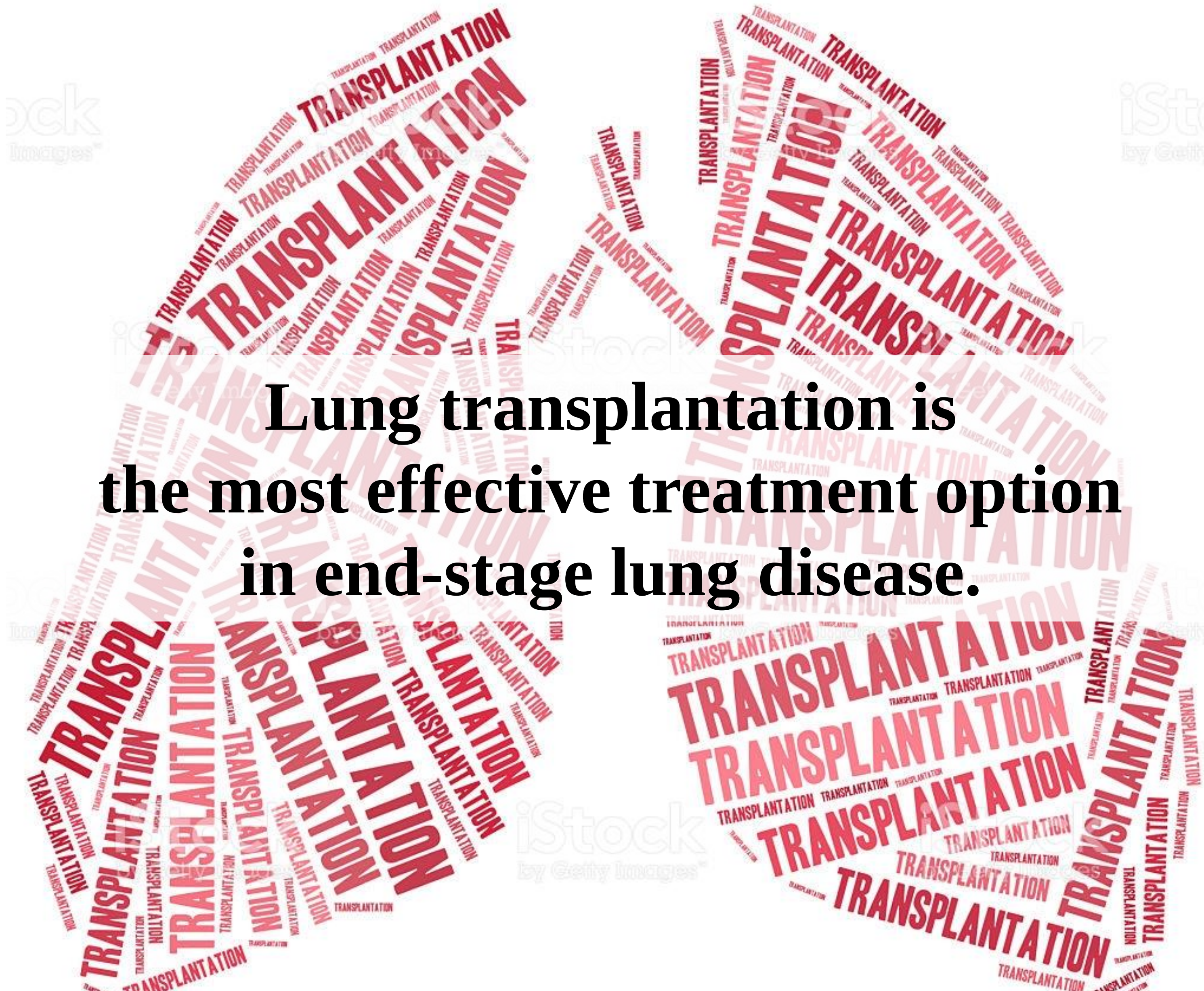
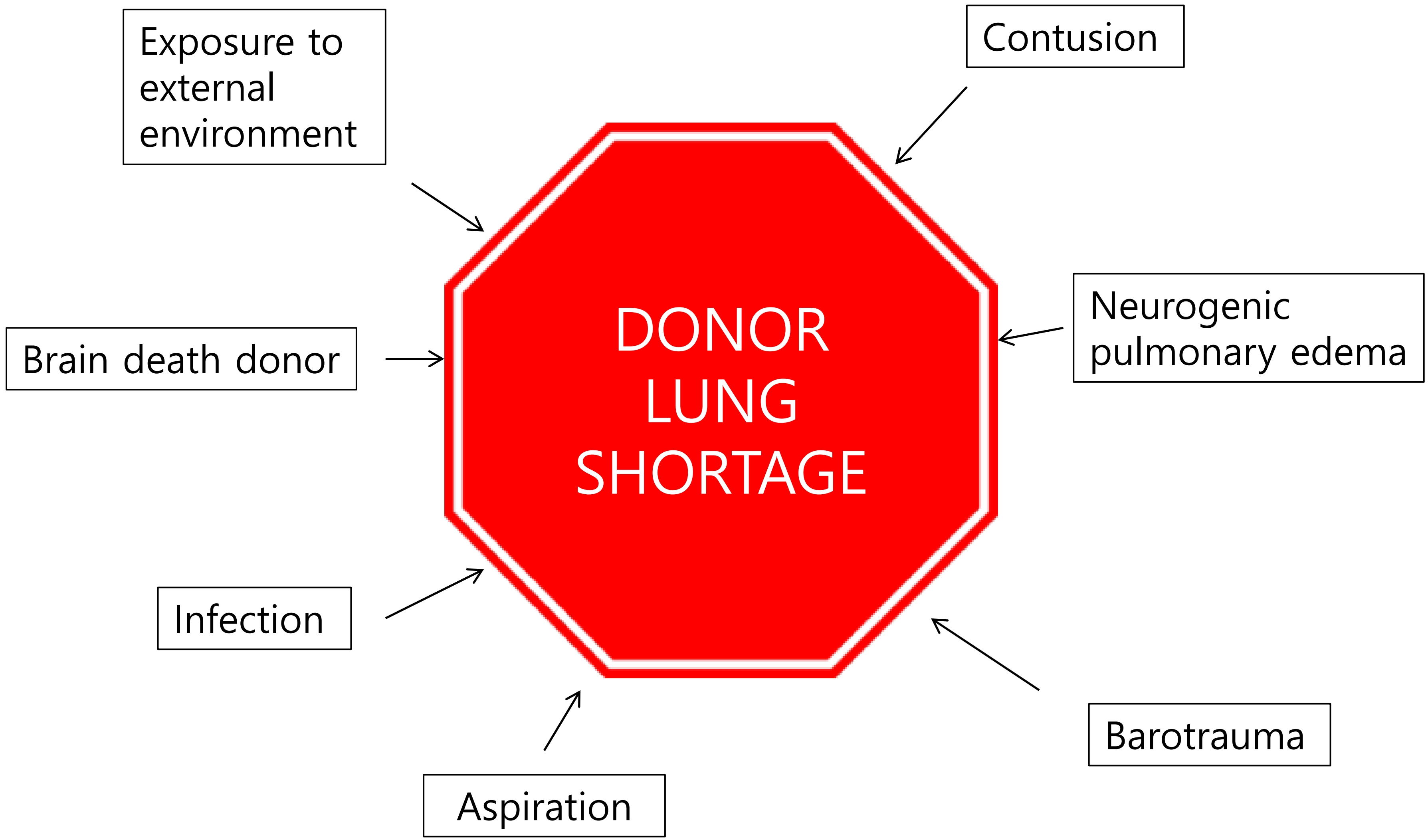
Ex Vivo Lung Perfusion in Lung Transplantation

함석진
아주대학교병원 흉부외과



**Lung transplantation is
the most effective treatment option
in end-stage lung disease.**


Exposure to external environment
Contusion
Neurogenic pulmonary edema
Brain death donor
DONOR LUNG SHORTAGE
Infection
Barotrauma
Aspiration

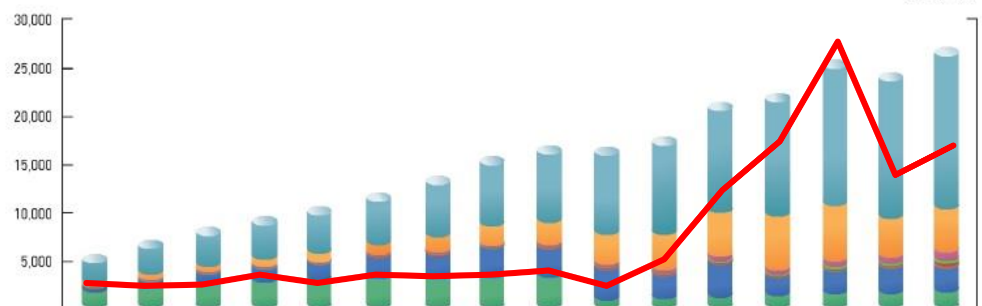
뇌사 이식 추이(주요 장기별) : 2000 - 2015

(단위 : 건)

	2000 (2.9~)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
신장	99	99	68	123	164	171	263	278	479	488	491	680	768	750	808	901
간장	34	37	28	50	64	66	118	128	233	236	242	313	363	367	404	456
췌장	11	5	8	12	10	12	29	18	22	22	25	43	34	57	55	57
심장	12	21	11	15	23	26	29	50	84	65	73	98	107	127	118	145
폐	1	-	2	2	3	7	3	9	7	8	18	35	37	46	55	64
계	157	162	117	202	264	282	442	483	825	819	849	1,169	1,309	1,347	1,440	1,623

장기등이식대기자 추이(장기별) : 2000 - 2015

(단위 : 명)



