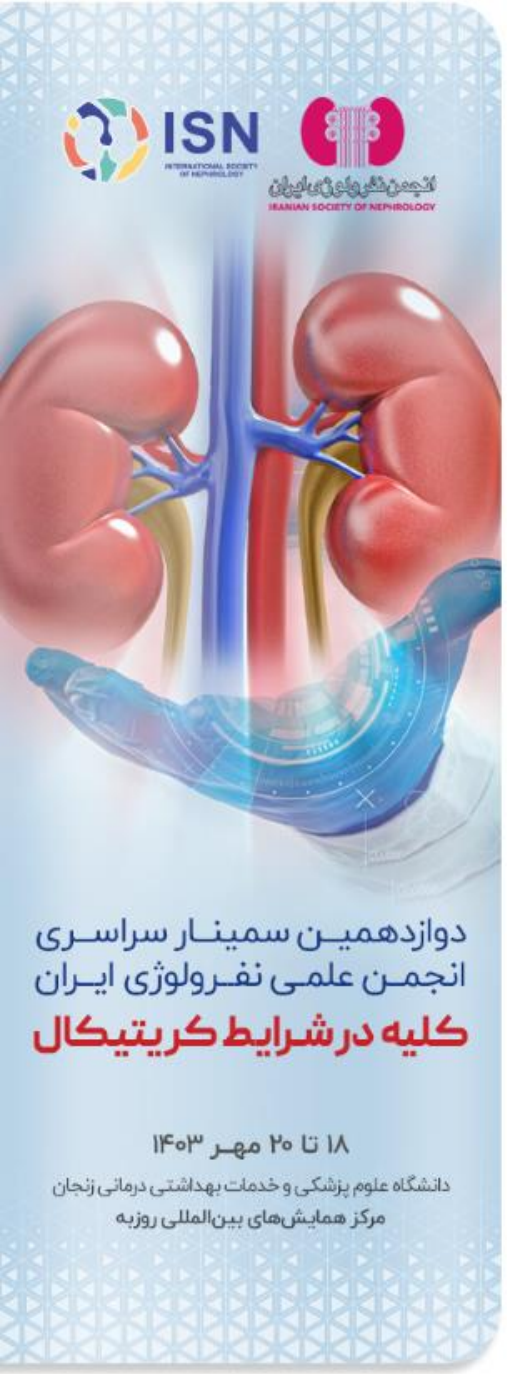


Organ Protection In Deceased DONORS

Farahnaz Dadras, MD

Iran University Of Medical Sciences

Firoozgar Hospital

Introduction

- **Mortality on the waiting list** for transplantation remains high.
- **Organs** from deceased potential donors are often refused because of **suboptimal quality.**
- **Adequate donor management** to **maximize the number of organs** that can be offered for donation is essential to expanding the donation pool.

Intensive Care Med (2019) 45:343–353

Management of the brain-dead donor in the intensive care unit

Jan Gunst[1]* and Michael J. Souter[2]

- **Optimal donor management** is essential in the intensive care unit and the operating room to **maximize the function** of transplanted organs.

- The **quality of life** and **survival benefits** are conveyed to the recipients.

Intensive Care Med (2024) 50:964–967

GENERAL CONSIDERATIONS

- Management of the potential organ donor primarily involves the use of **conventional therapeutic** and **supportive measures** to **reverse or mitigate** the **physiologic changes** that occur **after brain death,** including potentially severe **autonomic** and **inflammatory** responses.

Hemodynamic support and electrolyte management

- **Hemodynamic instability** is probably the **number one challenge**, or at least the most obvious one, in the management of the brain-dead donor.

- A **primary devastating injury to the brain** and/or brain stem results in a massive immediate **activation of the sympathetic nervous system**.

