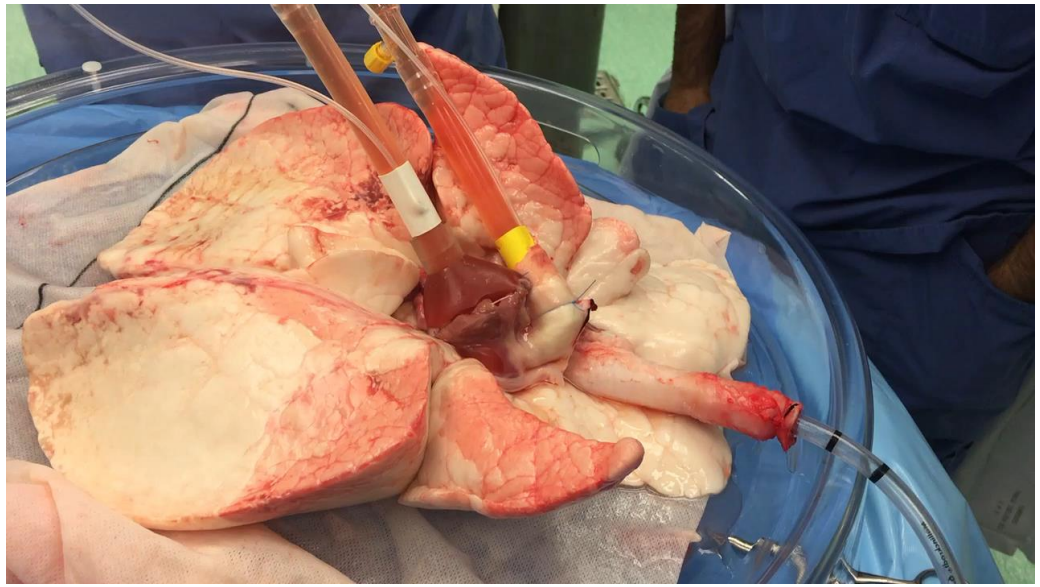
Updates on the results of recent clinical trials on organ perfusion prior to transplantation: Lung



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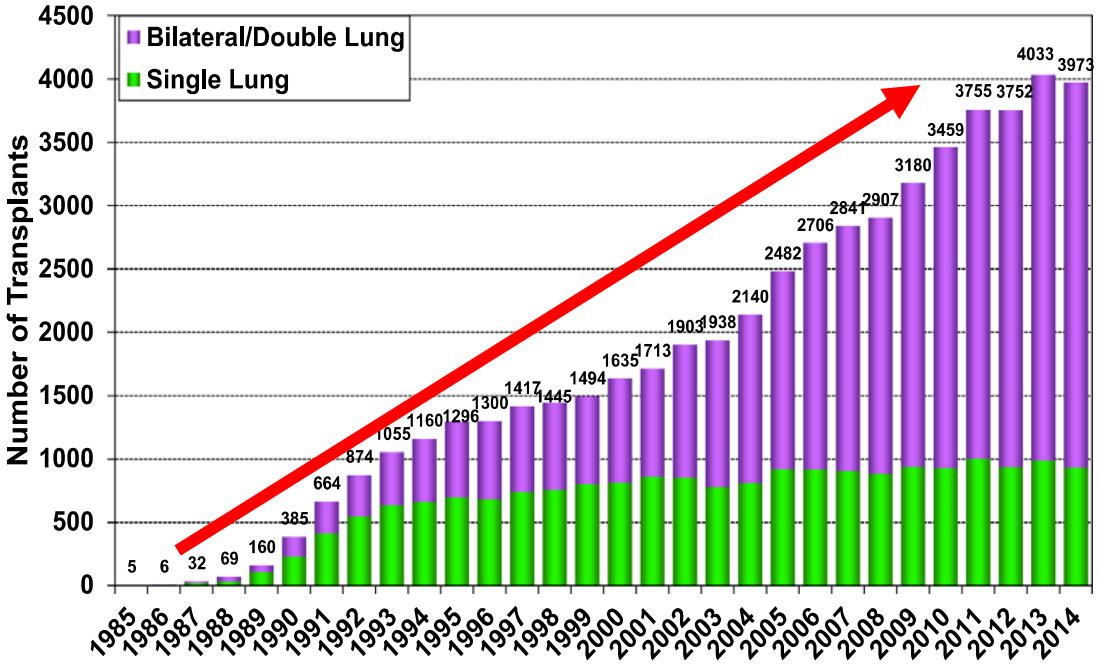
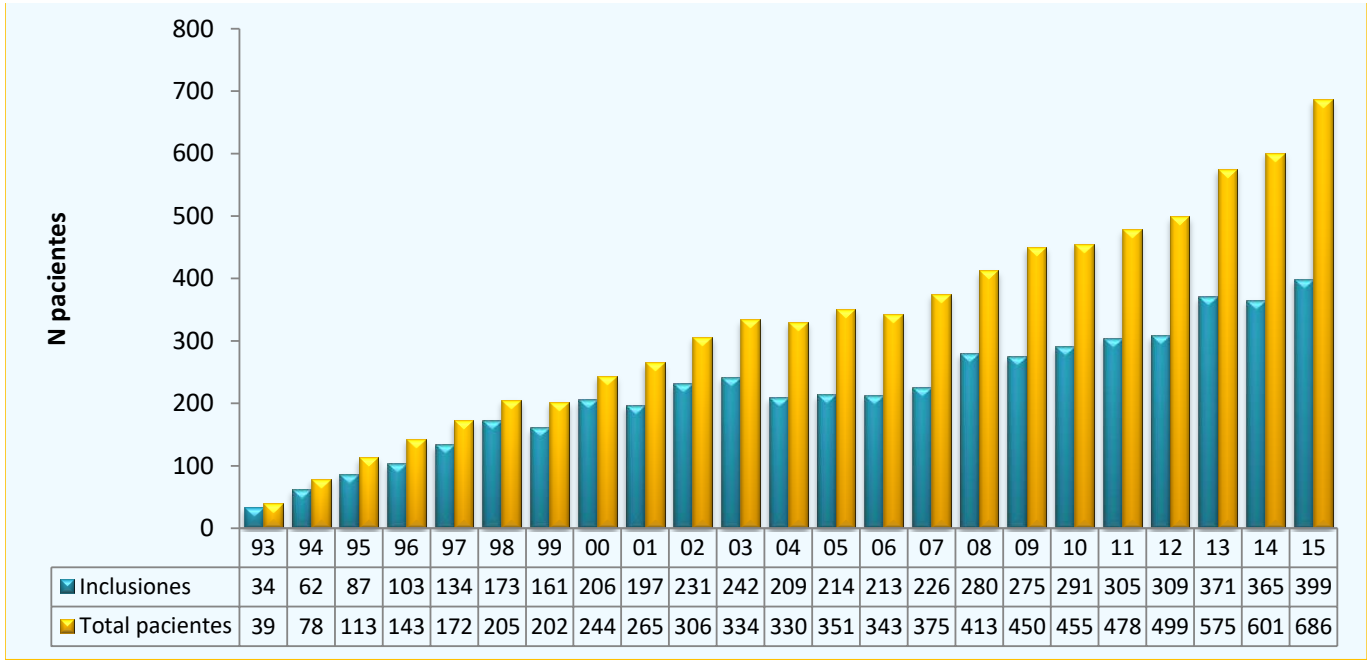
I have no conflict of interest to declare

- What happens with lung donors and waiting list?
- What can we do?
- *Ex vivo* lung perfusion systems
- What can we do with them?