	2000 (2.9~)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
신장	2,309	2,904	3,417	3,878	4,309	4,910	5,672	6,695	7,641	8,488	9,622	10,964	12,463	14,181	14,477	16,011
간장	367	541	627	786	975	1,279	1,598	2,108	2,596	3,501	4,279	4,895	5,671	6,334	4,422	4,774
췌장	72	101	123	142	162	187	225	257	314	373	435	532	603	715	766	890
심장	70	62	71	81	81	93	91	99	127	138	202	257	343	433	342	400
폐	22	20	21	28	22	28	27	28	31	20	39	88	123	194	99	120
췌도	-	-	-	-	-	1	1	-	4	4	6	18	23	23	25	28
소장	-	-	-	-	-	-	-	1	2	8	12	10	17	21	20	18
골수	509	818	1,213	1,540	1,829	2,198	2,665	3,168	3,073	3,426	2,390	3,746	1,941	2,448	2,761	3,323
안구	1,994	2,423	2,914	3,164	3,306	3,432	3,463	3,542	3,630	1,097	1,204	1,351	1,511	1,687	1,695	1,880
계	5,343	6,869	8,386	9,619	10,684	12,128	13,742	15,898	17,418	17,055	18,189	21,861	22,695	26,036	24,607	27,444

주) 각 연도말 누계

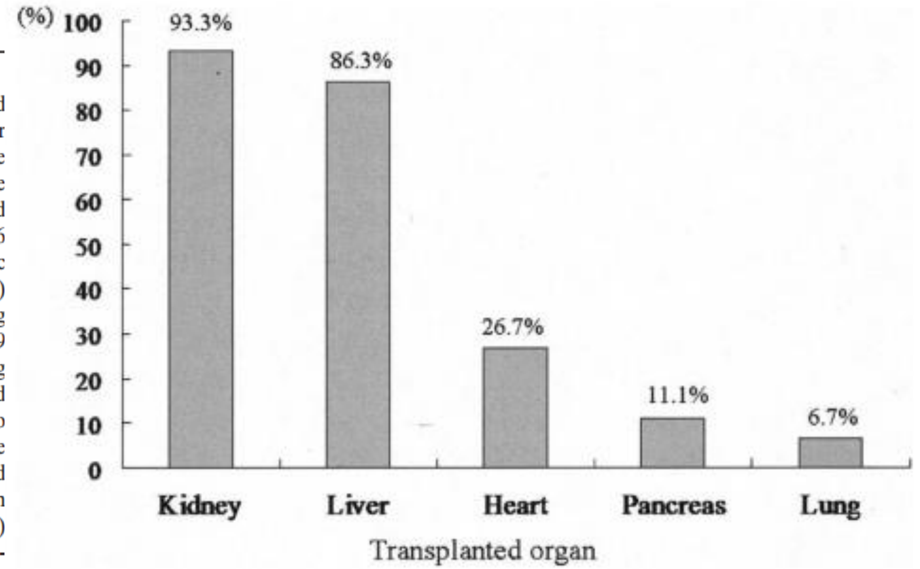
56?

The Fate of Patients on the Waiting List for Lung Transplantation in Korea

H.C. Paik, S.J. Haam, D.Y. Lee, G.J. Yi, S.W. Song, Y.T. Kim, C.H. Kang, K.M. Kim, S.I. Park, and S.H. Jheon

ABSTRACT

Lung transplantation for end-stage lung disease results in prolonged actuarial survival and improved pulmonary function. However, the shortage of donor lungs has been a major limiting factor in transplantation. The purpose of this study was to analyze the waiting time and mortality rate for each disease entity. The medical records of all patients listed in The Korean Network for Organ Sharing (KONOS) from May 1996 to May 2011 were analyzed to identify waiting times and causes of death. During the study period, 146 patients (86 males and 60 females) of mean age of 46.6 years (range; 5 to 73 years) showed idiopathic pulmonary fibrosis (IPF; n = 61), chronic obstructive pulmonary disease (COPD; n = 19) or bronchiectasis (n = 15). Sixty-five patients (44.5%) underwent lung or heart-lung transplantation. Sixty-two patients (42.5%) expired during the waiting period, and 19 patients are still on the waiting list. The mortality rate while waiting was highest among patients with primary pulmonary hypertension (62.5%) followed by IPF (57.4%), and acute respiratory distress syndrome (ARDS) (55.6%). The mean time from diagnosis to registration in KONOS was 15.5 months among the expired and 13.2 months in the transplanted group ($P = .455$). The mean time on waiting list was 8.2 months in the expired group and 3.7 months in the transplanted group ($P = .012$). In the expired group, the mean survival time was significantly shorter among patients with ARDS (2.2 months, $P = .004$) compared to IPF (7.9 months), COPD (10.7 months), and primary pulmonary hypertension (PPH) (30.0 months). The high mortality rate (42.5%) during the waiting period in Korea may result from the lack of donors and the delay in registration.



- The fate of patients on the waiting list for lung transplantation in Korea. Transplant Proc 2012;44:865-9
- Donor Evaluation for Lung Transplantation in Korea. Transplant Proc 2012;44:870–874

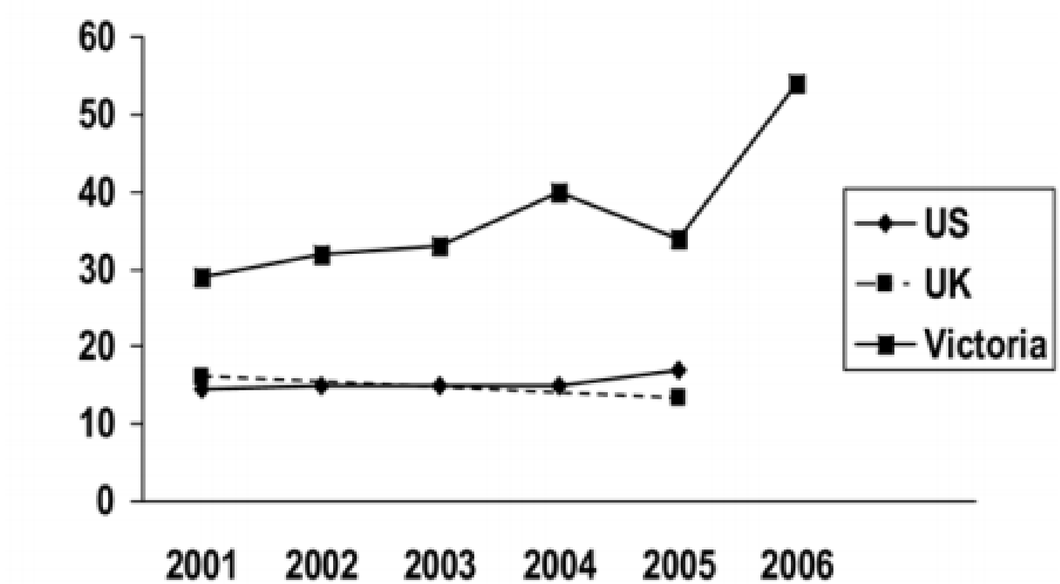
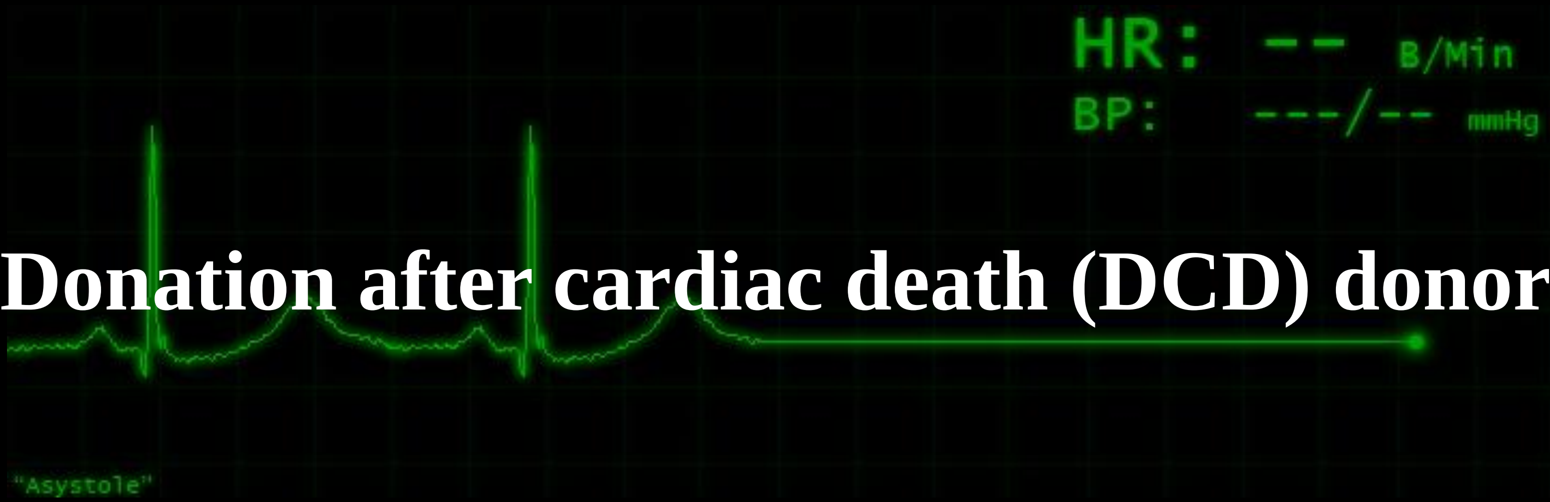