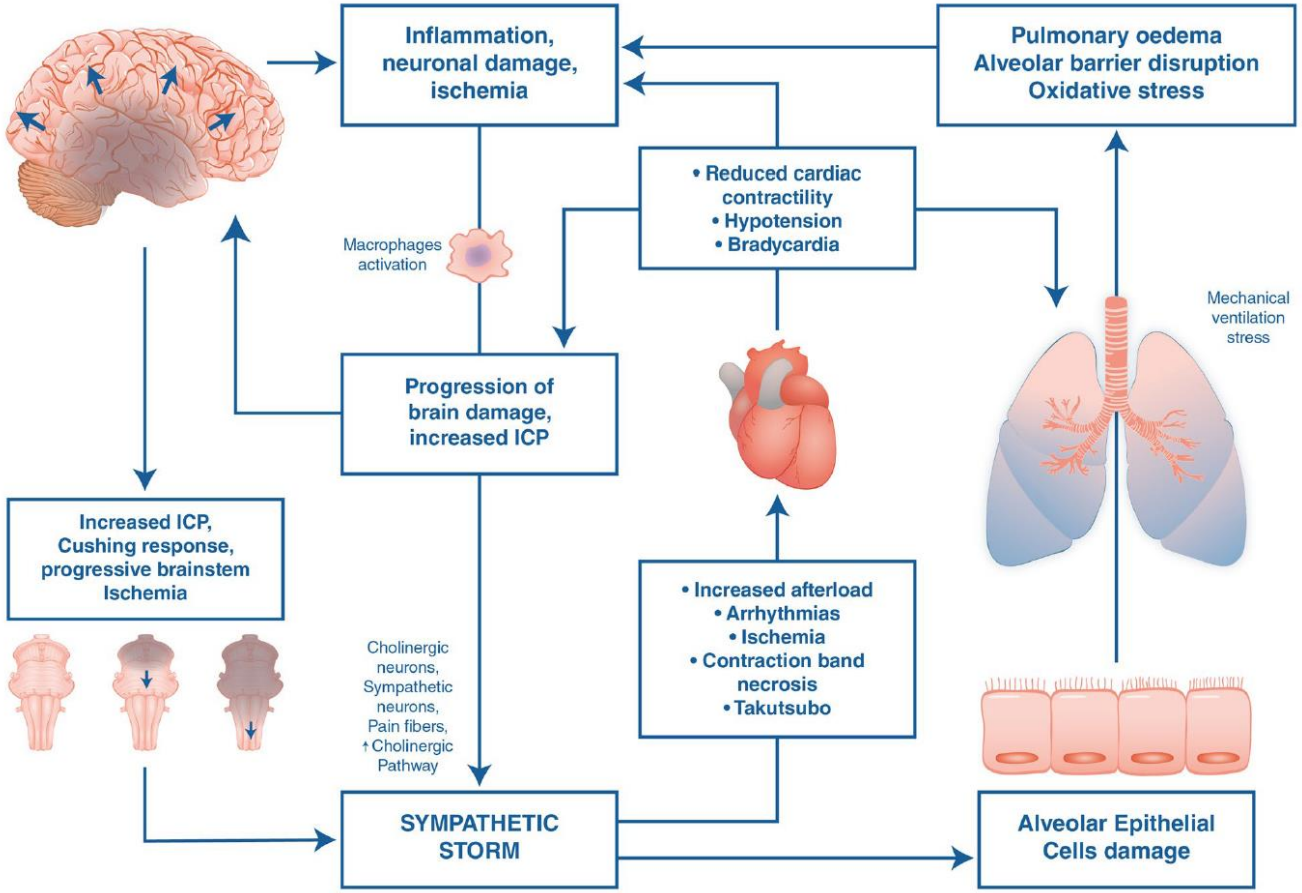
Intensive Care Med (2019) 45:343–353

Cardiovascular management

- The **catecholamine 'storm'** caused by cerebral injury leading to brainstem compression initially increases in:
- **arterial blood pressure,**
- **afterload,**
- **left atrial pressure**
- **pulmonary hydrostatic pressure**
- **pulmonary vasoconstriction,**
- **endothelial damage**
- **may lead to cardiac muscle damage(40-50%)**

Intensive Care Med (2019) 45:343–353

Overview of the sympathetic storm and the pro-inflammatory cascade caused by devastating brain injury with brain stem ischemia



- **Hypertensive autonomic storm**
- Beta-adrenergic antagonists such as esmolol may ameliorate the cardiovascular effects and preserve myocardial function.

