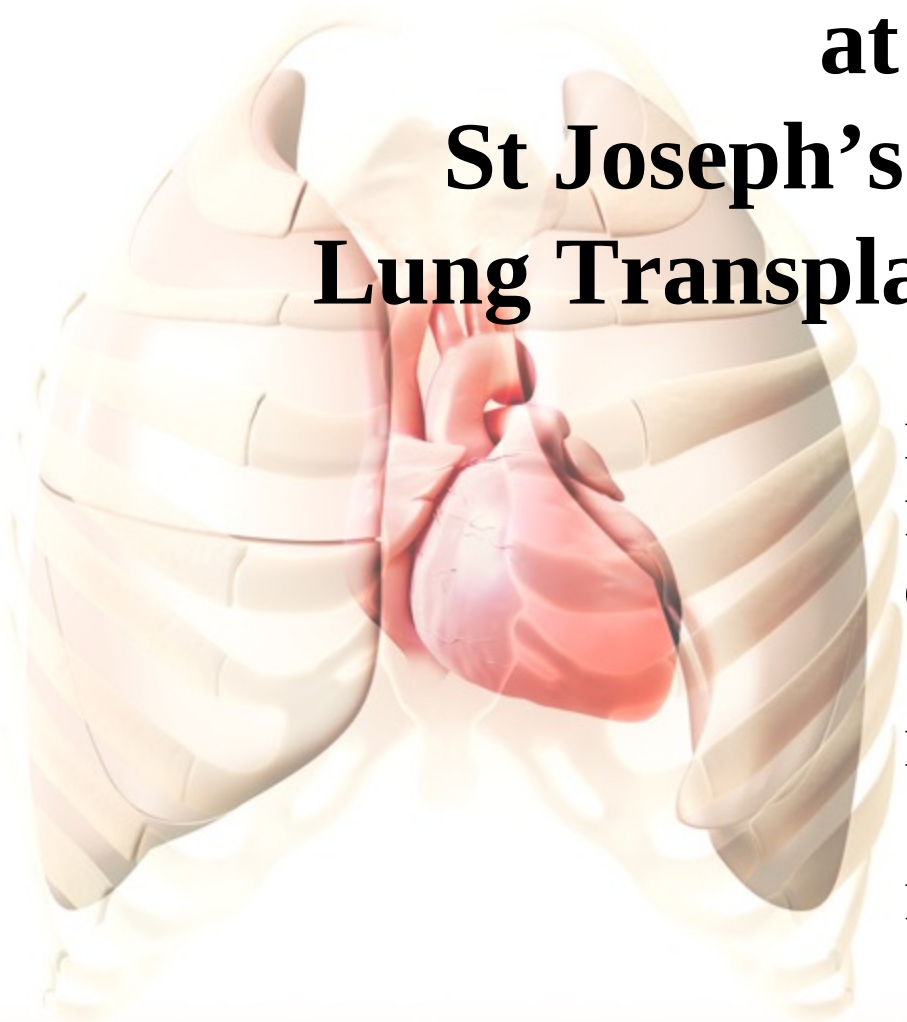
Ex Vivo Lung Perfusion
at
St Joseph's Hospital
Lung Transplant Program



Michael A Smith, MD
Professor of Surgery
Creighton University-Phoenix Campus
Surgical Director of Lung Transplantation
Norton Thoracic Institute
St Joseph's Hospital and Medical Center
Phoenix, AZ

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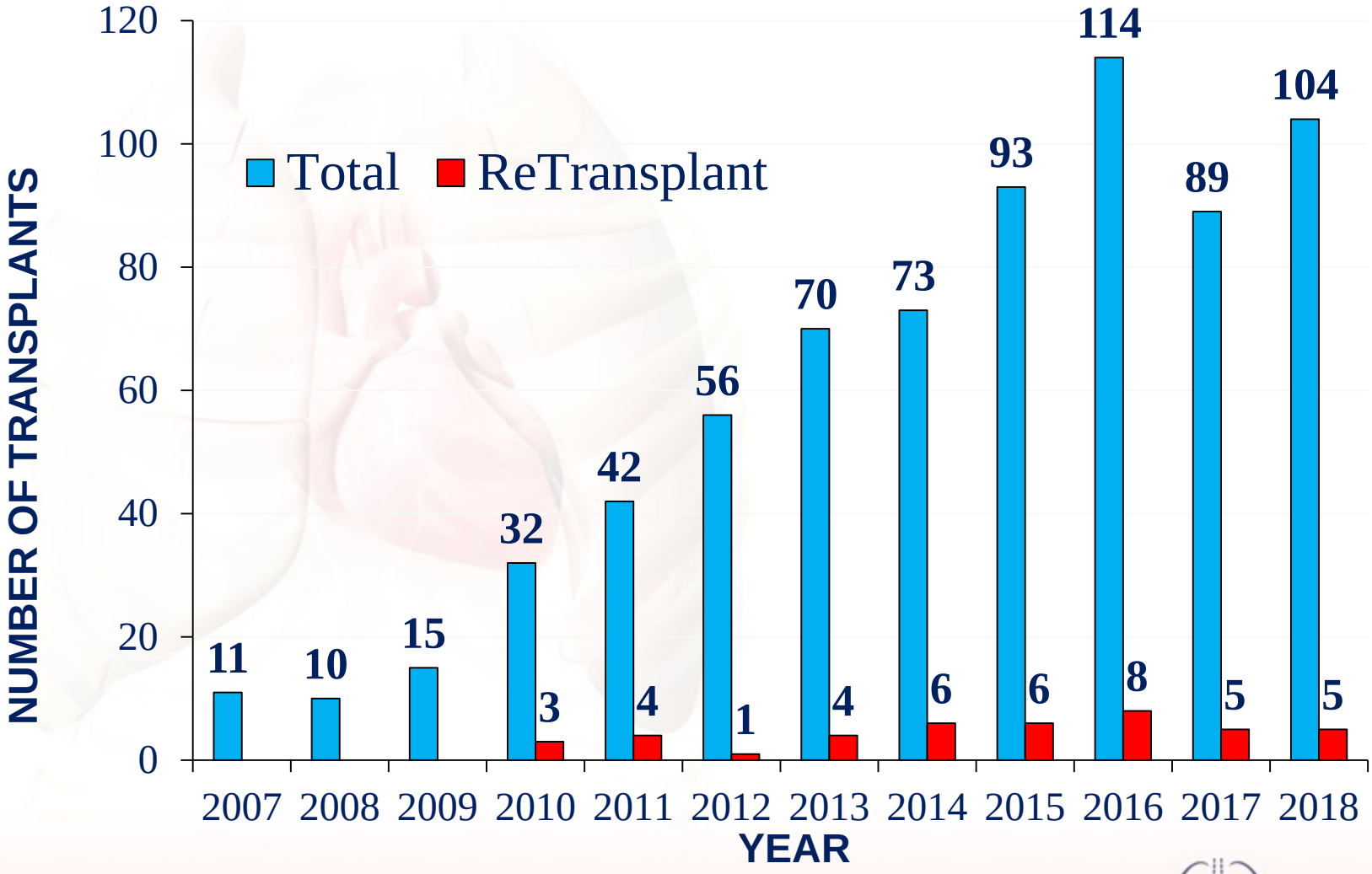
Thoracic Institute