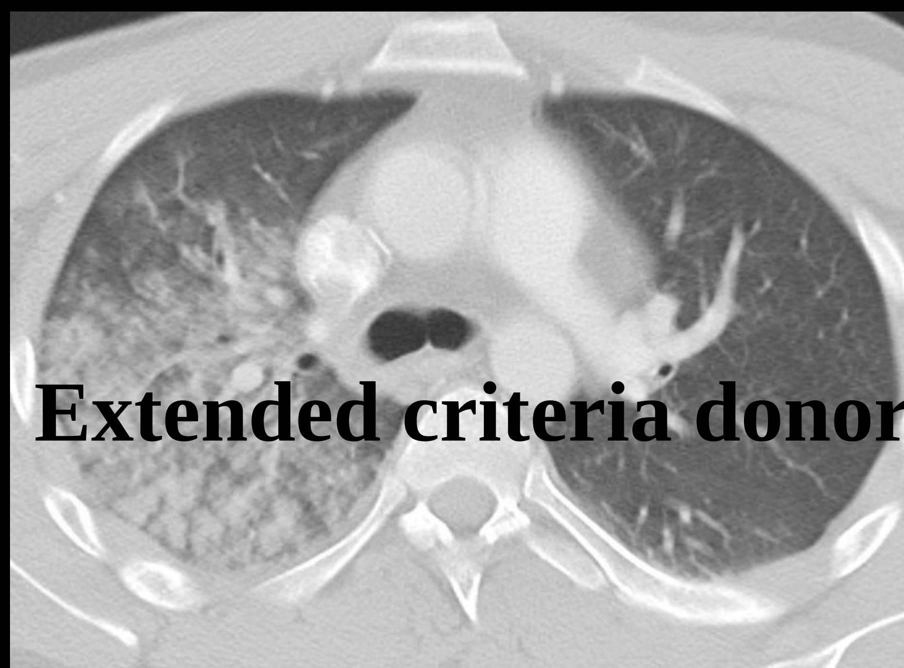
Figure 1. Lung utilization as a percentage of any organ donated for transplantation from the state of Victoria from 2001 to 2006. Known USA[1] and UK[12] data are included for comparison.

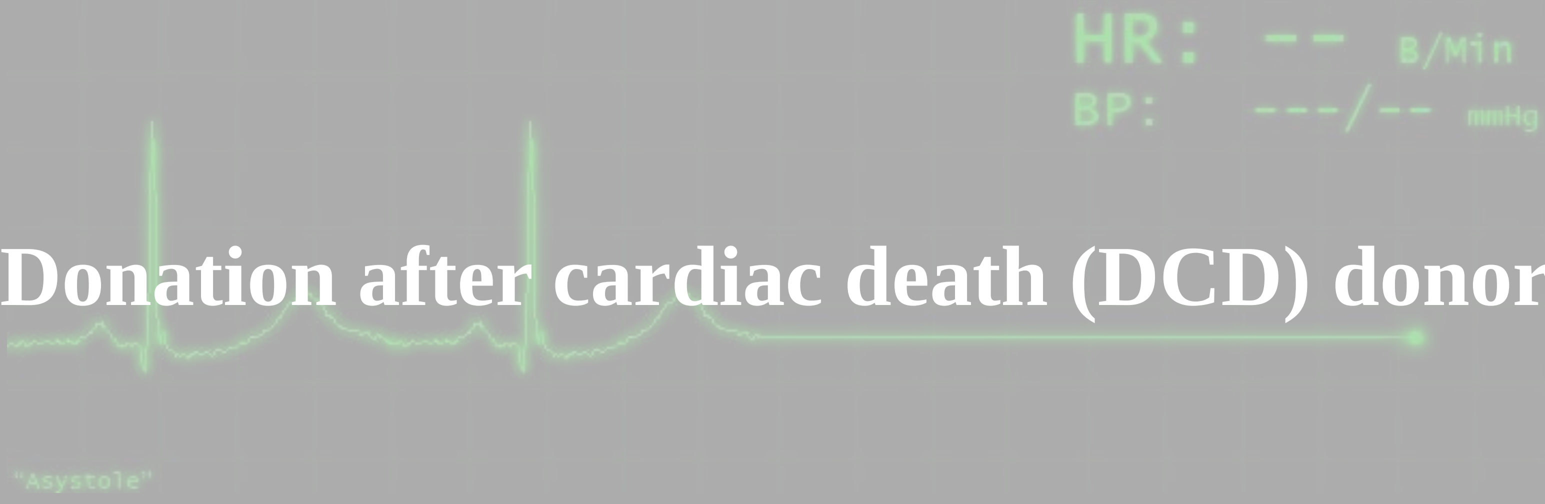
Availability of Lungs for Transplantation: Exploring the Real Potential of the Donor Pool. . J Heart Lung Transplant 2008;27:662–7

Donation after cardiac death (DCD) donors



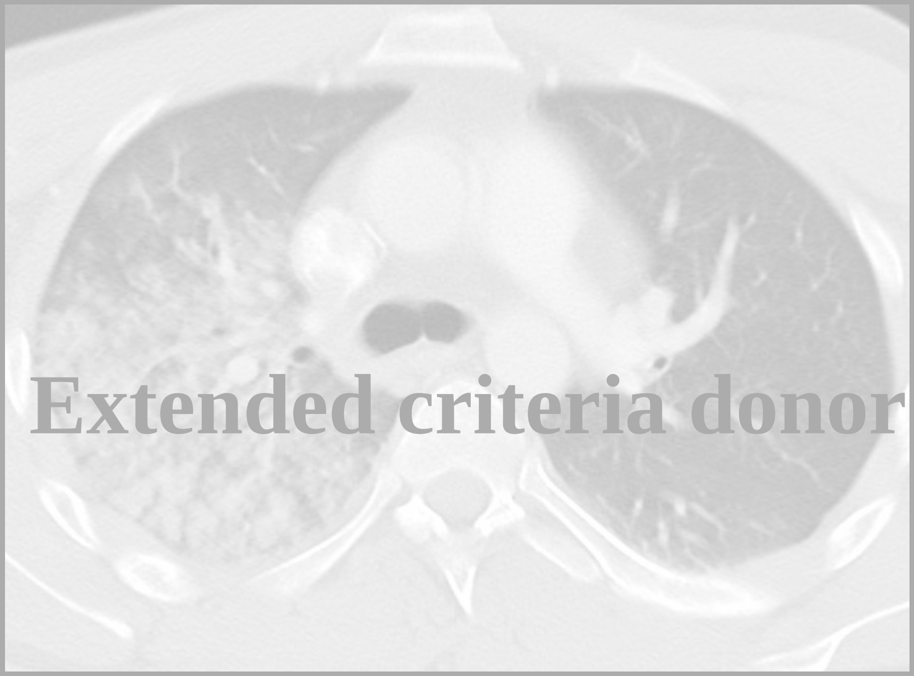
Extended criteria donor





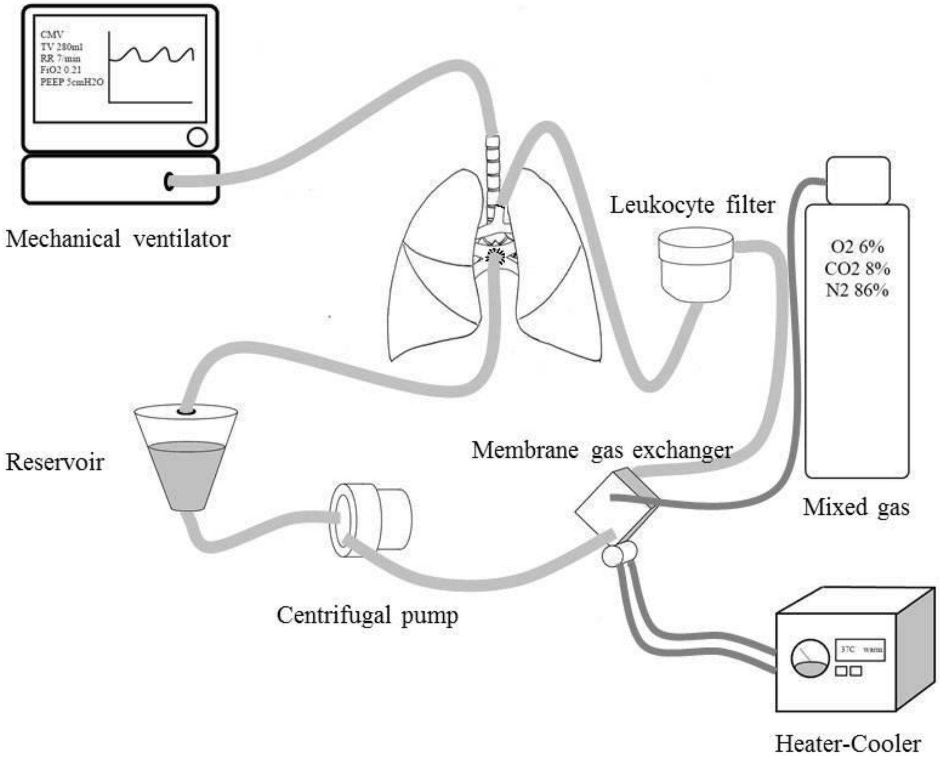
Donation after cardiac death (DCD) donors