- Transplantation 2006,82(8):p 1031-1036

- After **brainstem infarction**, **loss of sympathetic tone** frequently leads to profound **vasoplegia** and **hypotension**, which if left untreated, can lead to

  global hypoperfusion of all solid organs.

- Therefore, the **primary goal** of hemodynamic management is to maintain

  organ perfusion through judicious use of **intravenous fluids** and **vasopressors.**

- **Mean arterial pressure 60-65 mmHg**
-

Intensive Care Med (2019) 45:343–353

- As with every hemodynamic problem, **identification of the cause** of the instability (i.e. **fluid depletion**, **reduced cardiac output**, **vasoplegia**, …)

  is crucial to determine the right therapy.

- **Hemodynamic shock states** should be **evaluated** using
- **invasive arterial blood pressure** measurements**,**
- **lactate levels**,
- (**mixed) venous oxygen saturations**,
- **echocardiography** to evaluate myocardial contractility and exclude other cardiac pathology.

Protocolized fluid therapy in brain-dead donors: The multi-center randomized MOnIToR trial

Ali Al-Khafaji, MD, MPH[1,2], Michele Elder, RN[1,2], Daniel J Lebovitz, MD[3], Raghavan Murugan, MD, MS[1,2], Michael Souter, MB,ChB,FRCA[4], Susan Stuart, RN, MPM[5], Abdus S. Wahed, PhD[6], Ben Keebler, EMT-P, CPTC[7], Dorrie Dils, RN[8], Stephanie Mitchell, RN[9], Kurt Shutterly[5], Dawn Wilkerson, RN[11], Rupert Pearse, MD[10], John A Kellum, MD[1,2], and **on behalf of the Monitoring Organ Donors to Improve Transplantation Results (MOnIToR) Study Investigators[*]**

[1]Center for Critical Care Nephrology, Department of Critical Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA.

Intensive Care Med. 2015 March ; 41(3): 418–426

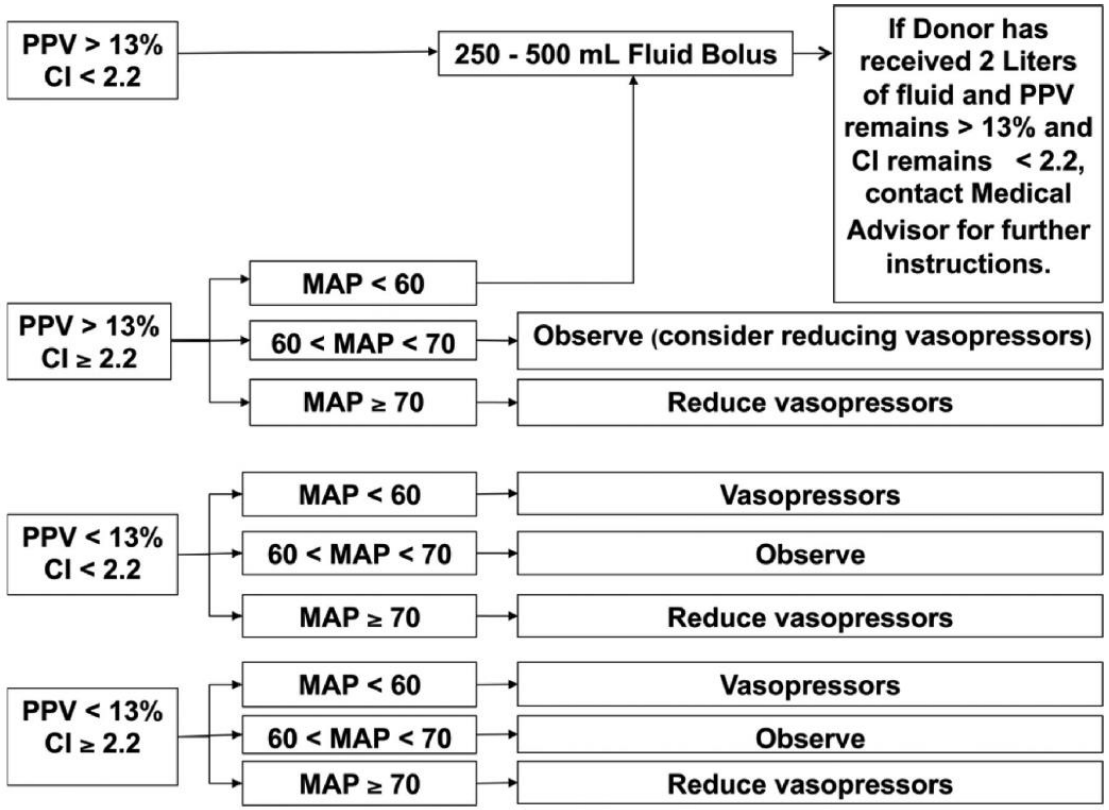


Figure 1.