What happens with lung donors and waiting list?

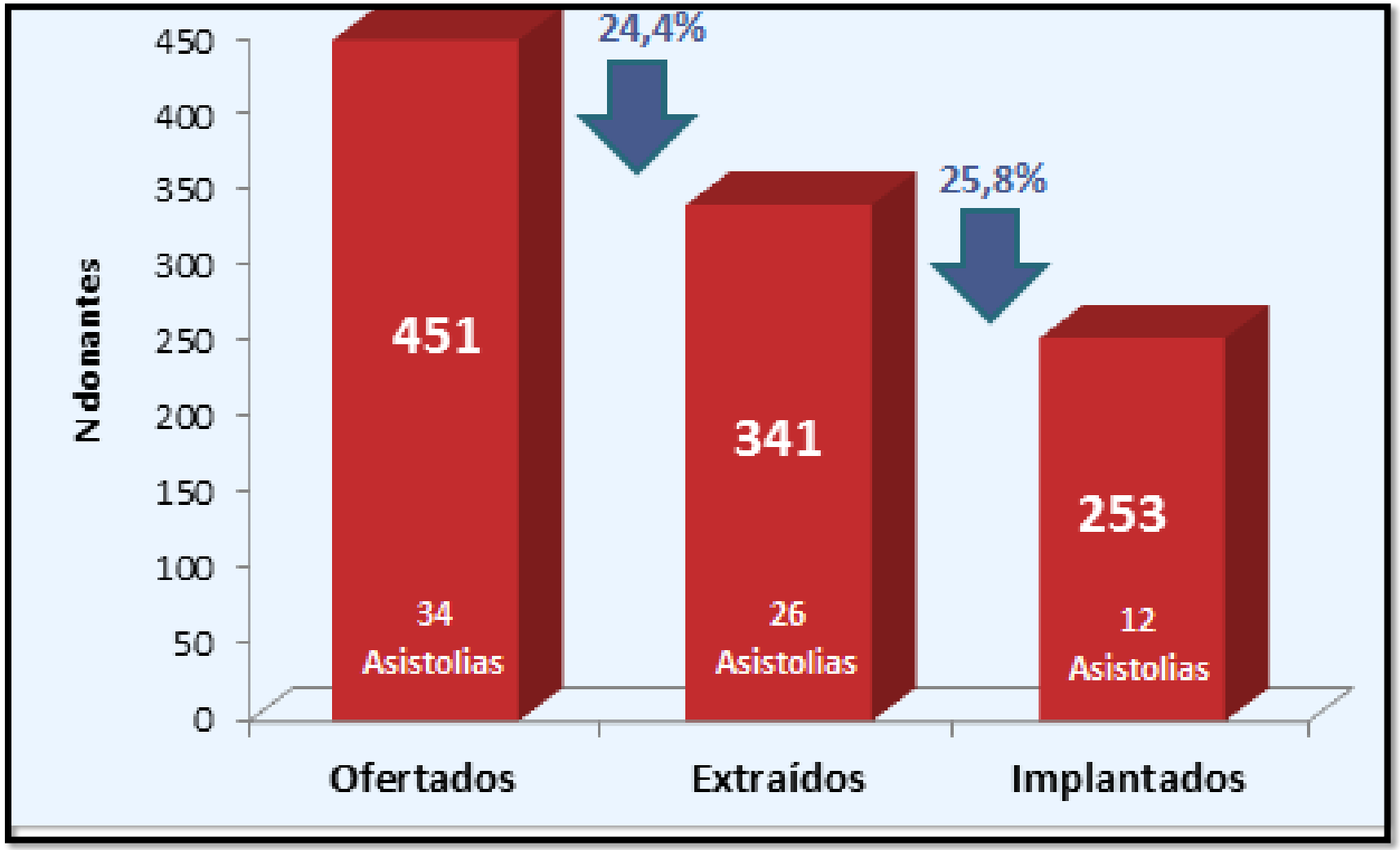




	93	94	95	96	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15
Inclusiones	34	62	87	103	134	173	161	206	197	231	242	209	214	213	226	280	275	291	305	309	371	365	399
Total pacientes	39	78	113	143	172	205	202	244	265	306	334	330	351	343	375	413	450	455	478	499	575	601	686

ORGANIZACIÓN NACIONAL DE TRASPLANTES

Yusen RD, Edwards LB, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Lung and Heart-Lung Transplant Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Hear Lung Transplant*. 2016;35(10):1170-1184.


N donantes
450
400
350
300
250
200
150
100
50
0
24,4%
25,8%
451
341
253
34
Asistolias
26
Asistolias
12
Asistolias
Ofertados
Extraídos
Implantados

What can we do?

Lung donor treatment protocol in brain dead-donors: A multicenter study

Eduardo Miñambres, MD, PhD,[a] Jose Miguel Pérez-Villares, MD, PhD,[b] Mario Chico-Fernández, MD, PhD,[c] Arturo Zabalegui, MD, PhD,[d] Jose María Dueñas-Jurado, MD,[e] Maite Misis, MD, PhD,[f] Fernando Mosteiro, MD,[g] Gil Rodriguez-Caravaca, MD, PhD,[h] and Elisabeth Coll, MD[i]

Extended criteria donor lungs and clinical outcome: Results of an alternative allocation algorithm

Wiebke Sommer, MD,[a] Christian Kühn, MD,[a] Igor Tudorache, MD,[a] Murat Avsar, MD,[a] Jens Gottlieb, MD,[b,c] Dietmar Boethig, MD,[d] Axel Haverich, MD,[a,c] and Gregor Warnecke, MD[a,c]

From the [a]Departments of Cardiothoracic, Transplant and Vascular Surgery; [b]Departments of Respiratory Medicine; [c]Member of the German Centre for Lung Research; and the [d]Department for Pediatric Cardiology and Intensive Care Medicine, Hannover Medical School, Hannover, Germany.

