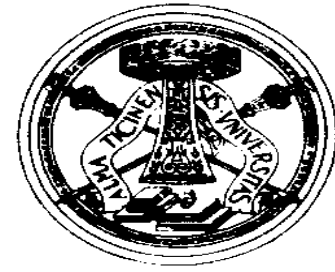




IRCCS - Policlinico "S. Matteo"
Cattedra di Anestesia e Rianimazione
Università degli Studi di Pavia



DONAZIONE A CUORE NON BATTENTE NELLA REALTA' ITALIANA

Dr. Marinella Zanierato
SSD Coordinamento Donazione e Trapianti
Rianimazione I



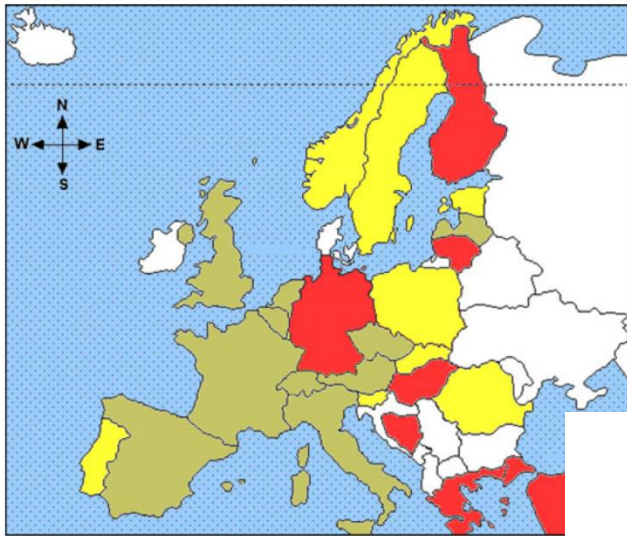
...very variable period of ischemic damage due to cardiac standstill (no-flow) followed by cardiac resuscitation (low-flow) with a varied degree of effectiveness.....**no-flow > 30 min** is associated to very poor graft survival.....

Donation after cardiac death: is a “paradigm shift” feasible in Italy?

V. FANELLI ¹, P. M. GERACI ², L. MASCIA ¹

This time negatively affects donation after cardiac death because warm ischemic time (WIT) – the most important predictor of grafts’ poor outcome – is prolonged. However, this time seems to be prudential to define the irreversibility of death and to respect the “dead donor rule”, as established by the National Committee of Bioethics. National reference protocols regulating DCD practice are therefore a compelling issue. (*Minerva Anesthesiol* 2013;79:534-40)

Italian DCD program started in 2007



10 yes 10 not yet 7 not

	No touch period (min)	Procurement protocol	Donation program	Allocation DCD organs
Austria	10	–	1 center	Local
Belgium	5	Super-rapid laparotomy and sternotomy with direct arterial cannulation	National	National
Czech Republic	10	DB	Centers	Special
France	5	ECMO, DB	Centers	Local
Italy	20	NECMO	National	Local
Latvia	15	DB	National	National
The Netherlands	5	Super-rapid laparotomy and sternotomy with direct arterial cannulation	National	National
Spain	5	ECMO, NECMO, DB	Centers	Local/special
Switzerland	10	–	Centers	Local
United Kingdom	5	Super-rapid laparotomy and sternotomy with direct arterial cannulation	National	Local

The possible scenarios

Category	Sub-category	Description	Type
Category I Uncontrolled Unwitnessed CA	I A – In-hospital	Sudden-unexpected-irreversible CA; no attempt of resuscitation by a medical team. WIT to be	Uncontrolled
Category II Uncontrolled Witnessed CA	II A – In-hospital	Sudden-unexpected-irreversible CA; unsuccessful resuscitation by a medical team. In- or out-of-hospital setting	Uncontrolled
	II B – Out-of-hospital		
Category III Controlled Awaiting circulatory death	III A – Uncontrolled end	Euthanasia Excluded Planned, expected CA; withdrawal of life-sustaining treatment; Euthanasia Excluded	Controlled
IV B - Death diagnosis during ECMO-ECLS		Death determination by circulatory (DCD) or neurologic (DBD) criteria	Partially controlled

ECLS

Program



Out of hospital

No-flow < 6 min

Good quality of CPR
(autopulse)- FV/TV

Assesment of time from
collapse to door



Time \leq 60 min

In hospital

Assesment of end-tidal CO₂

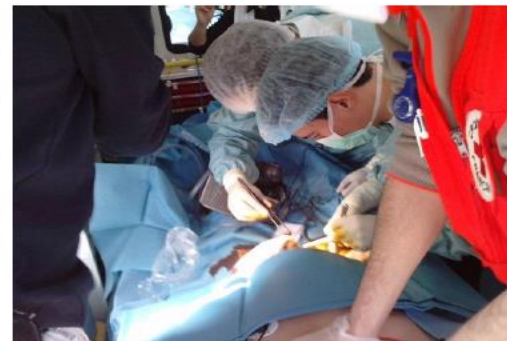
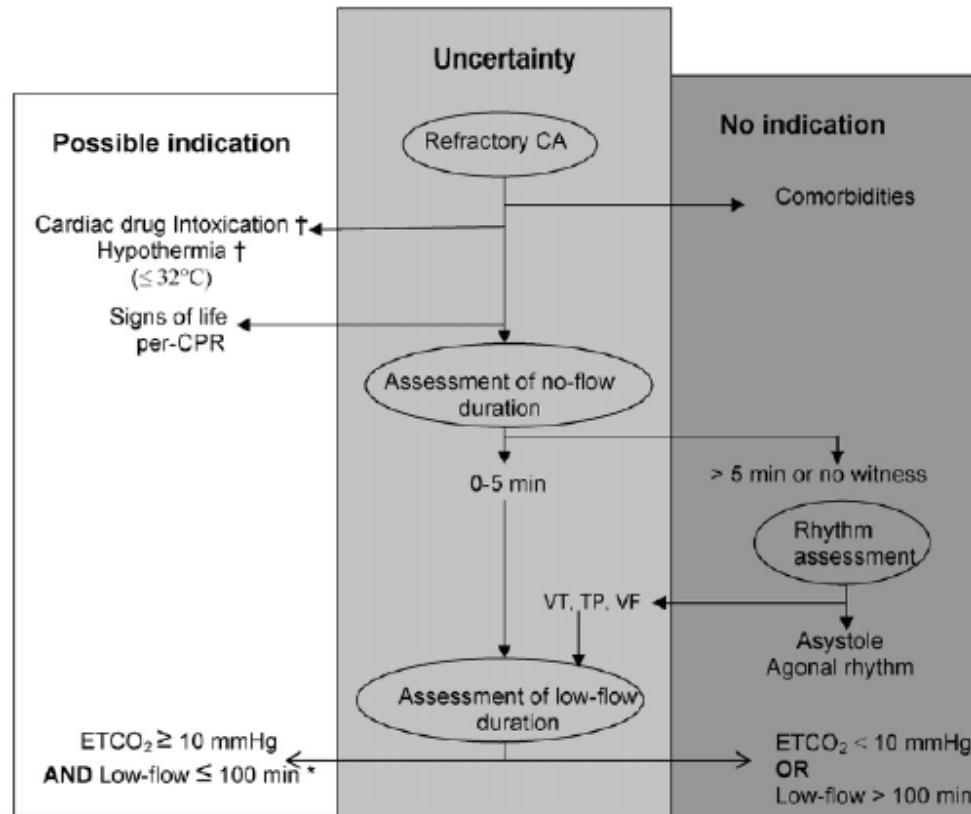
End-tidalCO₂> 10 mmHg

Now-flow < 80 min

Indication for ECMO support

Guidelines for indications for the use of extracorporeal life support in refractory cardiac arrest[☆]

Annales Françaises d'Anesthésie et de Réanimation 28 (2009) 187-190



Extracorporeal life support following out-of-hospital refractory cardiac arrest



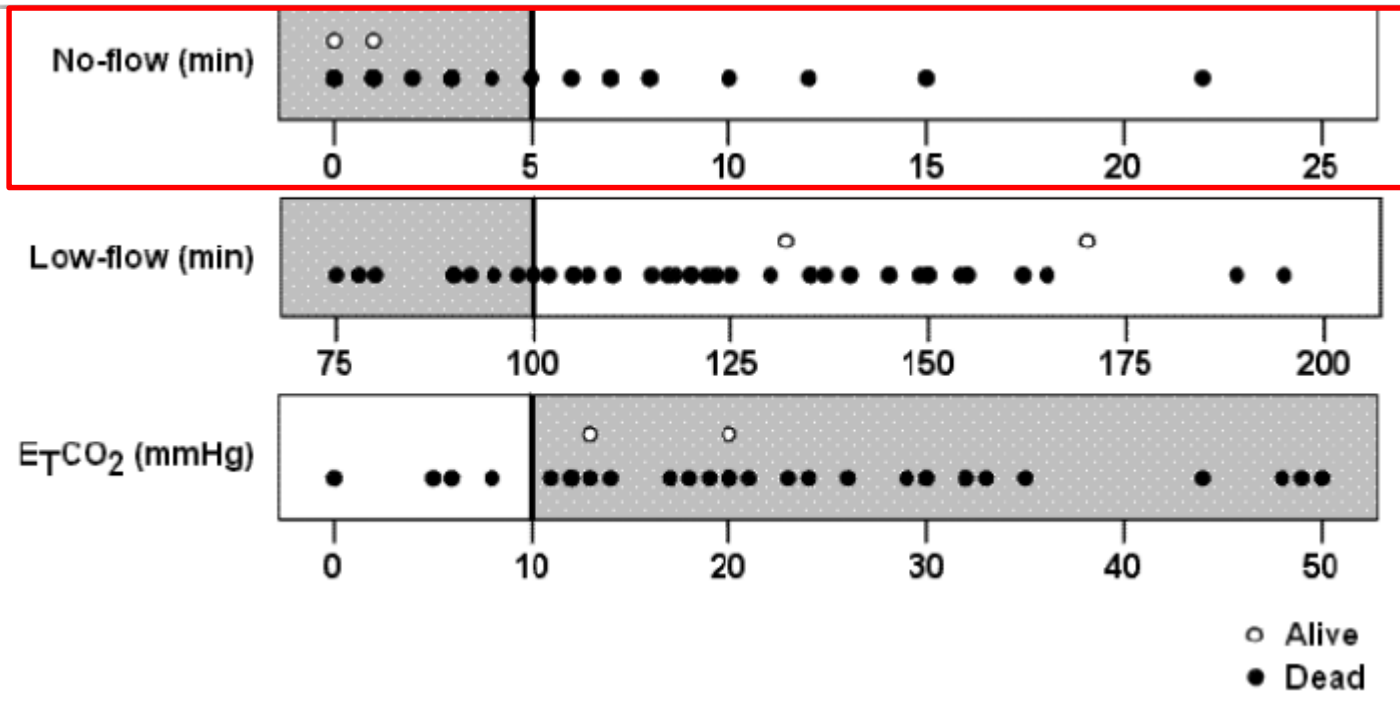
Morgan Le Guen¹, Armelle Nicolas-Robin¹, Serge Carreira¹, Mathieu Raux¹, Pascal Leprince², Bruno Riou^{3*}, Olivier Langeron¹

Critical Care 2011, 15:R29

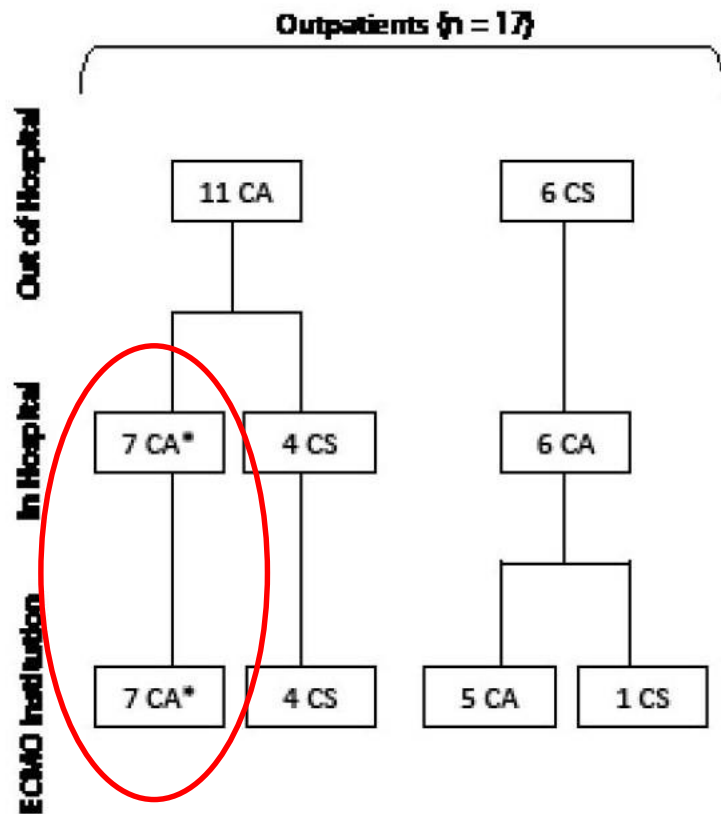
Abstract

Introduction: Extracorporeal life support (ECLS) has recently shown encouraging results in the resuscitation of in-hospital (IH) refractory cardiac arrest. We assessed the use of ECLS following out-of-hospital (OH) refractory cardiac arrest.

Methods: We evaluated 51 consecutive patients who experienced witnessed OH refractory cardiac arrest and received automated chest compression and ECLS upon arrival in the hospital. Patients with preexisting severe hypothermia who experienced IH cardiac arrest were excluded. A femorofemoral ECLS was set up on admission to the hospital by a mobile cardiothoracic surgical team.



Ineffective ECLS



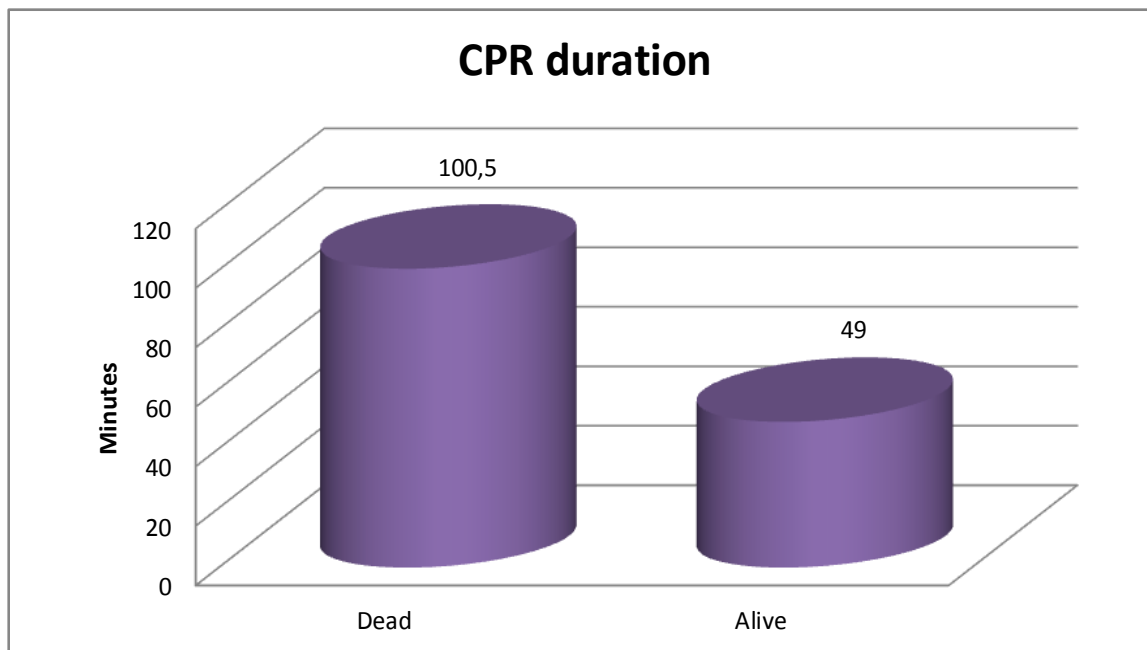
Median time to CRP 7 min (6-8)

Median time to ECMO 93 min (74-107)

After a median of 20 hours (16-22) of ECMO all pts of this subgroup died:

in 3 pts BD

in 4 pts ECMO was withdrawn because ineffective

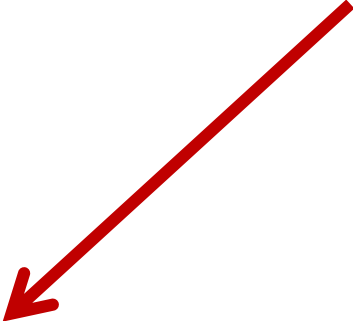


Significative correlation between CPR duration pre-ECLS and mortality (no flow/low flow)

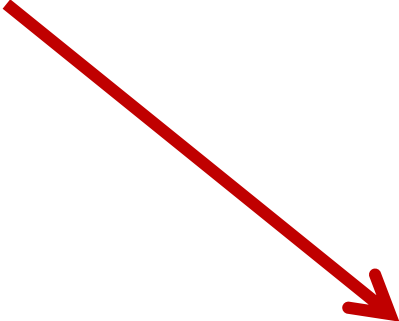
2015



**CRITERI CLINICI E RACCOMANDAZIONI PRATICHE INERENTI
L'ACCERTAMENTO DI MORTE IN SOGGETTI SOTTOPOSTI AD
ASSISTENZA CIRCOLATORIA EXTRACORPOREA**



DCD donors
Cardiocirculatory
criteria



DBD donors
Neurological
criteria



Diagnosi di morte

L'approccio diagnostico sarà diverso in base alla situazione emodinamica e circolatoria del paziente, determinanti ai fini del mantenimento della omeostasi:

- a) **Compenso emodinamico:** circolazione spontanea con battito cardiaco efficace o circolazione artificiale fornita da ECMO efficace (contesti 1:A, 2:A); omeostasi in equilibrio. La diagnosi di morte sarà basata su criteri neurologici.
- b) **Scompenso emodinamico:** circolazione spontanea assente o gravemente insufficiente e circolazione artificiale inadeguata per ECMO inefficace (contesti 1:B, 1:C, 2:B); omeostasi alterata. La diagnosi di morte sarà basata su criteri cardiaci.