MOnIToR protocol-guided hemodynamic management

PPV: pulse-pressure variation; CI: cardiac index; MAP: mean arterial pressure.

Number of organs transplanted by intervention arm

Number of Organs Transplanted	Intervention		Total (508)
	Protocolized Care N=249	Usual Care N=259	
0	20(8.03)	21(8.11)	41
1	28(11.24)	38(14.67)	66
2	28(11.24)	39(15.06)	67
3	65(26.1)	47(18.15)	112
4	38(15.26)	43(16.60)	81
5	28(11.24)	29(11.20)	57
6	24(9.64)	21(8.11)	45
7	15(6.02)	17(6.56)	32
8	3(1.20)	4(1.54)	7
Summary			Difference
Mean (sd) 95% CI	3.39 14, 3.63)	3,29 (3.04, 3.54)	0.10(2.01) (−0.25, 0.45)
p-value from t-test (pooled)			$t_{506} = 0.58$, p =0.56

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

ORIGINAL ARTICLE

A stroke volume-based fluid resuscitation protocol decreases vasopressor support and may increase organ yield in brain-dead donors

Gary F. Marklin ✉, William Dean Klinkenberg, Benjamin Helmers, Thomas Ahrens

- We studied a stroke volume-based fluid resuscitation and vasopressor weaning protocol **prospectively** on
- **64 hypotensive donors**,
- **30 hypotensive donors treated without** a protocol.
- **Stroke volume** was measured **every 30 minutes** for **4 hours** by **pulse contour analysis** or **esophageal Doppler**.
- Clin Transplant.2020 Feb;34(2):e13784

- The **protocol group** **received** **1937** **± 906 mL fluid** compared to **1323** **± 919 mL in the control group** (*P* = .003).
- **Mean time on vasopressors** **was** **decreased** from **957.6** ± 586.2 to **176.3** ± 82.2 **minutes** (*P*<.001).
- While **more organs** were transplanted **per donor in the protocol** group **(3.39** ± 1.52) than in the **control group (2.93** ± 1.44) (*P* = .268), the difference **did not reach statistical significance**.

ORIGINAL ARTICLE

Clinical outcomes of a prospective randomized comparison of bioreactance monitoring versus pulse-contour analysis in a stroke-volume based goal-directed fluid resuscitation protocol in brain-dead organ donors

Gary F. Marklin, Melissa Stephens, Elyssa Gansner, Gregory Ewald, William Dean Klinkenberg, Thomas Ahrens

- **Randomized prospective** comparative study of BR versus PCA
- **84 donors** (53.1%) were randomized to **BR**
- **74 donors to PCA** (46.8%).
- There was **no difference** in the **intravenous fluid infused over the 4-h** study period [BR 2271 ± 823 vs. PCA 2230 ± 962 mL; *p* = .77
- There was no difference in the time to **wean off vasopressors** [BR 108.8 ± 61.8 vs. PCA 150.0 ± 68 min *p* = .07
- There was no difference in the **total number of organs transplanted per donor** [BR 3.25 ± 1.77 vs. PCA 3.22 ± 1.75; *p* = .90
- Clin Transplant.2023 August;37

Volume Assessment

- The optimal methods to assess euvolemia and exact targets have not been determined.
- Traditional measures include achieving the **MAP** and **urine output** targets noted above**, CVP 4 to 10 mmHg**, or **PAOP 8 to 12 mmHg**.
- However, these measures can be misleading, so there is a growing use of noninvasive dynamic measures such as **PPV** or **SPV**.

Choices for fluid and electrolyte replacement

- Guidelines advocate use of **isotonic crystalloids**, such as lactated Ringer solution, PlasmaLyte, Normosol, or 0.9 percent saline.