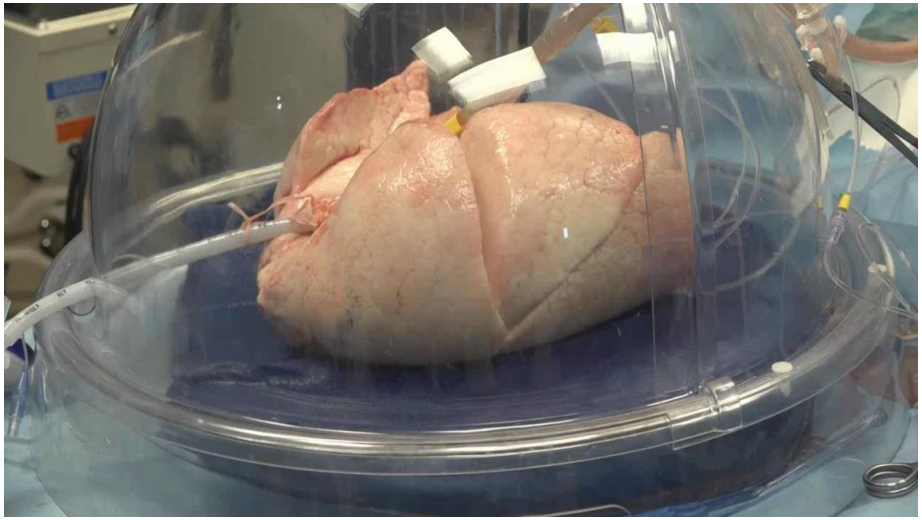
Ex Vivo Lung Perfusion



Extended criteria donor

Normothermic EVLP system





Cold static preservation

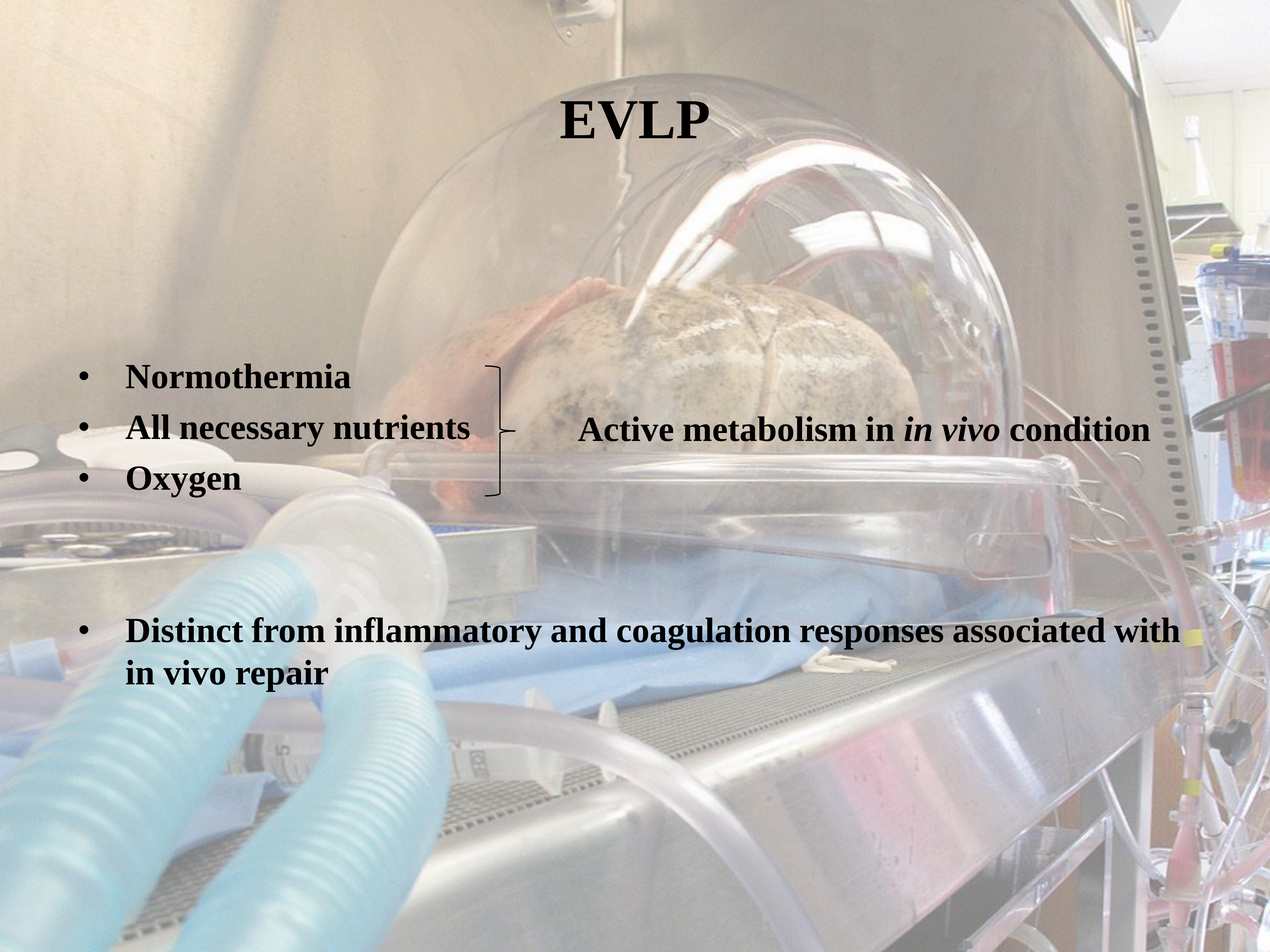
Preservation for extended periods (up to 12h)

Reduced cellular metabolism to about 5% in 4℃

No possibility of active metabolic processes and repair

Slowing down death

No recovery and regeneration



EVLP

- **Normothermia**
- **All necessary nutrients**
- **Oxygen**

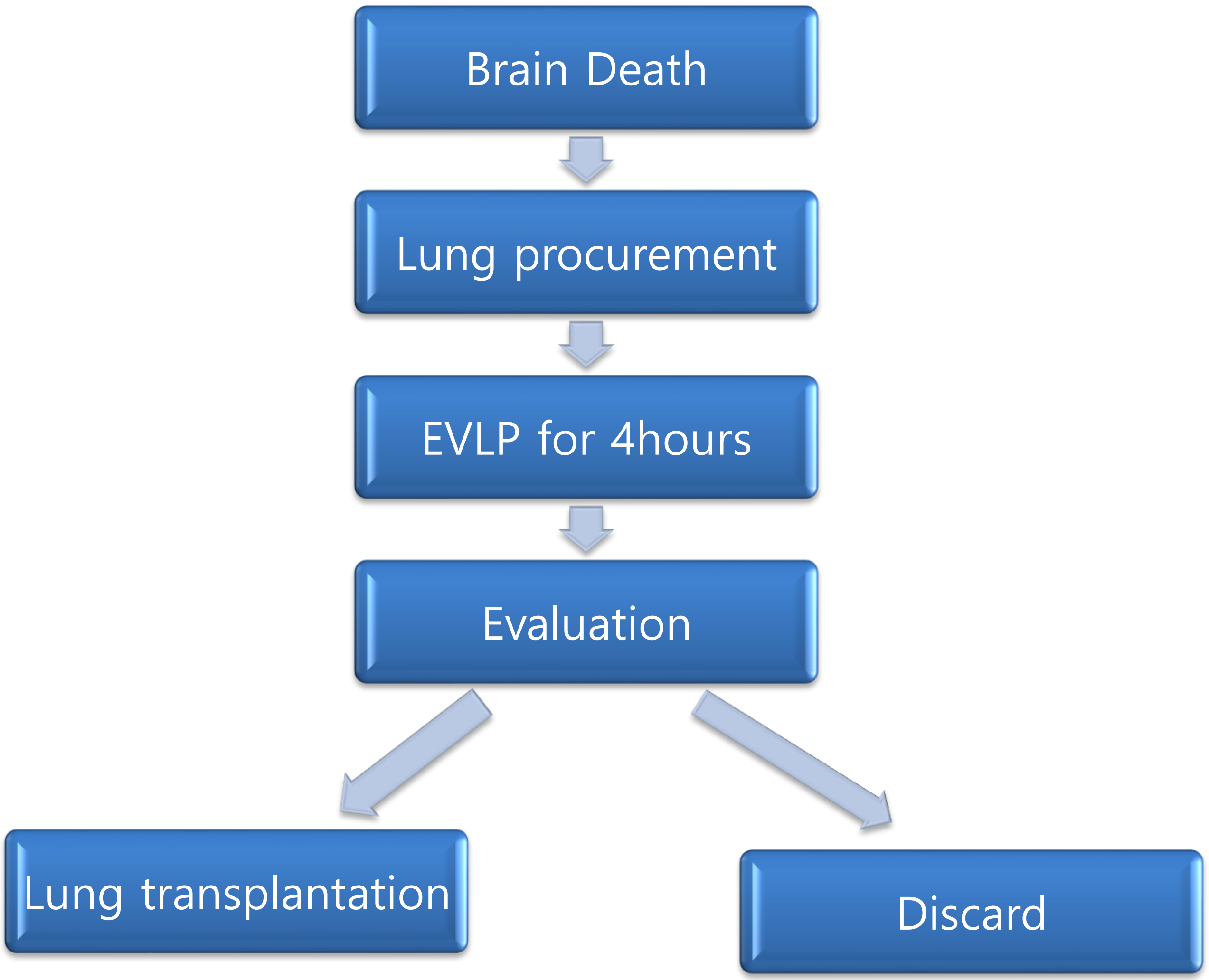
}→ **Active metabolism in *in vivo* condition**

- **Distinct from inflammatory and coagulation responses associated with in vivo repair**