THE ITALIAN “PROGRAMMA ALBA” FOR ORGAN DONATION AFTER CIRCULATORY DEATH

PAOLO M. GERACI¹, GIAMPAOLO AZZONI⁸, MASSIMO ABELLI², ELENA TICOZZELLI², TERESA RAMPINO³, VINCENZO SEPE³, MARCO SACCHI⁴, MAURIZIO RAIMONDI⁴, ANTONIO BRASCHI^{5a}, GIORGIO IOTTI^{5b}, MARCO MAURELLI^{5c}, MARIA ANTONIETTA BRESSAN⁶, ANTONIO DAL CANTON³, MARCO BOSIO⁷, CRISTIANO MARTINI⁹, ALESSANDRO NANNI COSTA¹⁰

Actions for organ protection before death

Table 3. *The 6-step protocols for organ donation in uncontrolled donation after circulatory death (Maastricht categories II)*

	Steps	Notes
1	<u>clinical decision</u> on treatment futility or inefficacy in the asystolic patient: intensive supports should be stopped, non-conventional ECLS is not indicated	<ul style="list-style-type: none"> the treating medical staff which identifies a potential organ donor must be different and independent from the on-call dedicated DCD Multidisciplinary Taskforce (DCD-MT)
2	<u>death diagnosis</u> by internationally accepted criteria (immediately after stop of life-support therapies)	<ul style="list-style-type: none"> invasive manoeuvres with proportional risk of complications (laboratory tests, I.V. heparin, vessel cannulation) are allowed with the aim of preserving the possibility of organ donation – in the meanwhile, consent/opposition should be verified
3	<u>declaration of death</u>	<ul style="list-style-type: none"> flat ECG must be recorded (for 20 minutes in Italy)
4	<u>information</u> to the family (treating doctors) and <u>donation proposal</u> (DCD-MT)	<ul style="list-style-type: none"> after declaration of death, organ retrieval organization and invasive manoeuvres (including ECMO) can be adopted with the aim of preserving organ functionality while the family may express non-opposition to donation (DCD-MT)
5	<u>complete evaluation of organ suitability</u> as soon as the family agrees with donation	
6	organ retrieval	<ul style="list-style-type: none"> ex situ perfusion if indicated

Alba program

WITNESSED CARDIAC ARREST (CA)

<15'

BLS/ACLS

**Multidisciplinary team evaluation: No-
flow >15 min, low-flow >60-80min,
Asystolia, ET CO₂ < 10 mmHg, no
indication to ECMO support**

DIAGNOSIS OF IRREVERSIBLE CA

Check for

exclusion criteria:

ARRIVAL IN

HOSPITAL

Age > 18 < 65 yrs

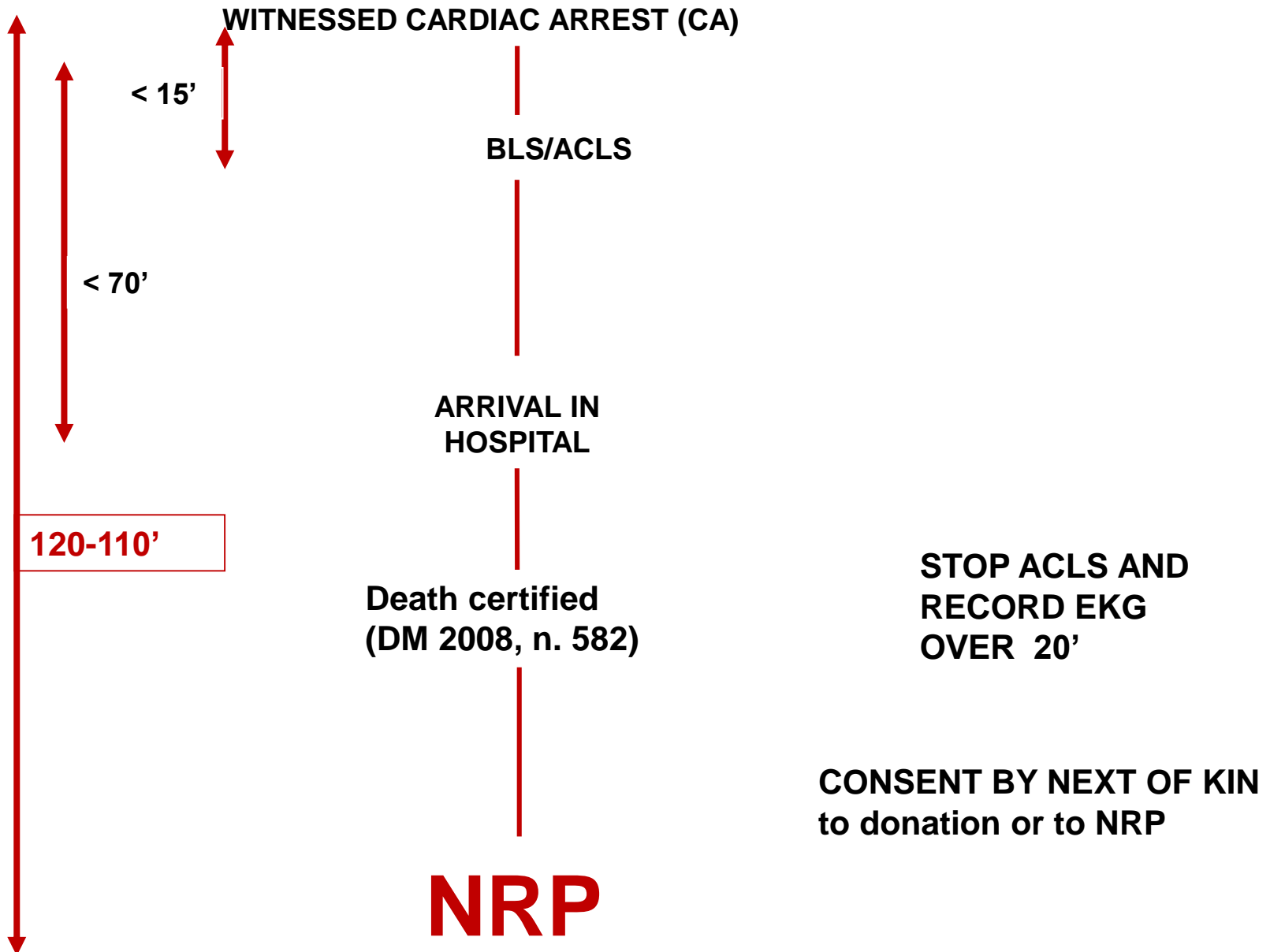
Past medical
history

STOP ACLS AND
RECORD EKG
OVER 20'

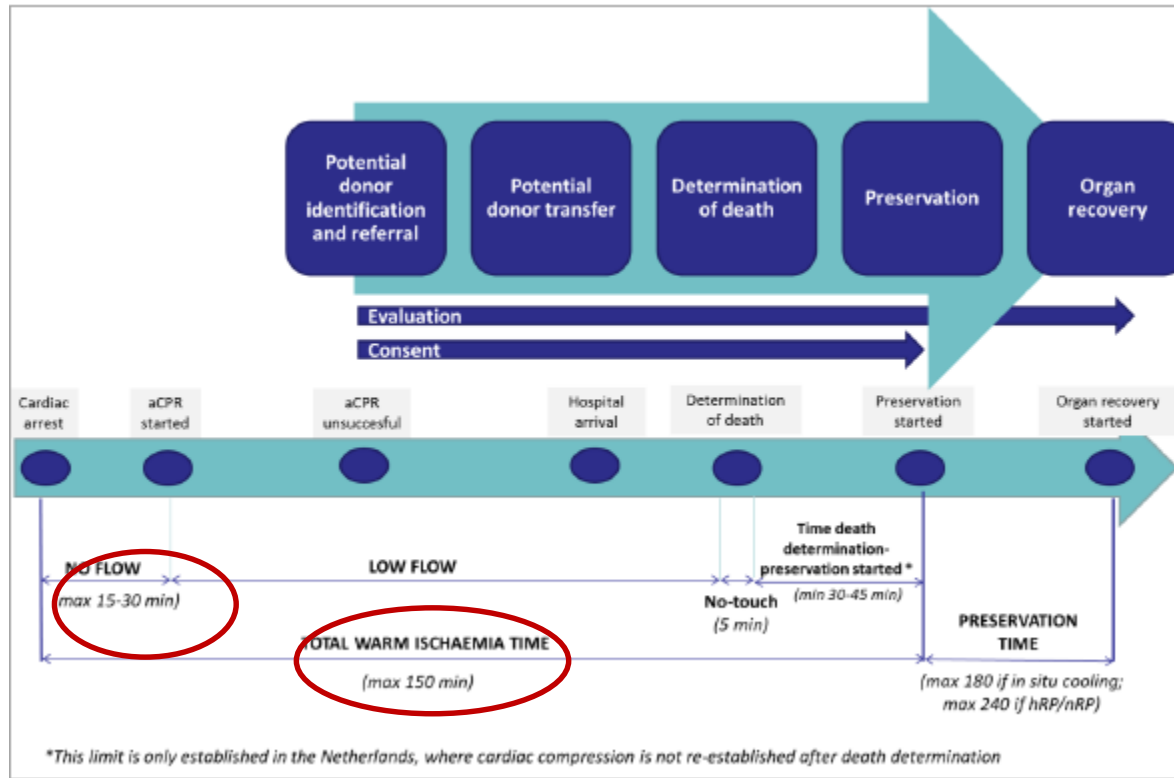
Heparin bolus
infusion

**Normothermic
Regional Perfusion
(NRP)**

Alba Program



The process of uncontrolled DCD



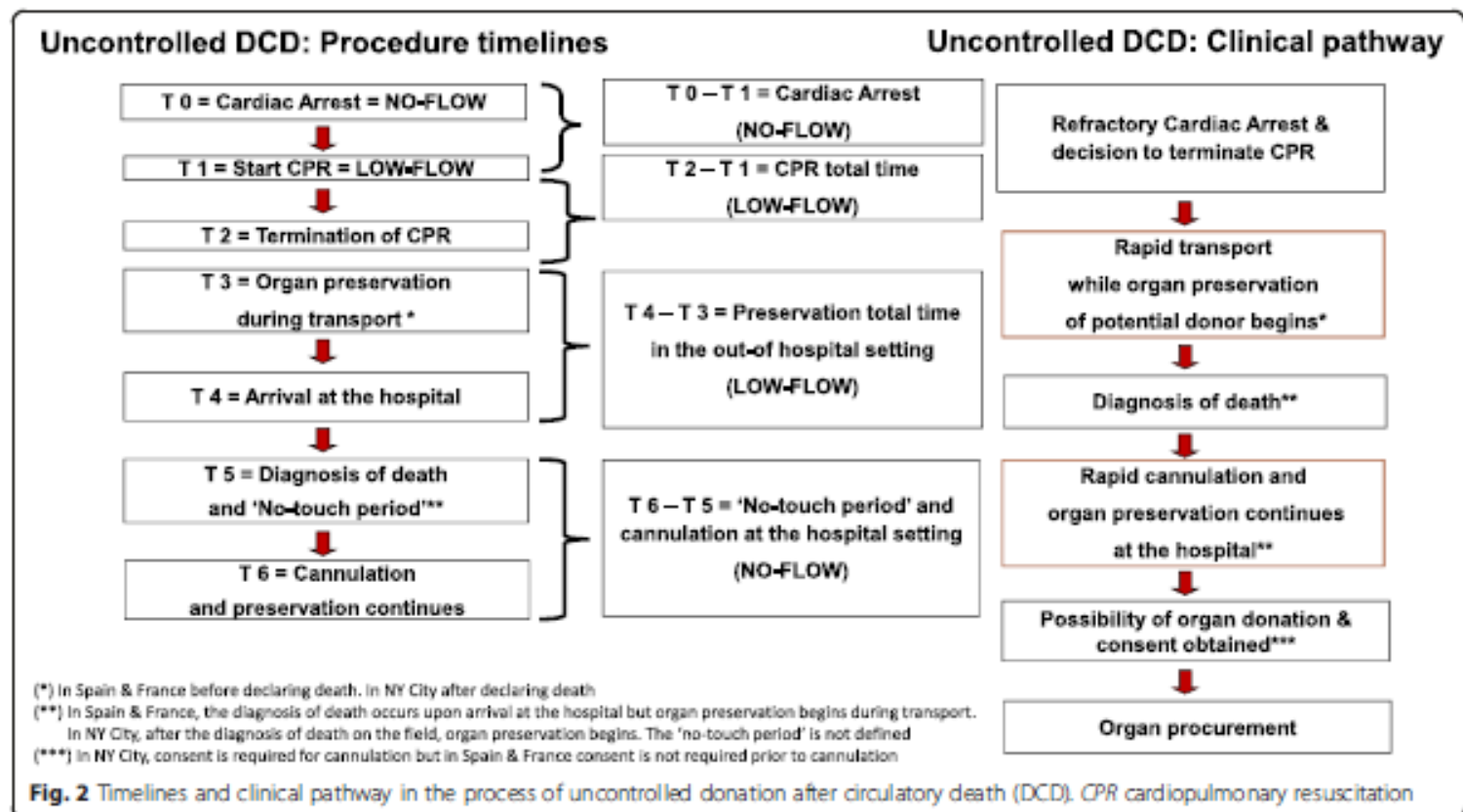


Protocols for uncontrolled donation after circulatory death: a systematic review of international guidelines, practices and transplant outcomes

Iván Ortega-Deballón^{1,2,3,4,5,6*}, Laura Homby^{7,8} and Sam D. Shemie^{8,9,10}



Spain
France
Italy
Switzerland
US, NY City

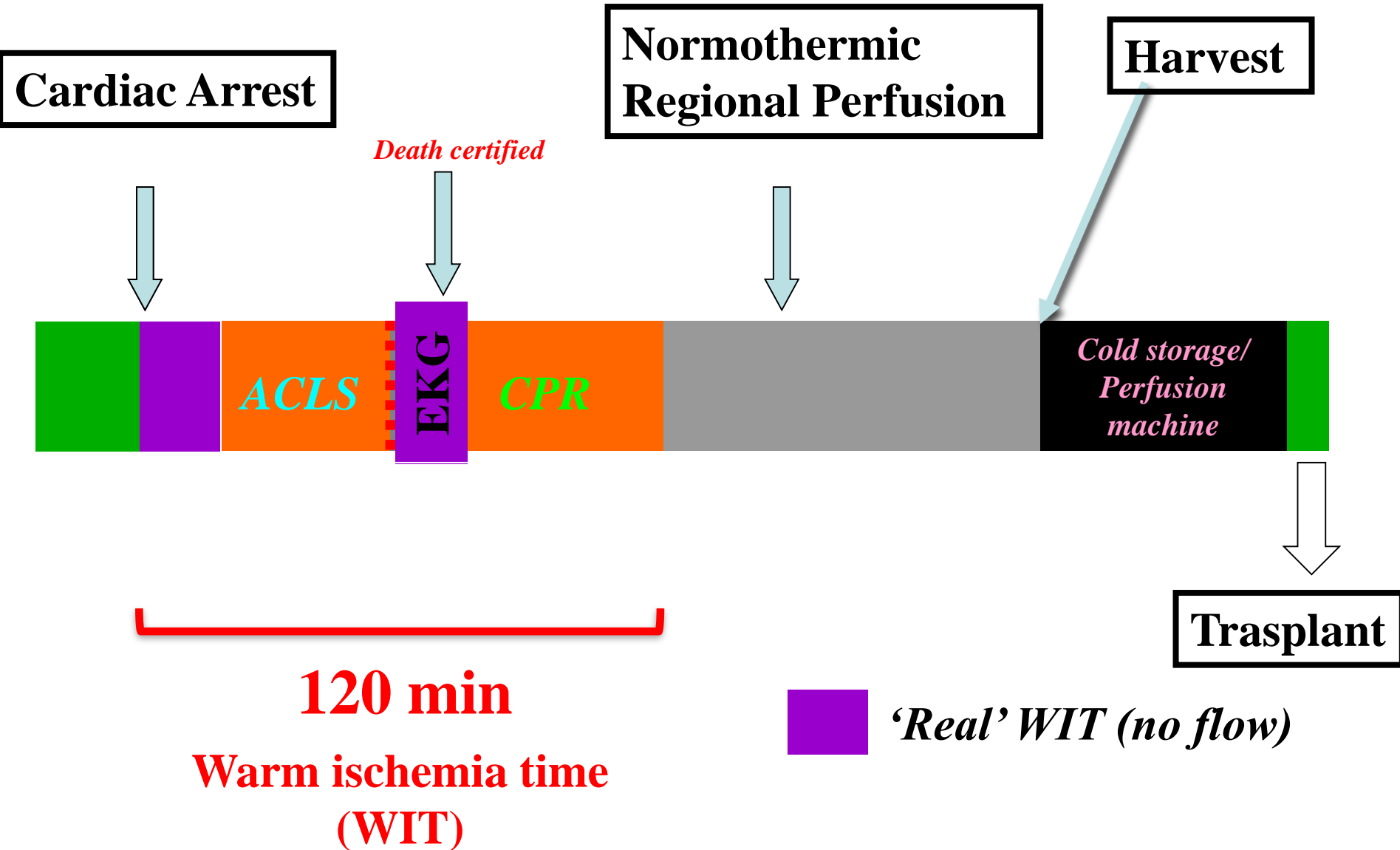


DCD PROTOCOL

DONOR ENROLMENT CRITERIA

- **Age 15 – 65 yrs**
- **Resuscitation start within 15 min**
- **Cardiac arrest witnessed by familiar or colleagues**
- **Refractory to acs**
- **Absence of hemodynamic instability for > 60 min or severe hypotension (< 60 mmhg) prior to cardiac arrest**
- **Known cause of death, ruling out violence**
- **Time to hospital arrival < 90 min**

