7° FORUM ITALIANO SULLA FIBROSI CISTICA

MOTESILVANO (PE), 22-24 NOVEMBER 2019

ANALISI DELLE PROCEDURE E CRITICITÀ DEL PROCESSO DI DONAZIONE-PRELIEVO-TRAPIANTO

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University Hospital Policlinico of Milan

Lung transplant program

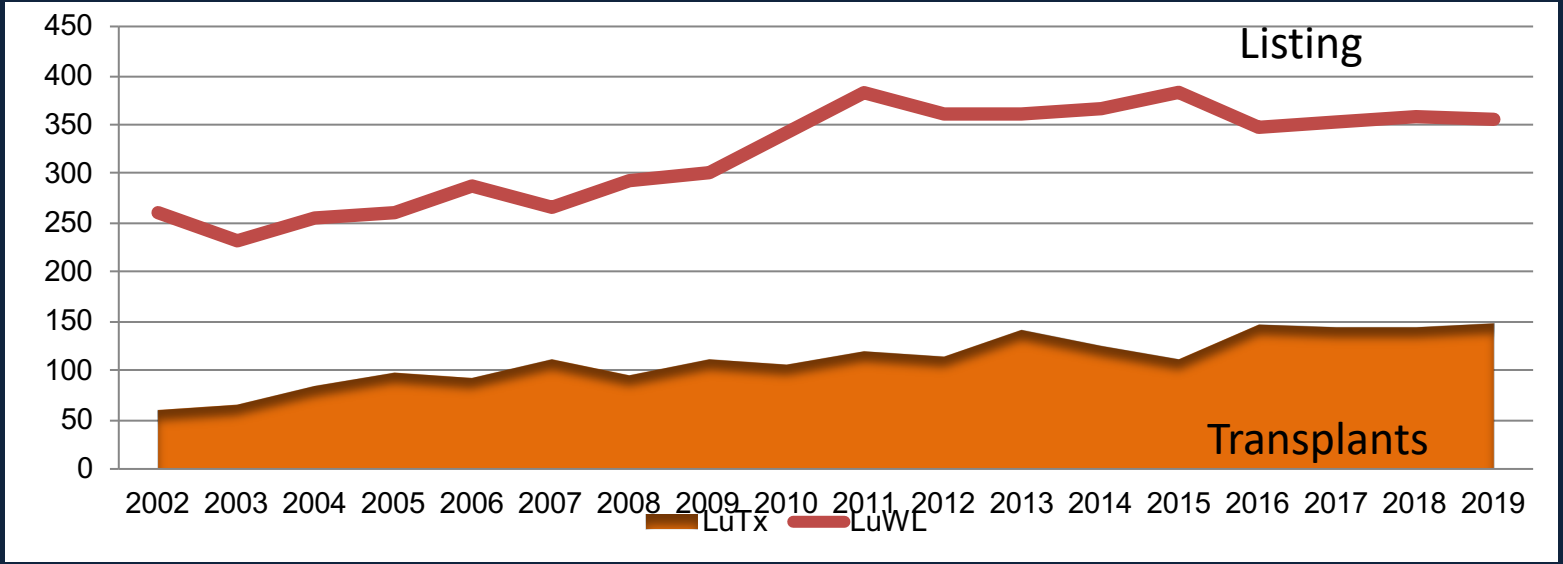
Success=

- *No waiting list mortality*
- *Optimal outcome in terms of quality of life and survival (graft and recipient)*

→ Role of thoracic surgeon

LUNG TRANSPLANT
Shortage of lung donors

*Exponential increase in the number of patients on waiting list, **without** a proportional amount of increase in the number of lung donors.*



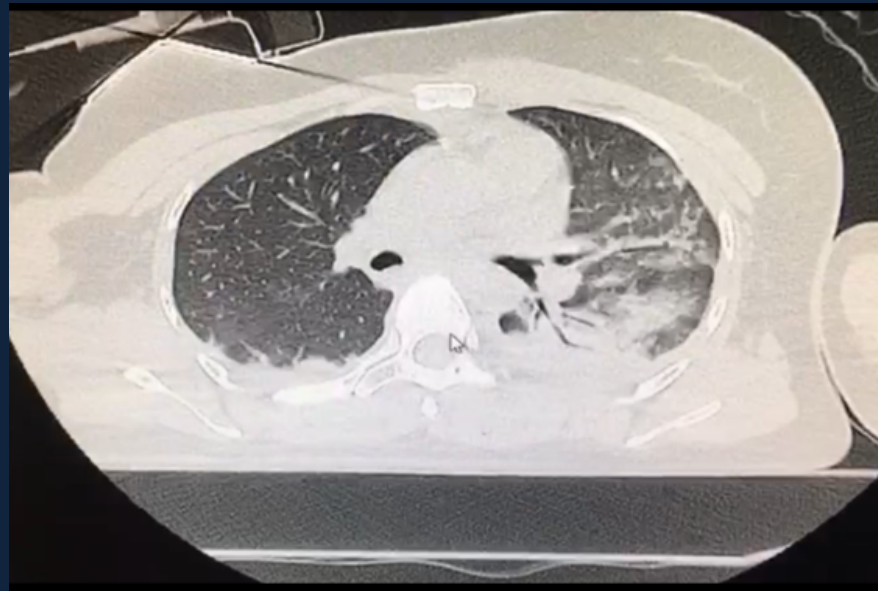
Transplant National Center

Donor pool strategies

- *Legislative system*
- *Public opinion*
- *Donor management*
- *Living donor*
- *Expanded criteria donor*
  - *MP*
  - *DCD*

Donor pool strategies

- Legislative system
- Public opinion
- Donor management (ICU)
- Living donor
- Expanded criteria donor
  - MP [EVLP]
  - DCD



Donor pool strategies

- Legislative system
- Public opinion
- Donor management

- Living donor – Lobar transplant
- Expanded criteria donor
  - MP
  - DCD

ELSEVIER CrossMark

Lobar Lung Transplantation From Deceased Donor: Monocentric Experience

P. Mendogni[a,*], A. Palleschi[a], D. Tosi[a], I. Righi[a], M. Montoli[a], F. Damarco[a], L.C. Morlacchi[b,c], L. Santambrogio[a,c], M. Nosotti[a,c], and L. Rosso[a]

Lobar Tx after right lower lobectomy

Back table

Inferior vein preparation

Fissure: lobectomy

- *2010-2019: 14 lobar transplants*
- *Lobar Tx versus Tx: same 3-yr survival*

Donor pool strategies

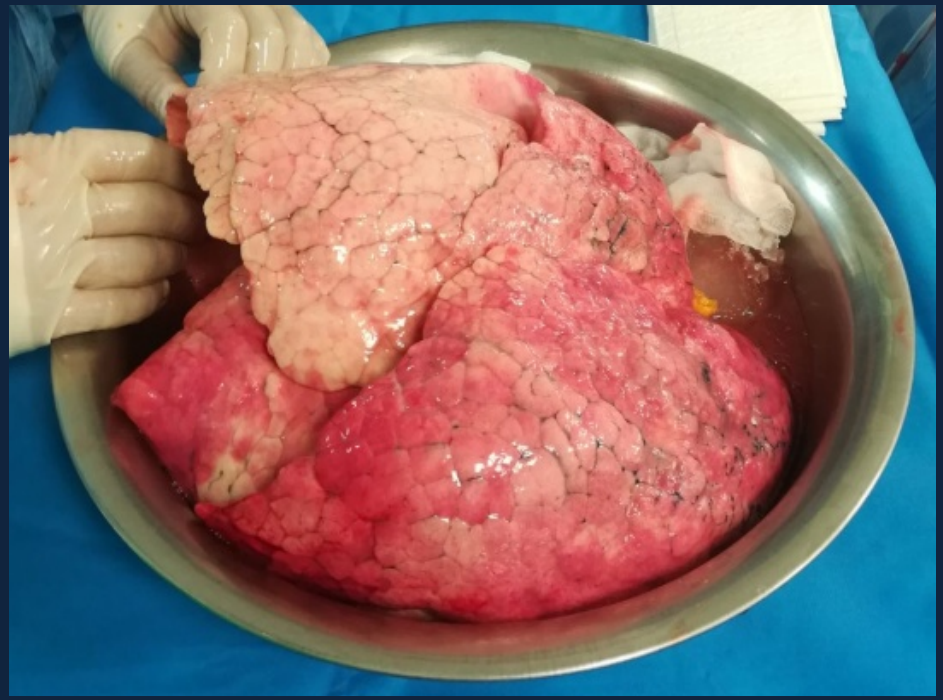
- Legislative system
- Public opinion
- Donor management
- Living donor
- Expanded criteria donor
  - MP
  - DCD

Indicator	"Ideal" Donor	"Standard" Criteria	Marginal Donor Progression	"Unusable" Donor
Age (years)	20 – 45	<55	60	65
PO_2/FiO_2	>350	>300	Donor Optimisation; Pulm. Vein Gas	200
Smoking History	Never	<20 p.y.	Cumulative; Current	? Upper limit
Chest x-ray	Clear	Clear	Neurogenic Pulm Edema; Donor Optimisation	Persistent Collapse; Dense Consolidation
Microbiology	Culture Negative	Gram-stain Negative	Antibiotics; ?HIV+	Pan-resistant Organism; Mycobaterial Disease
Bronchoscopy appearance	Clear	Non-Purulent	Purulent; Inflammation; Aspiration	Visualised Tumour

Donor pool strategies

- Legislative system
- Public opinion
- Donor management

- Living donor
- Expanded criteria donor
  - MP
  - DCD



First Human Transplantation of a Nonacceptable Donor Lung After Reconditioning Ex Vivo