Perfusate Solution

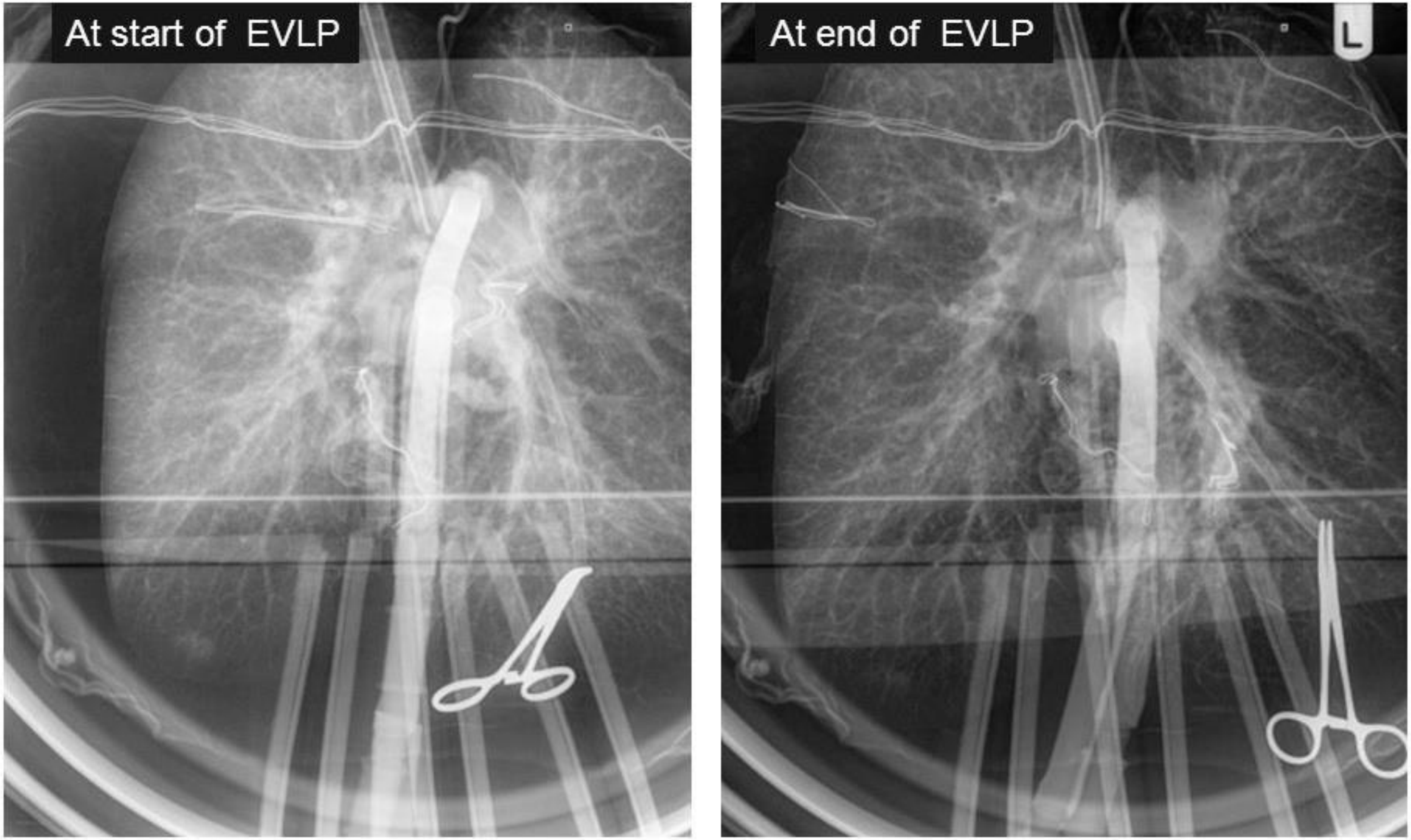
- Steen® (Vitrolife)
  - COMPOSITION
    - Dextran
      - Protection of endothelium from leukocyte interaction
    - Low potassium chloride
      - Reduction of free radical generation
      - Avoidance of vascular spasm
    - Human serum albumin: normal oncotic pressure
    - Glucose
    - $NaHCO_3$, $CaCl_2$, $MgCl_2$, $NaCl_2$
    - Water

EVLP protocol

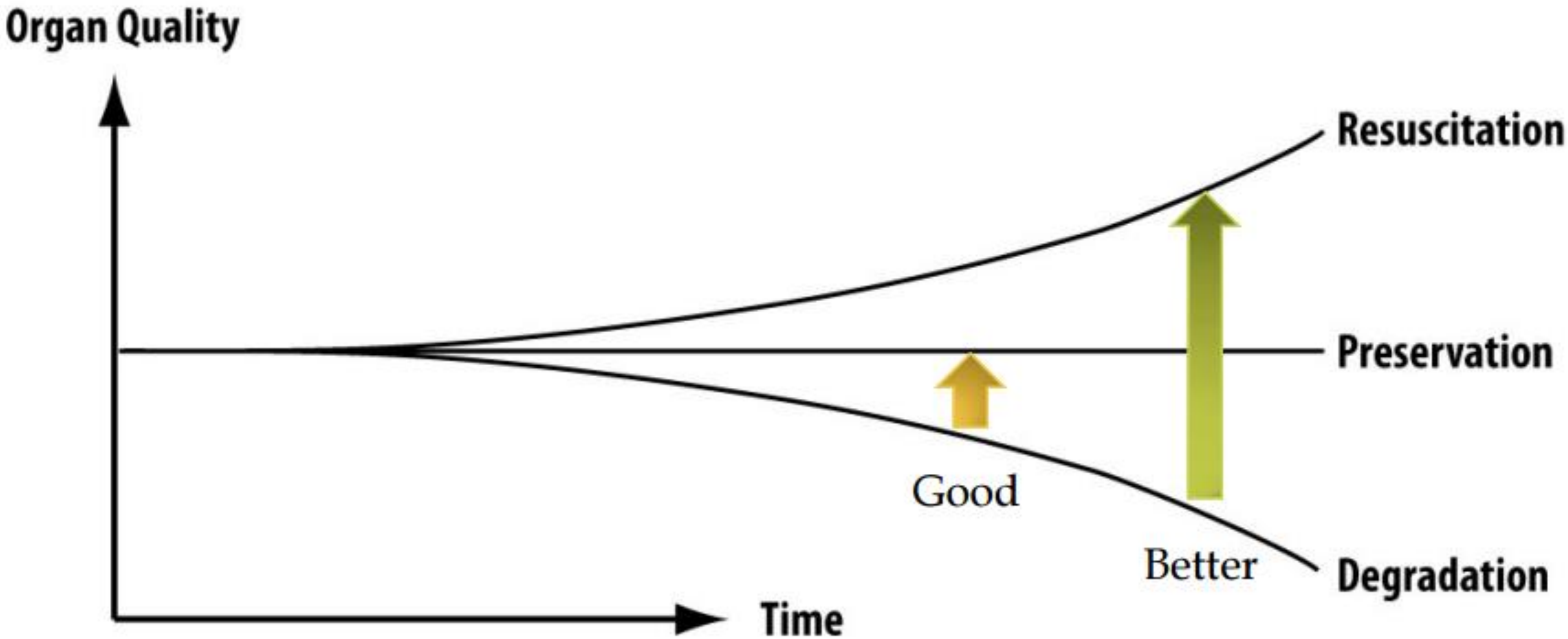


Advantages of EVLP

- Evaluation of the quality of grafts (e.g. DCD lung)
- Improvement of the organ function unsuitable for LTx
- Opportunity to reassess → confirm results of treatment


At start of EVLP
At end of EVLP
L

Improving outcomes in transplantation: Organ resuscitation and repair



Current clinical status of EVLP

- 2007
  - Steen
  - First LTx using EVLP
- 2011
  - Cypel and Lindstedt
  - EVLP in initially rejected lungs
- 2012
  - Aigner and Zych
  - Potential to improve the quality of donor lungs unsuitable for LTx
- 2013
  - Wallinder
  - Safety of EVLP and allowance of lungs rejected to be used in LTx

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.