Lung Transplant Volume
SJHMC



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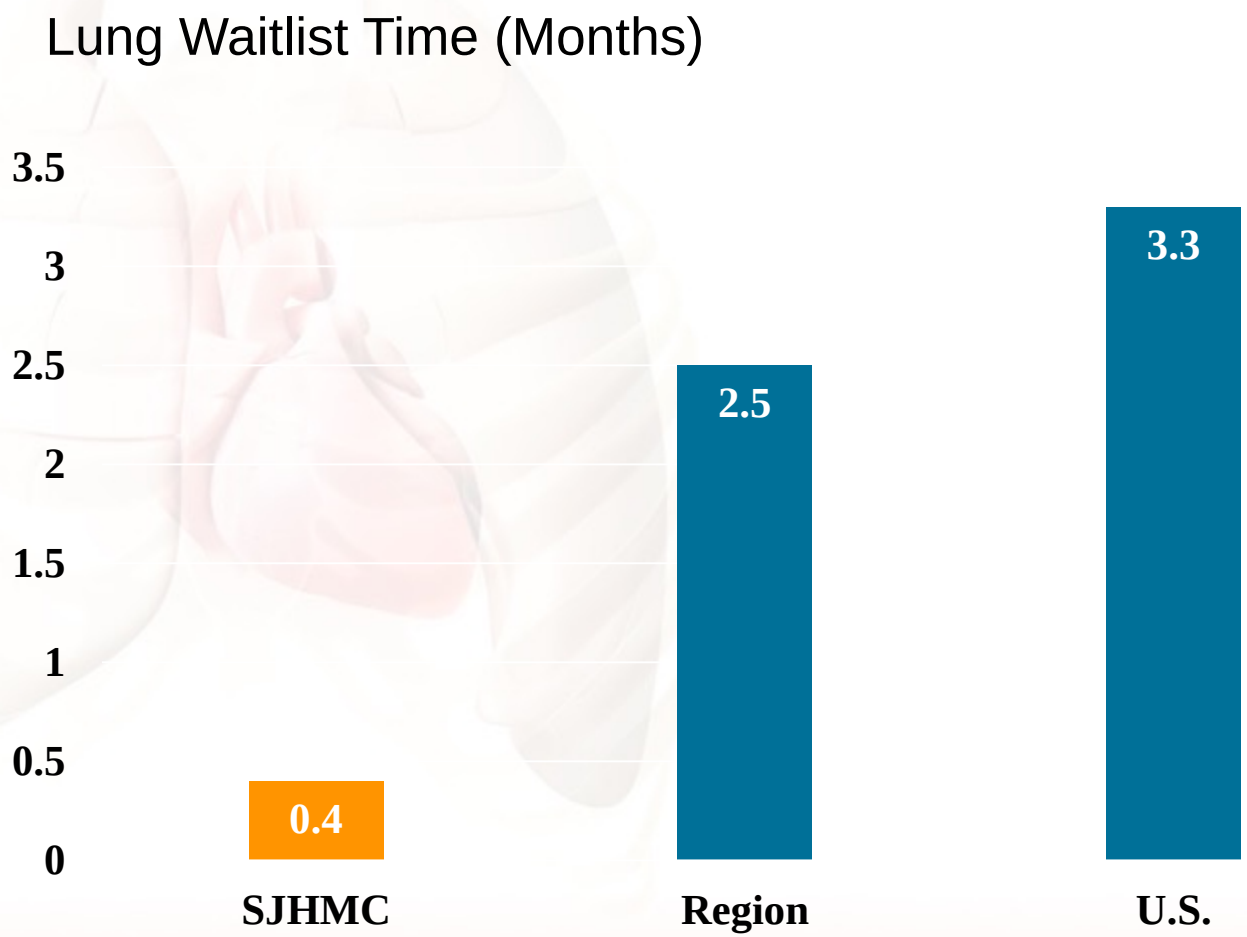
SJHMC Lung Transplant Program



Source: SRTR Jan 2019

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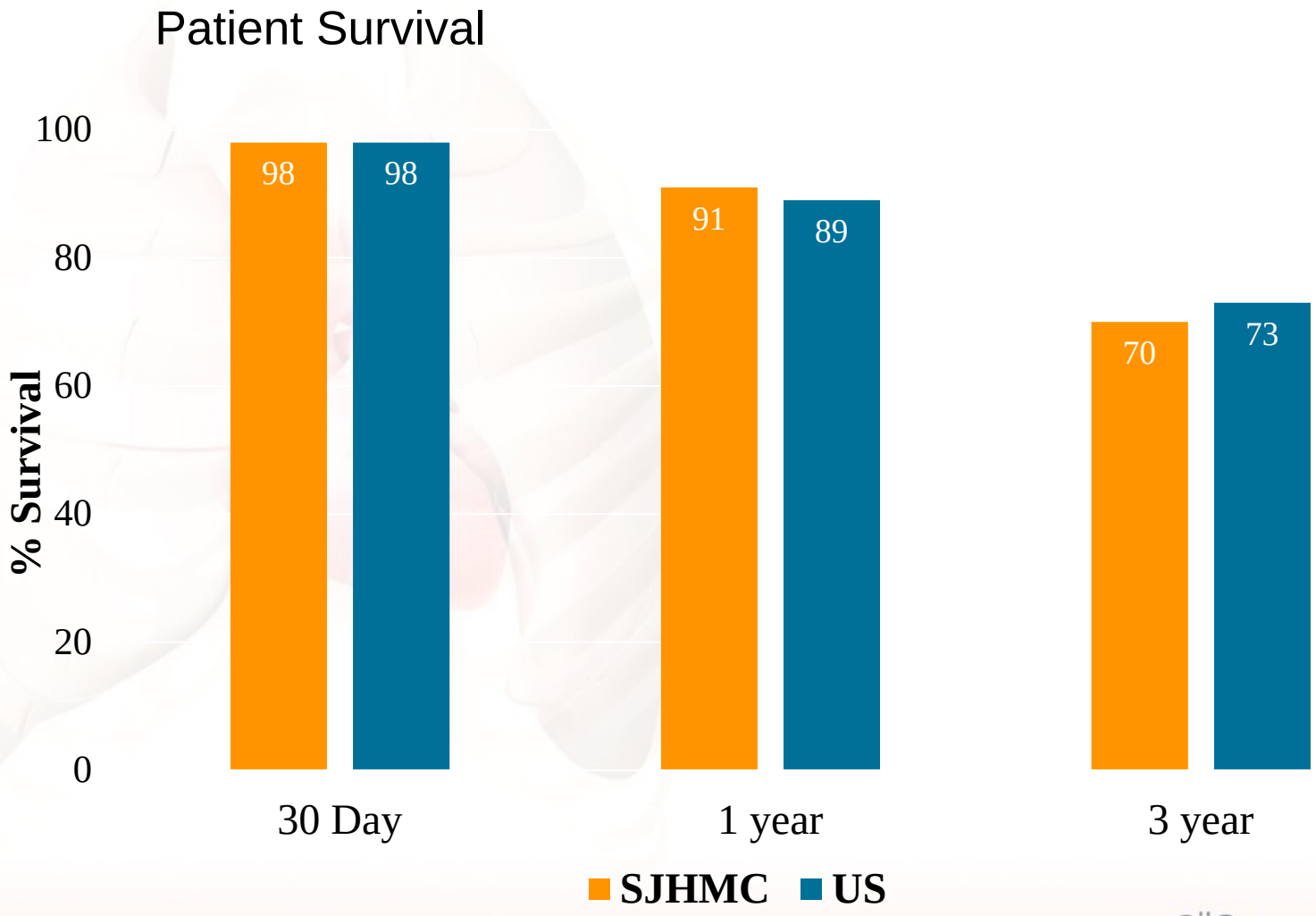
SJHMC Lung Transplant Program