Stig Steen, MD, PhD, Richard Ingemansson, MD, PhD, Leif Eriksson, MD, PhD, Leif Pierre, CPP, Lars Algotsson, MD, PhD, Per Wierup, MD, PhD, Qiuming Liao, MD, Atli Eyjolfsson, MD, Ronny Gustafsson, MD, PhD, and Trygve Sjöberg, PhD

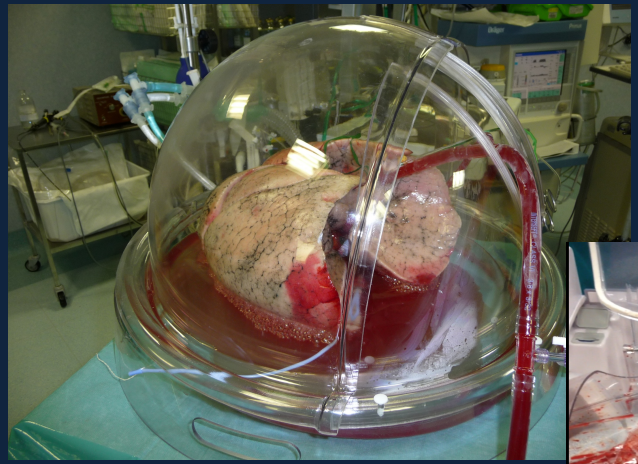
*…Rejected donor lungs may be successfully transplanted after being **reconditioned** ex vivo.*

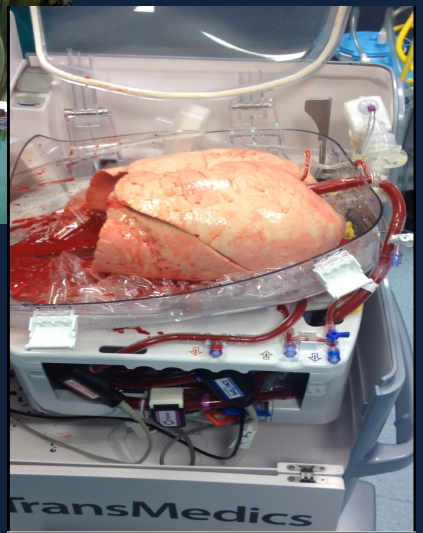
(Ann Thorac Surg 2007;83:2191–5)

Donor pool strategies

- Legislative system
- Public opinion
- Donor management

- Living donor
- Expanded criteria donor
  - MP= EVLP/OCS
  - DCD





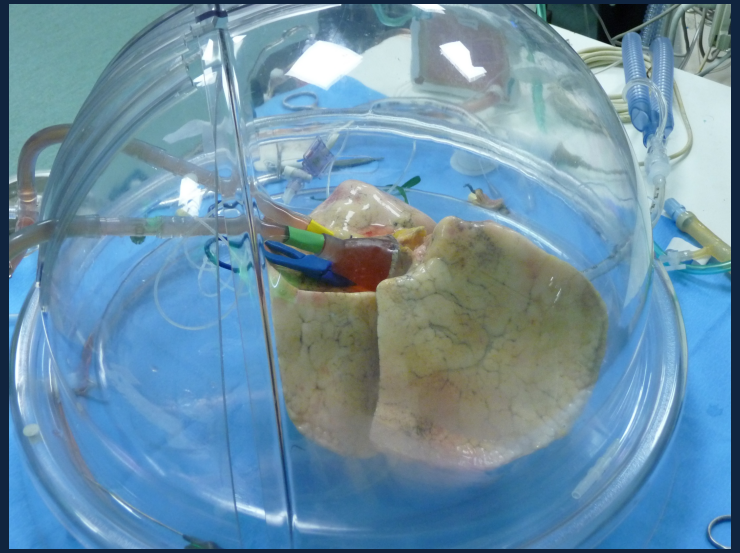
Ex-Vivo Lung Perfusion (EVLP)

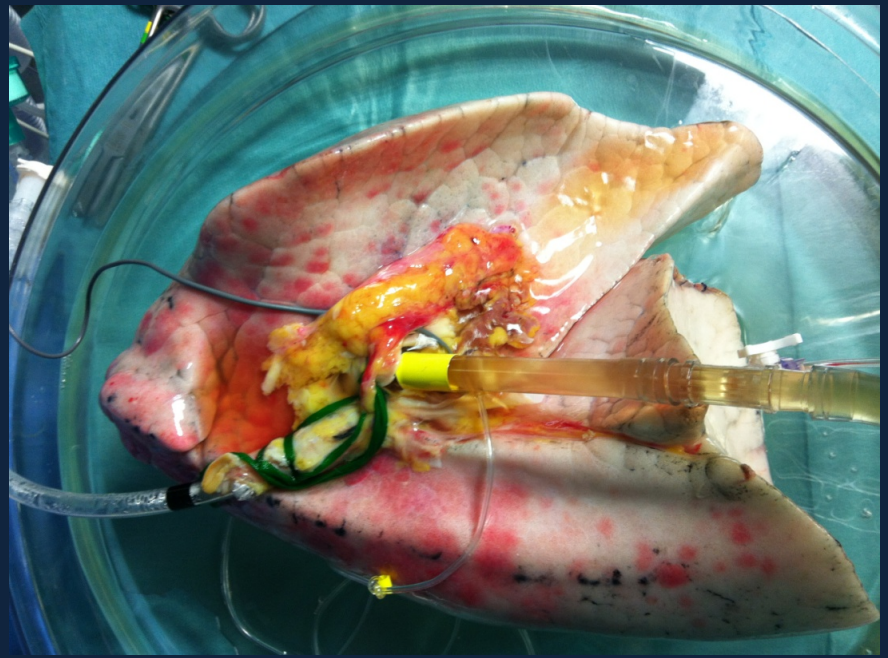
Questionable organs: better evaluation
Injured organs: treatment and repair
Time expansion

Organ preservation needs to occur at normothermic (or near-) conditions

Our experience

- *Experimental phase (2008)*





…We have set a standardized, reproducible pig model resembling the entire process of organ donation that may be used as a platform to test in vivo and ex vivo strategies of donor lung optimization before transplantation…

Valenza et al. Intensive Care Medicine Experimental 2014, 2:12
http://www.icm-experimental.com/content/2/1/12

RESEARCH Open Access

A standardized model of brain death, donor treatment, and lung transplantation for studies on organ preservation and reconditioning

Franco Valenza[1,2*], Silvia Coppola[1], Sara Froio[1], Giulia Maria Ruggeri[2], Jacopo Fumagalli[2], Alessandro Maria Villa[2], Lorenzo Rosso[3], Paolo Mendogni[3], Grazia Conte[4], Caterina Lonati[2], Andrea Carlin[2], Patrizia Leonardi[2], Stefano Gatti[5,6,8], Nino Stocchetti[1,2] and Luciano Gattinoni[1,2]

…We found that the worse the lung function, the greater the consumption of glucose during EVLP. This observation suggests the need to explore lung metabolism during EVLP to possibly obtain metrics for evaluation…

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Transplantation Proceedings, 43, 993–996 (2011)

The Consumption of Glucose During Ex Vivo Lung Perfusion Correlates With Lung Edema

F. Valenza, L. Rosso, M. Pizzocri, V. Salice, M. Umbrello, G. Conte, A. Stanzi, J. Colombo, S. Gatti, L. Santambrogio, G. Iapichino, and L. Gattinoni

…Glucose concentration in the perfusate was affected by salbutamol. Salbutamol was associated with lower pulmonary pressures and better lung mechanics. These data suggest a possible role for salbutamol as a pharmacologic adjunct during EVLP before transplantation…

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The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL PRE-CLINICAL SCIENCE

β-Adrenergic agonist infusion during extracorporeal lung perfusion: Effects on glucose concentration in the perfusion fluid and on lung function

Franco Valenza, MD,[a,b] Lorenzo Rosso, MD,[c] Silvia Coppola, MD,[a] Sara Froio, MD,[a] Jacopo Colombo, MD,[a] Roberto Dossi,[a] Jacopo Fumagalli,[a] Valentina Salice, MD,[a] Marta Pizzocri, MD,[a] Grazia Conte, MD,[d] Stefano Gatti, MD,[e] Luigi Santambrogio, MD, FRCP,[c,b] and Luciano Gattinoni, MD, FRCP[a,b]

Our experience

- *Experimental phase (2008)*
- *Clinical phase*
  - *March, 2011 first case*

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Ex vivo lung perfusion to improve donor lung function and increase the number of organs available for transplantation

Franco Valenza,[1,2] Lorenzo Rosso,[3] Silvia Coppola,[1] Sara Froio,[1] Alessandro Palleschi,[3] Davide Tosi,[3] Paolo Mendogni,[3] Valentina Salice,[1] Giulia M. Ruggeri,[1] Jacopo Fumagalli,[1] Alessandro Villa,[1] Mario Nosotti,[2,3] Luigi Santambrogio[2,3] and Luciano Gattinoni[1,2]

EX VIVO LUNG PERFUSION (EVLP)
Our experience: clinical phase

1st CASE

- M – 24 yrs
- Medical history
  - CF (Pseudomonas)
  - 2000 left pleurodesis
  - 2011 put on waiting list for Tx