International Society for Heart and Lung Transplantation Donation After Circulatory Death Registry Report

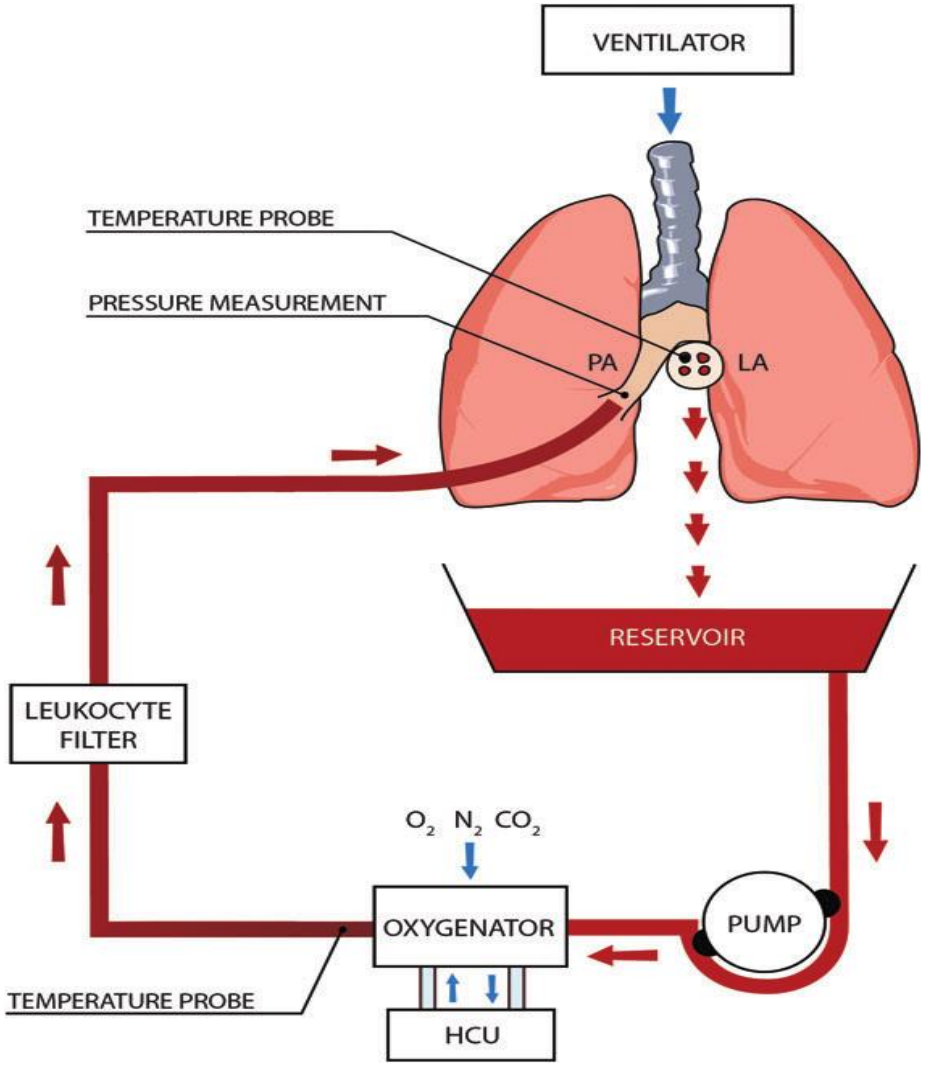
Marcelo Cypel, MD, Bronwyn Levvey, RN, Dirk Van Raemdonck, MD, Michiel Erasmus, MD, John Dark, MB, FRCS, Robert Love, MD, David Mason, MD, Allan R. Glanville, MD, Daniel Chambers, MD, Leah B. Edwards, PhD, Josef Stehlik, MD, Marshall Hertz, MD, Brian A. Whitson, MD, Roger D. Yusen, MD, Varun Puri, MD, Peter Hopkins, MD, Greg Snell, MD, and Shaf Keshavjee, MD; for the International Society for Heart and Lung Transplantation

From the International Society for Heart and Lung Transplantation Donation after Circulatory Death Registry, Dallas, Texas.

An Exciting New Era in Donor Organ Preservation and Transplantation: Assess, Condition, and Repair!

James P. Hunter, MBChB, MD[1] and Rutger J. Ploeg, MD, PhD, FRCS[1]

EX VIVO LUNG PERFUSION SYSTEMS



Steen S, Sjöberg T, Pierre L, Liao Q, Eriksson L, Algotsson L. Transplantation of lungs from a non-heart-beating donor. *Lancet*. 2001;357:825-829.
Andreasson ASI, Dark JH, Fisher AJ. Ex vivo lung perfusion in clinical lung transplantation-State of the art. *Eur J Cardio-thoracic Surg*. 2014;46(5):779-788

	Lund	Toronto	OCS
Perfusion			
Target flow	100% of cardiac output (70 ml/kg/min)	40% of cardiac output	2–2.5 l/min
Pulmonary arterial pressure (mmHg)	≤20	≤15	≤20
Left atrial pressure (mmHg)	0 (open LA)	3–5	0 (open LA)
Pump	Roller	Centrifugal	Piston (pulsatile)
Perfusate	2 l Steen Solution™ with red-cell concentrates (heamatocrit 10–15%)	2 l Steen Solution™	1.5 l 'OCS lung solution'[a] with red-cell concentrates (heamatocrit 15–25%)
Ventilation			
Mode	Volume controlled	Volume controlled	Volume controlled
Tidal volume (ml/kg)	6–8	7	6
Frequency (bpm)	10–15	7	10
Peak end-expiratory pressure (cmH_2O)	5	5	5
Fraction of inspired oxygen (%)	50	21	21
Temperature (°C)			
Start of ventilation	32	32	32
Start of perfusion	15	25	32
Start of evaluation	37	37	37

Andreasson ASI, Dark JH, Fisher AJ. Ex vivo lung perfusion in clinical lung transplantation-State of the art. *Eur J Cardio-thoracic Surg*. 2014;46(5):779-788

