettina Wiegmann, Wiebke Sommer, Arne Neyrinck, Marco Schiavon, Fiorella Calebrese, Nichola Santeimo, Anne Olland, Pierre-Emanuel Falcoz, Andre R Simon, Andres Varela, Joren C Madsen, Marshall Hertz, Axel Haverich, Abbas Ardehali

Summary

Background Severe primary graft dysfunction (PGD) of grade 3 (PGD3) is a common serious complication following lung transplantation. We aimed to assess physiological donor lung preservation using the Organ Care System (OCS) Lung device compared with cold static storage.

Methods In this non-inferiority, randomised, controlled, open-label, phase 3 trial (INSPIRE) recipients were aged

18 years or older and were registered as standard criteria primary double lung transplant candidates. Eligible donors

Lancet Respir Med 2018;

6: 33/-0/ Published Online April 9, 2018 http://dx.doi.org/10.1016/ 52213-2600(18)30136-X

See Comment page 319

were younger than 65 years old with a ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen of more than 300 mm Hg. Transplant recipients were randomly assigned (1:1) with permuted blocks, stratified by centre to receive standard criteria donor lungs preserved in the OCS Lung device (OCS arm) or cold storage at 4°C. Vacuus Knower







OCS EXPAND I Lung Clinical Trial

Evaluating OCSTM Lung for recruiting, preserving & assessing donor lungs that may not meet current standard donor lung acceptance criteria for transplantation

Analysis will Include:

- Patient survival at Day 30 post-transplant
- Absence of PGD (Primary Graft Dysfunction) in the first 72 hours posttransplantation
- Duration of initial post-transplant invasive mechanical ventilation, ICU stay and hospital stay
- Incidence of BOS at 6 and 12 months post-transplantation
- Incidence of lung graft-related Serious Adverse Events through Day 30 posttransplant



EXPAND I Lung Trial Centers OCS™ **EXPAND** Lung **University of Minnesota** Leuven, Belgium **Medical Center** MGH **UCSF Medical Center** Hannover, Germany **UCLA Medical Center Temple University** St. Joseph's Hospital and **Medical Center Duke University**



EXPAND I Lung Trial Status Completed on Oct. 2016



79 Transplants

- 32.9 % DCD
- 39.2% Age \geq 55 y.o.
- 26.6% $PaO_2/FiO_2 \le 300 \text{ mmHg}$
- 34.2% Expected cross-clamp time > 6 hrs
- >1 Eligibility criteria
- 89% Utilization Rate



EVLP at St Joseph's Current Status

- OCS Lung received FDA Pre Market Approval 5/2017
 - Commercial distribution of the device has begun
 - Indication is for standard donor lungs
- EXPAND II trial for Extended Criteria Donors Enrolling
- Post Approval Study Currently Enrolling
 - Thoracic Organ Perfusion registry
 - Prospective, single arm, multi-institutional study
 - Evaluate device performance in real-world setting



EVLP in Lung Transplantation Summary

- Expand the donor pool
 - Assess marginal donors
 - Distant donors
 - DCD donors
 - Rehabilitate/treat inferior donor lungs
- Reduce primary graft dysfunction
 - Limit ischemia
 - Superior preservation
- Extend long term survival