EX VIVO LUNG PERFUSION (EVLP)
Our experience: clinical phase

03/2011 Exacerbation of infection

↓

Hypoxic-hypercapnic respiratory failure

↓

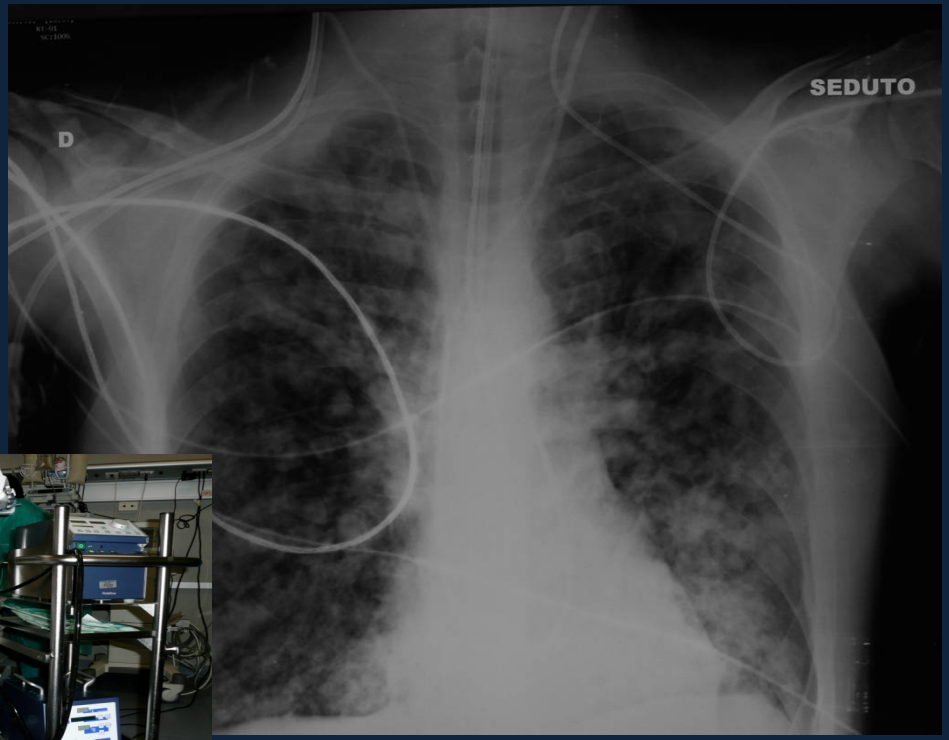
Admission in ICU and non-invasive ventilation

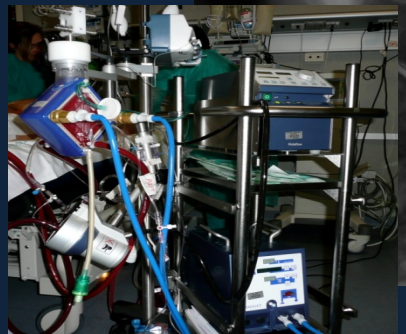
↓

Awake ECMO

↓

Urgent lung transplant list

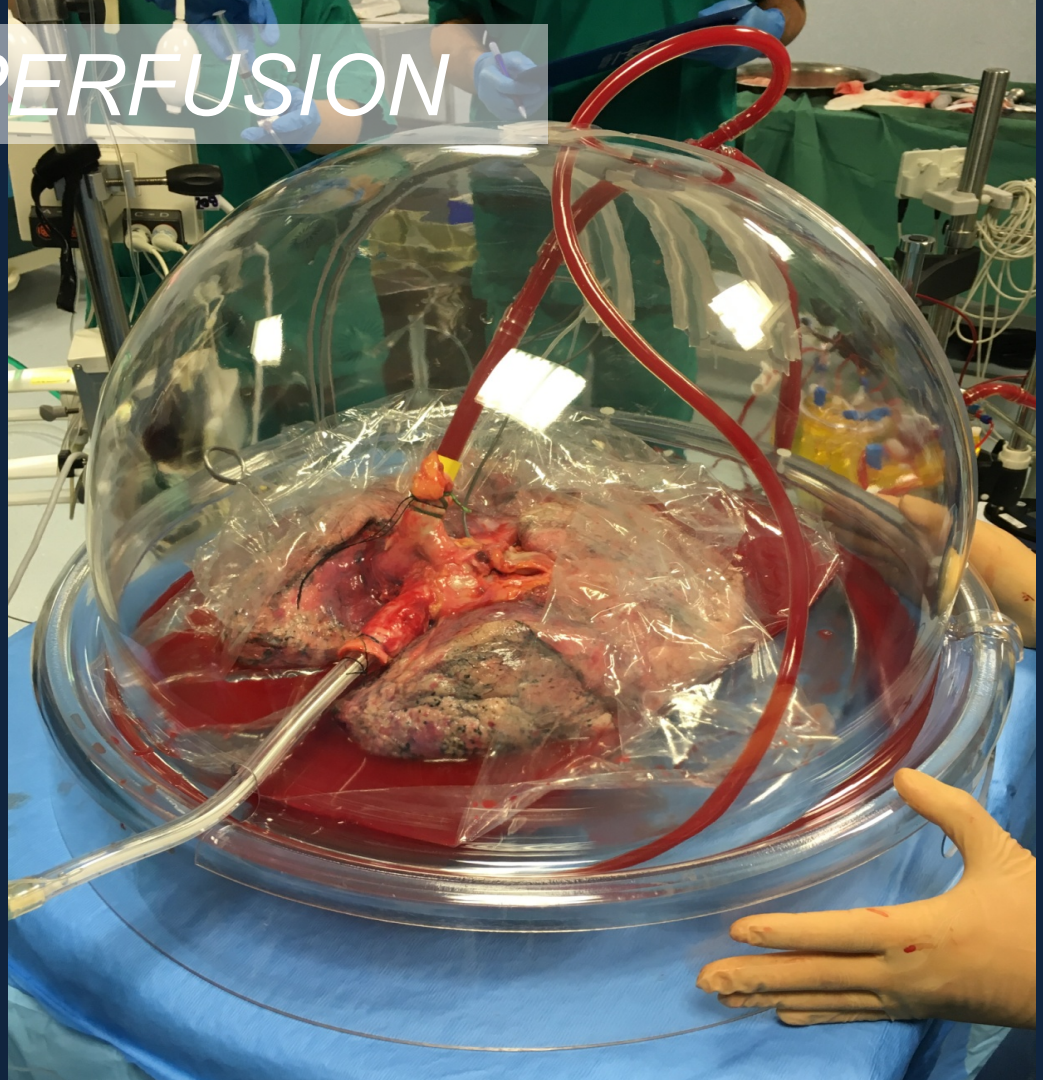




EX VIVO LUNG PERFUSION (EVLP)

Marginal potential donor alert after 12 ECMO days

START PERFUSION



RECRUITMENT

[redacted]

EX VIVO LUNG PERFUSION (EVLP)

BLTx on vv-ECMO (1st in the world)

14 marzo 2011

Avanguardia Rivitalizzati organi già scartati da altri ospedali

Trapianto di polmoni «riciclati» Policlinico, intervento di 16 ore

Poche parole, sussurrate da un letto di rianimazione, a 24 anni, che rendono l'idea di un'impresa mai realizzata in Italia: «Sono vivo grazie ai polmoni che nessuno voleva».

Le pronuncia Marco, impiegato di Milano, nato con la fibrosi cistica, da settimane ricoverato per gravi problemi respiratori e il 7 marzo finito

una tecnica imparata a Toronto dal ricercatore Franco Valenza, 46 anni, mai applicata in Italia — e poi di trapiantarli.

L'intervento complessivamente dura 16 ore: sono le 3 di notte del 15 marzo quando scatta la disponibilità dei due polmoni, Marco esce dalla sala operatoria alle 7 di sera. Da

negli anni Settanta inventa l'Ecmo — adesso si apre una nuova frontiera per il trapianto di polmoni. «Sfortunatamente oggi la necessità di organi supera di gran lunga la loro disponibilità. Così molti pazienti muoiono in attesa del trapianto — spiega Franco Valenza —. L'obiettivo è rinvigorire i polmoni compromessi

16 hours after CC

EX VIVO LUNG PERFUSION (EVLP)
Post-operative course

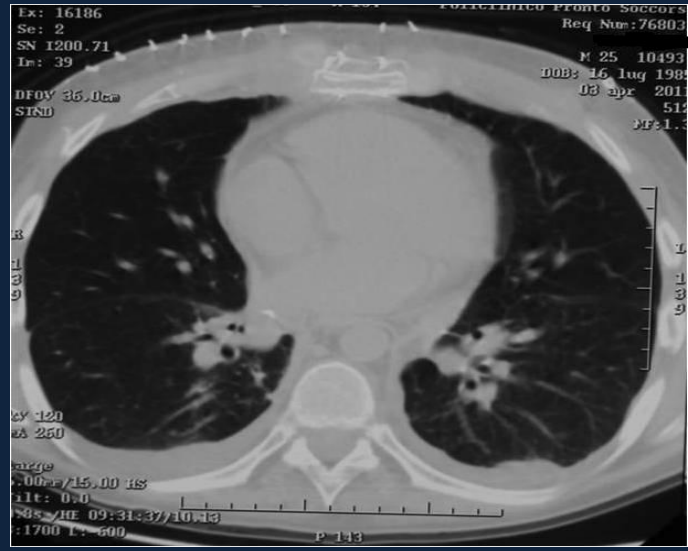
- *Immediate functional recovery of transplanted organs*
- *Extubation after 12 hrs*
- *Patient removed from ECMO after 24 hrs from lung transplant*
- *Discharge (18 days after Tx)*

PFR:

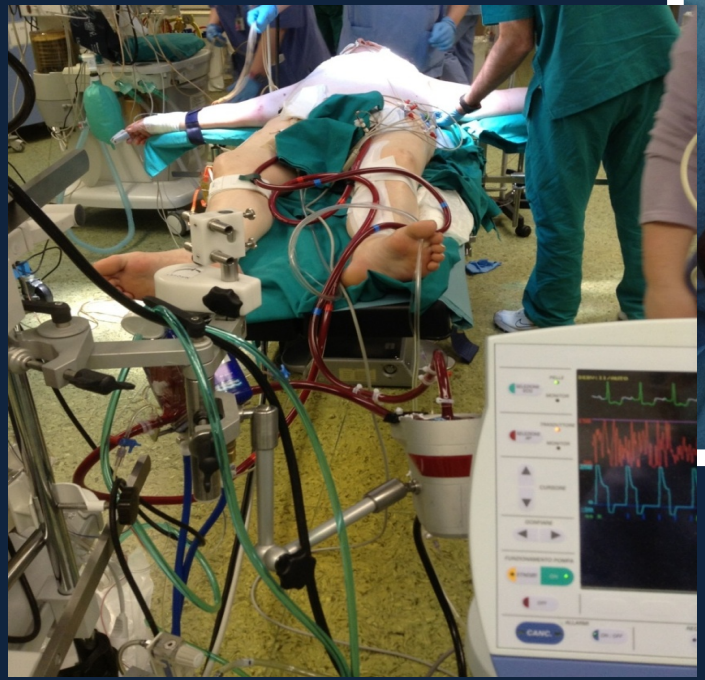
- *FVC 3,01 l (53%)*
- *FEV_1 2,90 l (61%)*

EGA in aa:

- *pO_2 76 mmHg*
- *pCO_2 43 mmHg*
- *pH 7,46*
- *sO_2 97,3%*

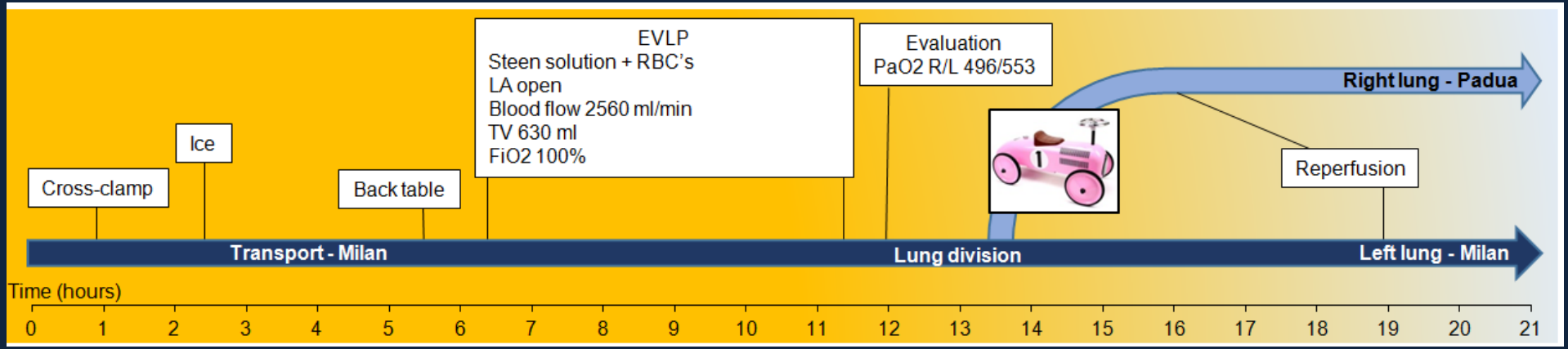


EVLP: ECMO donor



1/2013: lung proposal from donor on VA-ECMO after myocardial infarction and by-pass

EVLP: hub repair centre



EVLP: graft downsizing

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Graft Downsizing During Ex Vivo Lung Perfusion: Case Report and Technical Notes

M. Nosotti[a], L. Rosso[a], P. Mendogni[a,*], D. Tosi[a], A. Palleschi[a], I. Righi[a], S. Froio[b], F. Valenza[b], and L. Santambrogio[a]

Donor pool strategies

- *Legislative system*
- *Public opinion*
- *Donor management*

- *Living donor*
- *Expanded criteria donor*
  - *MP*
  - *DCD*

Why DCD?
Brain Death

Instability:

- *Loss of vasomotor control / perfusion deficit*
- *Loss of thermoregulation*
- *Hormonal imbalance (diabetes insipidus, hypothyroidism, cytokine cascade)*

→ *Neurogenic polmonary edema*

(interstitial edema + alveolar hemorrhage)

Donation after cardiac death (DCD)

Italian legal problem

Table 5 Items described in the protocols

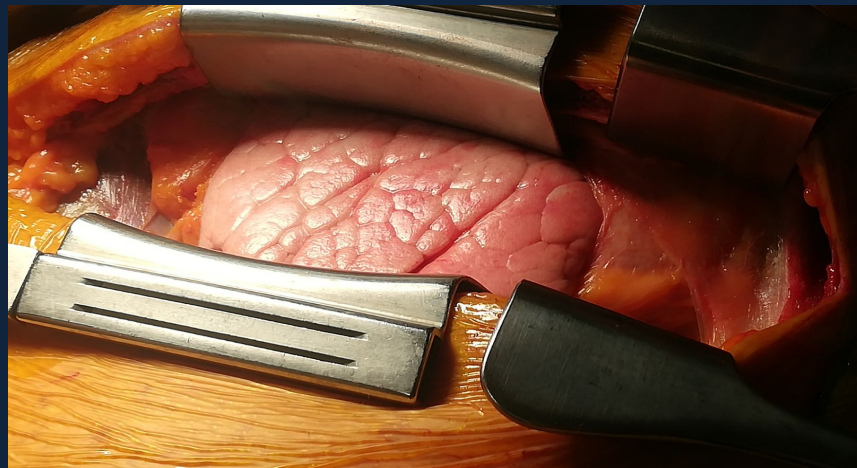
Country	Criteria for determination of death and diagnostic procedures	Death determined by	No-touch time (minutes)	Preservation method
Austria	Asystole, not specified	Treating physician with *jus practicandi*	10	Laparotomy with direct cannulation
Belgium	Cardiorespiratory criteria, according to most recent standard[a]	Three independent physicians	5	Laparotomy with direct cannulation
Czech Republic[b]	Not described	Independent physician, not involved in donation	10	DBTL catheter
France	Cardiorespiratory criteria, unconsciousness, absence of brainstem reflexes. ECG	Independent physician, not involved in donation	5	nECMO, DBTL catheter
Italy	Asystole, isoelectric ECG to confirm	Treating physician	20	nECMO
Latvia[b]	Not described	Intensivist	15	Laparotomy with direct cannulation, DBTL catheter
The Netherlands	Cardiocirculatory arrest, not specified	Treating physician	5	Laparotomy with direct cannulation, DBTL catheter
United Kingdom[a]	Cardiocirculatory arrest, unconsciousness. Intra-arterial pressure monitoring, ECG during 5 minutes. After 5 minutes, absence of brainstem reflexes confirmed	Treating physician	5	Laparotomy with direct cannulation, DBTL catheter
Spain	Asystole, apnea, no response to stimuli. ECG to confirm	Treating physician	5	ECMO, nECMO, DBTL catheter
Switzerland	*Lege artis*, referred to specific guidelines, TTE to confirm asystole	Two independent physicians	10	Laparotomy with direct cannulation

DBTL, double balloon, triple lumen; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; nECMO, normothermic extracorporeal membrane oxygenation; TTE, transthoracic echocardiogram.
[a]Variation in regional protocols. [b]Donation after circulatory death not described in a protocol.

Donation after cardiac death (DCD)

Lung parenchyma does not depend on blood supply for its oxygenation

→ lung ISCHEMIA does not necessarily equate to tissue HYPOXIA



Donation after cardiac death (DCD)

First case (1/11/2014)

American Journal of Transplantation 2016; 16: 1312–1318
Wiley Periodicals Inc.

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doi: 10.1111/ajt.13612

Case Report

Successful Transplantation of Lungs From an Uncontrolled Donor After Circulatory Death Preserved *In Situ* by Alveolar Recruitment Maneuvers and Assessed by *Ex Vivo* Lung Perfusion

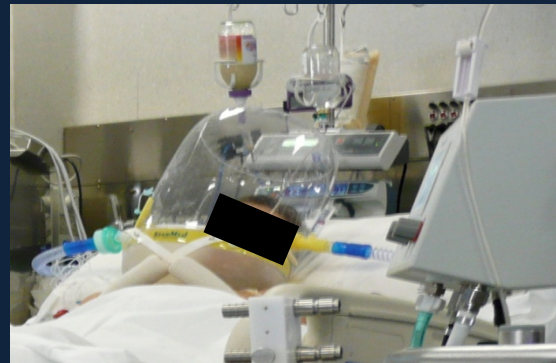
F. Valenza[1,2,*], G. Citerio[3,4], A. Palleschi[5], A. Vargiolu[4], B. Safaee Fakhr[1], A. Confalonieri[4], M. Nosotti[2,5], S. Gatti[6], S. Ravasi[7], S. Vesconi[8], A. Pesenti[3,4], F. Blasi[2,9], L. Santambrogio[2,5] and L. Gattinoni[1,2]

and protective mechanical ventilation is applied to the donor. After procurement, *ex vivo* lung perfusion (EVLP) is performed. From November 2014, 10 subjects were considered potential donors; one of these underwent the full process of procurement, EVLP, and transplantation. The donor was a 46-year-old male who died because of thoracic aortic