Source: SRTR Jan 2019

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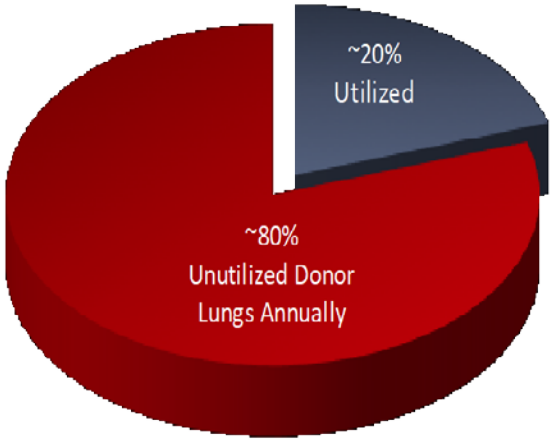
Challenges in Lung Transplantation

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



Significant Underutilization of Donor Lungs

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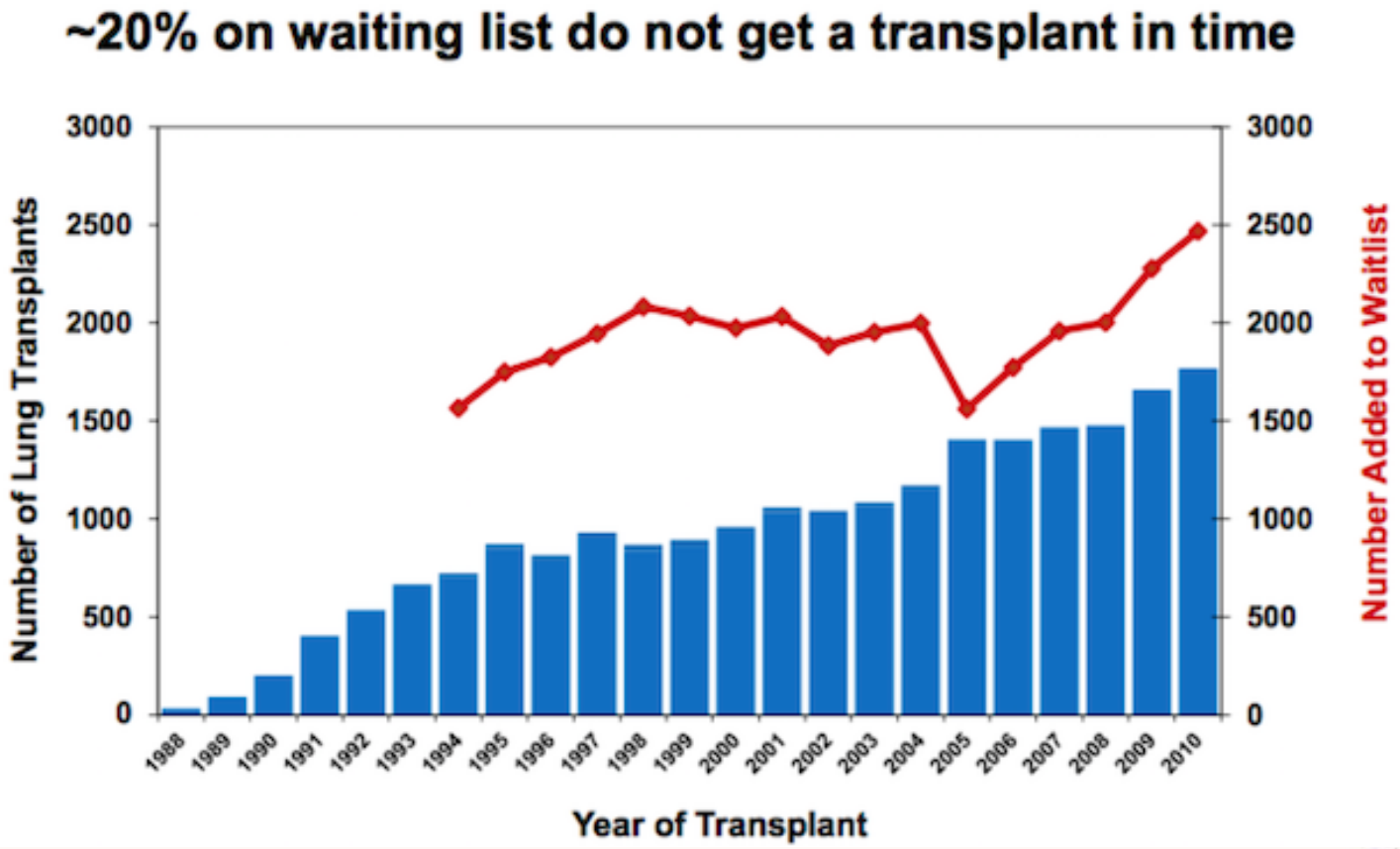
Lung Donor Shortage

The need continues to grow…



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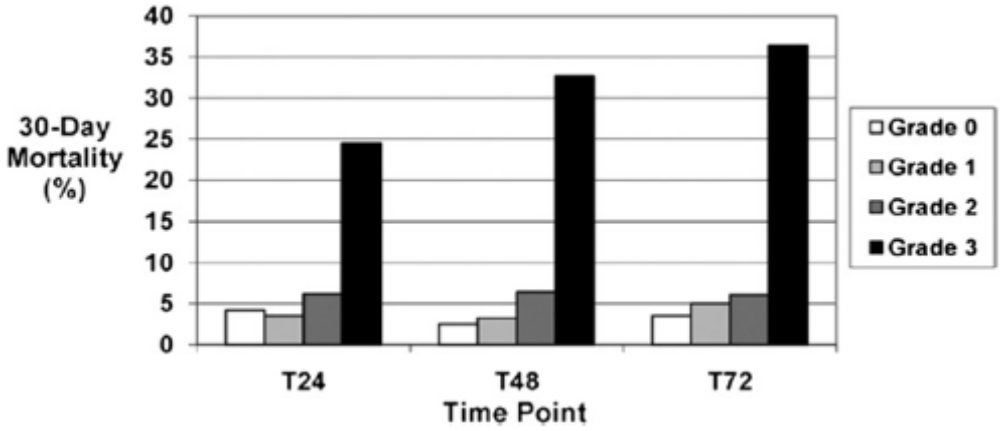
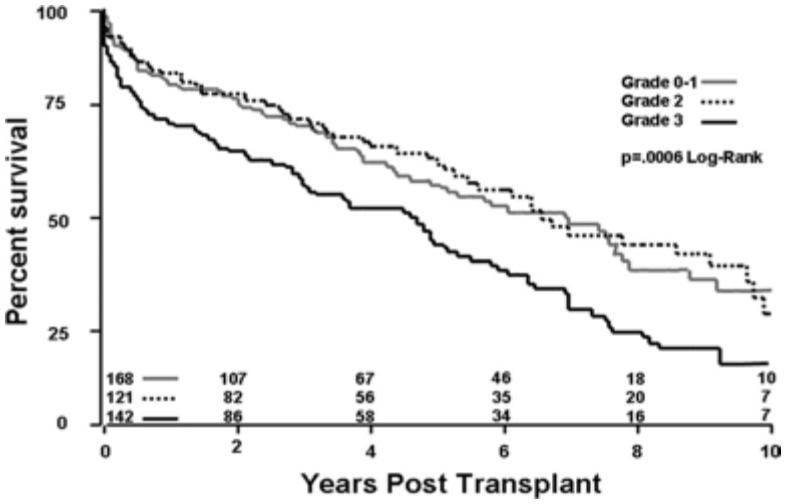
Primary Graft Dysfunction
Short & Long Term Impact

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).