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

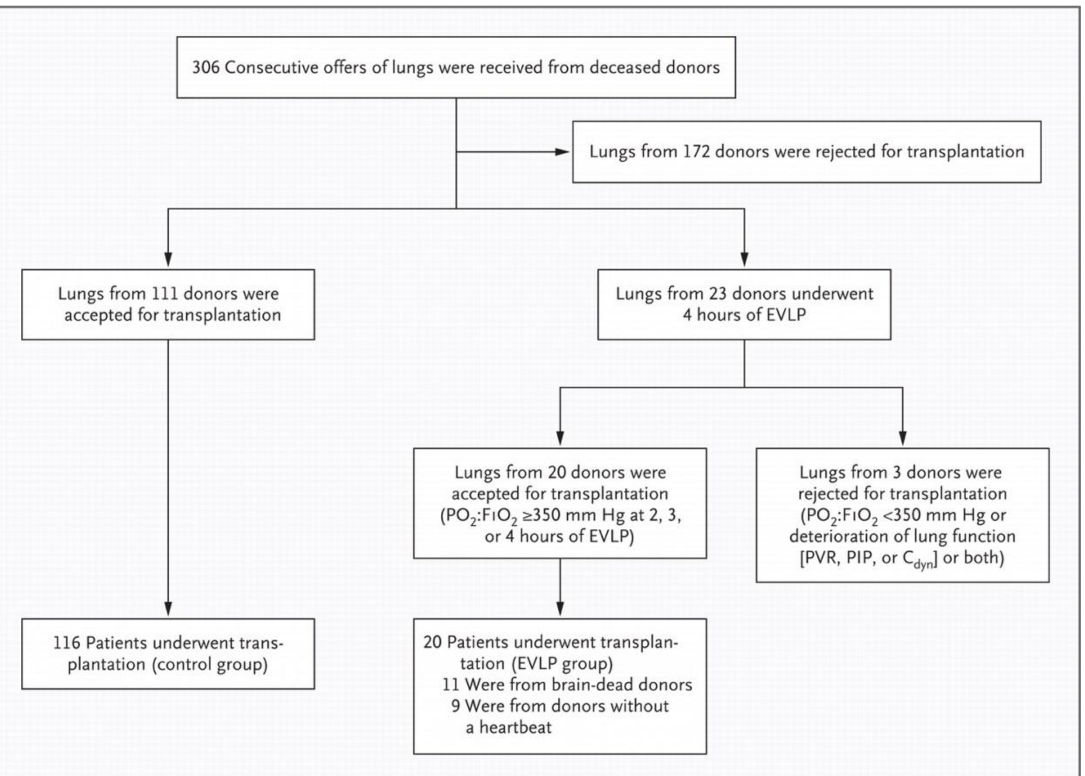


Table 2. Outcomes in the EVLP and Control Groups.*

End Point	EVLP Lungs (N=20): Donors without a Heartbeat (N=9)	EVLP Lungs (N=20): Brain-Dead Donors (N=11)	EVLP Lungs (N=20): Total (N=20)	Control Lungs (N=116)	Absolute Difference† *percentage points (95% CI)*	P Value‡
Primary end point§						
PGD grade 2 or 3 at 72 hr (%)	11	18	15	30	15 (−3 to 33)	0.11
Secondary end points§						
PGD grade 2 or 3 at ICU arrival (%)	33	18	25	30	5 (−15 to 26)	0.30
PGD grade 2 or 3 at 24 hr (%)	11	18	15	36	21 (3 to 39)	0.07
PGD grade 2 or 3 at 48 hr (%)	33	27	30	35	5 (−17 to 27)	0.46
ECMO (%)	0	0	0	4		0.37
PaO_2:FIO_2 on arrival in ICU (mm Hg)						0.51
Median	420	423	422	372		
Range	85–518	86–538	85–538	49–591		
Mechanical ventilation after transplantation (days)						0.15
Median	2	2	2	2		
Range	1–27	1–101	1–101	1–43		
ICU stay after transplantation (days)						0.68
Median	4	5	4	4		
Range	1–34	1–101	1–101	1–103		
Hospital stay after transplantation (days)						0.39
Median	19	34	23	27		
Range	7–54	11–101	7–101	9–156		
Airway complications (%)¶	11	0	5	4	−1 (−10 to 10)	1.0
Mortality at 30 days (%)	22	0	10	5	−5 (−19 to 9)	0.33

* ECMO denotes extracorporeal membrane oxygenation, ELVP ex vivo lung perfusion, ICU intensive care unit, and PGD primary graft dysfunction.

† The differences between all EVLP lungs and control lungs are shown in percentage points (with 95% confidence intervals [CI]) for each study end point.

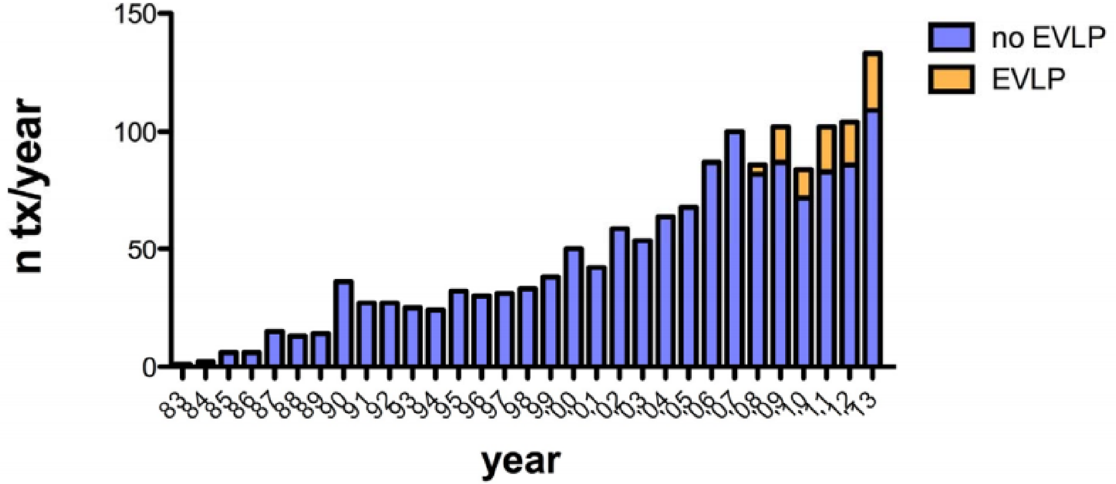
‡ P values were calculated with the use of Fisher's exact test for discrete variables and the Mann–Whitney test for continuous variables and are for the comparison between all EVLP lungs and control lungs.

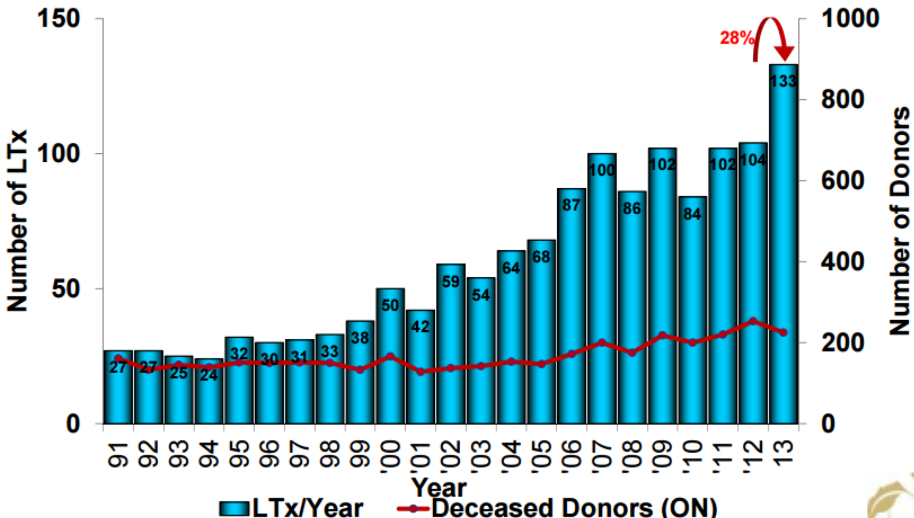
§ Primary graft dysfunction was defined as a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FIO_2) of less than 300 mm Hg, according to the International Society for Heart and Lung Transplantation classification.[25] Grade 0 indicates PaO_2:FIO_2 ≥300 mm Hg with clear chest radiographs, grade 1 PaO_2:FIO_2 ≥300 mm Hg with infiltration on chest radiographs, grade 2 PaO_2:FIO_2 ≥200 but <300 mm Hg, and grade 3 PaO_2:FIO_2 <200 mm Hg.

¶ Airway complications were defined as those requiring interventions, such as bronchial dilation.

EVLP Activity /Year

1983-2013





UHN Toronto Lung Transplant Program

Standard donor lung procurement with normothermic ex vivo lung perfusion: A prospective randomized clinical trial

J Heart Lung Transplant

Table 2 Comparison of Durations Between Both Groups

	EVLP group (n = 35)		Control group (n = 41)		p-values
	Median	Range	Median	Range	1 vs 2
Aortic cross clamp to EVLP (CIT1)	220	119–379			
Duration of EVLP	266	245–329			
End of EVLP to first reperfusion	133	80–238			
End of EVLP to second reperfusion (CIT2)	212	119–325			
Aortic clamp to first reperfusion	642	517–766	291	212–456	$<$**0.001**
Aortic clamp to second reperfusion	716	566–894	370	270–568	$<$**0.001**
Total CIT of the first side	372	235–499	291	212–456	$<$**0.001**
Total CIT of the second side	437	305–629	370	270–568	**0.001**
Duration of surgery[a]	277	172–541	275	184–390	0.69

CIT, cold ischemic time; EVLP, ex vivo lung perfusion.

All data are given in minutes.

Table 4 Oxygen Partial Pressure/Fraction of Inspired Oxygen Ratios and Primary Graft Dysfunction Grades

	EVLP group (n = 35)		Control group (n = 41)		
	Median	Range	Median	Range	p-values (Fisher)
T12 PaO_2, mm Hg	488	341–578	469	114–576	0.17
T12 PGD >1, n (%)	2 (5.7%)		8 (19.5%)		0.10
T24 PaO_2, mm Hg	516	280–557	491	352–575	0.63
T24 PGD >1, n (%)	2 (5.7%)		7 (17.1%)		0.17
T48 PaO_2, mm Hg	477	362–530	490	247–547	0.92
T48 PGD >1, n (%)	1 (2.9%)		4 (9.8%)		0.37
T72 PaO_2, mm Hg	403	341–558	451	295–590	0.96
T72PGD >1, n (%)	1 (2.9%)		1 (2.4%)		1.00