EVLP – DCD NOVEMBER 2014

1st CASE

- F – 36 yrs
- Medical history
  - CF (Pseudomonas)
  - 2014 put on waiting list for Tx
  - Hospitalized
  - NIV 24/24

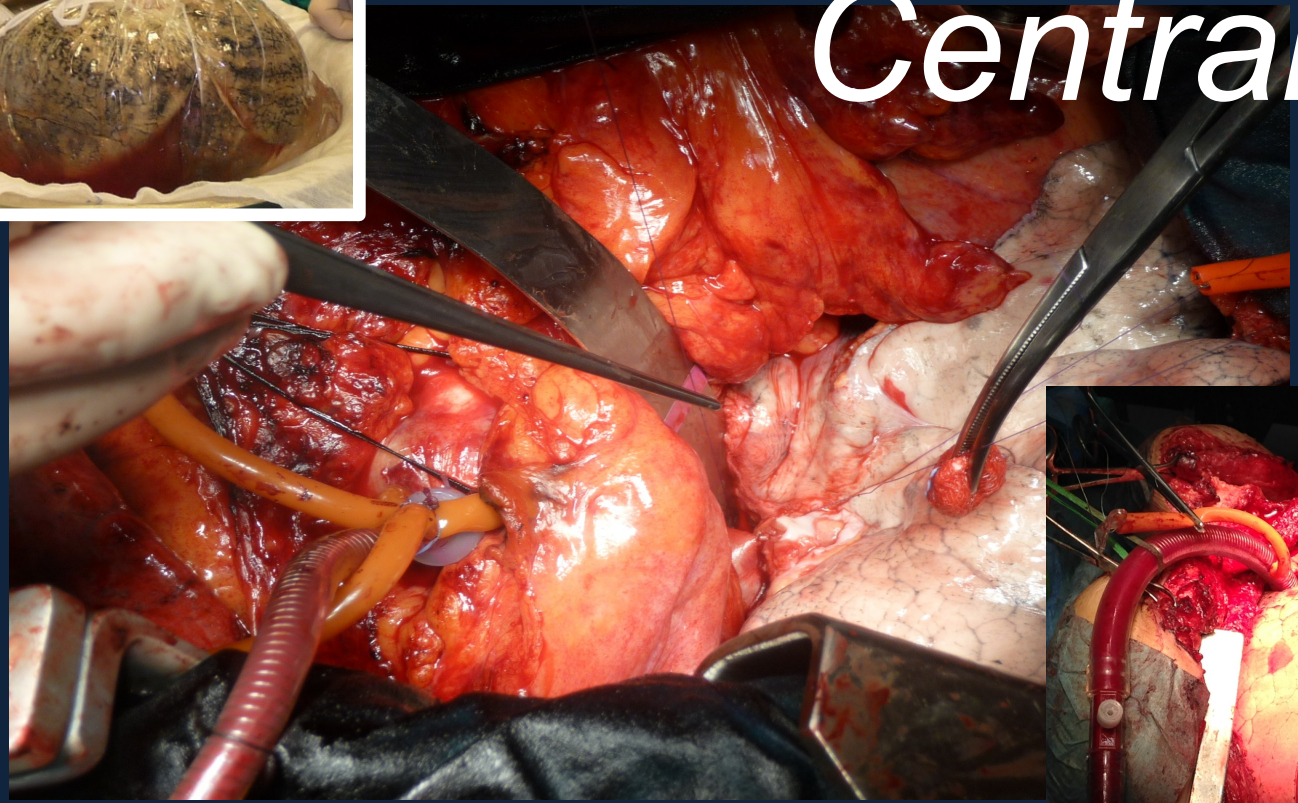


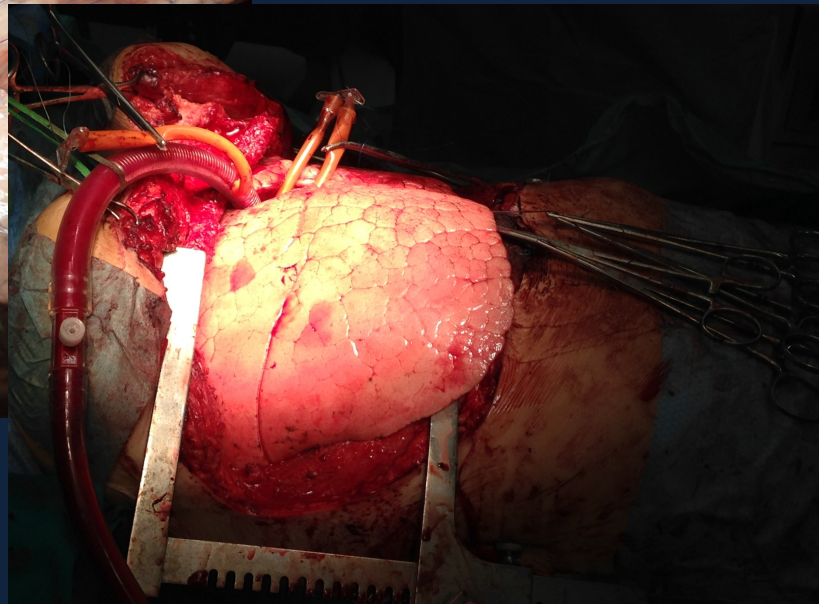
EVLP – DCD
First case

DCD aortic rupture

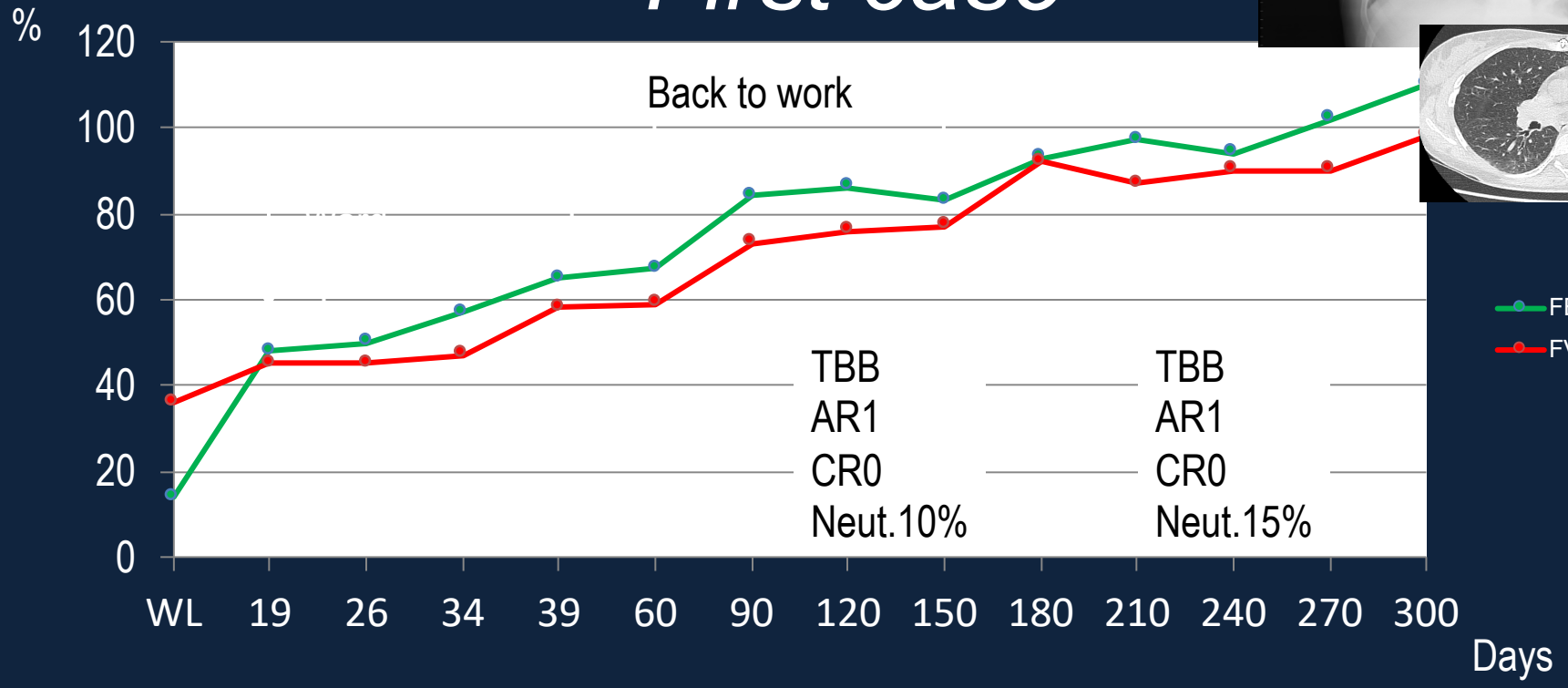
16 hours of surgery
8 hours of CEC
28 blood transfusion