EX VIVO LUNG PERFUSION SYSTEMS

Author	Transplant centre	Year of transplant	EVLP protocol	No. of EVLP assessments	Conversion rate to transplant	Median PaO_2/FiO_2 in donor (kPa)	Rate of ECMO post-Tx (non-elective)	Rate of PGD Grade 3 at 72 h	30-day survival (%)	1-year survival (%)
Ingemansson *et al.* [34]	Lund	2006–7	Lund	8	75% (6)	21.1	17% (1)	NK	100	67
Fildes *et al.* [35]	Manchester	2008–10	Lund	NK	NK (8)	NK	NK	NK	87.5[a]	NK
Cypel *et al.* [11]	Toronto	2008–11	Toronto	58	86% (50)	44.5[b]	2% (1)	2% (1)	96	87
Dark *et al.* [36]	Newcastle	2009–11	Toronto	18	39% (7)	34.6[b]	0% (0)	14% (1)	100	86
Zych *et al.* [37]	Harefield	2009–10	Toronto	13	46% (6)	47.0[b]	33% (2)	NK	100	NK
Aigner *et al.* [38]	Vienna	2010–11	Toronto	13	69% (9)	28.8	0% (0)	0% (0)	100	NK
Moradiellos *et al.* [39]	Madrid	NK	Toronto	8	50% (4)	NK	0% (0)	0% (0)	100	NK
Valenza *et al.* [40]	Milan	2011	Toronto[c]	NK	NK (2)	24.5	0% (0)	0% (0)	100	NK
Warnecke *et al.* [20]	Hannover/ Madrid	2011	OCS	12	100% (12)	61.5	0% (0)	0% (0)	100	92
Wallinder *et al.* [21]	Gothenburg	2011–12	Lund	11	100% (11)	27.9	9% (1)	9% (1)	100	NK
Hopkins *et al.* [41]	Brisbane	2011–12	Lund	5	80% (4)	25.2[b]	0% (0)	0% (0)	100	NK
Boffini *et al.* [42]	Turin	2011–13	Toronto	NK	NK (8)	NK	25% (2)	0% (0)	NK	NK
Sage *et al.* [43]	Paris	2011–12	Toronto	21	95% (20)	34.1	NK	10% (2)	95	95
Cypel *et al.* [30][d]	Toronto/ Vienna/ Paris	2008–12	Toronto	125	82% (103)	35.7[b]	NK	5% (5)	96	88
Steen *et al.* [22]	Lund	2000	Lund	1	100% (1)	NK	0% (0)	0% (0)	100	NK
Steen *et al.* [23]	Lund	2005	Lund	1	100% (1)	12.9	NK	NK	100	0
Wigfield *et al.* [32]	Chicago/ Toronto	2011	Toronto	1	100% (1)	34.4	0% (0)	NK	100	NK
García Sáez *et al.* [44]	Harefield	2012	Toronto	1	100% (1)	24.0	0% (0)	NK	100	100
Patil *et al.* [45]	Harefield	2012	Toronto	1	100% (1)	>40.0	NK	NK	100	NK
Wallinder *et al.* [46]	Gothenburg	2012	Lund	1	100% (1)	10.0	0% (0)	0% (0)	100	NK
Methangkool *et al.* [47]	UCLA	2012	OCS	1	100% (1)	NK	0% (0)	NK	100	NK
Zamel *et al.* [48]	Toronto	2013	Toronto	1	100% (1)	35.5	0% (0)	NK	100	NK

Andreasson ASI, Dark JH, Fisher AJ. Ex vivo lung perfusion in clinical lung transplantation-State of the art. *Eur J Cardio-thoracic Surg*. 2014;46(5):779-788

WHAT CAN WE DO WITH THEM?

WHAT CAN WE DO WITH THEM?: Assessment

International Society for Heart and Lung Transplantation Donation After Circulatory Death Registry Report

Marcelo Cypel, MD, Bronwyn Levvey, RN, Dirk Van Raemdonck, MD, Michiel Erasmus, MD, John Dark, MB, FRCS, Robert Love, MD, David Mason, MD, Allan R. Glanville, MD, Daniel Chambers, MD, Leah B. Edwards, PhD, Josef Stehlik, MD, Marshall Hertz, MD, Brian A. Whitson, MD, Roger D. Yusen, MD, Varun Puri, MD, Peter Hopkins, MD, Greg Snell, MD, and Shaf Keshavjee, MD; for the International Society for Heart and Lung Transplantation

From the International Society for Heart and Lung Transplantation Donation after Circulatory Death Registry, Dallas, Texas.

Table 1 Characteristics of DCD Practices in Participating Centers

Center	Transplants 2012 to 2014 (n)	Percentage of Transplants from DCD (%)	Use of heparin pre-mortem	Use of Bronchoscopy Pre-mortem	Selective use of EVLP	Stand-off period	Maximum time allowed for WLS T to arrest
Toronto	352	15	Yes	Yes	Yes	[illegible] min	180 min
Sydney	139	23	No	No	Yes	[illegible] min	90 min
Melbourne	214	23	Yes[a]	Yes	No	[illegible] to 5 min	90 min
Brisbane	93	15	No	No	Yes	[illegible] min	90 min
Leuven	199	14	Yes	No	Yes	[illegible] min	120 min
Groningen	112	32	No	Yes	Yes	[illegible] min	90 min
Minnesota	126	7	Yes	Yes	Yes	[illegible] min	90 min
St. Louis	191	<1	Yes	Yes	No	5 min	30 min
Cleveland	302	8	Yes	Yes	No	5 min	60 min

Andreasson ASI, Dark JH, Fisher AJ. Ex vivo lung perfusion in clinical lung transplantation-State of the art. *Eur J Cardio-thoracic Surg*. 2014;46(5):779-788

REVIEW

DCD lung donation: donor criteria, procedural criteria, pulmonary graft function validation, and preservation

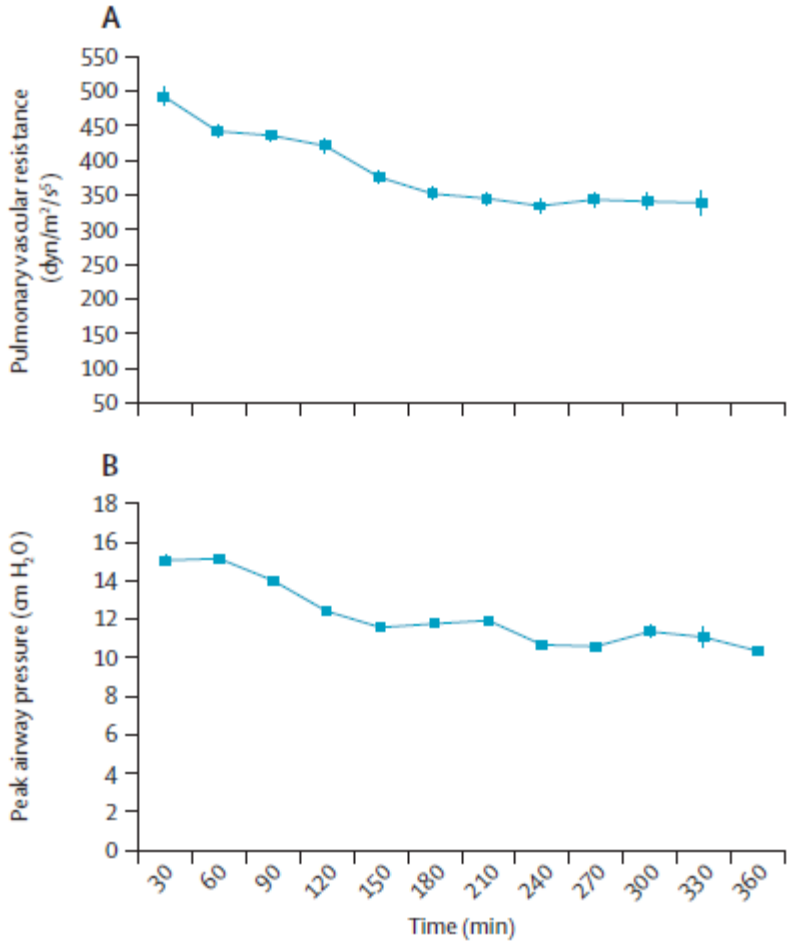
Michiel E. Erasmus[1], Dirk van Raemdonck[2], Mohammed Zeeshan Akhtar[3], Arne Neyrinck[2], David Gomez de Antonio[4], Andreas Varela[4] & John Dark[5]