Time point uncontrolled DCD



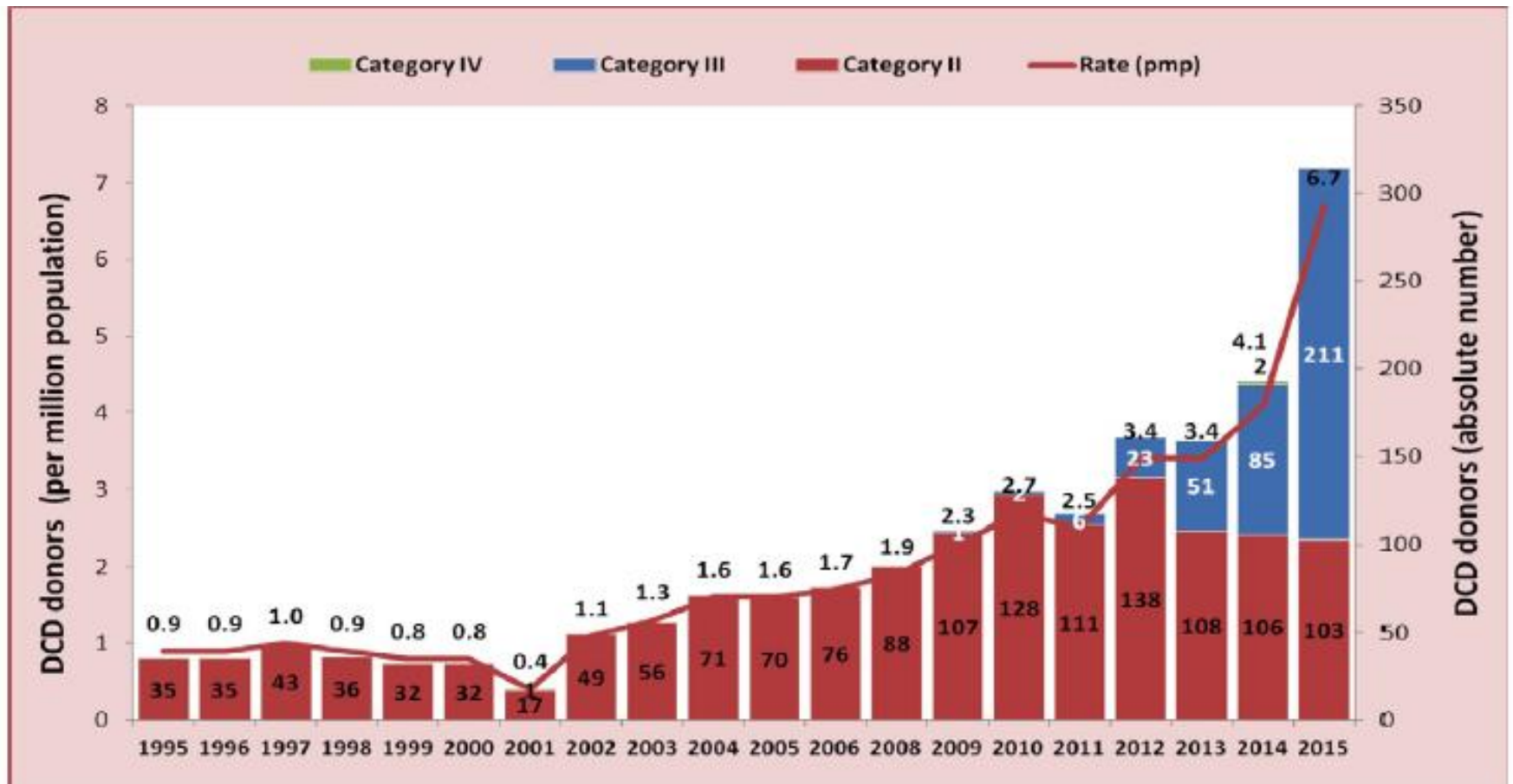
Maastricht Classification

	Definition	Where
Category I Uncontrolled	Unwitnessed circulatory arrest I A - In-hospital I B - Out-of-hospital	Sudden-unexpected CA, no attempt of resuscitation by a medical team WIT to be considered according national recommendations in place In- or out-of-hospital setting
Category II Uncontrolled	Witnessed circulatory arrest II A - In-hospital II B - Out-of-hospital	Sudden-unexpected-irreversible CA, unsuccessful resuscitation by a medical team In- or out-of-hospital setting
Category III Controlled	Awaiting circulatory death	Planned, expected CA, withdrawal of life-sustaining treatment Euthanasia excluded
Category IV Uncontrolled and controlled	Circulatory arrest while brain dead	Sudden or planned CA during or after brain death diagnosis process but before retrieval

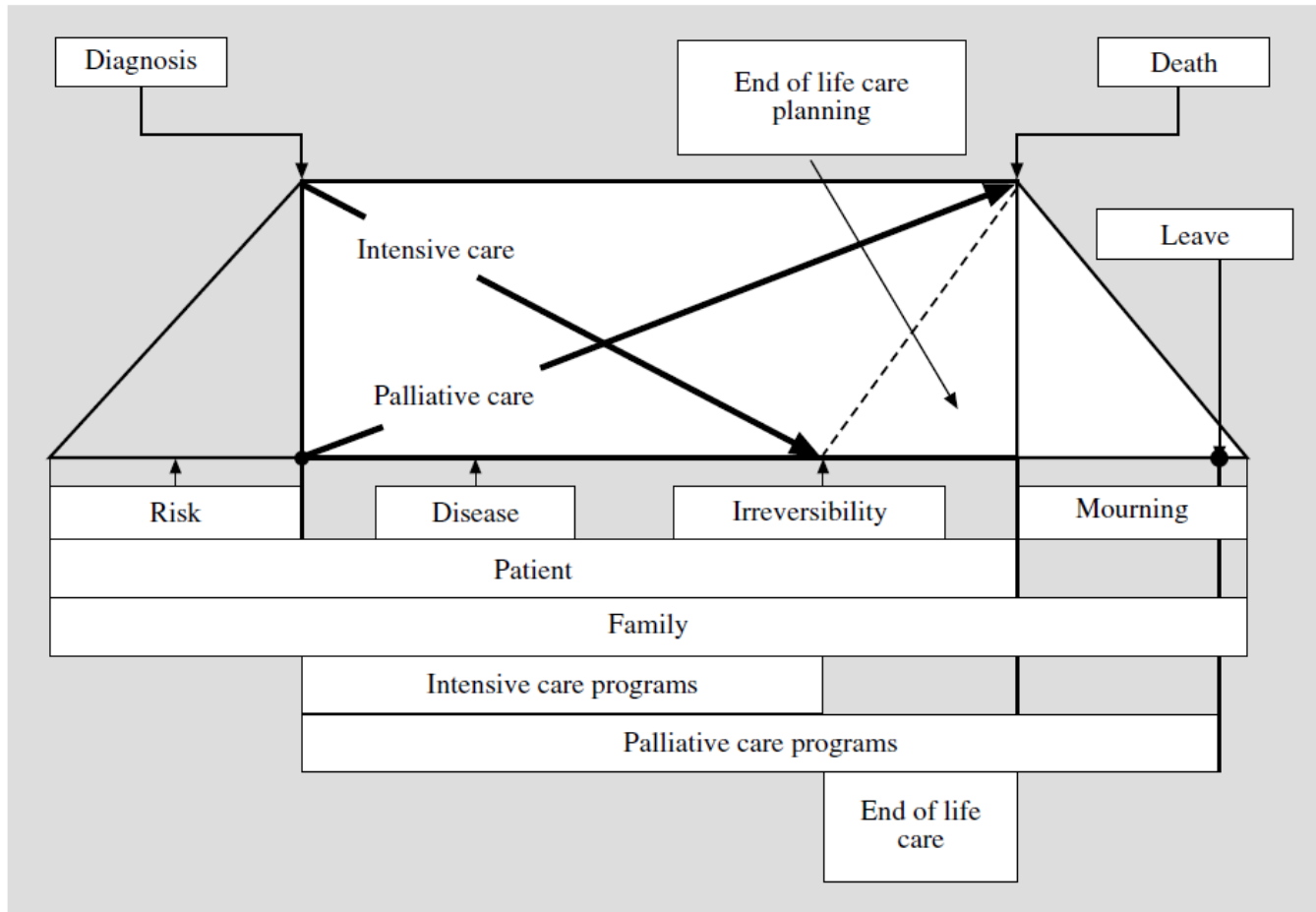
I, II, uncontrolled

III, IV: controlled

Controlled Donation After Circulatory Determination of Death in Spain



End-of-life care and intensivist





- three guiding principles:
 - the decision to withdraw life-sustaining treatment (WLST) must be independent of the possibility of organ donation. The family will not be approached about organ donation until the decision to withdraw life-sustaining treatment has been made and independently agreed, and the family has been involved in the decision and had accepted it,
 - “the dead donor rule and organ transplantation” must be strictly respected. This states that patients must be declared dead before any organs are removed and that interventions after WLST do not accelerate death [18],
 - if a patient had agreed to donate organs after their death, these patients should be offered the possibility to donate their organs in the case of planned end of life;

Treatment Futility

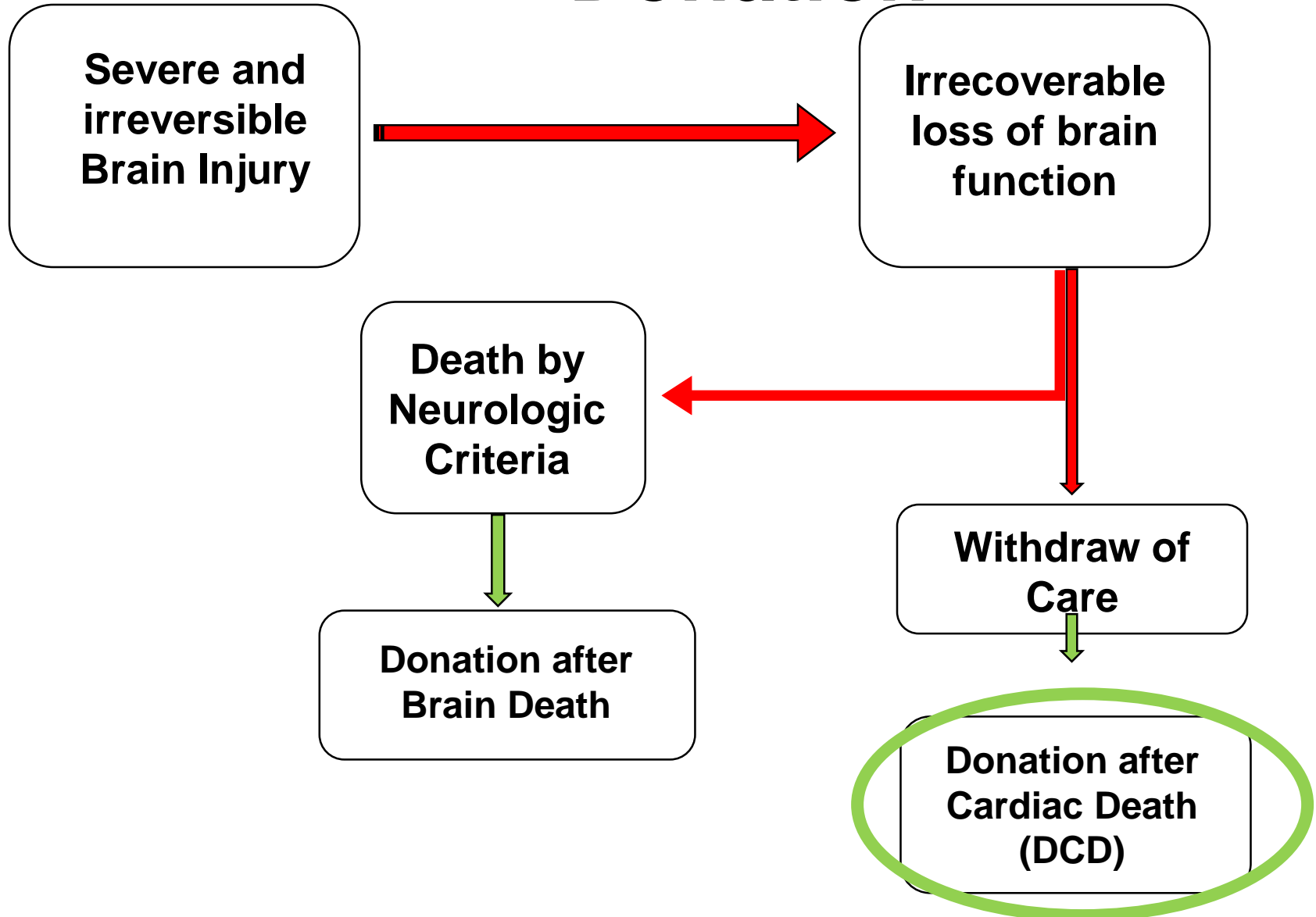
LINEE GUIDA SIAARTI

MINERVA ANESTESIOLOGIA 2003;69:101-18

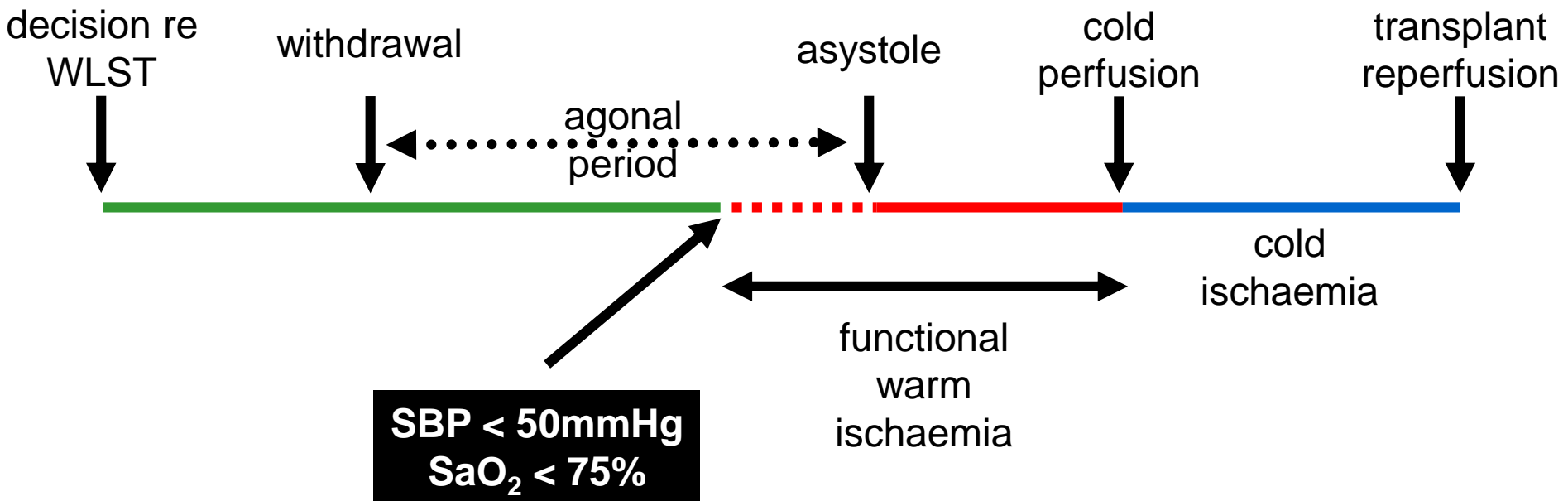
SIAARTI guidelines for admission to and discharge from Intensive Care Units and for the limitation of treatment in intensive care