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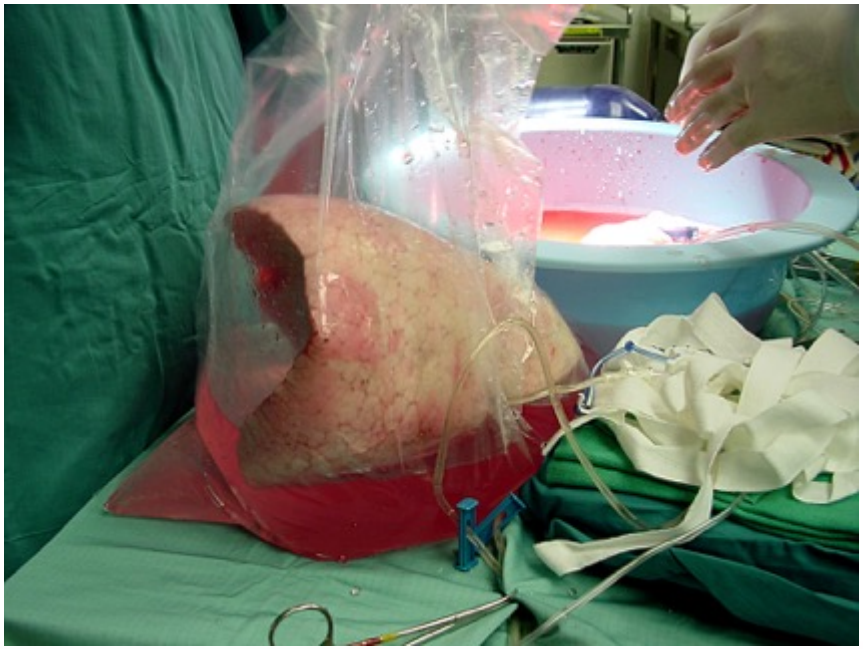
STRATEGIES TO MAXIMIZE LUNG RECOVERY

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



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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

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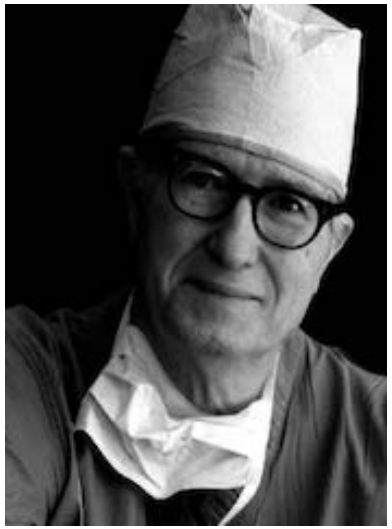
STRATEGIES TO MAXIMIZE LUNG RECOVERY

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



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

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

❖ ***Modified Maastricht - Paris DCD Work Group - 2013***

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DCD Lung Expansion

U.S. OPO Experience – Organ Donors / DCDs 1995 – 2015

Year Donor Recovered	Total Donors (includes DCDs)	Total DCDs	DCD Percent of Total	Number of OPOs 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.

GIFT of LIFE DONOR PROGRAM

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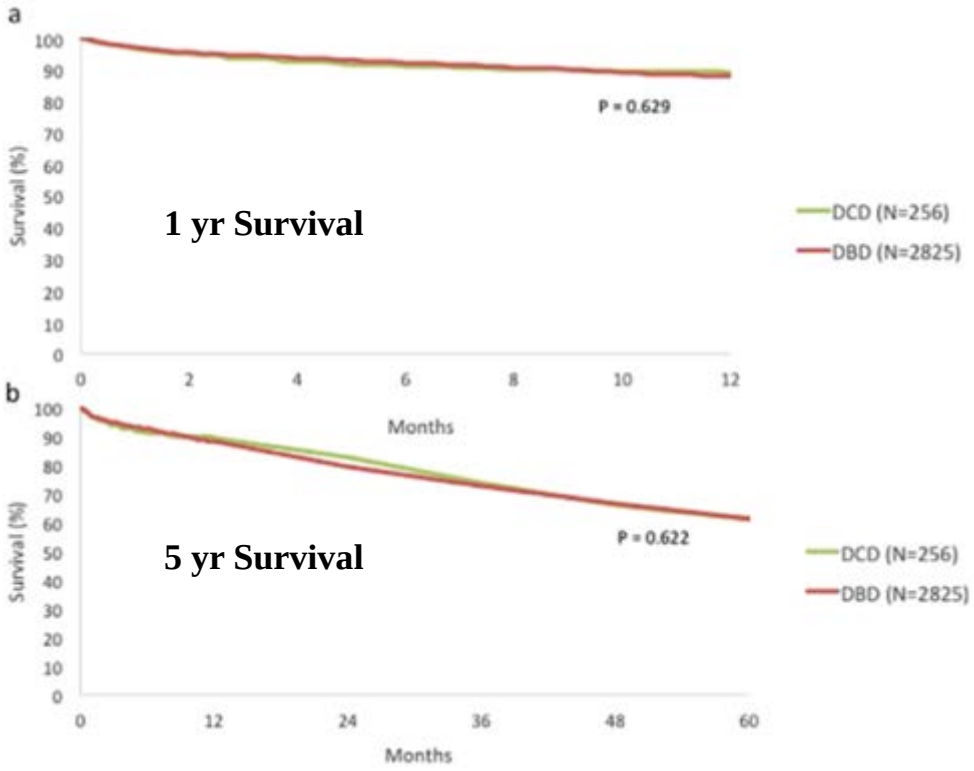
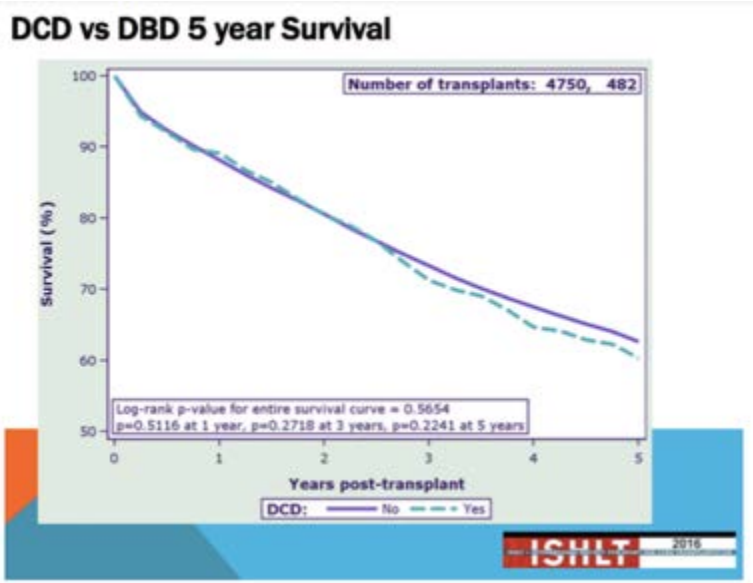
DCD vs DBD Outcomes





- ***DCD- 95% Category III (Controlled)***

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

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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

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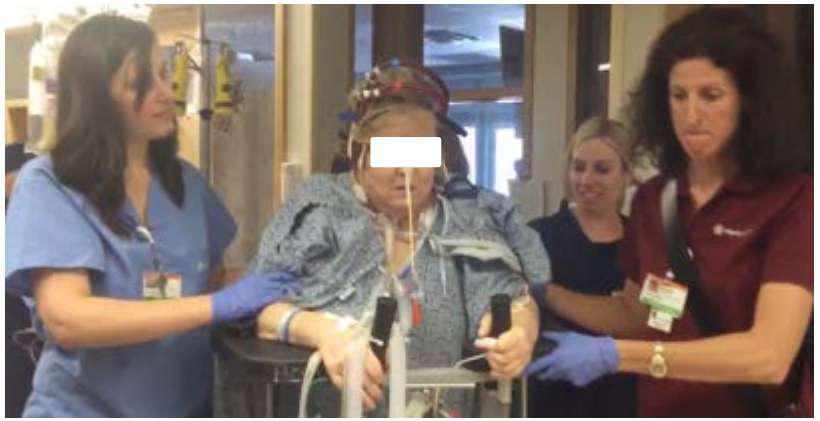
STRATEGIES TO MAXIMIZE LUNG RECOVERY