Central CEC

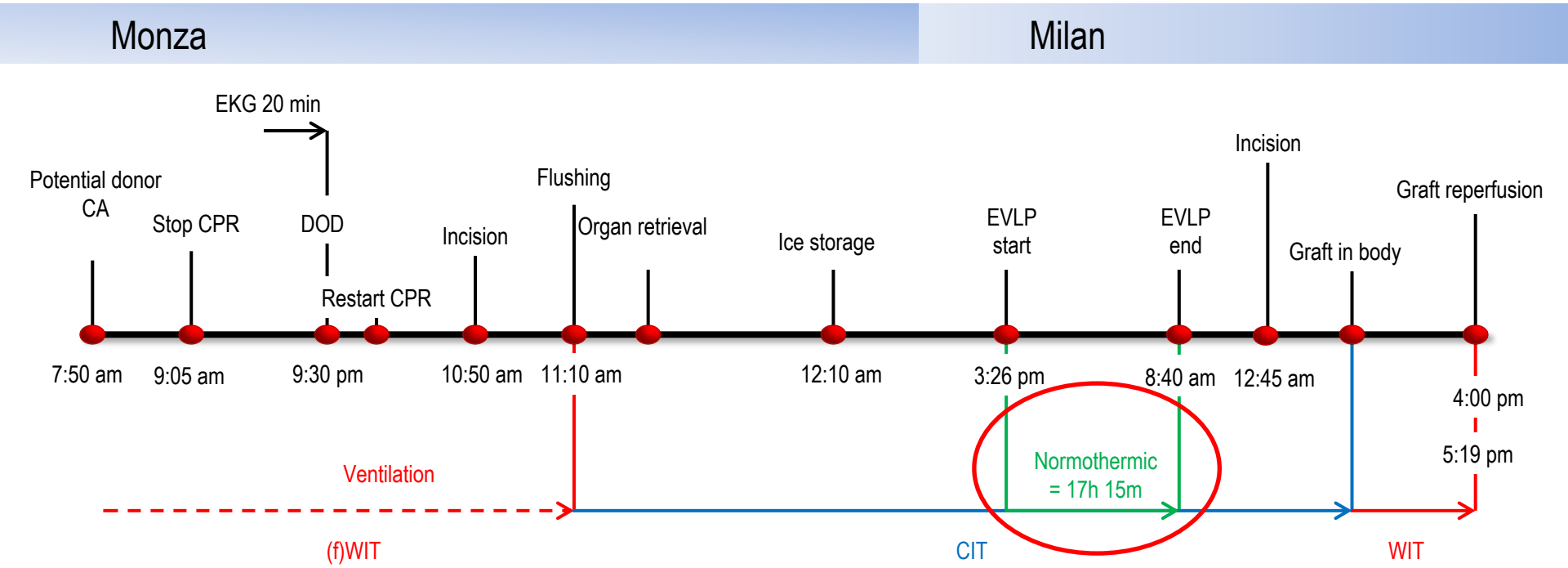




EVLP – DCD
First case



3th Successful case [01/2019]: timeline



Donor: AB group
M; 57 yrs; BMI= 27.68; Smoke= 0;
Moderate secretions

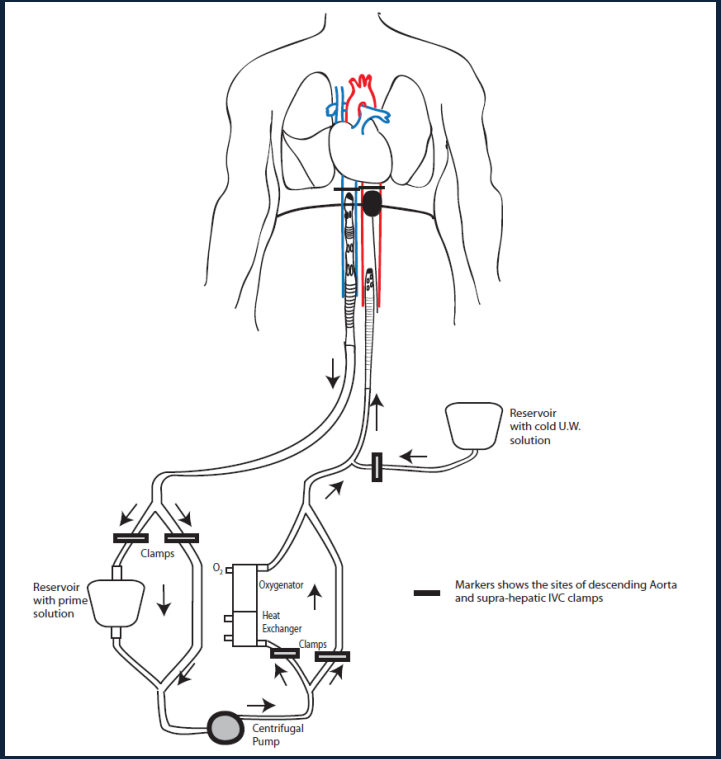
Suspect of lymphoprolipherative disorder

Recipient:
M; 32 yrs; CF; LAS= 37.12; O_2-therapy;
MV= 48 h

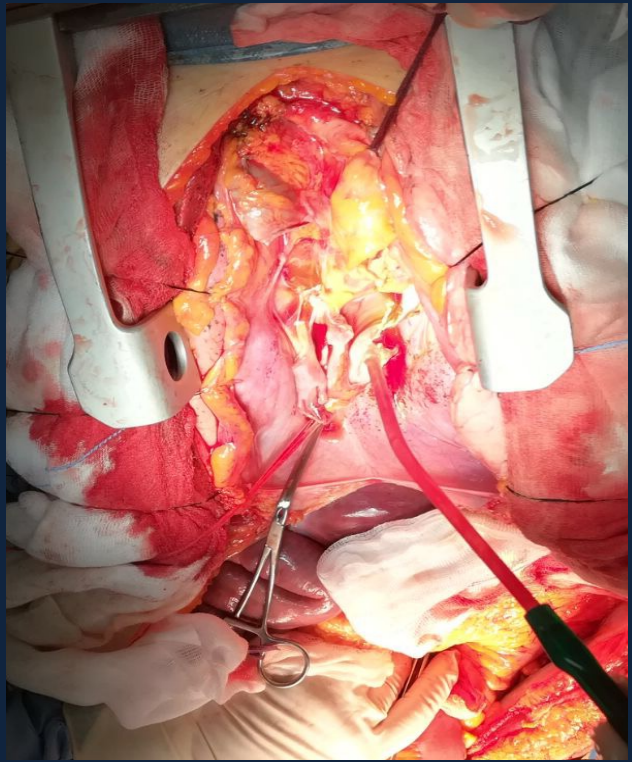
Procurement of lungs + liver + kidneys from cDCD

First case (30/10/2017)

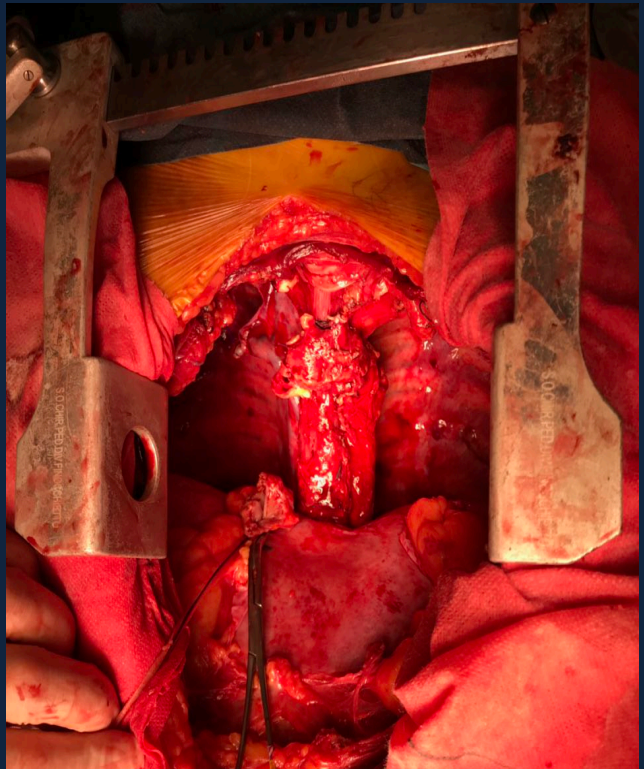
Normothermic Regional Perfusion



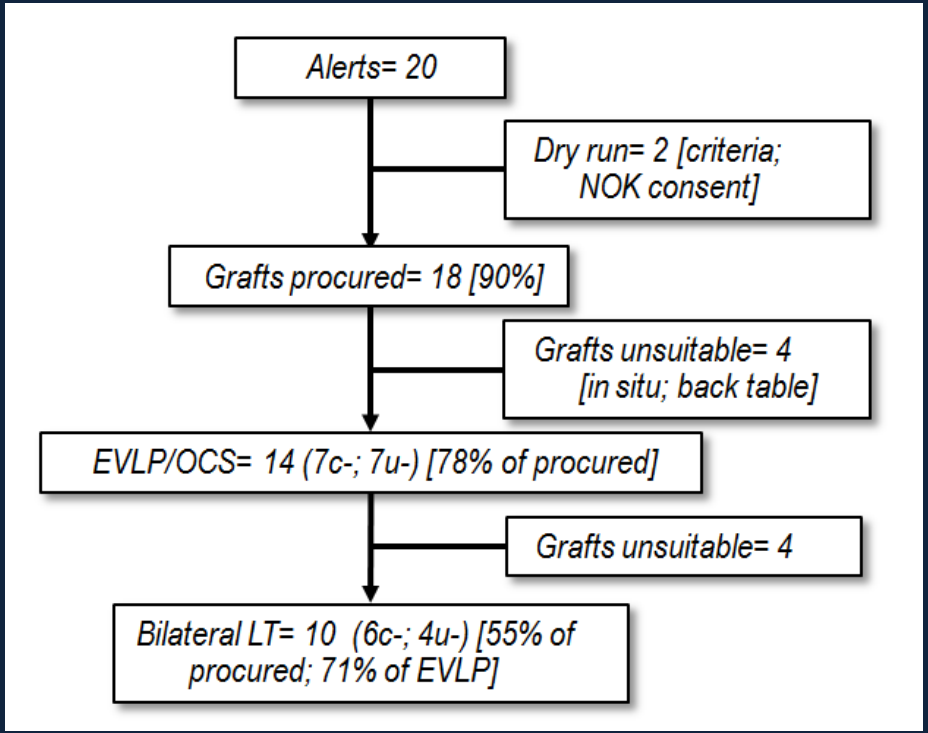
Procurement of lungs + liver + kidneys from cDCD