Technical considerations

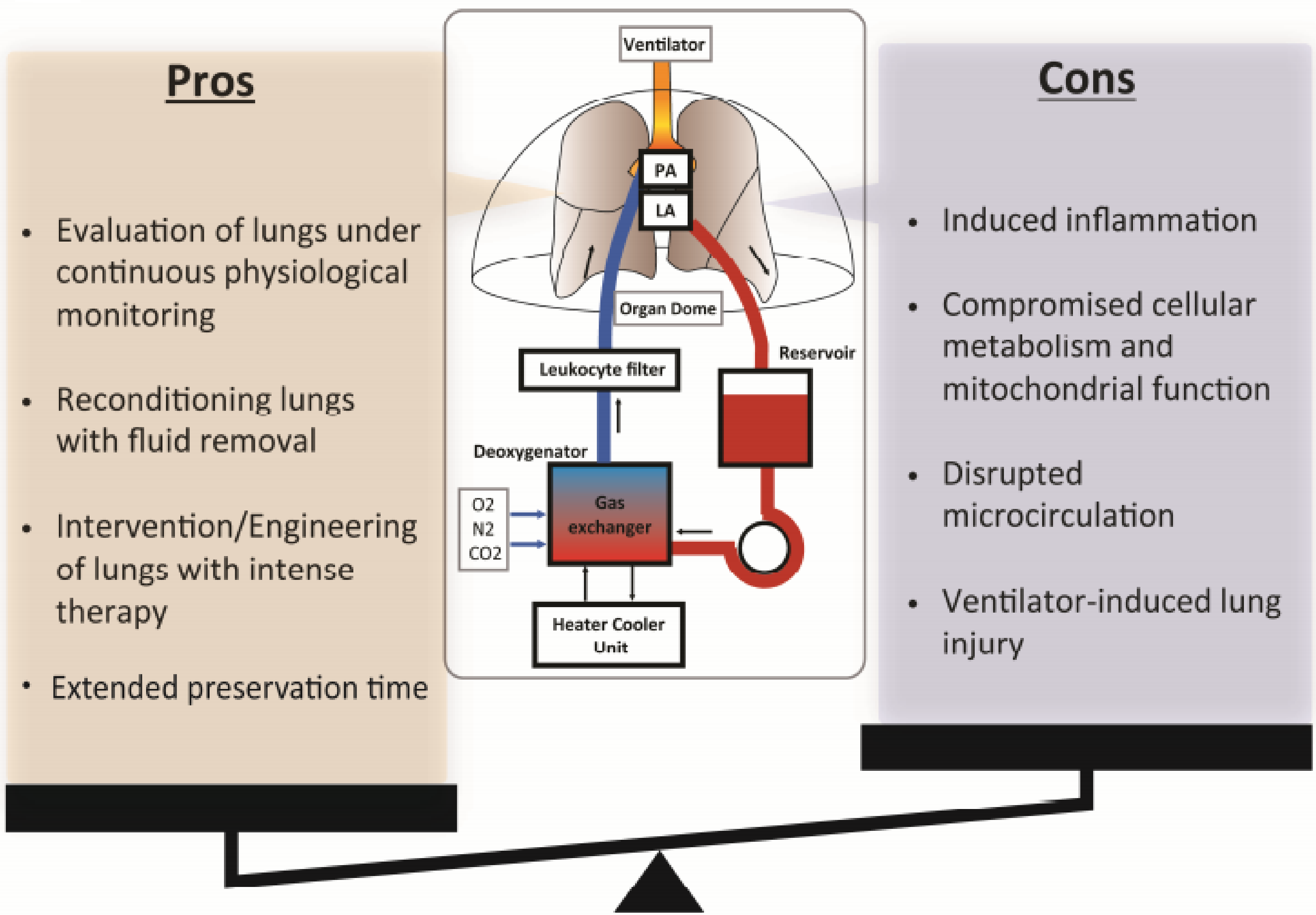
	Protocol		
Parameter	Toronto	Lund	OCS™[a]
Perfusion			
Target flow (leadtime)	40% CO (1 h)	100% CO (1 h)	2.0–2.5 L/min (15–30′)
Start flow	10% of the target flow	100 mL/min	200 mL/min
Flow characteristic	Continuous	Continuous	Pulsatile
PAP	Flow dictated ≤ 15 mmHg	≤ 20 mmHg	≤ 20 mmHg
LA	Closed	Open	Open
LA pressure	3–5 mmHg	0 mmHg	0 mmHg
Perfusate	Steen™ solution	Steen™ solution + RBC's hct 14%	OCS™ solution + RBC's hct 15–25%
Ventilation			
Start temperature	32°C	32°C	34°C
TV	7 mL/kg donor bw	5–7 mL/kg donor bw	6 mL/kg donor bw
RR	7 bpm	20 bpm	10 bpm
PEEP	5 cmH_2O	5 cmH_2O	5–7 cmH_2O
FiO_2	21 %	50 %	21 %
Timing of EVLP			
Beginning of EVLP	Static device: recipient site or specialized EVLP centers	Static device: recipient site	Mobile device: donor site
Perfusion time	4–6 h; until 12 h	2 h	Duration of transport

PAP, pulmonary artery pressure; LA, left atrium; CO, cardiac outpout; RBC's, red blood cells; TV, tidal volume; RR, respiratory ratio; bpm, breaths per minute; PEEP, positive end-expiratory pressure; FiO_2, inspired fraction of oxygen; bw, ideal body weight.

[a]OCS, Organ Care System™ (Transmedics).

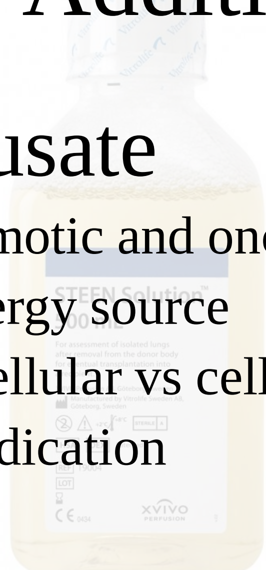
Commercialized Devices

OCS

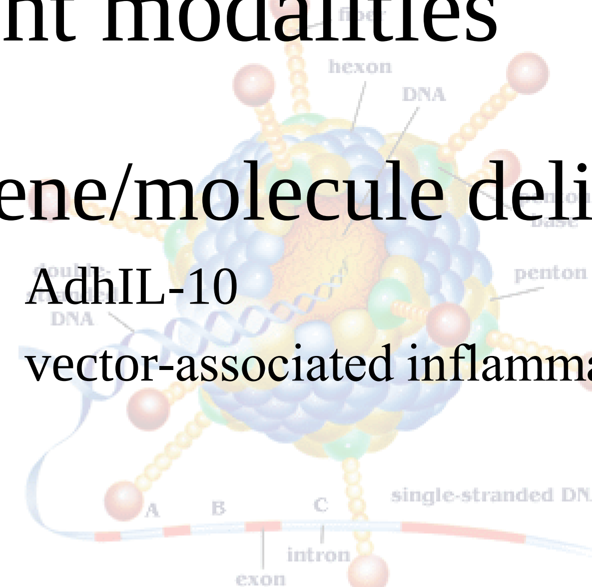


Pros
Evaluation of lungs under continuous physiological monitoring
Reconditioning lungs with fluid removal
Intervention/Engineering of lungs with intense therapy
Extended preservation time
Ventilator
PA
LA
Organ Dome
Reservoir
Leukocyte filter
Deoxygenator
O2
N2
CO2
Gas exchanger
Heater Cooler Unit
Cons
Induced inflammation
Compromised cellular metabolism and mitochondrial function
Disrupted microcirculation
Ventilator-induced lung injury

Additional treatment modalities



- Perfusate
  - Osmotic and oncotic pressure
  - Energy source
  - Acellular vs cellular
  - Medication



- Gene/molecule delivery
  - AdhIL-10
  - vector-associated inflammation↓

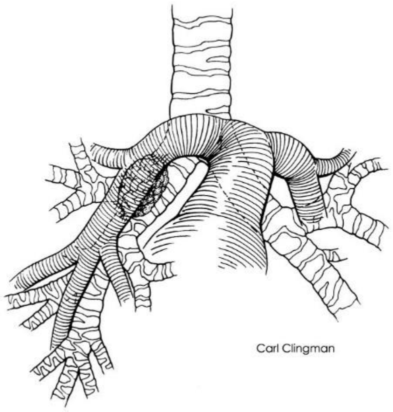
- Trans-tracheal and aerosolized agent delivery
  - Delivery of biodegradable nanoparticle containing drugs
  - Medical gas

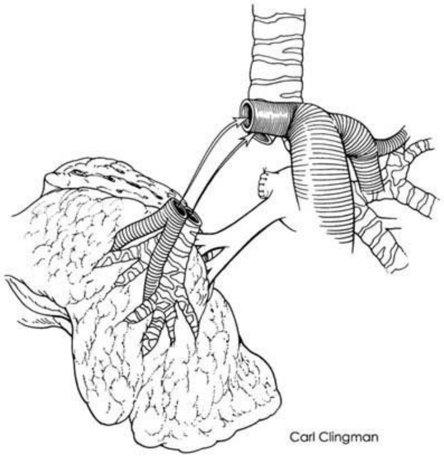
EVLP in specific injured donor lungs

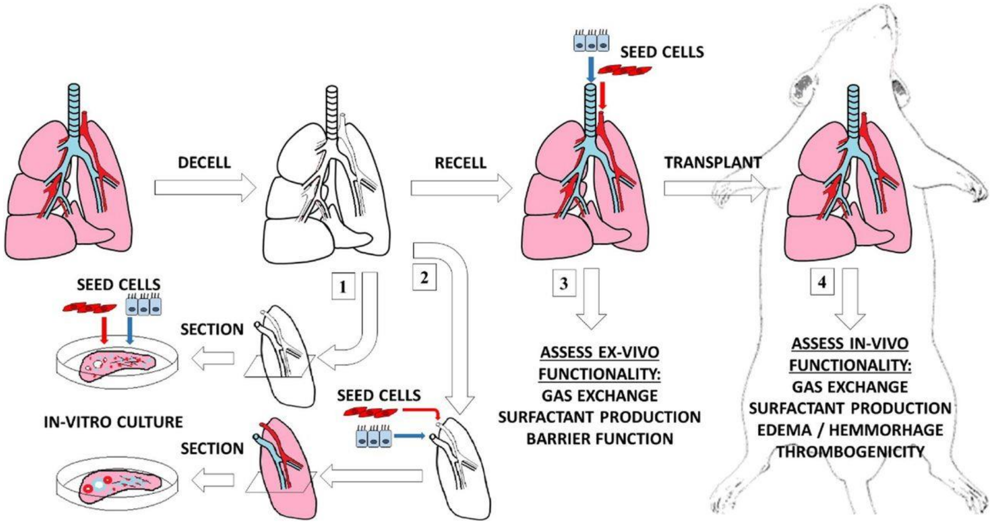
- Edema
  - Basal alveolar fluid clearance: 19±10% per hr during EVLP
  - Franck: Airway instillation of terbutaline→ 43±13% per hr
  - Gattinoni: Infusion of salbutamol →PAP↓, compliance↑
- Inflammation
  - Cypel: Intra-airway AdhIL-10
  - Matthay: Instillation of MSC
- Infection
  - Toronto group: High-dose antibiotics
  - Instillation of MSC →bacterial killing mechanism↑(via keratinocyte growth factor)
- Gastric aspiration
  - Zurich group: Positive effect of lavage with surfactant
  - Leuven group: Pre-emptive treatment with steroid
- Pulmonary embolism
  - Inci: Urokinase in DCD →PVR↓, oxygen capacity↑, edema↓
  - Toroto group: Clinical EVLP using alteplase