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

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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,[e] Paul Kang, MPH,[f] Katherine E. Varsch, RN, MSN, CCTC,[g] Barry E. Steinbock, BS,[a] Jasmine Huang, MD,[c] Ashraf Omar, MD,[h] Vipul Patel, MD,[b] Rajat Walia, MD,[b] Michael A. Smith, MD,[c] and Ross M. Bremner, MD, PhD[c]

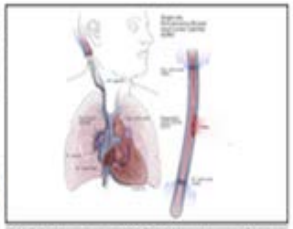
ABSTRACT

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 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. Long-term 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, Arizona.

Central Message

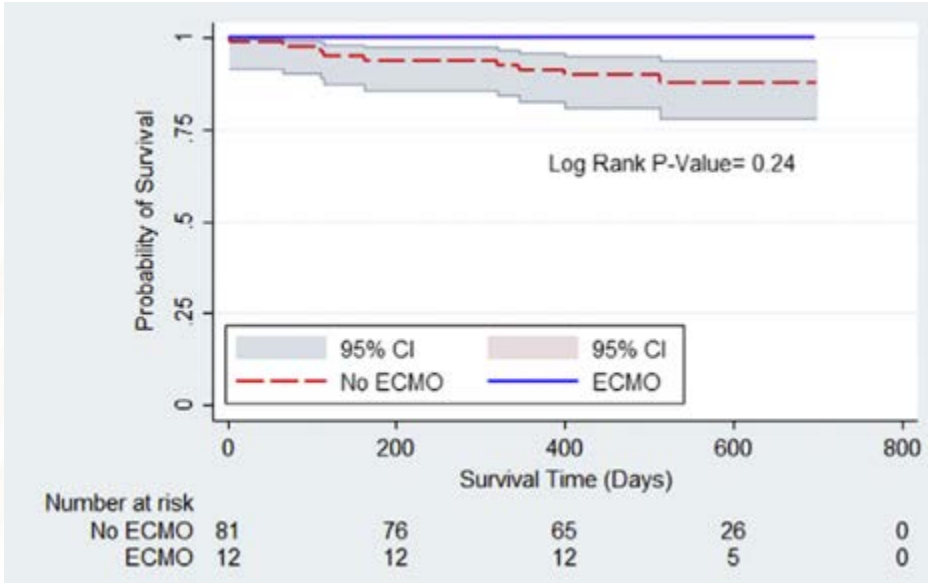
ECMO can be safely used as a bridge to LTx with high success rates and good short-term survival in select high-acuity patients with end-stage lung disease.

Perspective

ECMO can be used as bridge therapy in select critically ill patients who experience acute deterioration while awaiting LTx. Good short-term 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.



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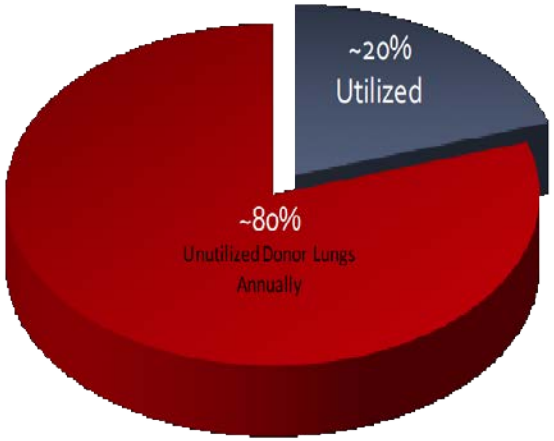
Advances in Lung Transplantation

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



Significant Underutilization of Donor Lungs

- What is the role of EVLP?

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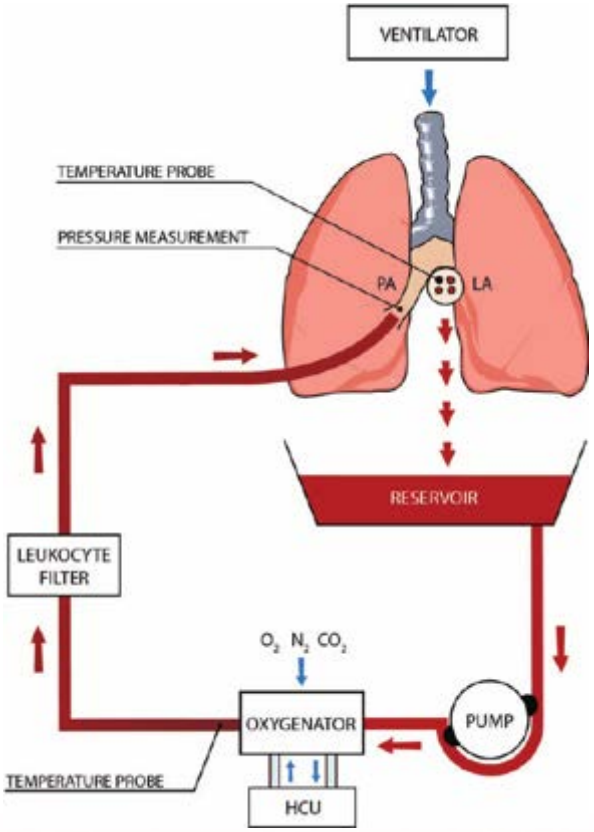
Advances in Lung Transplantation

Donor Lung Preservation



- Perfusion circuit
- Pump to drive perfusate
- Ventilator

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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

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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)

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Advances in Lung Transplant
Donor Lung Preservation

(Failed Resuscitation)

Transplantation of lungs from a non-heart-beating donor

Stig Steen, Trygve Sjöberg, Leif Pierre, Qiuming Liao, Leif Eriksson and Lars Algotsson

Heart-Lung Division, University Hospital of Lund, S-22185 Lund, Sweden

THE LANCET

Volume 357, Issue 9259 , 17 March 2001, Pages 825-829

S. Steen
Lund, SE

- 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

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Landmark Clinical Series from Toronto

- Extended criteria donor lungs underwent EVLP for 4 hours
- 20/23 EVLP lungs 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

BACKGROUND

More than 80% of donor lungs are potentially injured and therefore not considered suitable for transplantation. With the use of normothermic ex vivo lung perfusion (EVLP), the retrieved donor lung can be perfused in an ex vivo circuit, providing an opportunity to reassess its function before transplantation. In this study, we examined 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_2:FIO_2) less than 300 mm Hg. 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. Secondary end points were 30-day mortality, bronchial complications, duration of mechanical ventilation, and length of stay in the intensive care unit and hospital.

From the Toronto Lung Transplant Program (M.C., J.C.Y., M.L., M.A., F.C., W.K., M.S., J.L., S.A., M.M., C.-W.C., C.C., M.H., L.G.S., K.Y., M.P., A.F.P., T.K.W., S.K.) and the Interdepartmental Division of Critical Care Medicine (A.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 Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital (A.S.S.) — all in Toronto. Address reprint requests to Dr. Keshavjee at Toronto General Hospital, 200 Elizabeth St., 9N946, Toronto, ON M5G 2C4, Canada, or at shaf.keshavjee@uhn.on.ca.