Procurement of lungs + liver + kidneys from cDCD (30/10/19)



DCD: clinical experience (9/2017-9/2019)



DCD: clinical experience (9/2017-9/2019)

	9/2017-	2018	-9/2019	Total
DBD	6	29	20	55
cDCD	3	1	2	6
uDCD	0	1	3	4
DCD	3	2	5	**10 [15%]**
Total	9	31	25	65

DCD: clinical experience (9/2017-9/2019)

Variables	DCD group	DBD group
Number of lung transplantations	10	41
Donor		
Gender, male	9 (90%)	28 (68.3%)
Age, years, median (95% CI)	54 (47.3 to 60.1)	50 (37.7 to 53.0)
uDCD CA-PA flush, min, mean (95%CI)	245 (173 to 305)	NA
cDCD ISHLT-int 3, min, median (95%CI)	176 (122 to 191)	NA
PA flush-1st lung reperfusion, min, mean (95%CI)	640 (505 to 775)	435 (386 to 483)
Recipients		
Gender, male	23 (56%)	5 (50%)
Age, years, median (95% CI)	42 (24.9 to 51.5)	37 (31.7 to 48.4)
Disease: CF, COPD, IPF	7; 2; 1 (70%; 20%; 10%)	27; 4; 10 (66%; 10%; 24%)
LAS, median (95% CI)	40 (34.9 to 49.3)	40.5 (38.4 to 45.5)
Machine perfusion rate	100%	17.6%
Intraoperative ECMO	6 (60%)	20 (50%)
Postop. MV, days, median (95% CI)	2 (1 to 4)	1 (1 to 1)
30-day mortality rate	0%	0%
1-year mortality rate	0%	2%
Best FEV1, mean (95% CI)	82.7 (69.5 to 96.0)	90.1 (84.2 to 95.9)
Airway complication	2 (20%)	3 (7.3%)

2011-2018

35 DBD-Donors

15 DCD-Donors

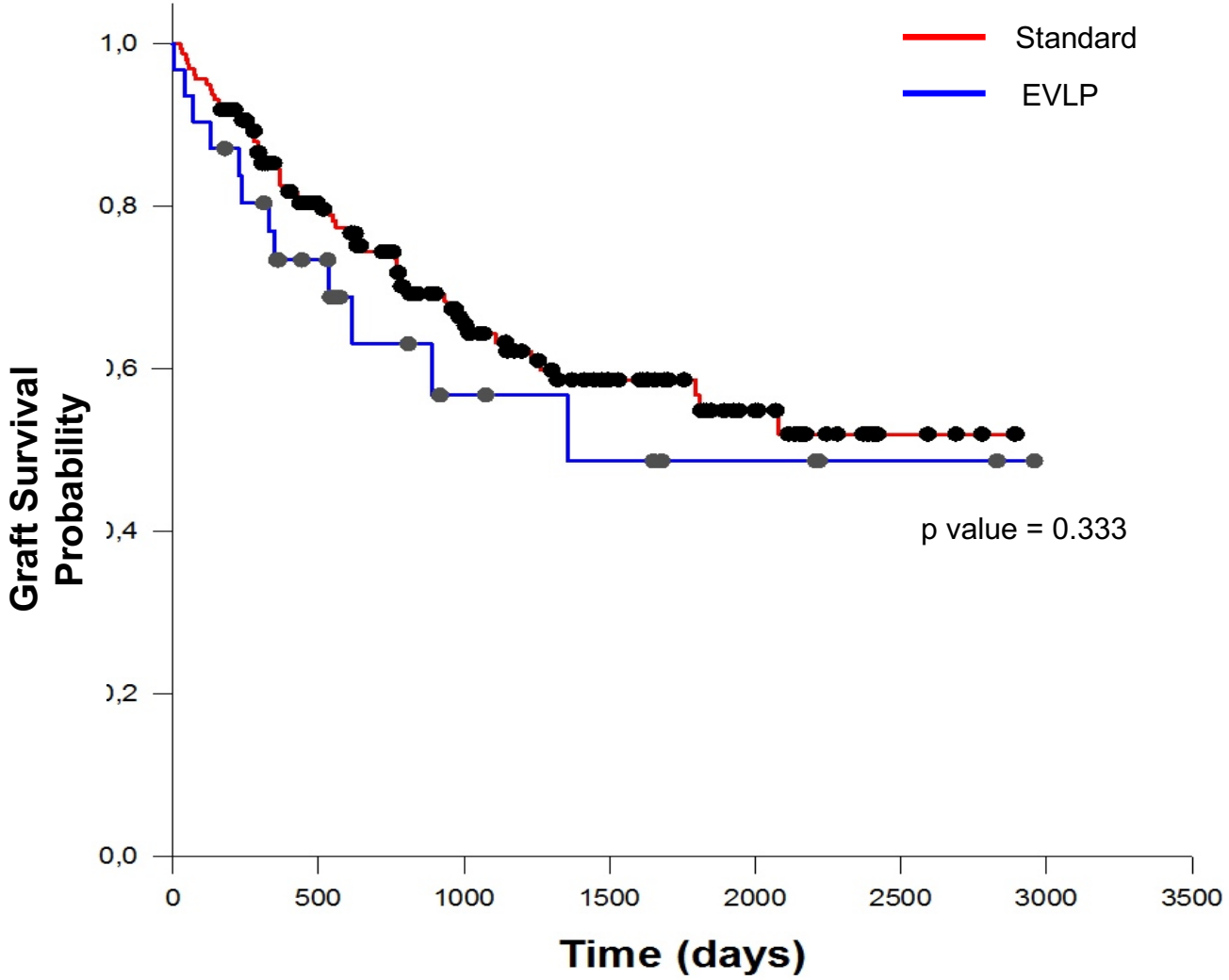
EVLP

Exclusion:
11 DBD (5 edema; suspected infection; 1 parenchymal bleeding)
8 DCD (7 edema; 1 parenchymal bleeding)

31 EVLP-Donors **(16%)**

162 Standard-Donors

193 LUNG TRANSPLANTATION


2011-2018
Standard
EVLP
p value = 0.333
Graft Survival Probability
1,0
0,8
0,6
0,4
0,2
0,0
0
500
1000
1500
2000
2500
3000
3500
Time (days)

ECMO:
Emergency National Program 2010

ELSEVIER

Bridge to Lung Transplantation by Venovenous Extracorporeal Membrane Oxygenation: A Lesson Learned on the First Four Cases

M. Nosotti, L. Rosso, A. Palleschi, A. Lissoni, S. Crotti, C. Marenghi, C. Colombo, D. Costantini, and L. Santambrogio

Our experience: 31 bridge → bilateral lung Tx

Lung Allocation Score
Variables

Age (years)

Height (cm)

Weight (kg)

Diagnosis of lung disease

Functional status (without support, mild support, full support)

Diabetes status (unknown, insulin-dependent, no diabetes, non-insulin-dependent)

Mechanical ventilation [none, continuous positive airway pressure (CPAP), bilevel Positive airway pressure (BiPAP), continuous invasive, intermittent invasive]

Oxygen treatment (none, at rest, only at night, only under stress)

Oxygen requirement at rest (L/min or %)

Forced vital capacity (% predicted)

Systolic pulmonary arterial pressure (mmHg)

Mean pulmonary arterial pressure (mmHg)

Mean pulmonary capillary closing pressure (mmHg)

Current carbon dioxide partial pressure (mmHg or kPa)

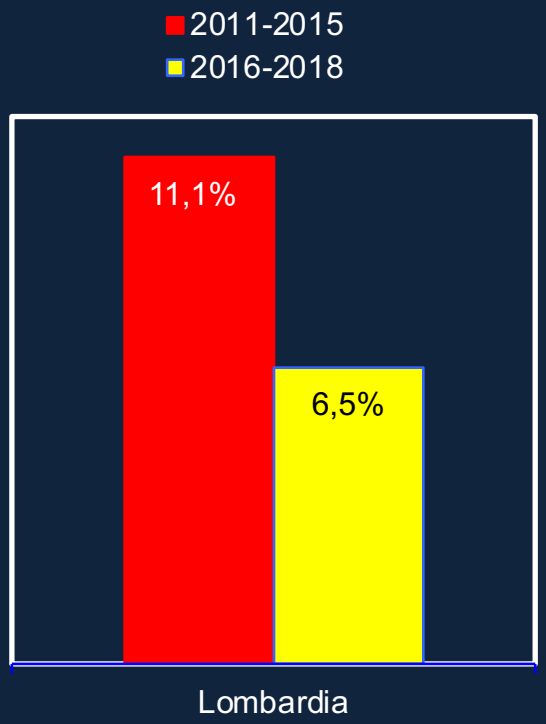
Rise in carbon dioxide partial pressure (%) in relation to minimal carbon dioxide partial pressure

6-min walking test (m)