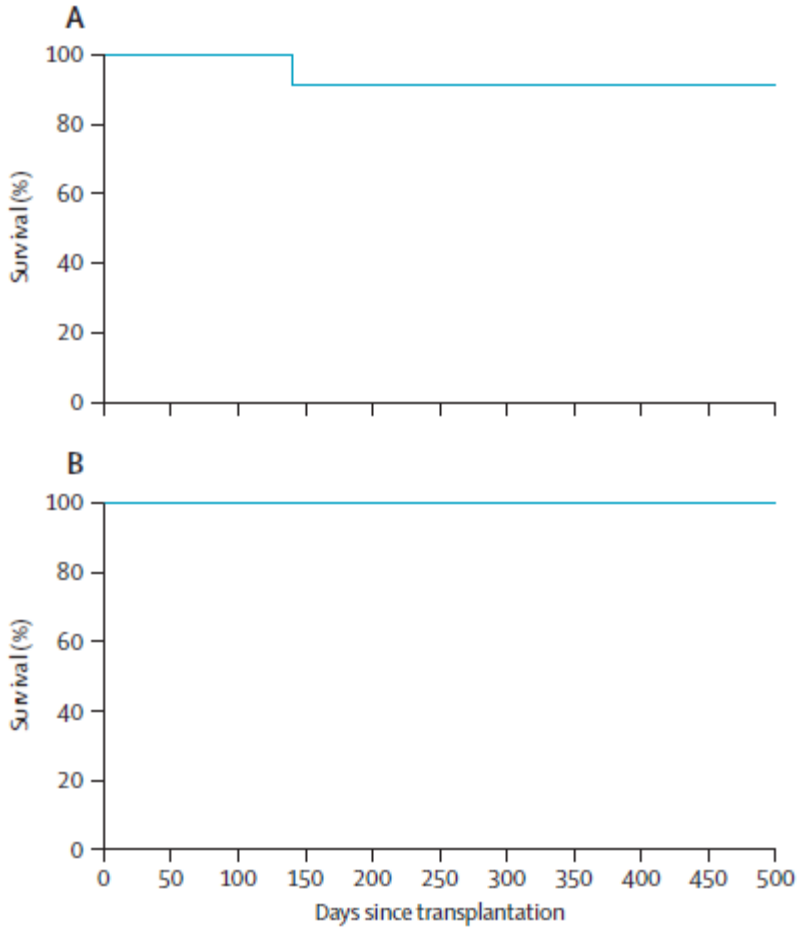
Uncontrolled DCD lung donation

In uncontrolled DCD lung donation, a method to validate lung function after donation is a necessity as lung function is unknown before donation. EVLP is thought to be a good method to evaluate lungs from uncontrolled DCD donors. However, the largest experience with lung validation in uncontrolled DCD is with an *in vivo* single flush technique as described by the Madrid group.

Erasmus ME, van Raemdonck D, Akhtar MZ, et al. DCD lung donation: donor criteria, procedural criteria, pulmonary graft function validation, and preservation. *Transpl Int*. 2016;29(7):790-797

WHAT CAN WE DO WITH THEM?: Transport





Warnecke G, Moradiellos J, Tudorache I, Kühn C, Avsar M, Wiegmann B, et al. Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lung before bilateral transplantation: A pilot study of 12 patients. Lancet 2012;380(9856):1851–8

WHAT CAN WE DO WITH THEM?: Reconditioning

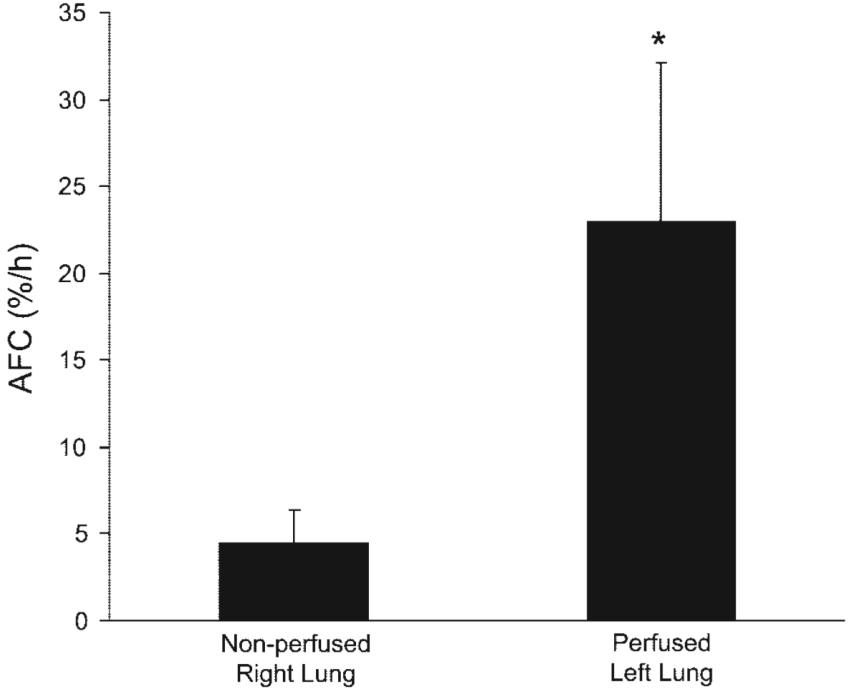
- Some causes to refuse grafts are:
  - Edema
  - Inflamation
  - Infection
  - Aspiration
  - Pulmonary Embolism
  - Atelectasis
  - …