GRUPPO DI STUDIO AD HOC DELLA COMMISSIONE DI BIOETICA DELLA SIAARTI

The Pathway to Organ Donation



Ischaemic injury

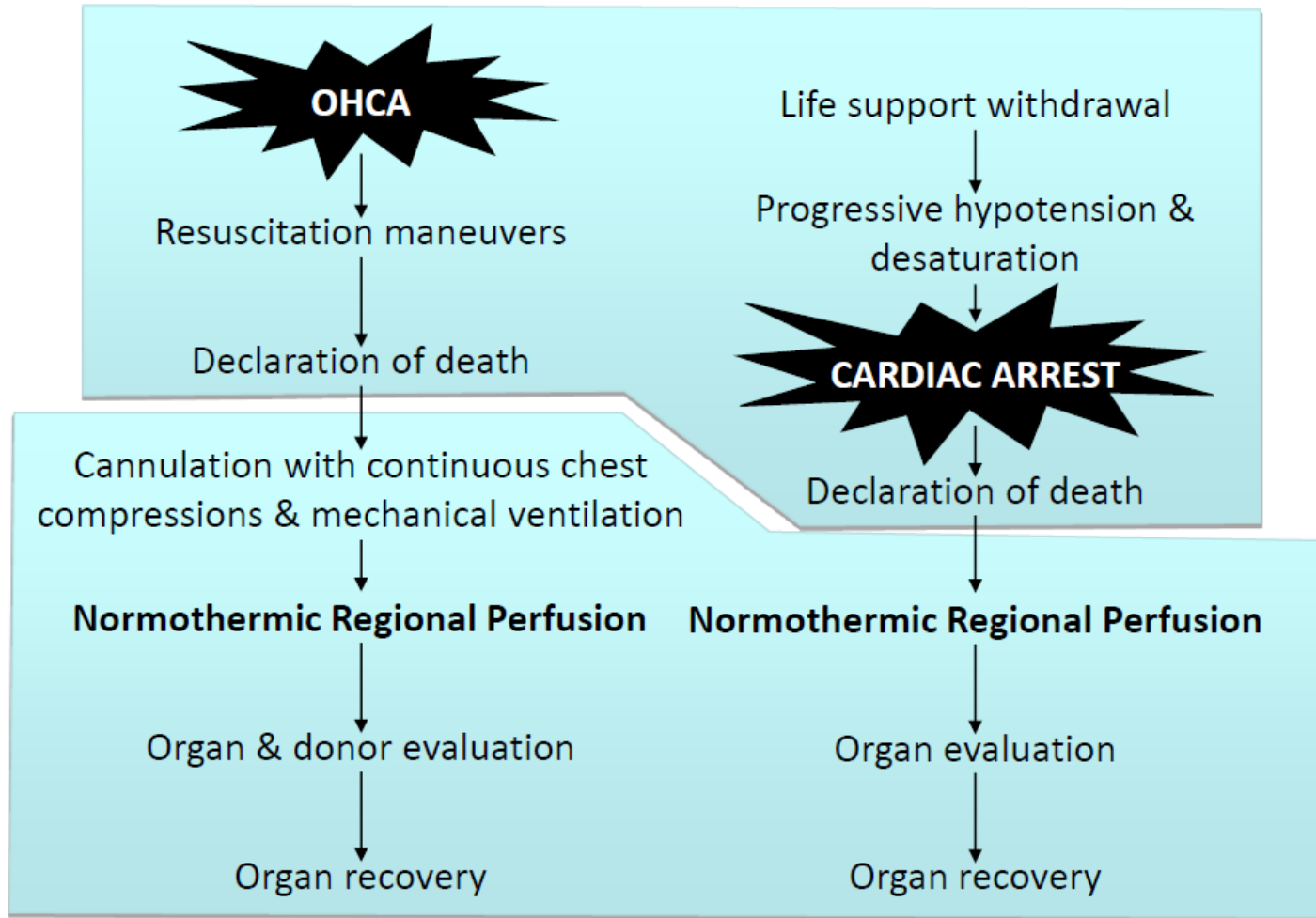


ISCHEMIA

Reconditioning

UNCONTROLLED DCD

CONTROLLED DCD



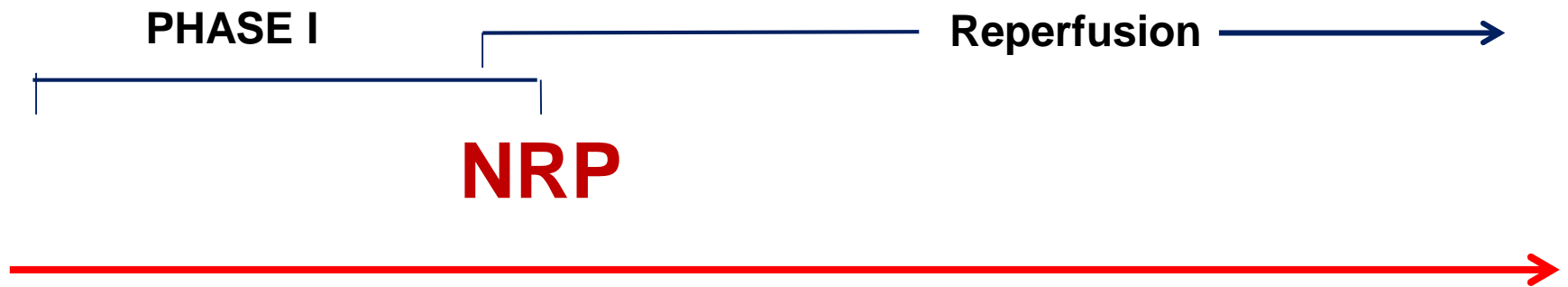


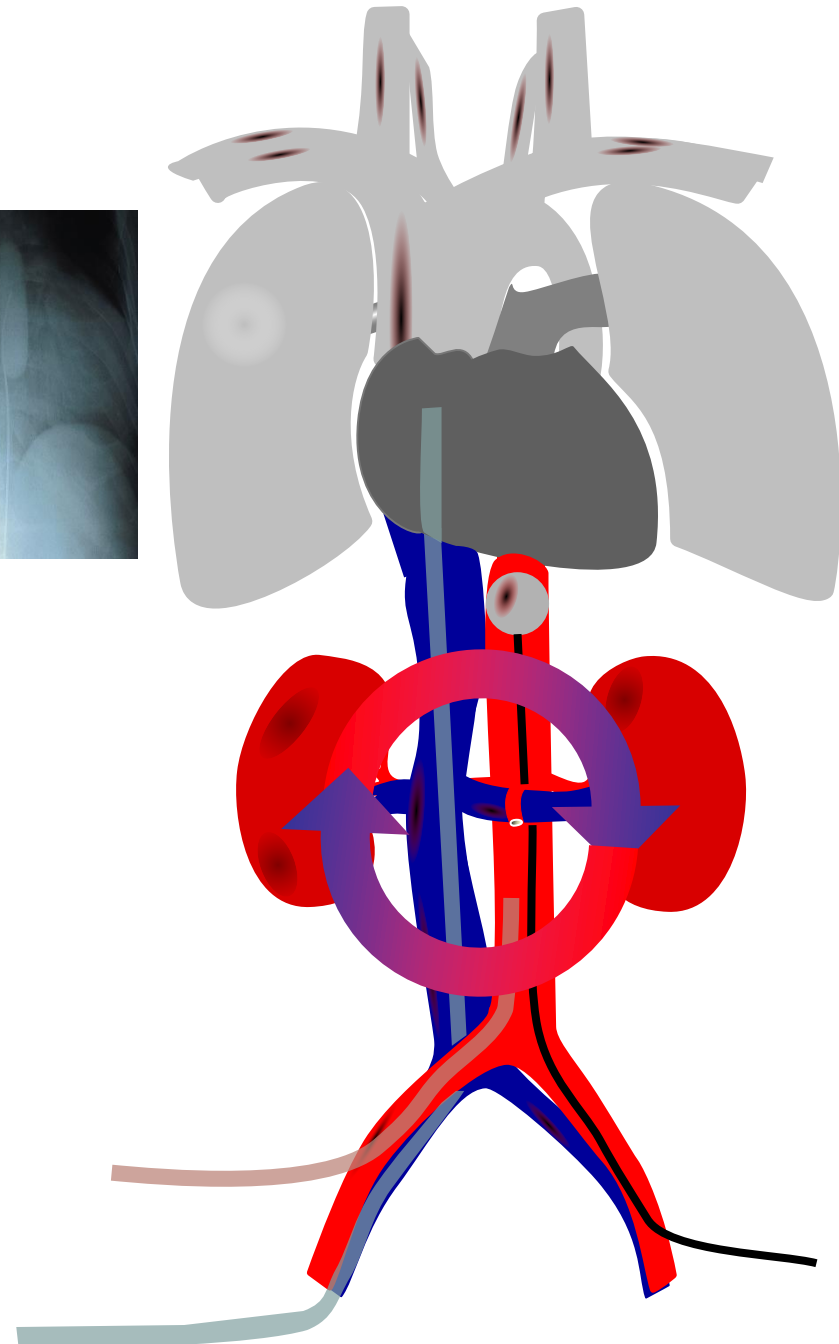
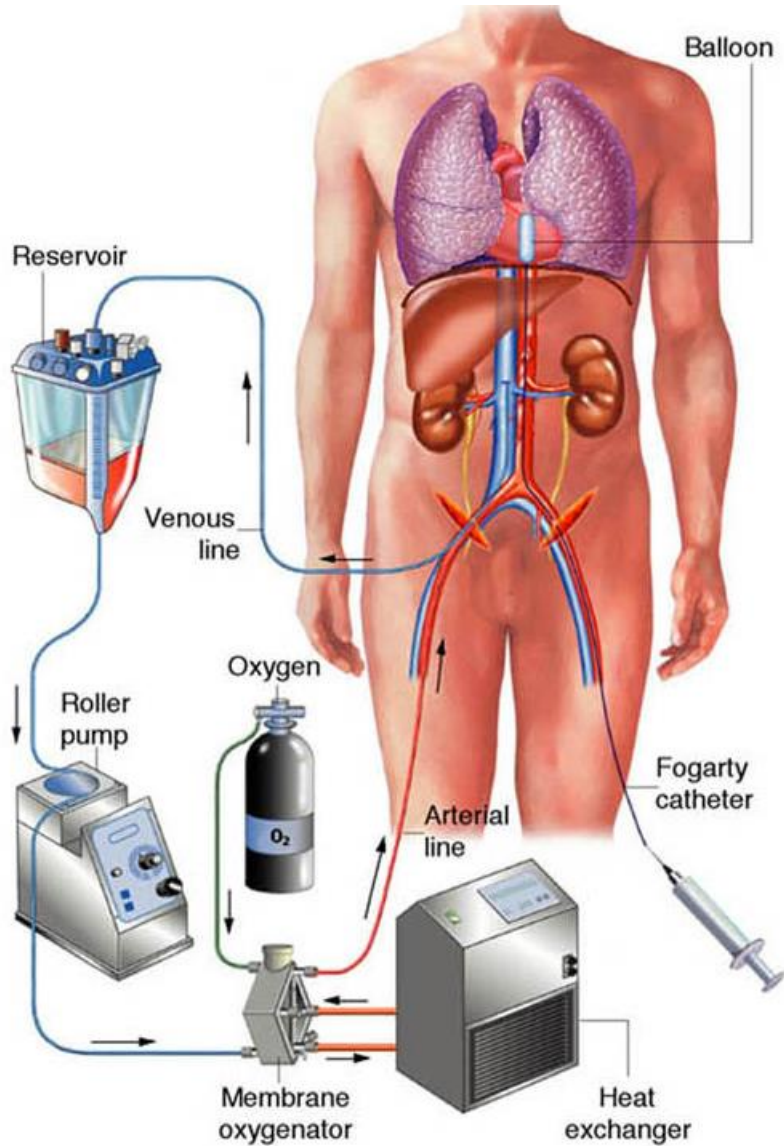
Table 1 Derangements in Cardiac Arrest

GLOBAL ISCHEMIA

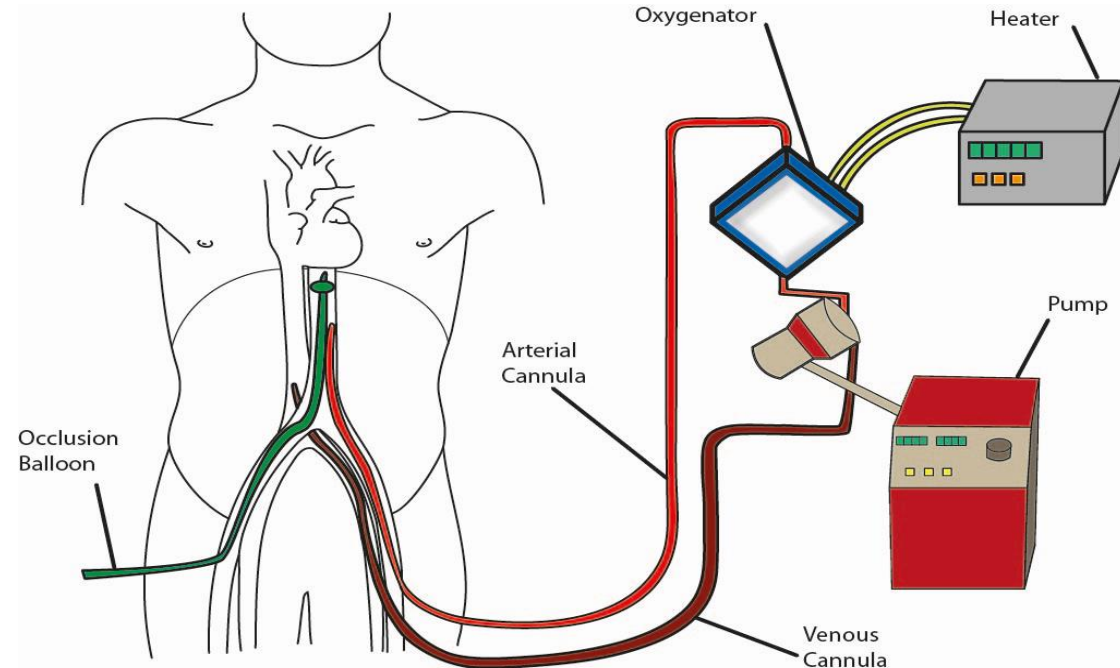
During Circulatory Arrest	After Circulatory Arrest
Potassium extracellular	Potassium intracellular
Calcium influx	Calcium outflow
Lactic acidosis, hydrogen ions	Free radical formation
Glutamate release	Glutamate release
Release of proteases, lipases, nucleases	Nitric oxide release
Flow arrest	Impaired microcirculation

RIPERFUSION INJURY

NORMOTHERMIC RECIRCULATION



Normothermic Regional Perfusion (NRP)



- Heparin bolus (300 UI/kg) before no touch period
- Femoral artery and vein cannulation
- Fogarty catheter inflated at the supraceliac aorta
- Pump flow during NRP : 1.7-3 l/min
- NRP time: 240-480 min

NRP could shift the warm ischemia time to an ischemic preconditioning



Aortic Balloon

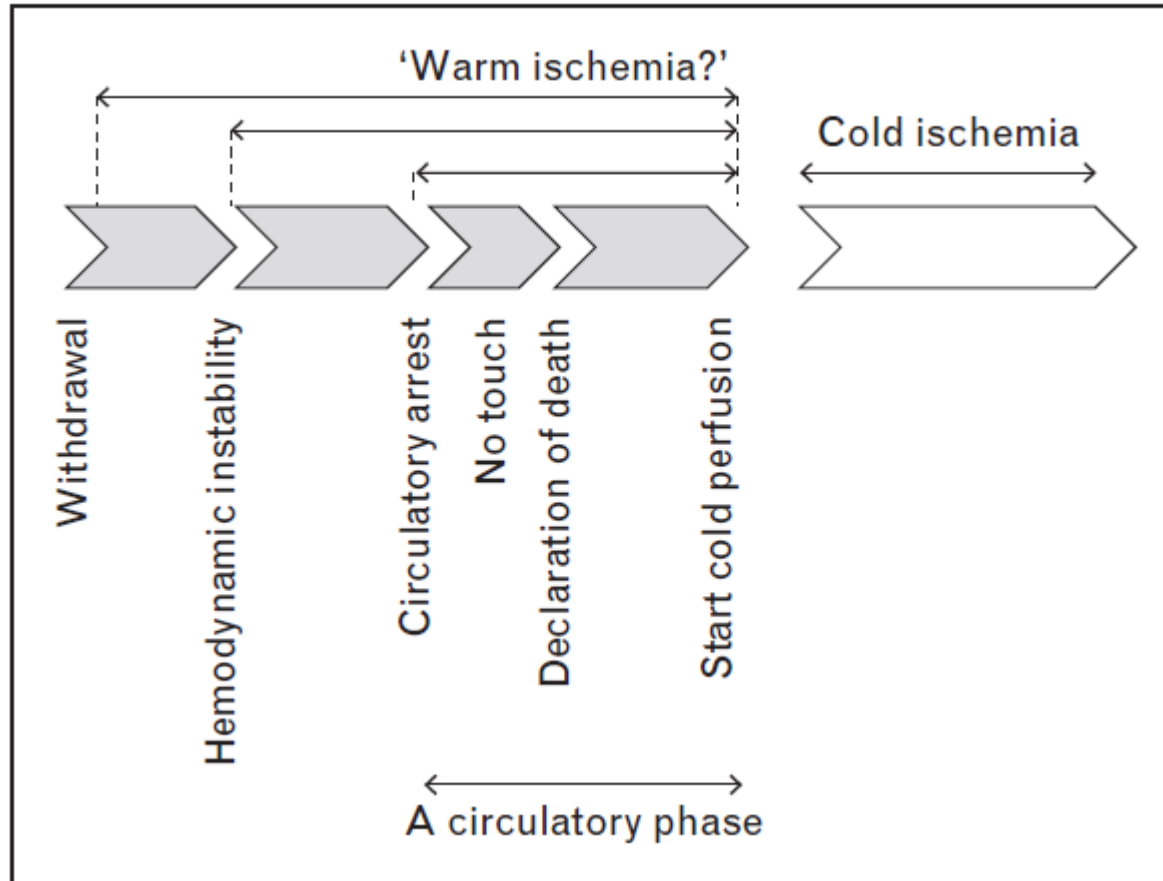
WHICH ARE THE BEST PREDICTORS OF SUBSEQUENT ORGAN FUNCTION, DURING NRP?

All studies examine short-term markers

**WARM
ISCHEMIA
TIME**

...very variable period of ischemic damage due to cardiac standstill (no-flow) followed by cardiac resuscitation (low-flow) with a varied degree of effectiveness.....**no-flow > 30 min** is associated to very poor graft survival.....