N Engl J Med 2011;364:1431-40.

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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

- Control Group
  - Historical
  - Standard criteria lungs

	EVLP (n=42)	Control (n=42)	p
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

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

Flavors of EVLP

Ingredients

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

Recipes

- Lund
  - Static EVLP
  - Steen Solution™ with RBC
- Toronto
  - Static EVLP
  - Steen Solution™ alone
- Organ Care System™
  - 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)

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Flavors of EVLP

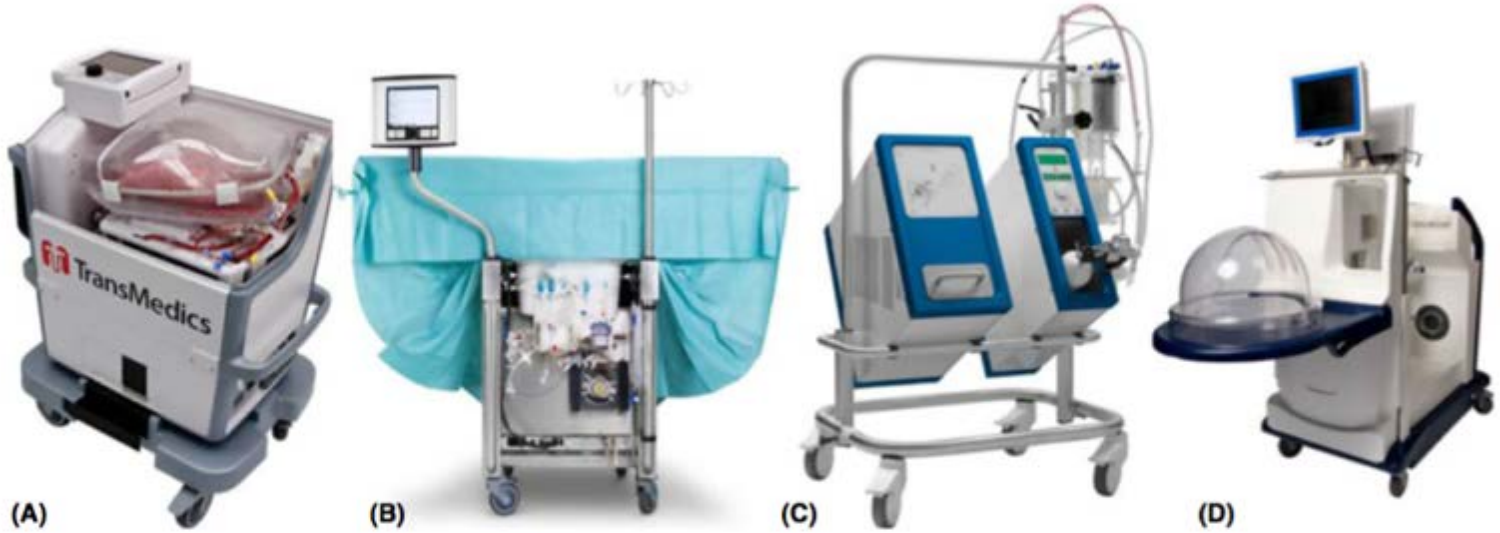

Figure 3 Commercial devices for *ex vivo* lung perfusion. (A) OCS™ Lung (Transmedics); source: www.transmedics.com. (B) Vivoline® LS1 (Vivoline Medical); source: www.vivoline.se. (C) Lung Assist® (Organ Assist); source: www.organ-assist.nl. (D) XPS™ (XVIVO Perfusion AB); source: www.xvivoperfusion.com.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

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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-OCS™
    - Lungs placed immediately on device at donor site
    - Then placed on ice prior to implantation

  - Data?

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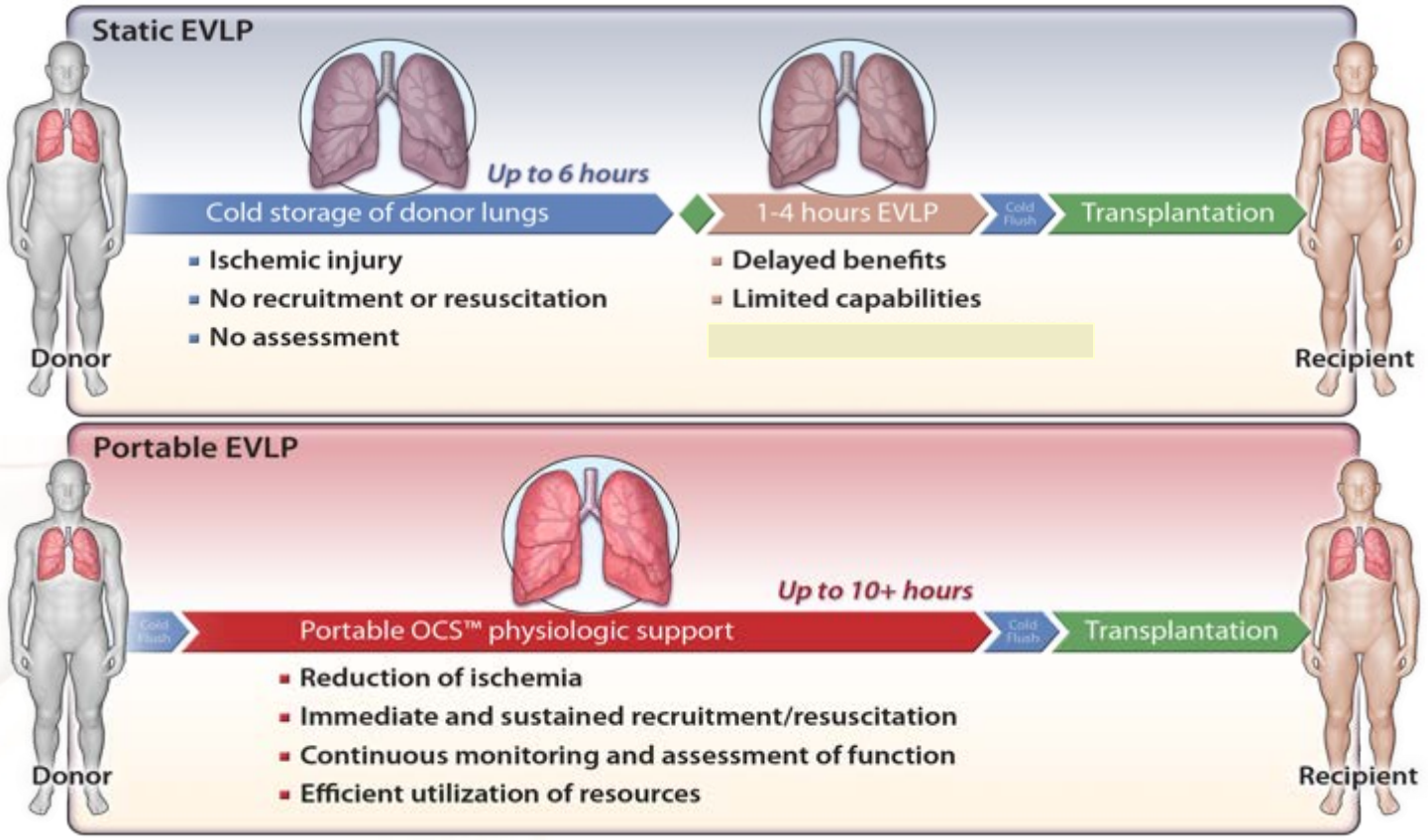
Best Timing for EVLP?