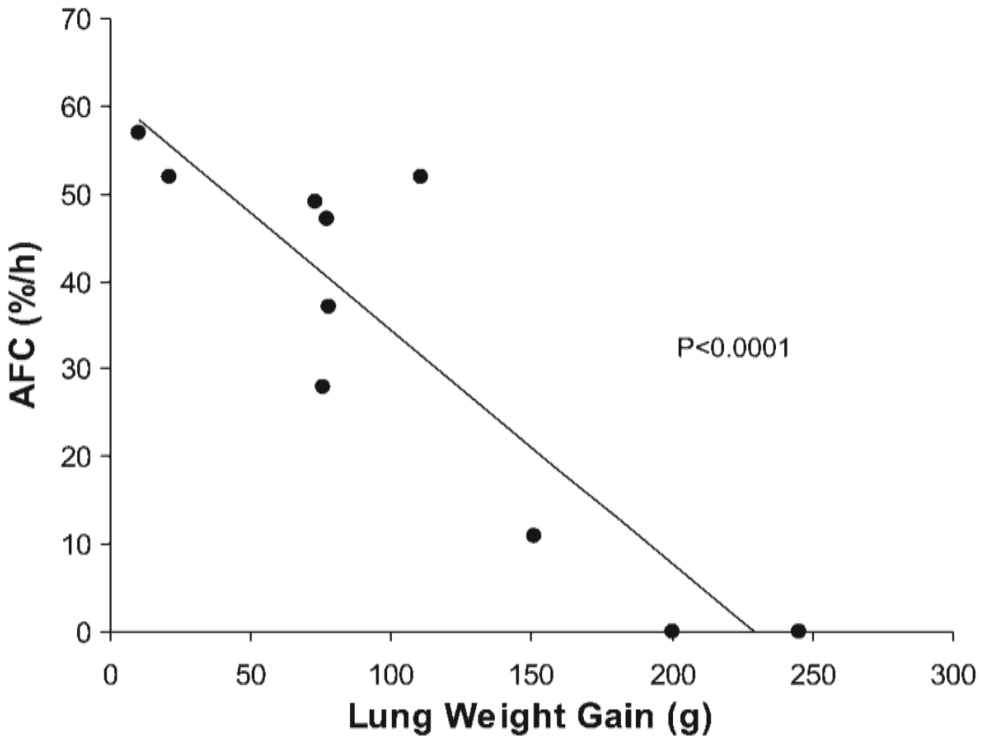
Edema

Physiological and biochemical markers of alveolar epithelial barrier dysfunction in perfused human lungs

James A. Frank[1,3,4,5], **Raphael Briot**[3], **Jae Woo Lee**[2,3], **Akitoshi Ishizaka**[6], **Tokujiro Uchida**[7], and **Michael A. Matthay**[1,2,3]

Published in final edited form as:
Am J Physiol Lung Cell Mol Physiol. 2007 July ; 293(1): L52–L59

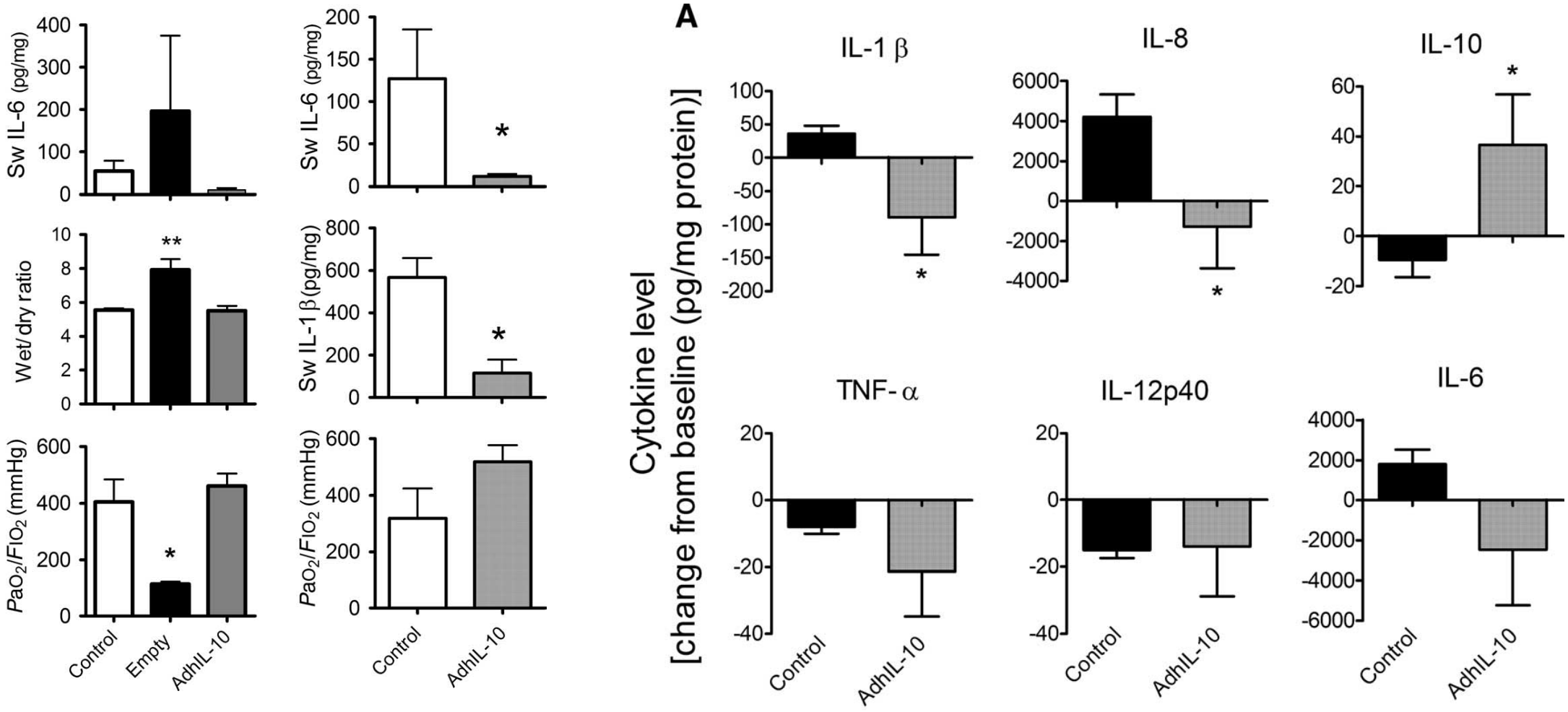




Frank JA, Briot R, Lee JW, et al. Physiological and bio- chemical markers of alveolar epithelial barrier dysfunction in perfused human lungs. Am J Physiol Lung Cell Mol Physiol 2007: 293: L52