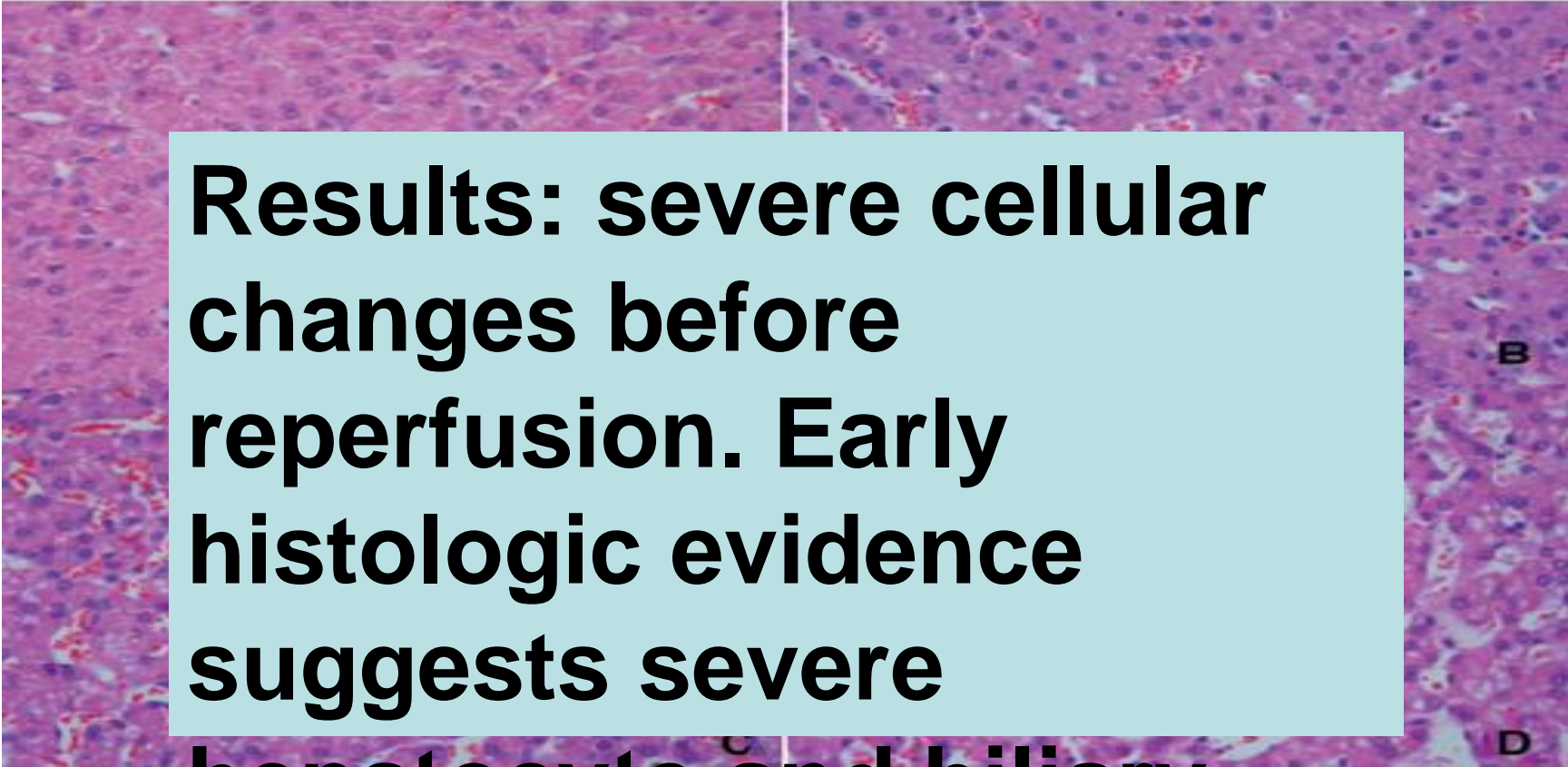
Definition of warm ischemia time



Curr Opin Anesthesiol 2013, 26:382–390

Donation after circulatory death: current status Neyrinck *et al.*

Relationship of hepatic circulation, renal circulation with oxygen saturation and mean arterial pressure in DCD III

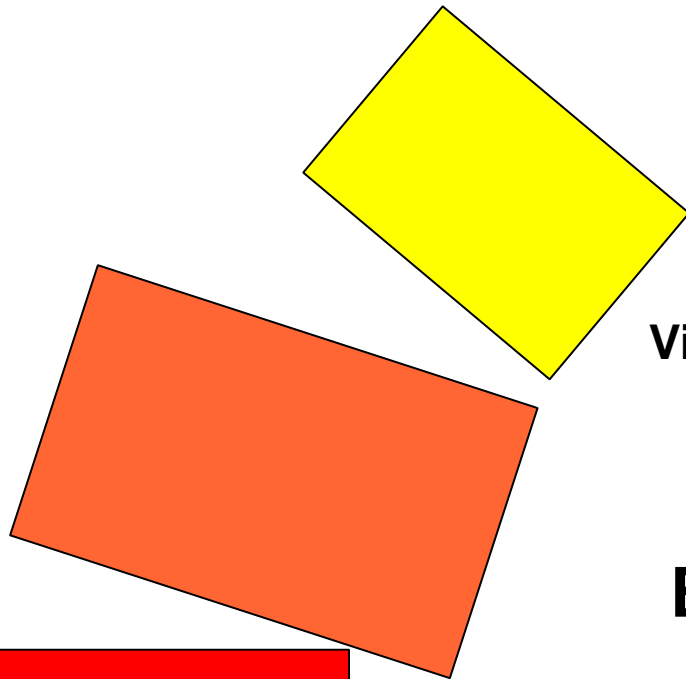


The image displays four panels (A, B, C, D) of liver tissue stained with hematoxylin and eosin (H&E). Panel A shows normal liver architecture with distinct hepatocyte cords and a central vein. Panel B shows early signs of cellular damage, including ballooning and nuclear changes. Panel C shows more pronounced cellular disruption and loss of normal architecture. Panel D shows severe cellular damage and significant architectural disorganization. A central text box overlays the images, summarizing the findings.

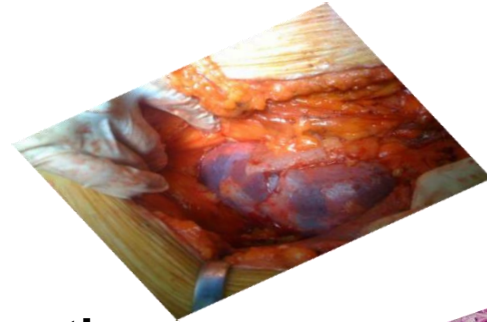
Results: severe cellular changes before reperfusion. Early histologic evidence suggests severe hepatocyte and biliary cell disruption

American Journal of Transplantation 2011; 11: 1169–1175

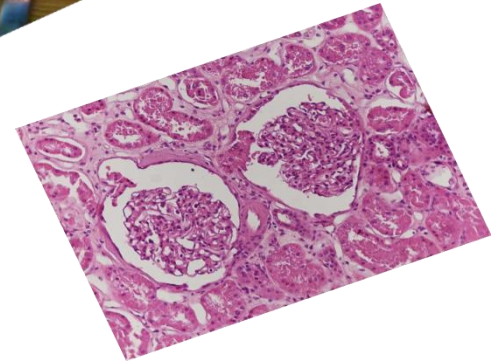
Viability assessment



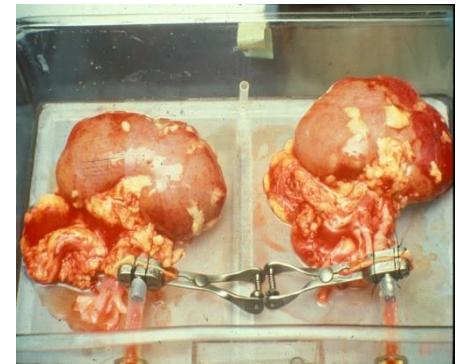
Visual inspection



Biopsy



Perfusion Machine

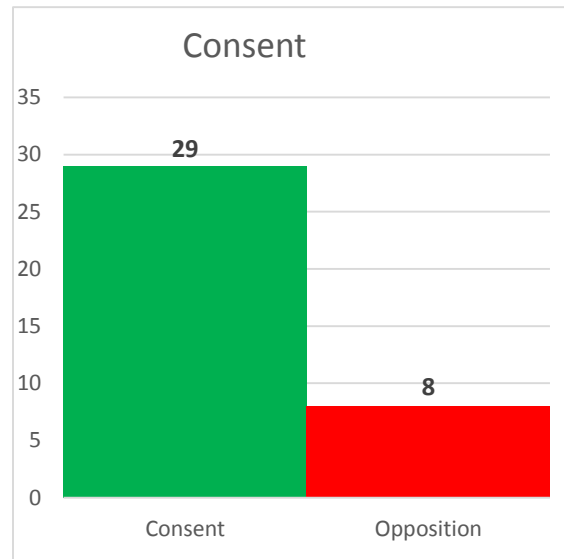


Results (sept 2008-march 2016): 65 potential DCD

63 unreversible CA/
2 severe brain injury

62 Male/3 female

Mean age 50yrs (36-63)