Toronto/Lund Protocols

OCS ™ Protocol



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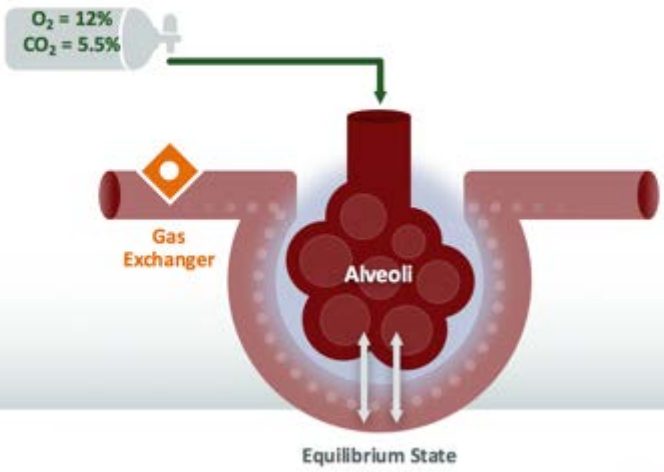
OCS™ Lung Perfusion – Two Operating Modes

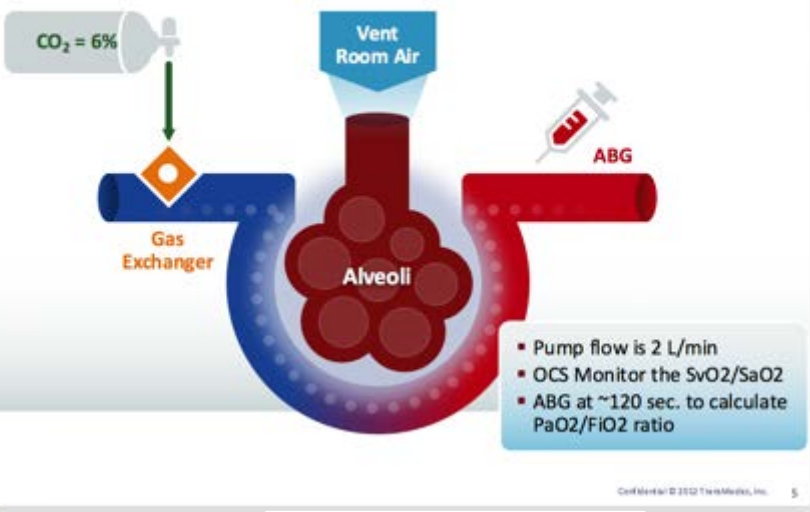
Preservation Mode

Ventilation in Preservation Mode



Monitoring/Assessment Mode

Continuous Monitoring



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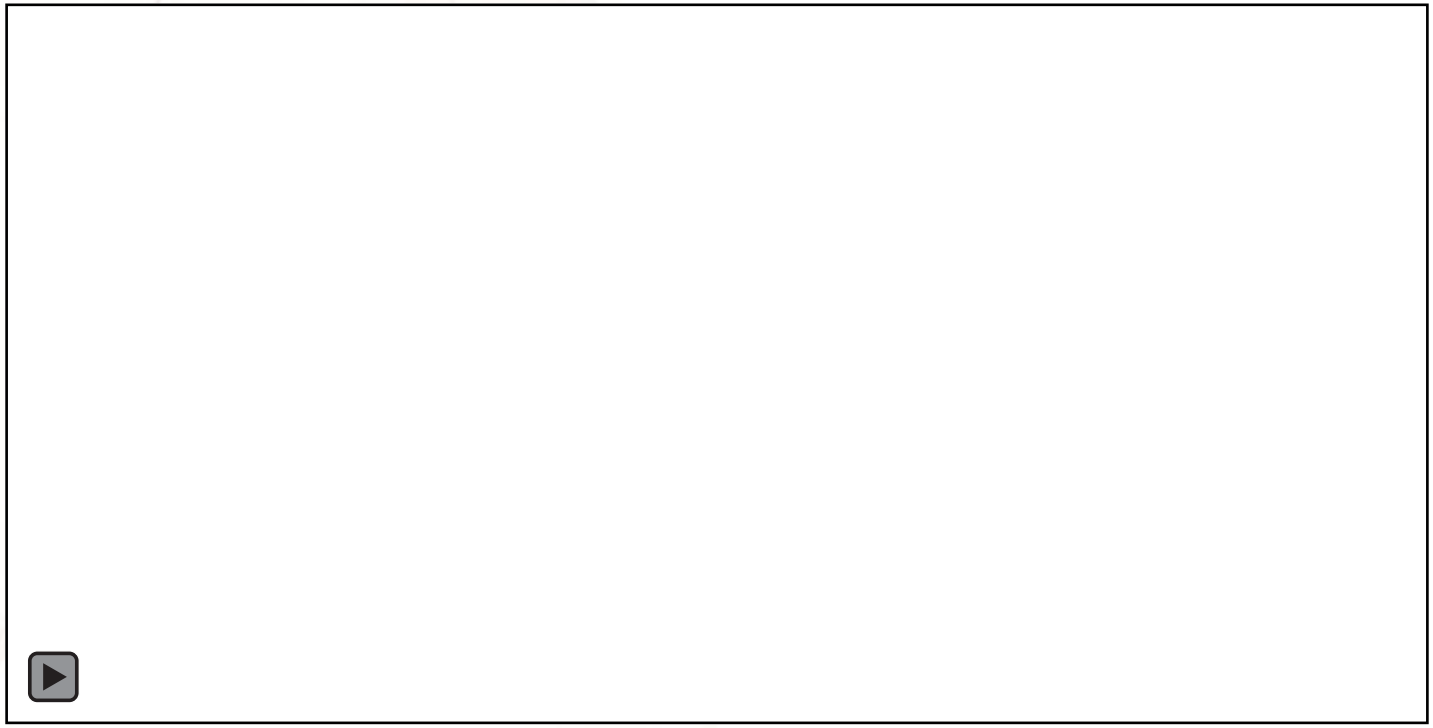
The OCS™ Lung System



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ICU for the Donor Lungs
Monitored Parameters

PAWP (Peak Airway Pressure)

Pump Flow

PAP (Pulmonary Artery Pressure)

VR (Vascular Resistance)

Critical Trends (Perfusion & Ventilation Parameters)