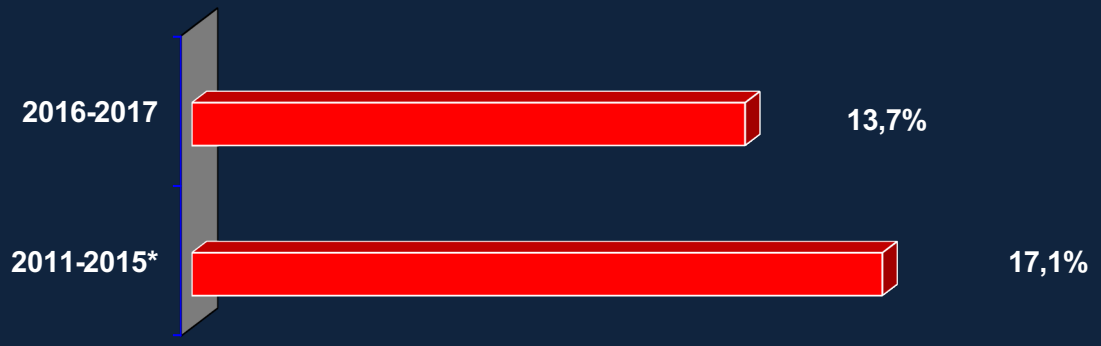
Serum creatinine (μmol/L or mg/dL)

Lung Allocation Score

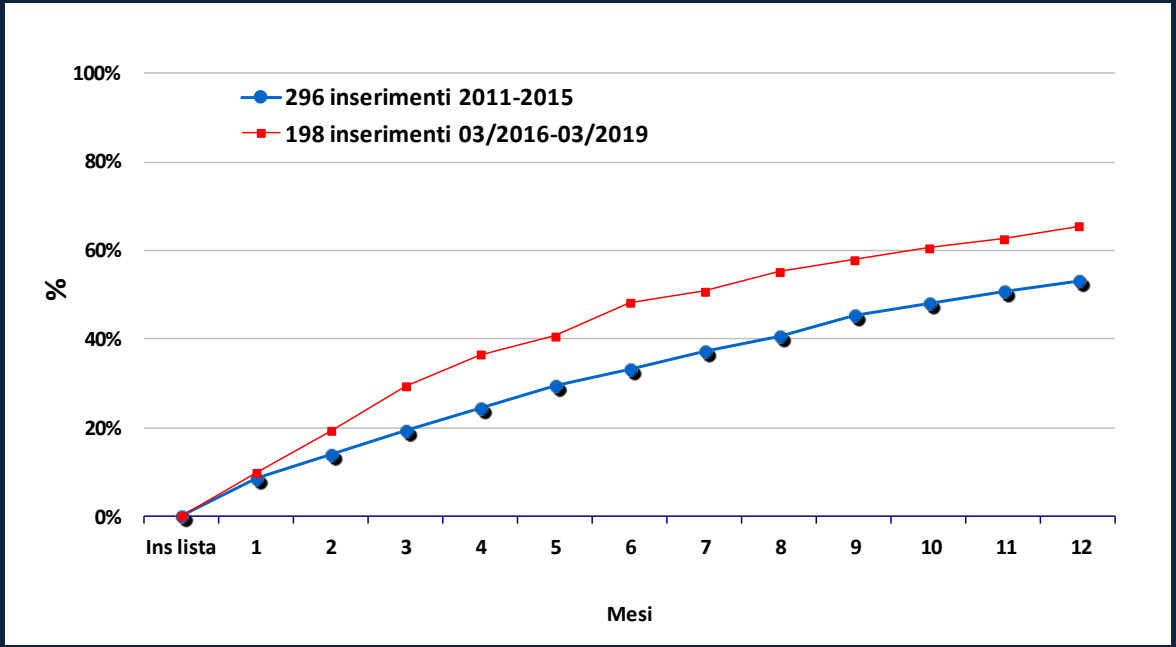
List mortality



Lung Allocation Score
Post-transplant mortality



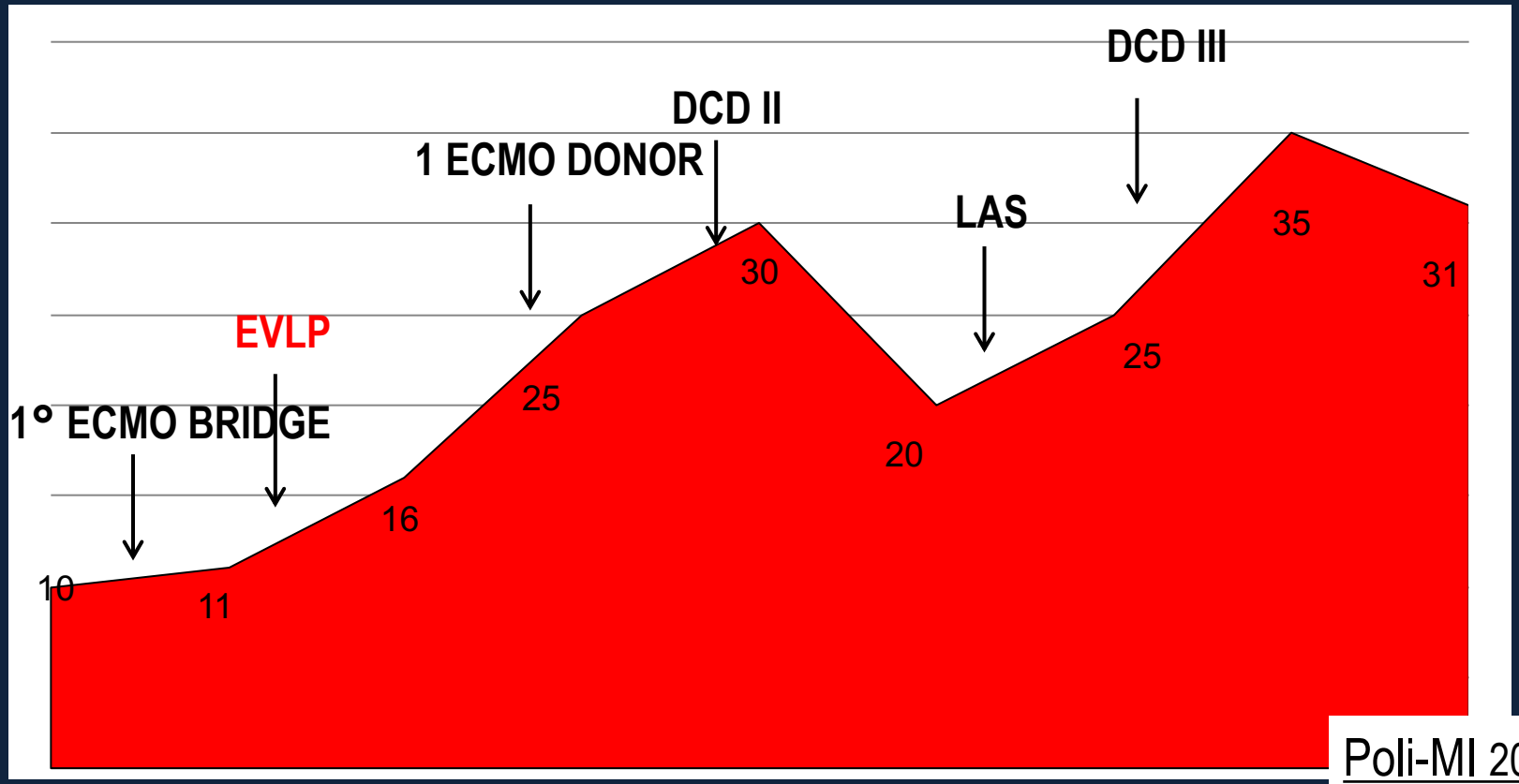
Lung Allocation Score
Transplant probability



Lung Allocation Score
Pre- and Post-transplant variables

	2011-2015		15 marzo 2016- 15 marzo 2017		p-value
	N	**%**	***N***	***%***	
Emergenze	**38**	**19,8%**	***3***	***5,9%***	***0,018***
ECLS preop	**36**	**18,7%**	**2**	**3,9%**	***0,009***
ECLS intraop	73	38,0%	24	47,1%	*0,241*
ECLS postop	38	19,8%	4	7,8%	***0,044***
Decessi entro 90 gg	33	17,1%	*7*	*13,7%*	*0,553*
Gg ICU (media,sd)	13,6 (17,2)		10,8 (13,2)		*0,285*
Trapianti analizzati	**192**		***51***		

The EVLP side effect



Poli-MI 2008-2018

TRAPIANTO DI POLMONE OSPEDALE POLICLINICO: STORICO

Conclusions

Open problems	Research Guidelines
• *Decrease in mortality of patients on waiting list*	• *ECMO-URGENCY* • *LAS*
• *Increase of organ procurement*	• *MARGINAL DONOR* • ***EVLP – DCD***
• *Increased survival of transplanted organs*	• *LESS BOS – (PHOTOPHERESIS)* • *NEW ANTI-REJECTION DRUGS*

Cosa significa per il nostro centro la fibrosi cistica?

- *1/1/2016-20/11/2019: 89 pz messi in nota → 65 Tx*
- *1° trapianto in Italia dopo ricondizionamento (EVLP)*
- *1° trapianto in Italia da donatore DCD*
- *Tx-FC miglior sopravvivenza (>80% a 5 anni)*

Cosa significano per il nostro centro le Onlus-FC?

- *Ricerca scientifica (grant)*
- *Contratti per fisioterapisti*
- *Assistenza a pazienti e famiglie*
- *Supporto per EVLP , OCS e fotoferesi*

Tutto questo esteso a tutti i pazienti e non solo ai pazienti FC

Italia

DRG (rimborso) per trapianto di polmone:

- *Nazionale= 72.000 euro (ex. Piemonte, Veneto, Sicilia)*
- *Lombardia= 32.760 euro*