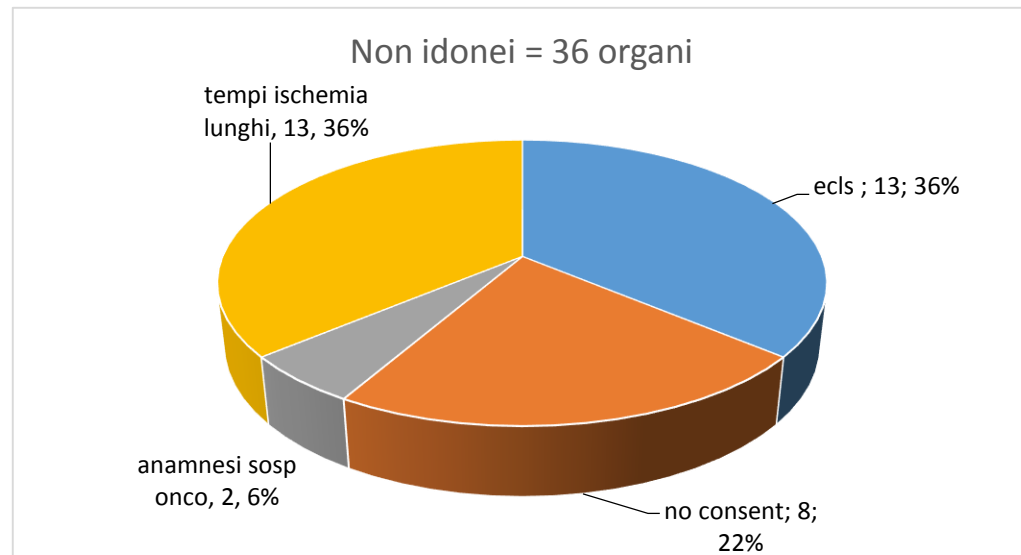


Mean no-flow 10,4 min

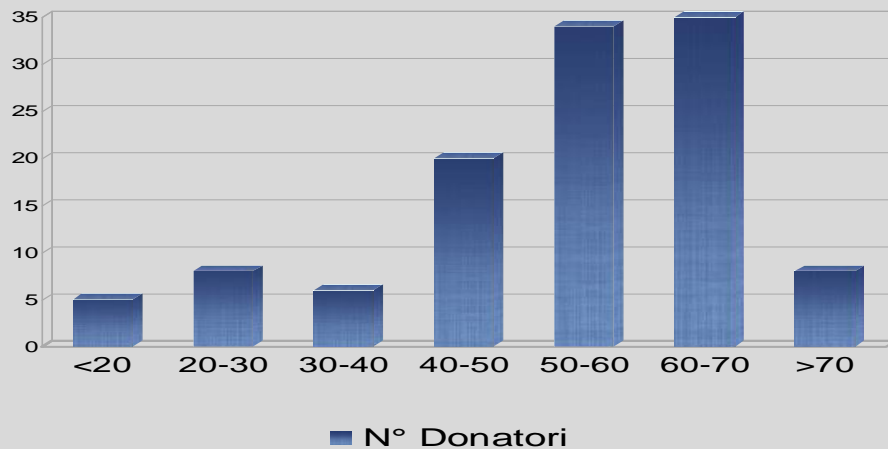
Mean low flow 72,8 min

Low-flow > 120 min 17 pts

29 effective DCD donors

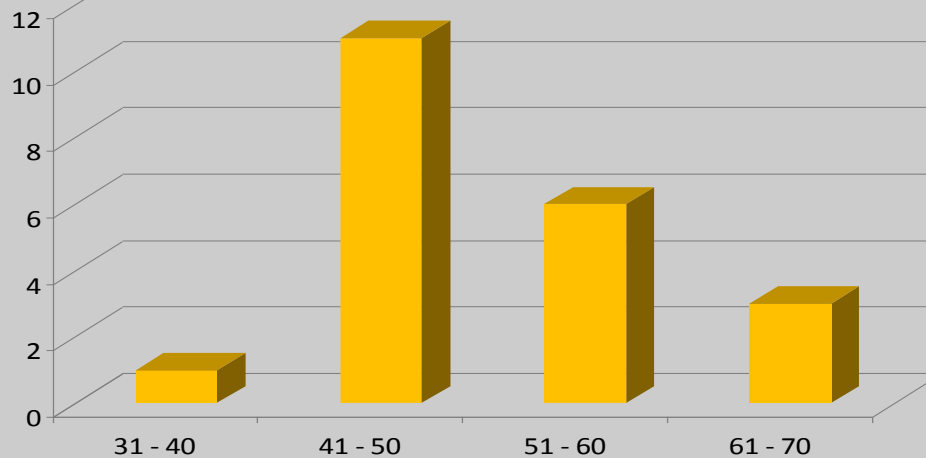


DBD AGE

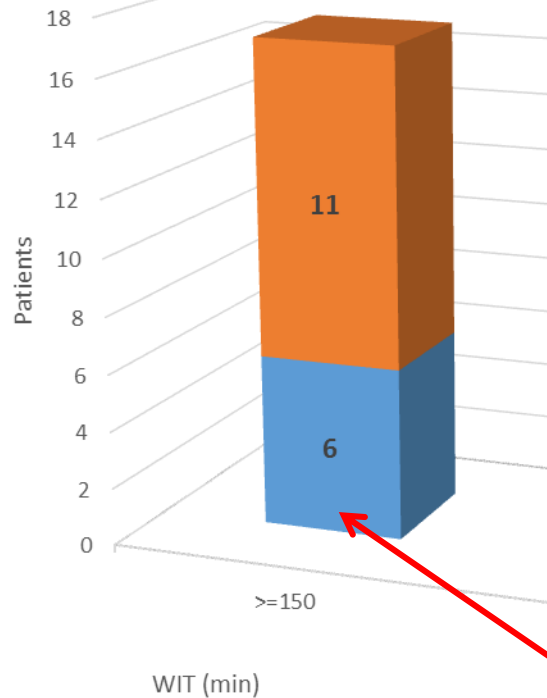


DCD AGE

Distribuzione per età



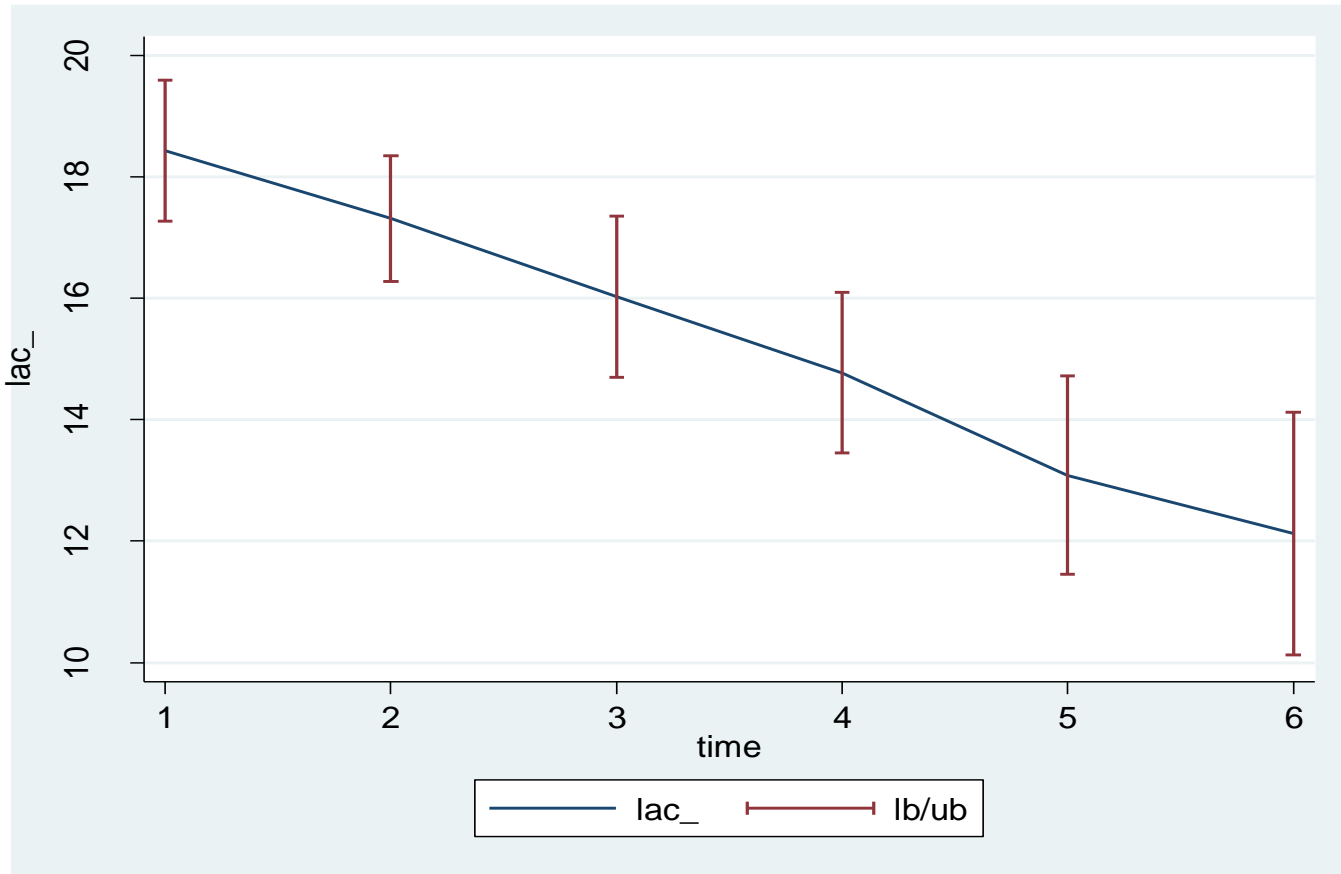
PAVIA
Donors' Age
HBD / DCD
2009/2016



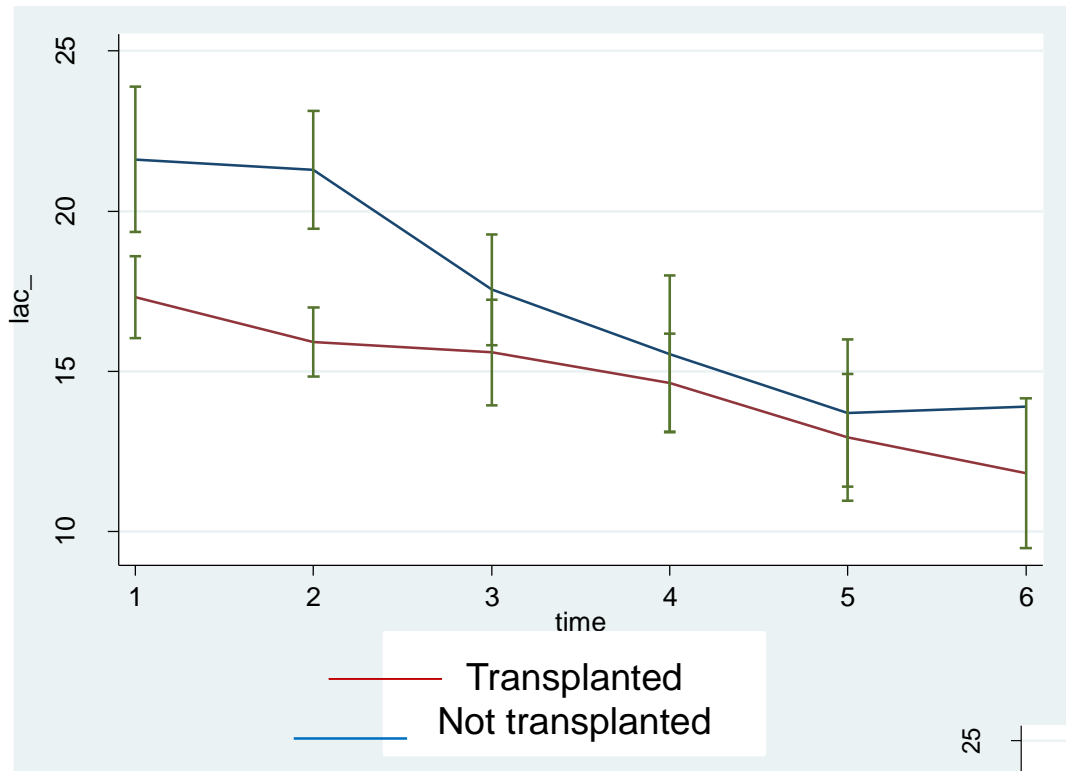
mean WIT 183,33 min

Mean WIT 163 min in effective donors

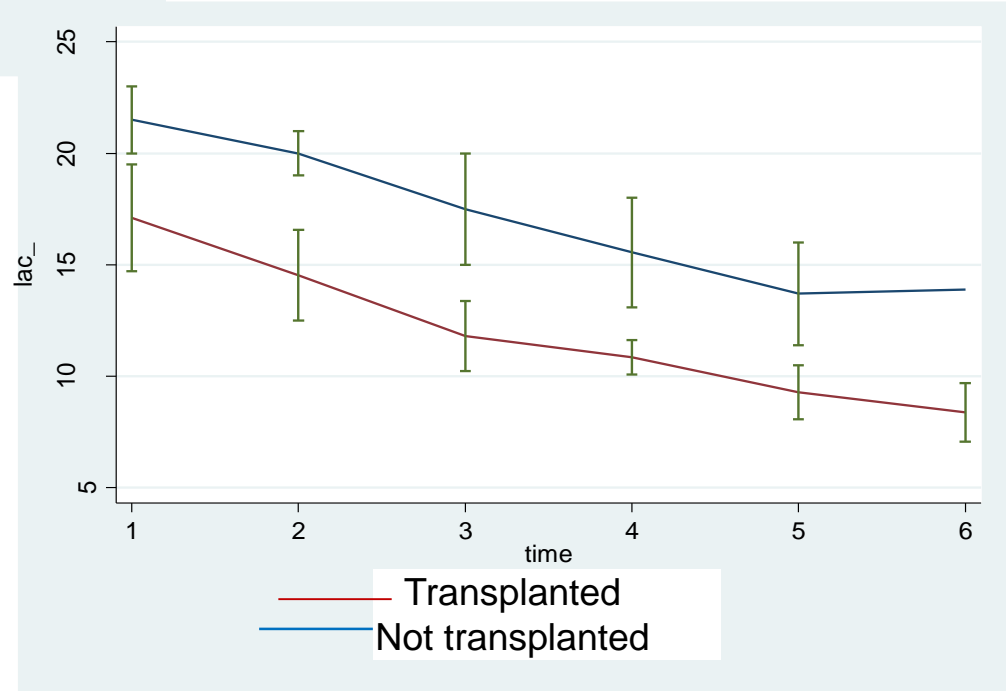
Lactate trend during NRP

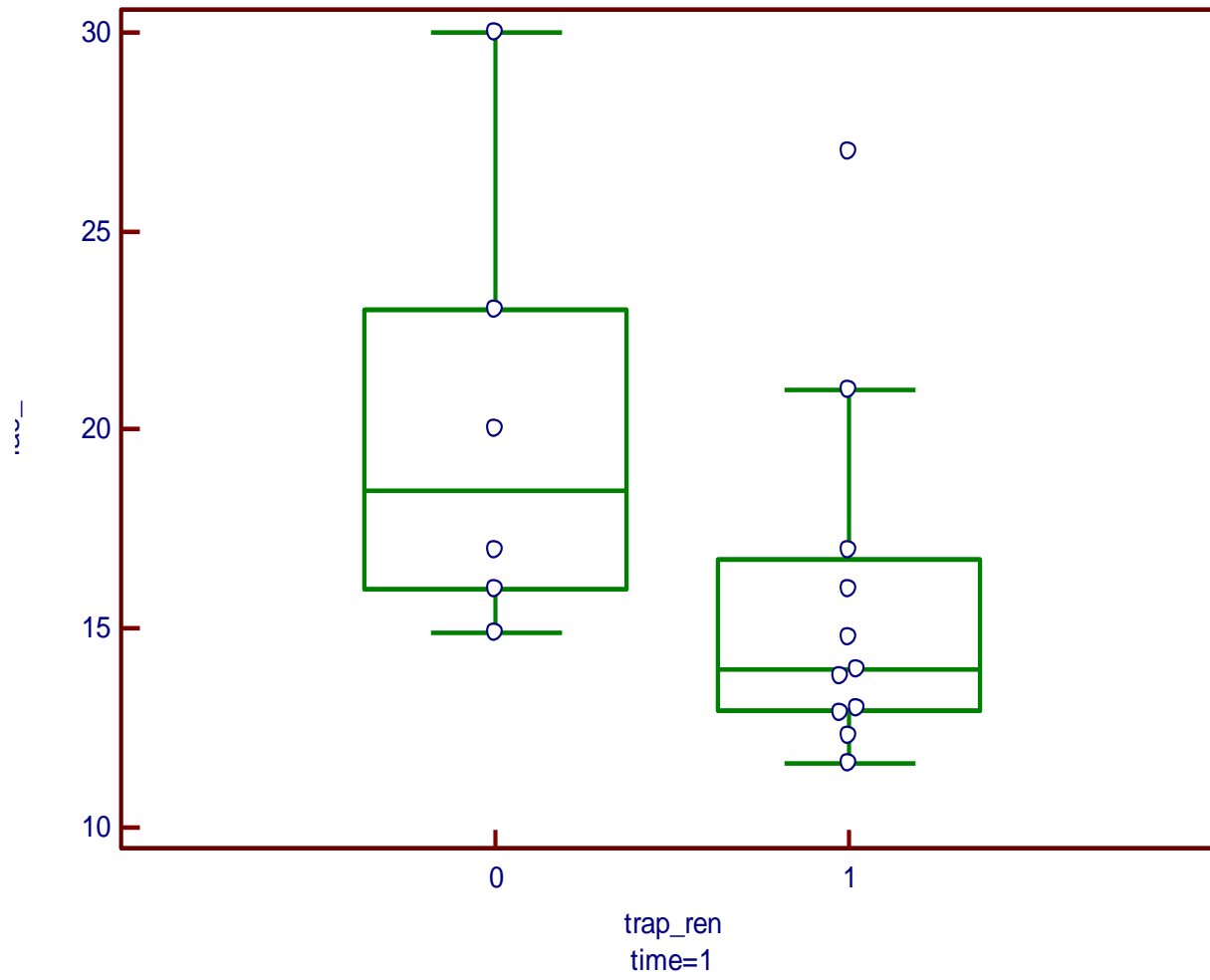


Lactate trend in kidneys transplant



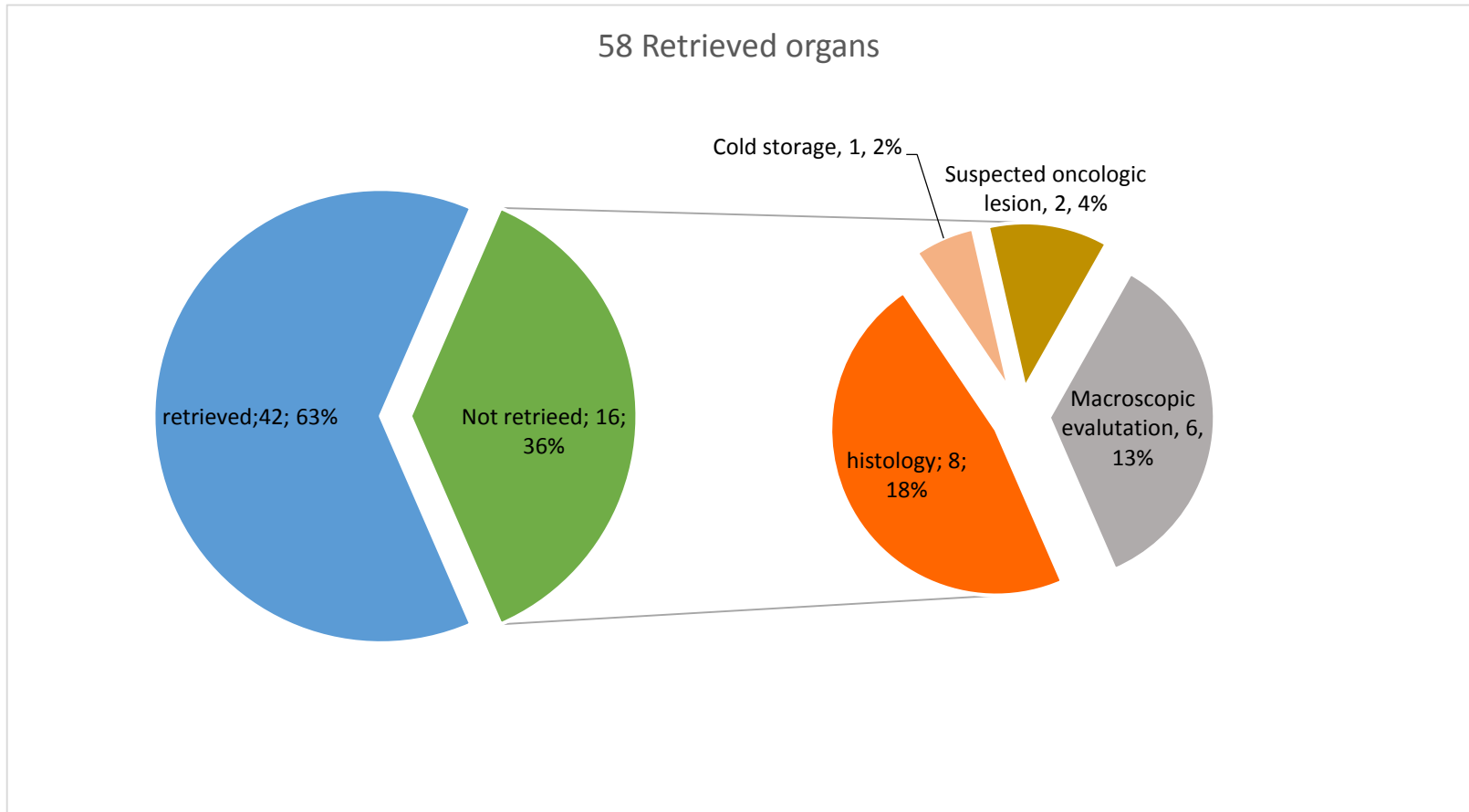
Lactate trend in livers transplant





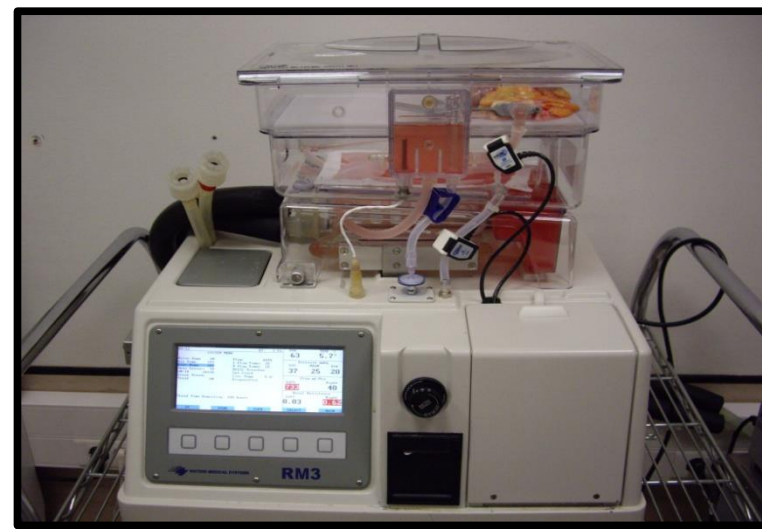
Data in press

Kidneys (58 grafts, 29 pts)



42 kidneys
retrieved
underwent Machine
Perfusion(4-18 hs)

Kidneys with
resistance > 0.4
were excluded



- 30 grafts were transplanted:
 - 21 in Pavia
 - 5 in other center
 - 4 no recipients

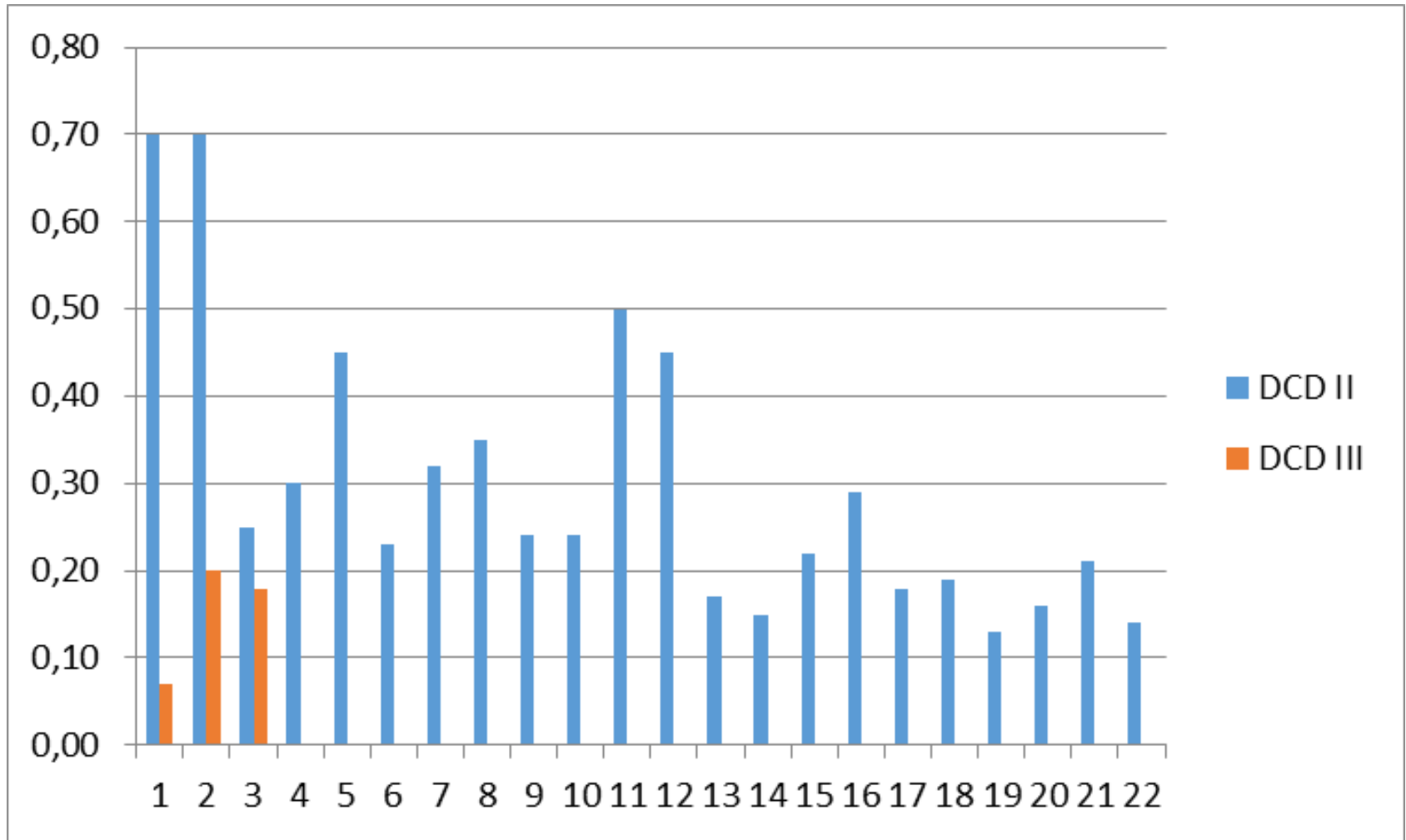
Advantages

Lower incidence of DGF
Continuous monitoring of
parameters during perfusion
Decreased intrarenal vasospasm
Ability to provide metabolic support
during perfusion
Potential for pharmacological
manipulation