SaO_2 & SvO_2

Tidal Volume

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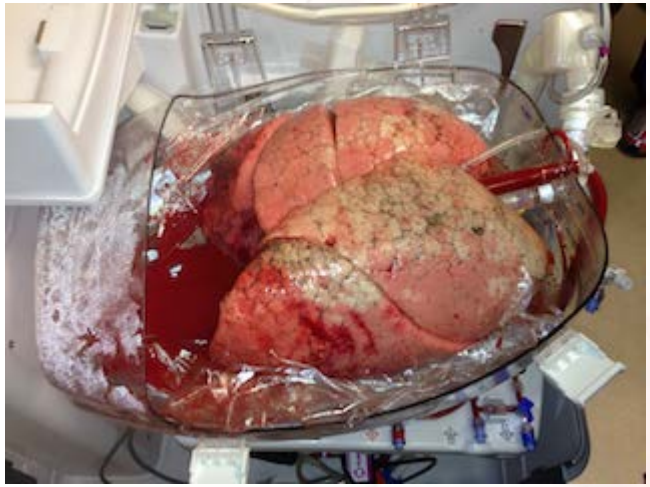
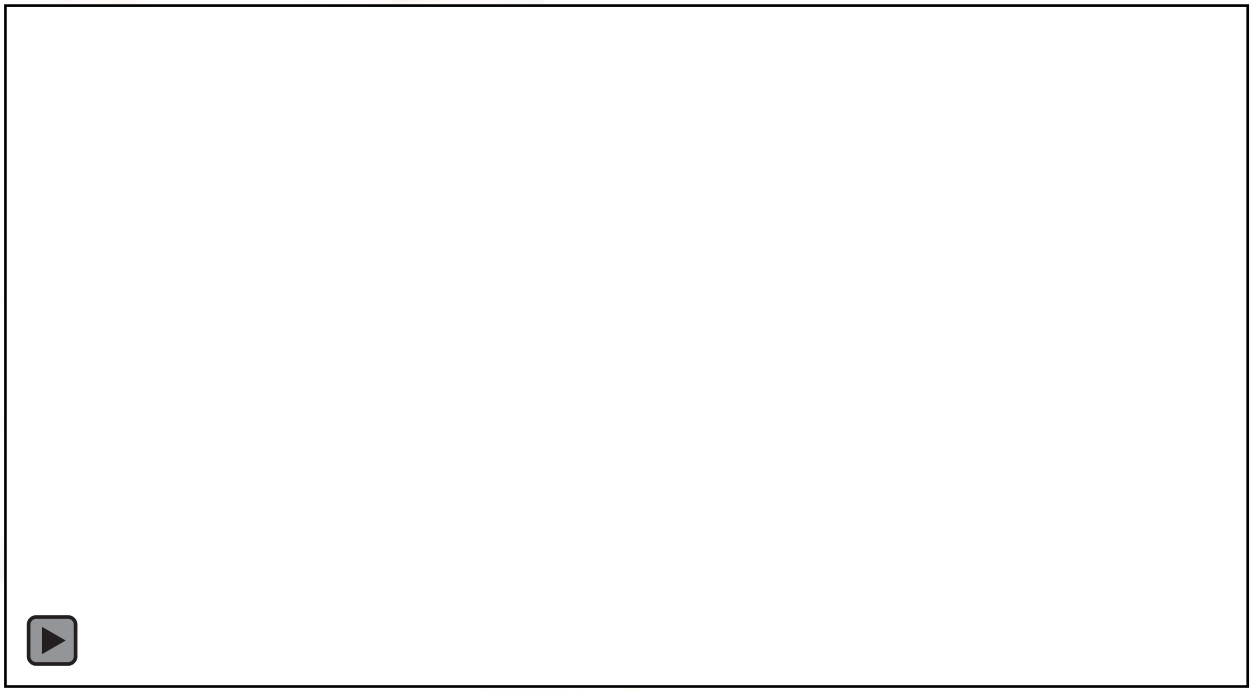
Designed for Maximum Portability

- 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



Bronchoscopy Assessment Capability



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OCS Lung Clinical Data Highlights

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THE LANCET
Respiratory Medicine

Articles

Normothermic ex-vivo preservation with the portable Organ 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 Santelmo, 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 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

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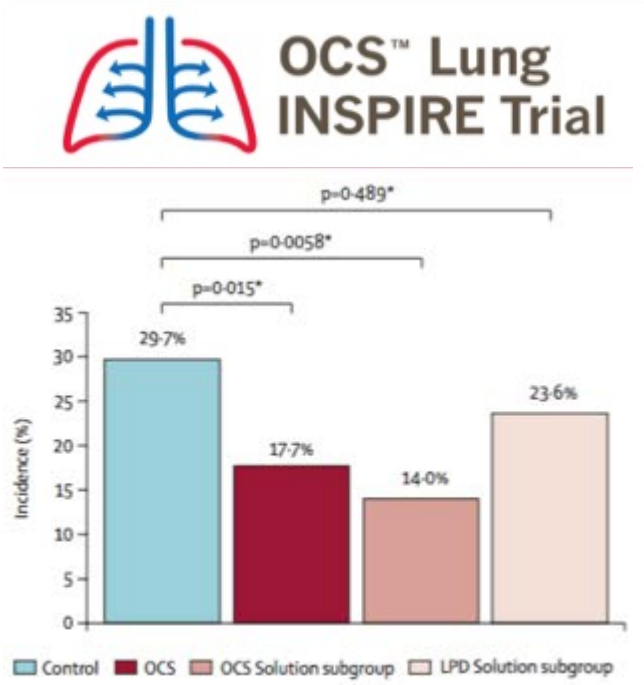

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OCS EXPAND I Lung Clinical Trial

Evaluating OCS™ 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 post-transplantation
- 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 post-transplant

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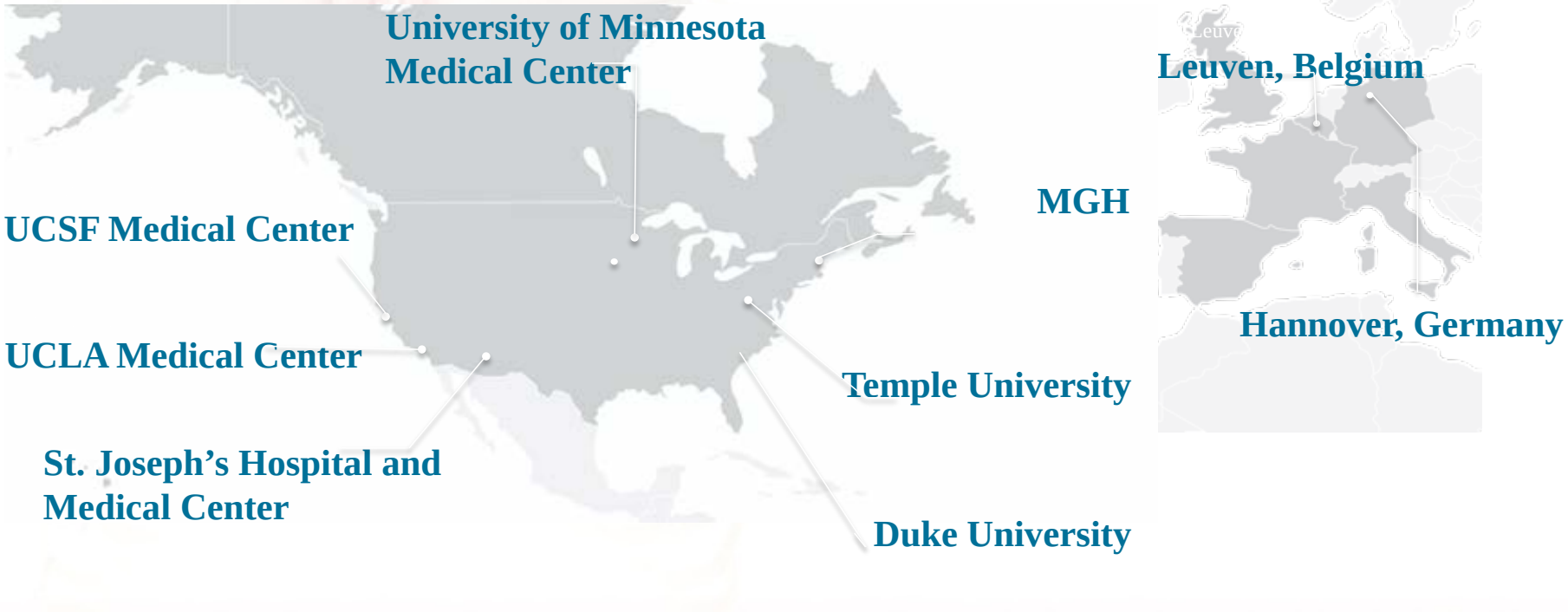
EXPAND I Lung Trial Centers



EXPAND I Lung Trial Status
Completed on Oct. 2016

OCS™
EXPAND Lung

79
Transplants

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

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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

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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

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