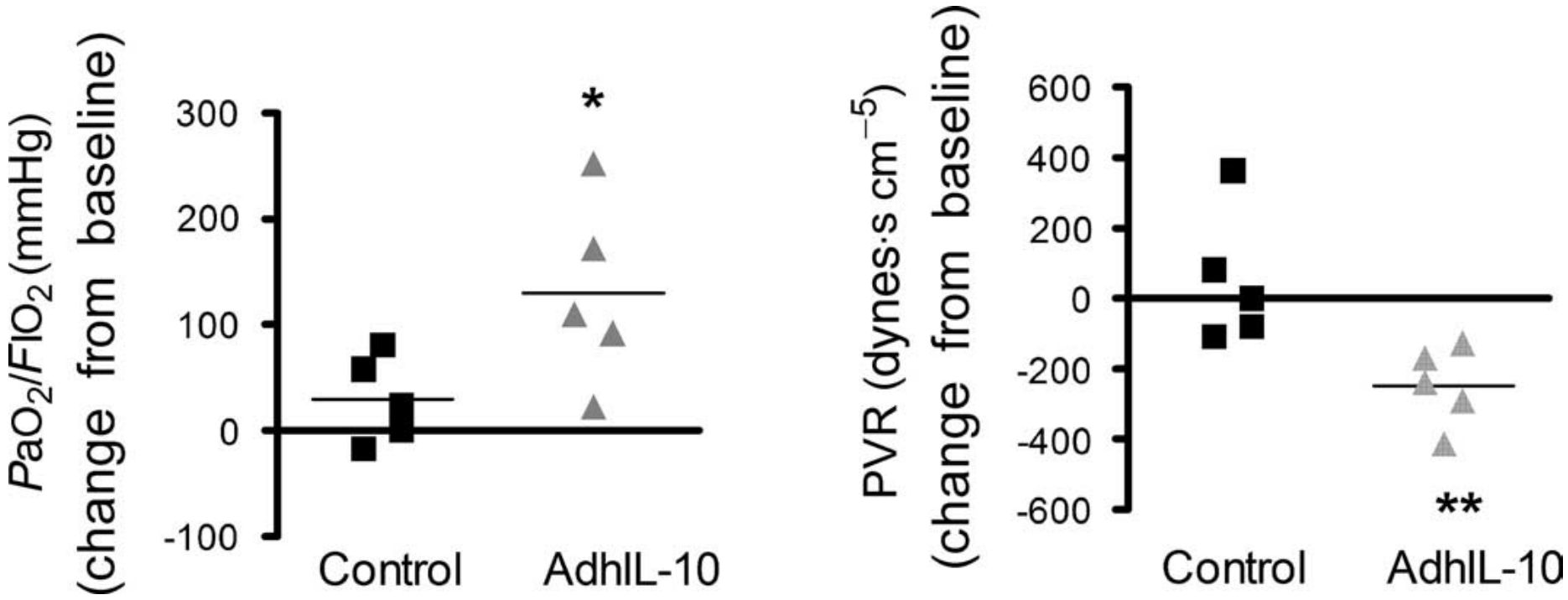
Valenza F, Rosso L, Coppola S, et al. β-Adrenergic agonist infusion during extracorporeal lung perfusion: Effects on glucose concentration in the perfusion fluid and on lung function. *J Hear Lung Transplant*. 2012;31(5):524-530

Inflamation



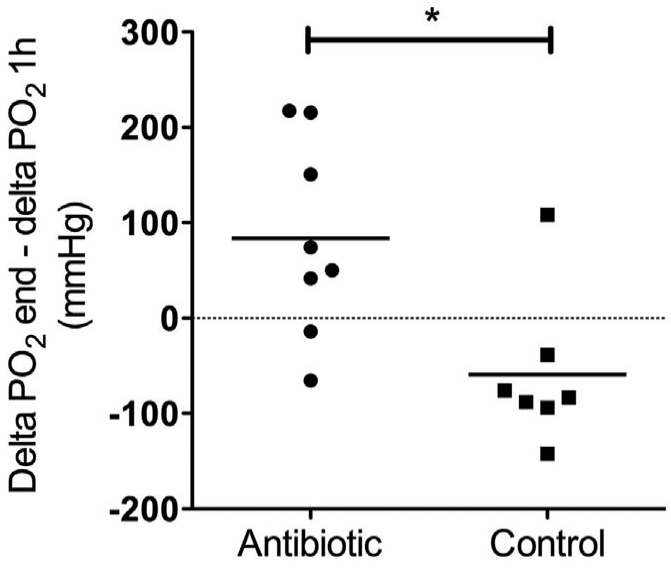
Cypel M, Liu M, Rubacha M, et al. Functional repair of human donor lungs by IL-10 gene therapy. *Sci Transl Med*. 2009;1(4):4ra9

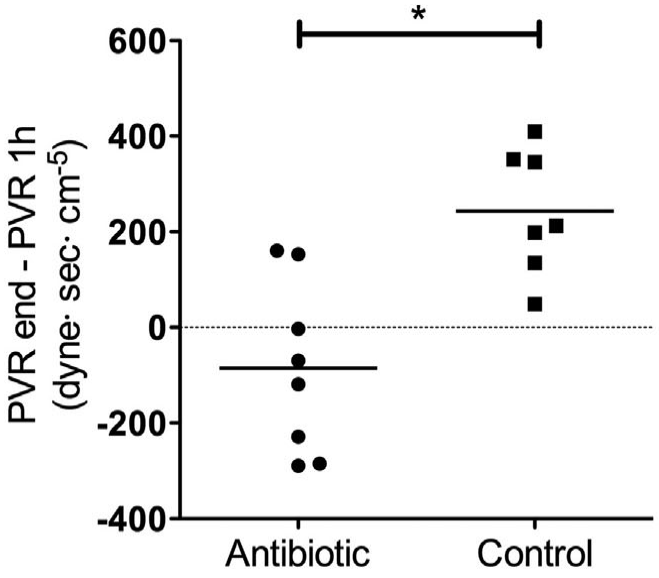
Inflamation

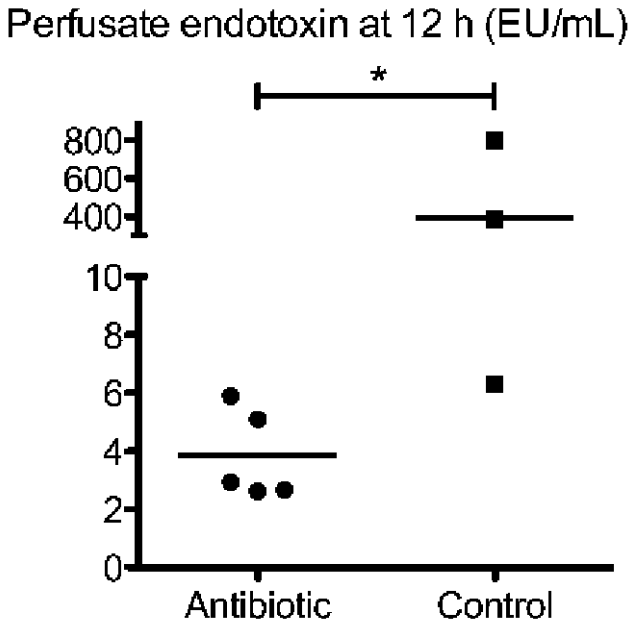


Cypel M, Liu M, Rubacha M, et al. Functional repair of human donor lungs by IL-10 gene therapy. *Sci Transl Med*. 2009;1(4):4ra9