Disadvantages

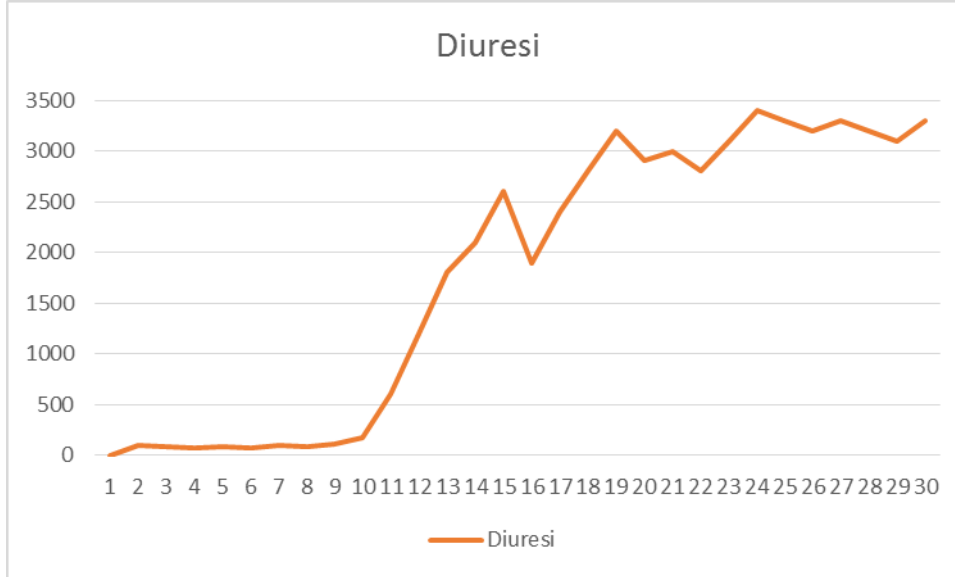
Higher cost in the short term^a
Endothelial injury is possible
Possibility of graft damage^b
Logistically more complex
Possible equipment failure

PERFUSION PARAMETERS



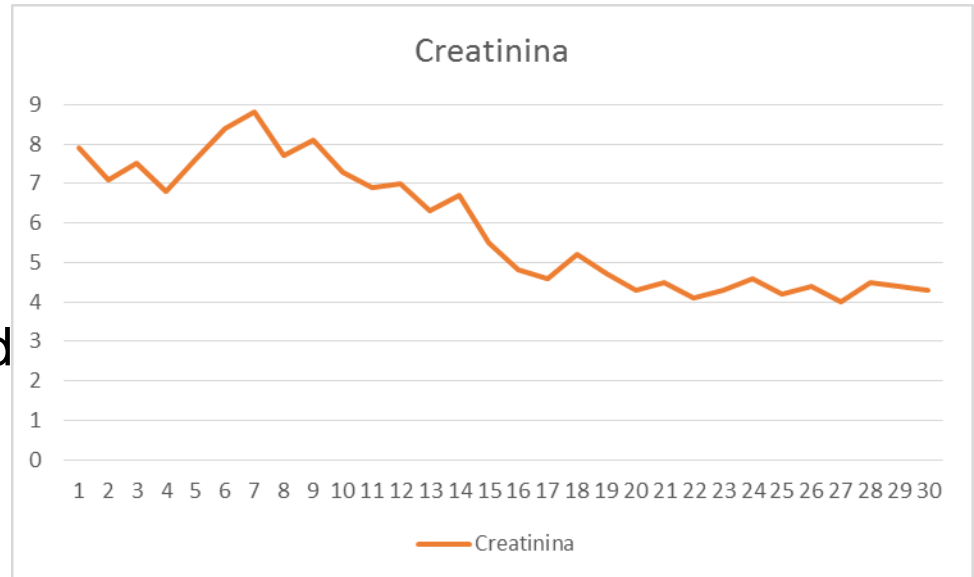
Mean resistance: 0.22
Mean flow: 0.95 ml/min

Kidney function assessment at 30 days



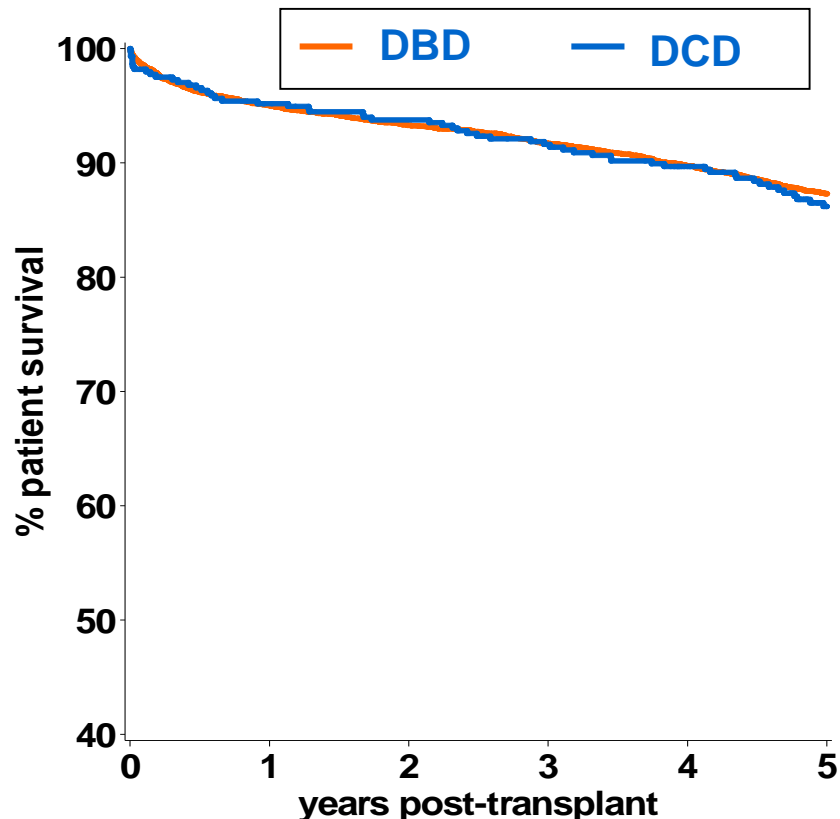
Histology showed severe tubular necrosis

During the first month serum creatinine is high, but this improves with time as renal tubular epithelium is regenerated



OUTCOME

Mean follow up was 4 years (min 1 yr,max 8 yrs)



PNF: 4% (1 pts)

DGF :75%

Acute rejection: 0%

1-year graft survival
98%

1-year patient survival
98%

Actuarial patient
survival:93,4%

Mean GFR during follow up was 43 ml/min without any statistical difference with BDD

Standard versus expanded versus DCD

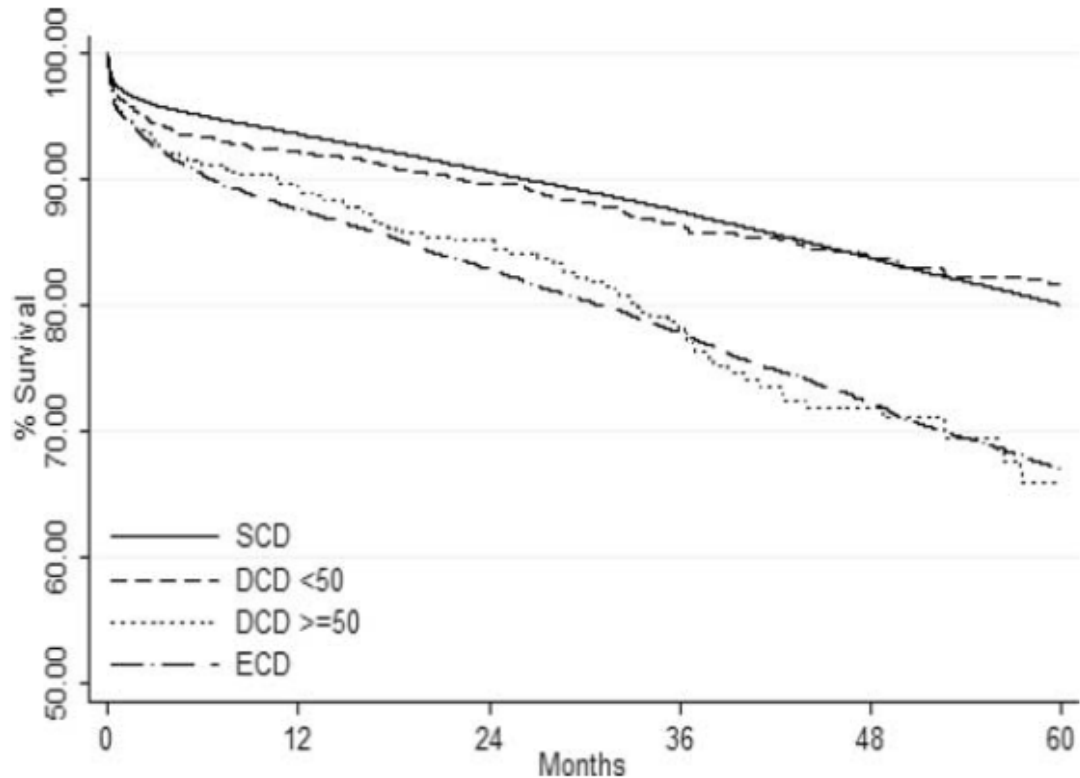
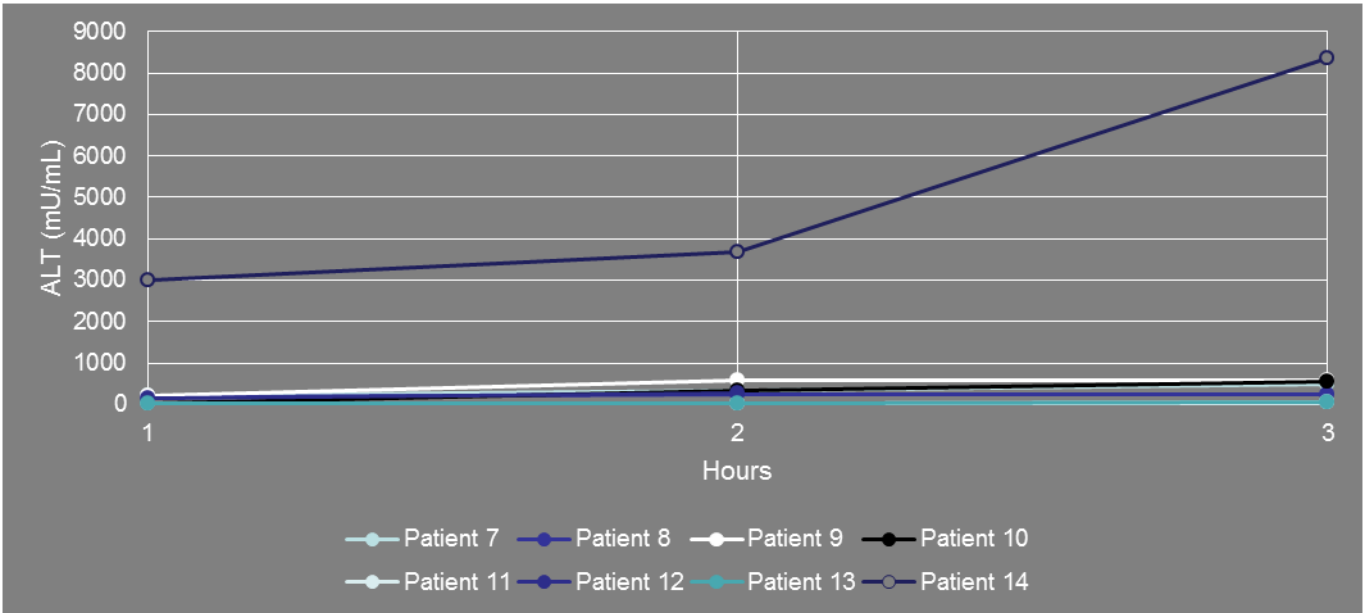
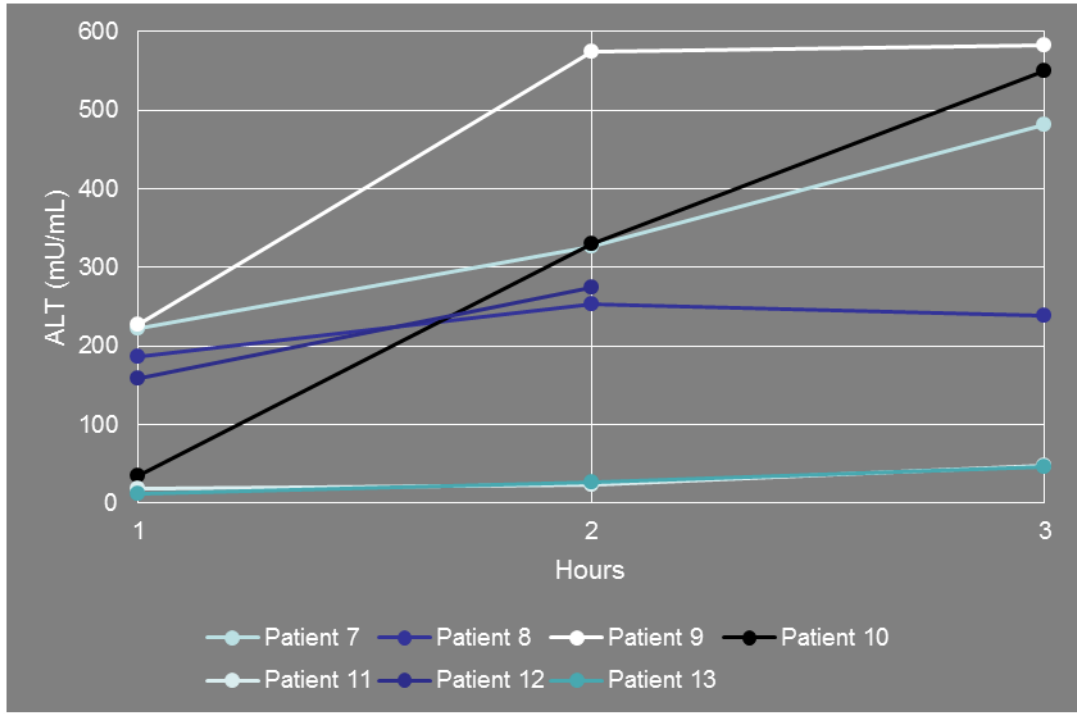


Figure 3. Kaplan–Meier (KM) death-censored graft survival (DCGS) curves for recipients of standard criteria donor (SCD) kidneys, donation after cardiac death (DCD) kidneys from donors younger than 50 years, DCD kidneys from donors older than 50 years and expanded criteria donor kidneys (ECD). With regard to 5-year DCGS, SCD kidneys and DCD kidneys from donors younger than 50 years have equivalent outcomes, and ECD kidneys and DCD kidneys from donors older than 50 years have equivalent outcomes.

Liver

9 cases: 7 DCD II
2 DCD III



**ALT TRENDS
DURING NRP**

TABLE 2. Histological Evaluation of Biopsies From 127 DCD Liver Grafts

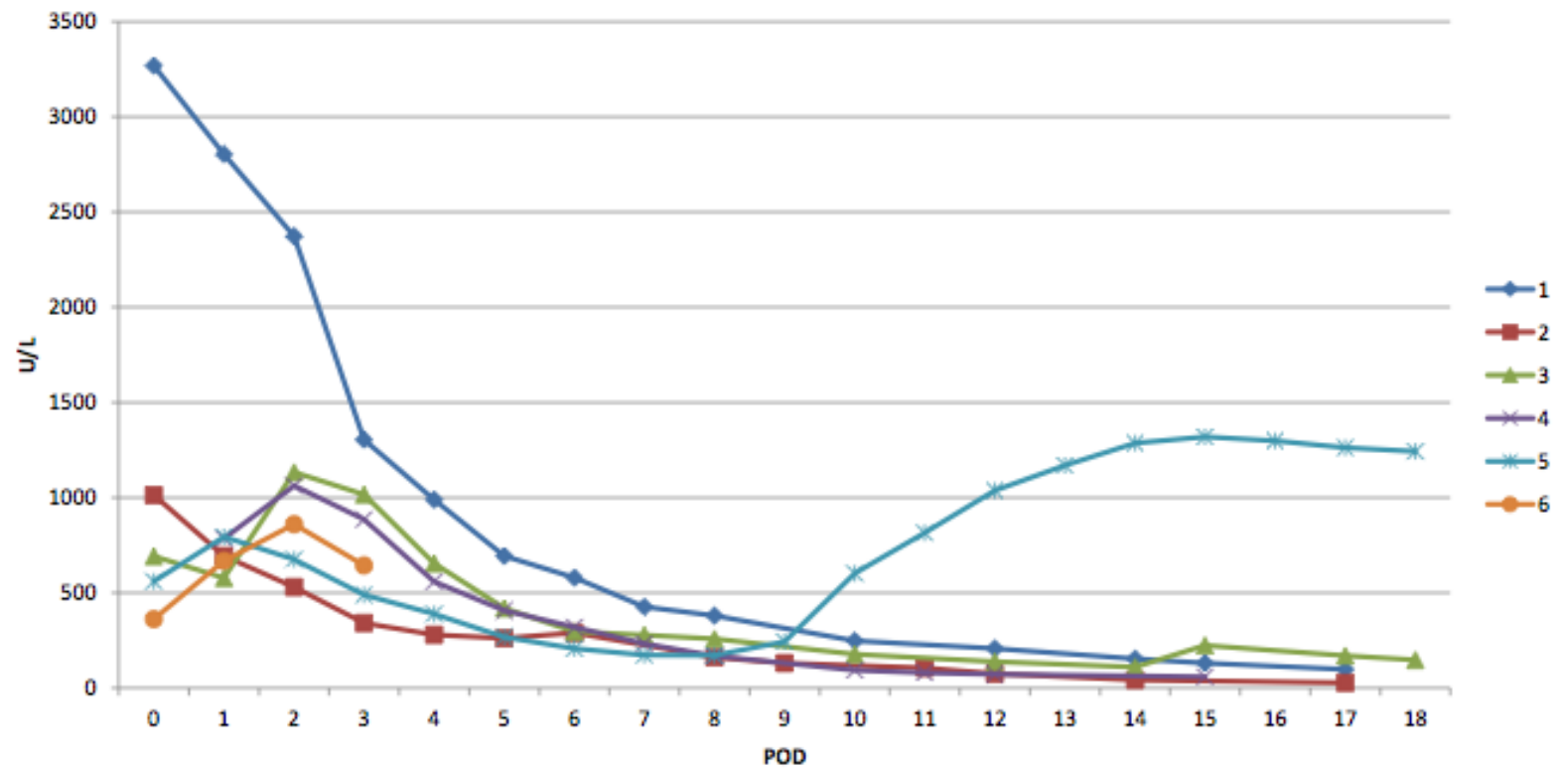
Characteristics	Classification (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Macrovesicular steatosis*	111 (87.4%)	6 (4.7%)	10 (7.9%)	0
Hepatocellular swelling	27 (21.3%)	30 (23.6%)	42 (33.1%)	28 (22.0%)
Hepatocellular vacuolation*	118 (92.9%)	5 (3.9%)	4 (3.1%)	0
Hepatocyte necrosis	96 (75.6%)	21 (16.5%)	10 (7.9%)	—
Sinusoidal neutrophilic infiltrate*	118 (92.9%)	5 (3.9%)	2 (1.6%)	2 (1.6%)

Micro: Pur con i limiti legati alla procedura di congelamento, la struttura lobulare appare conservata. Steatosi macrovescicolare (35-40% circa) e microvescicolare (40-50%).
 Infiammazione cronica portale di grado lieve della maggior parte degli spazi portalici.
 Infiammazione cronica periportale di grado lieve della maggior parte degli spazi portalici.
 Necrosi confluyente centrolobulare (zona 3): 15-20% circa.