Useful tool for translational research

- **In medical oncology**

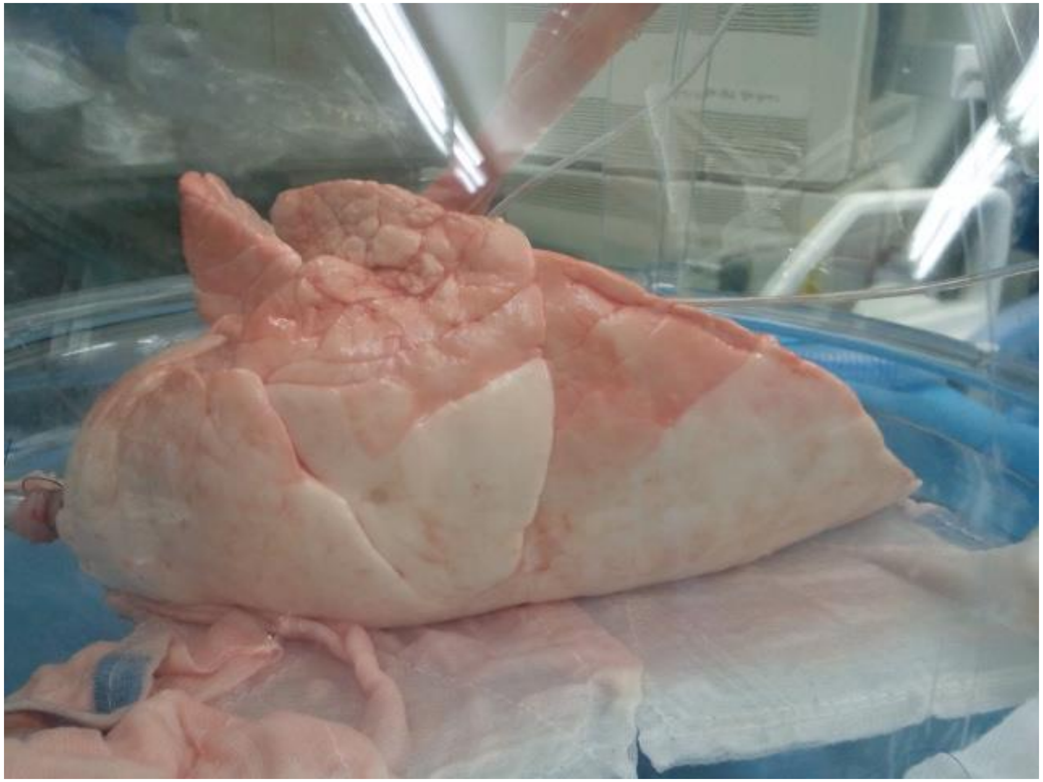


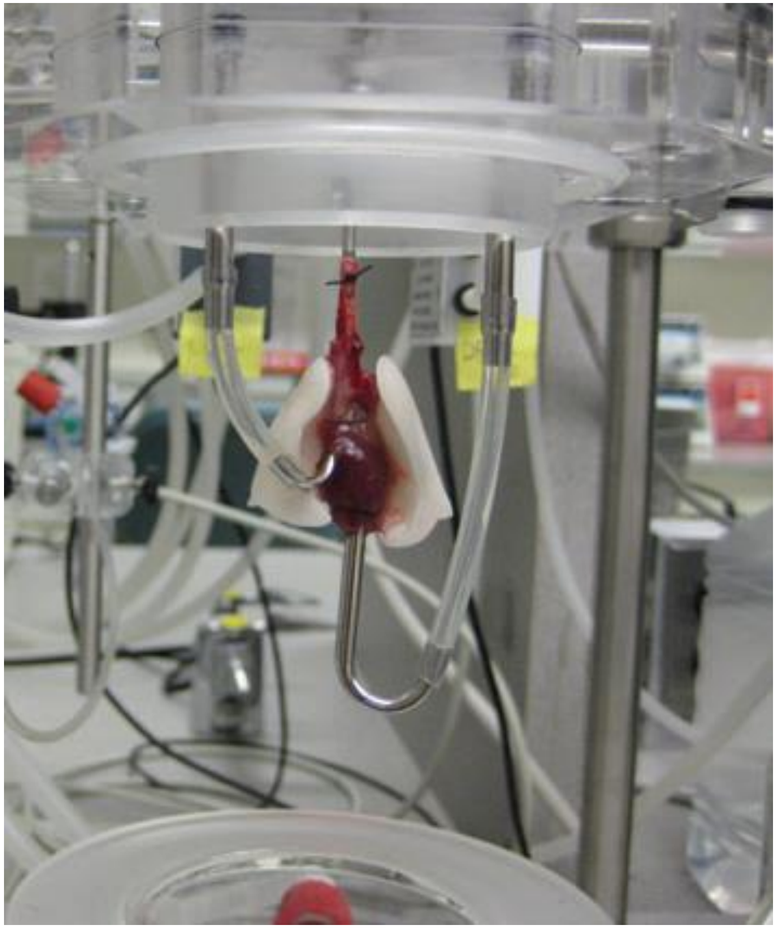




- **In thoracic surgery**
- **In lung bio-engineering**

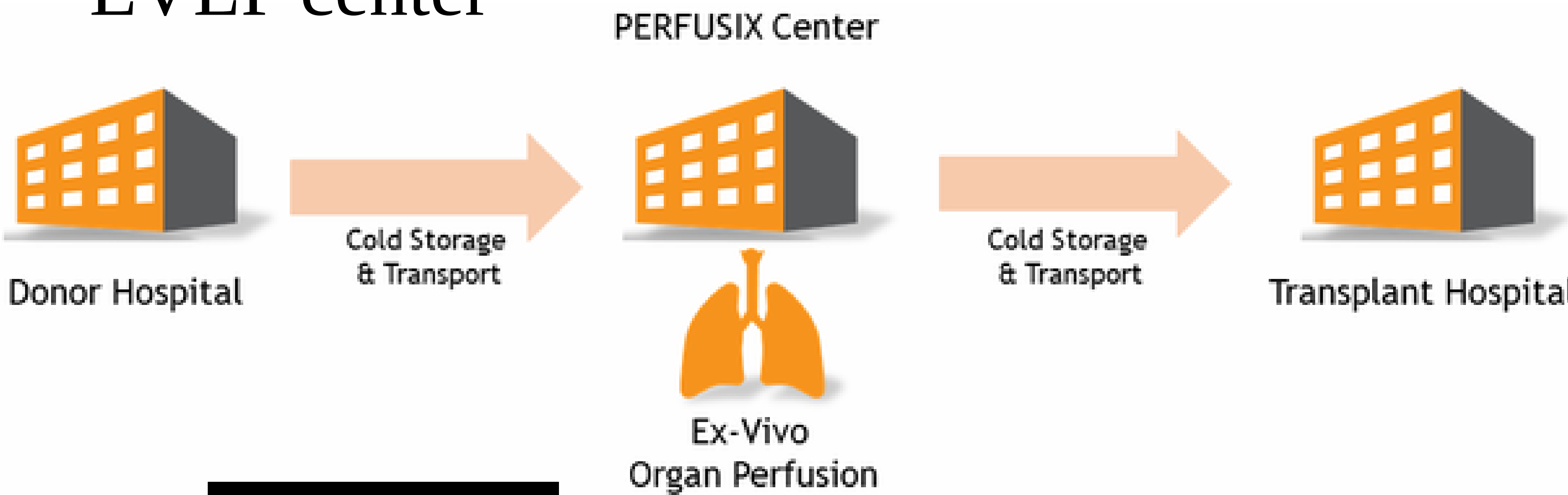
EVLP in animal model

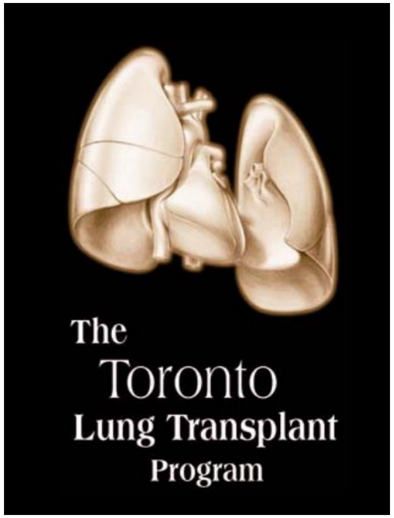




The future of EVLP

- EVLP center





Conclusions

- EVLP
  - Useful tool for lung evaluation and reconditioning
  - Reconditioning of extended criteria and DCD donor lungs
  - Application to translational research

감사합니다.