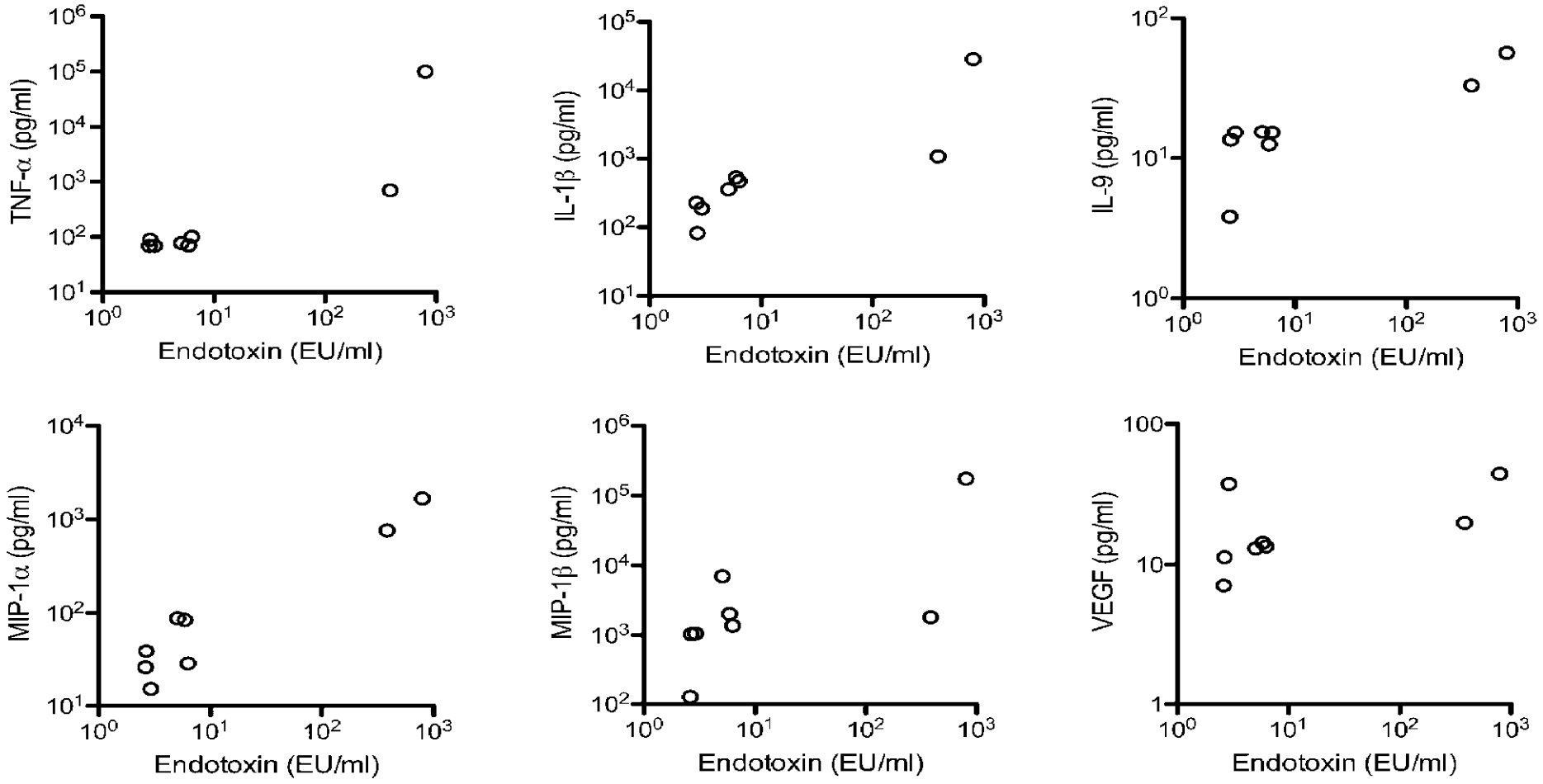
Infection







Nakajima D, Cypel M, Bonato R, et al. Ex Vivo Perfusion Treatment of Infection in Human Donor Lungs. *Am J Transplant*. 2016;16(4):1229-1237



Nakajima D, Cypel M, Bonato R, et al. Ex Vivo Perfusion Treatment of Infection in Human Donor Lungs. *Am J Transplant*. 2016;16(4):1229-1237

Ex Vivo Reconditioning of Marginal Donor Lungs Injured by Acid Aspiration

Ilhan Inci, MD,[a] Luca Ampollini, MD,[a] Stephan Arni, PhD,[a] Wolfgang Jungraithmayr, MD,[a] Demet Inci, MD,[b] Sven Hillinger, MD,[a] Boris Leskosek, MD,[a] Peter Vogt, MD,[c] and Walter Weder, MD[a]

Pulmonary embolism

Successful Lung Transplantation After Donor Lung Reconditioning With Urokinase in Ex Vivo Lung Perfusion System

Ilhan Inci, MD, Yoshito Yamada, MD, PhD,
Sven Hillinger, MD, Wolfgang Jungraithmayr, MD, PhD,
Michael Trinkwitz, and Walter Weder, MD

Departments of Thoracic Surgery and Cardiovascular Surgery,
University Hospital, Zurich, Switzerland

Inci I, Yamada Y, Hillinger S, Jungraithmayr W, Trinkwitz M, Weder W. Successful lung transplantation after donor lung reconditioning with urokinase in Ex vivo lung perfusion system. *Ann Thorac Surg*. 2014;98(5):1837-1838.
Inci I, Ampollini L, Arni S, et al. Ex Vivo Reconditioning of Marginal Donor Lungs Injured by Acid Aspiration. *J Hear Lung Transplant*. 2008;27(11):1229-1236. doi:10.1016/j.healun.2008.07.027.

IN CONCLUSION

- They exist differents models of EVLP systems, the better of them depends on the use and the needs.
- The EVLP system is safe and increases the grafts avaibles to transplant.
- The EVLP is needed in uDCD lung donors.
- Health systems with long distances and long time of cold ischaemia can use EVLP systems to preserve the grafts with similar outcomes.
- More studies and research is necessary to keep advancing and reconcition greater proportion of lungs.


THOUSANDS OF PEOPLE OWE
THEIR LIVES TO ORGAN DONORS
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ADOT
Sign up for your donor's card at france-adot.org