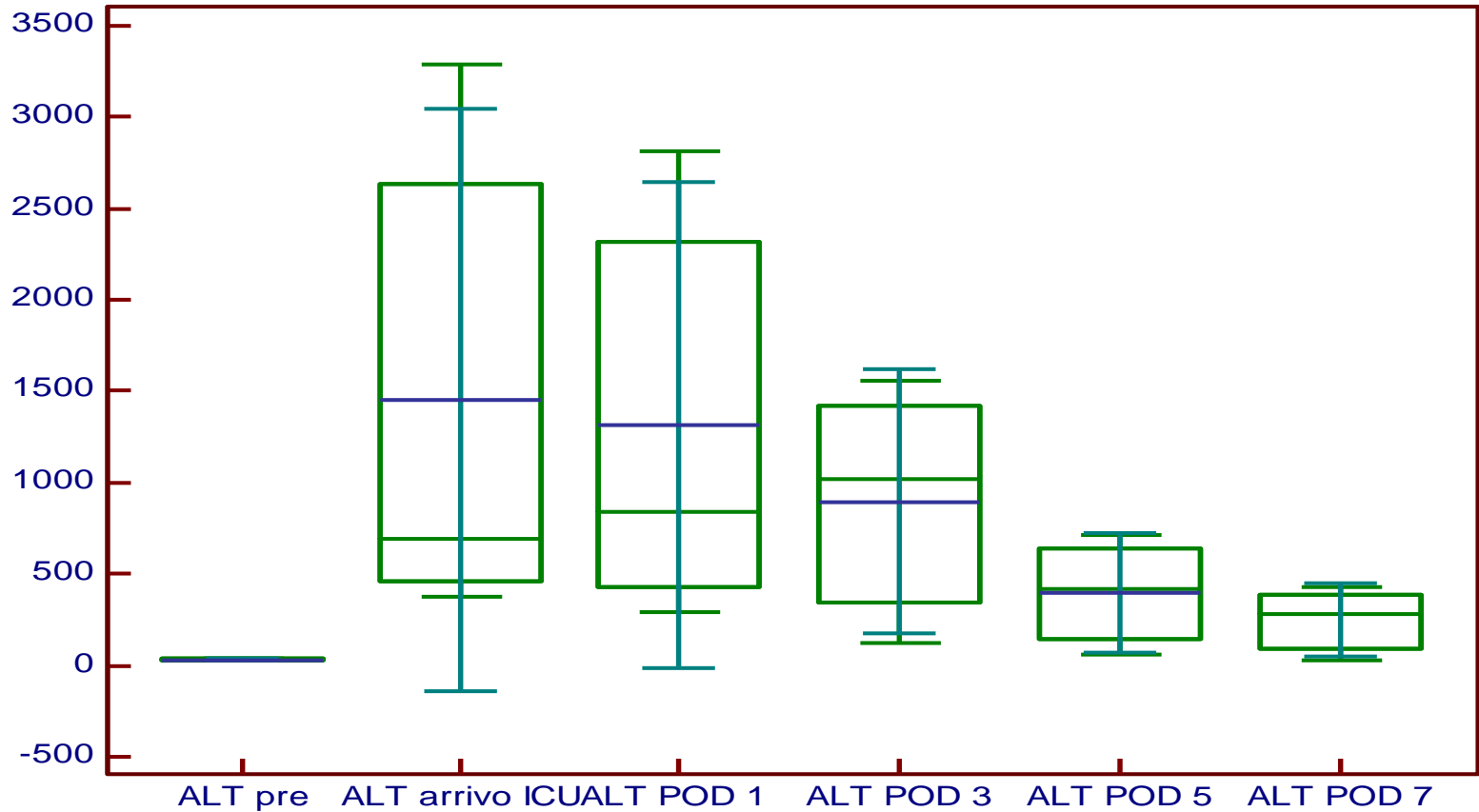
Hepatocellular vacuolation	0.044 (0.000-110.844)	0.23
Hepatocellular swelling		
Grade 1 (reference)	—	—
Grade 2	0.995 (0.270-3.666)	0.53
Grade 3	1.261 (0.338-4.703)	0.08
Grade 4	0.255 (0.046-1.412)	0.97
Hepatocyte necrosis		
Spotty (reference)	—	—
Confluent	0.397 (0.085-1.853)	0.35
Zonal	0.681 (0.121-3.838)	0.20

Postoperative course

ALT



Postoperative course ALT



liver grafts experience inferior graft survival mainly related to higher rates of biliary strictures. In con-

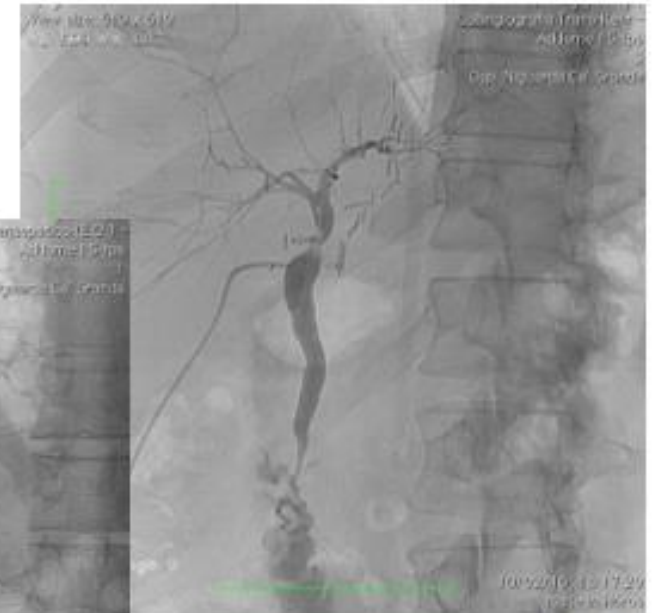
3-months trans-Kehr cholangiogram



case 1



case 2

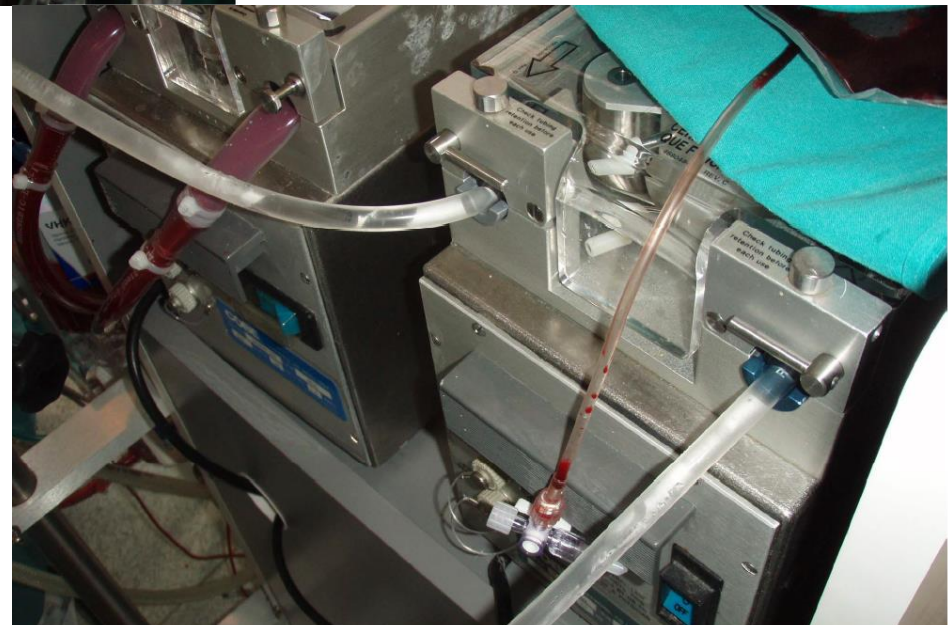


case 3

No biliary complications during the 3-months follow-up

**.....And the
lungs?**

Dual preservation



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

Franco Valenza^{1,2,*}, Giuseppe Citerio^{3,4},

Issue



Cardio-circulatory death

absence of respiration and pulse pressure after 5 min of no-touch
20 minutes of asystole on EKG.



Exclusion criteria

un-witnessed collapse, no flow > 15 min, low flow > 60 min



In situ Preservation

recruitment maneuvers - CPAP - low frequency protective ventilation



Ex Vivo Lung Perfusion

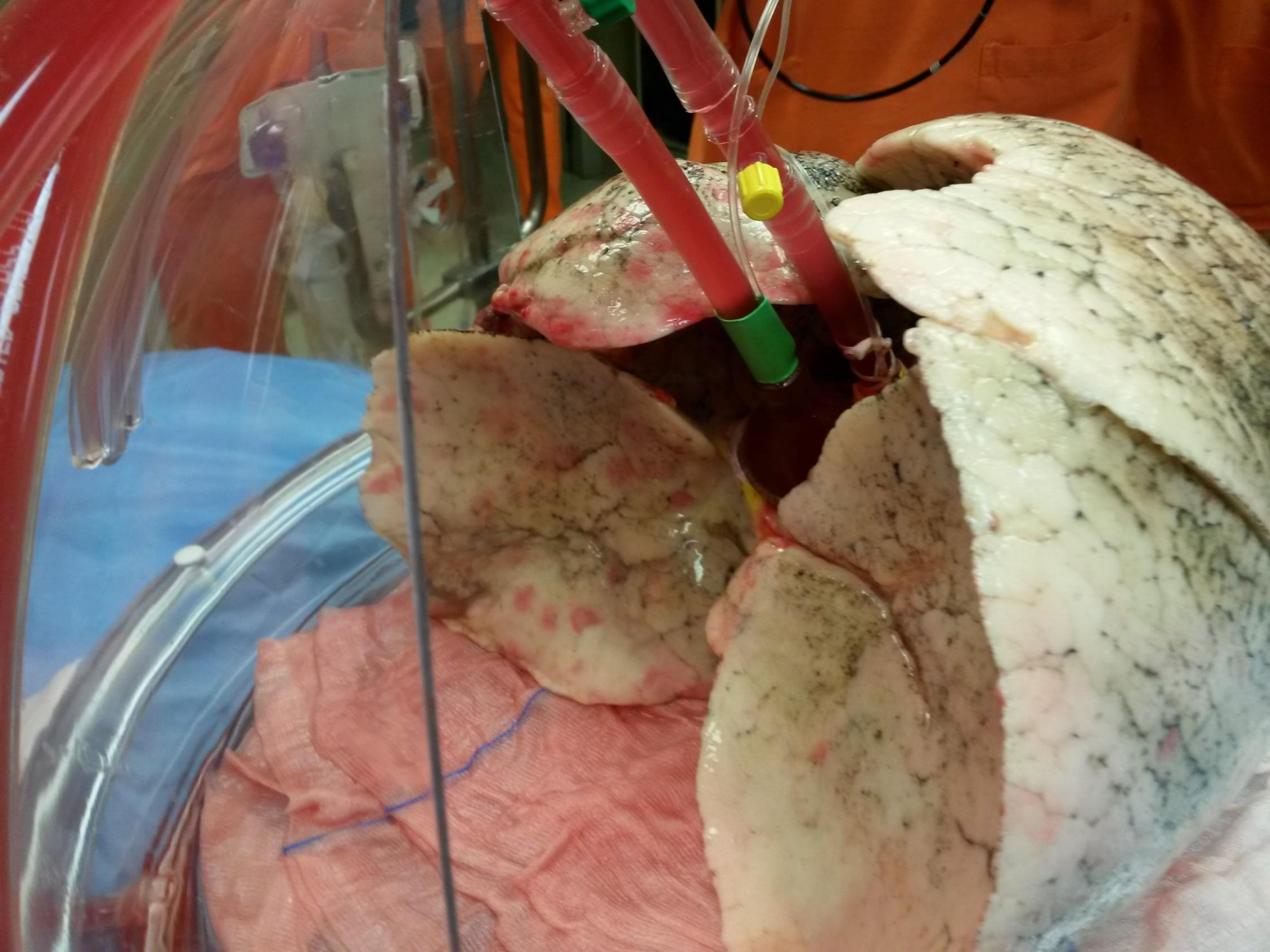
reconditioning - evaluation



Transplantation

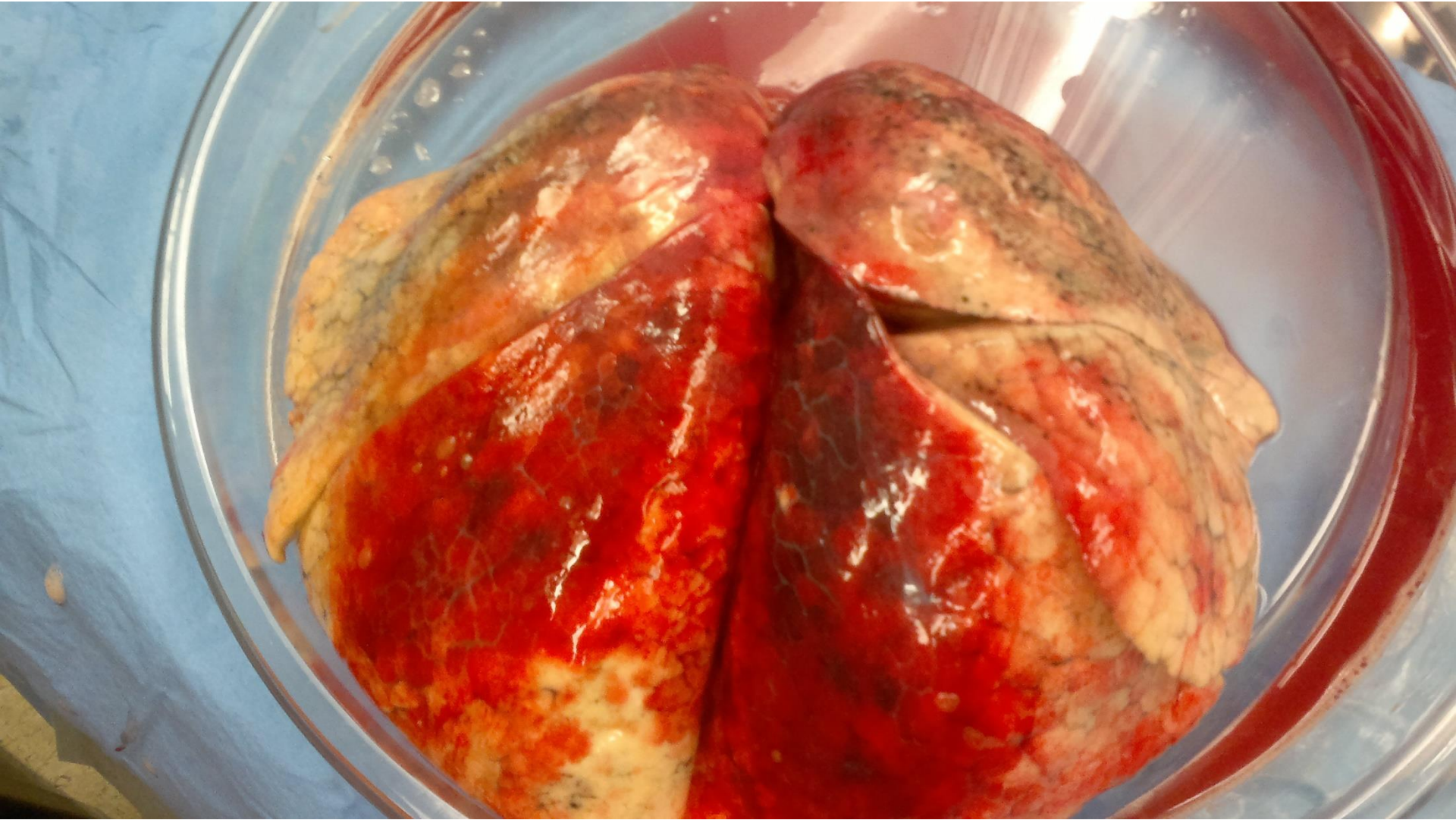


Follow-up









Conclusion 1

First, the question emerged about a conflict of interest between patient care and potential organ procurement. In this cohort, resuscitation duration was always longer than recommended. Secondly, to avoid any potential conflict of interest,

Specific time and legal constraints of this emergency procedure implied a highly coordinated multidisciplinary teamwork in order to preserve organ function.

Conclusion 2

The key element of **in-situ NRP** is to maintain the organs in a normal physiological state providing oxygen and nutrients to support aerobic metabolism

There is the need to improve the quality of these graft by **ex-situ preservation technique** which increases the chance of immediate function after transplantation