- The presence of a hyperchloremic acidosis may prompt selection of lactated Ringer solution or other bicarbonate-containing solutions.

Effects of Dopamine Donor Pretreatment on Graft Survival after Kidney Transplantation: A Randomized Trial

Peter Schnuelle, Wilhelm H. Schmitt, Christel Weiss, Antje Habicht, Lutz Renders, Martin Zeier, Felix Drüschler, Katharina Heller, Przemyslaw Pisarski, Bernhard Banas, Bernhard K. Krämer, Matthias Jung, Kai Lopau, Christoph J. Olbricht, Horst Weihprecht, Peter Schenker, Johan W. De Fijter, Benito A. Yard, and Urs Benck

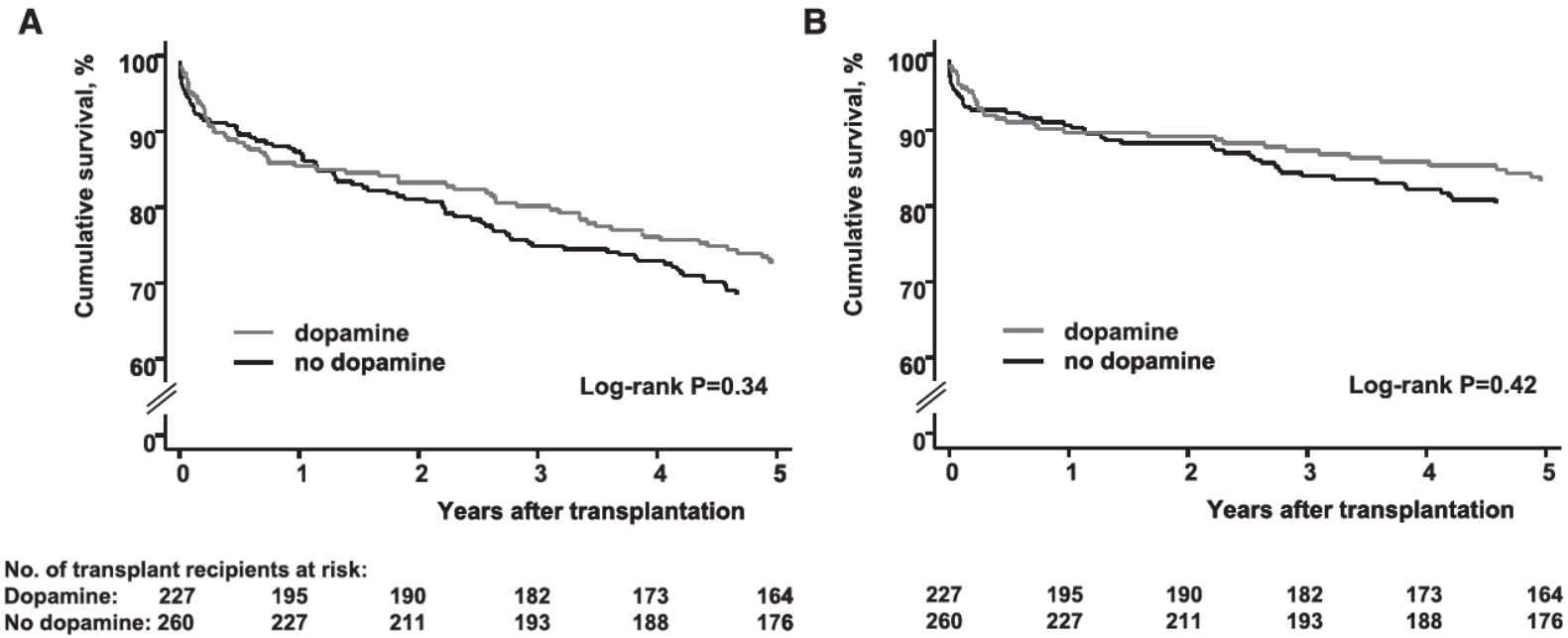


Figure 2. | Kaplan–Meier estimates of kidney graft survival until 5 years after transplantation according to trial group assignment failed to show a significant benefit of dopamine. (A) Overall graft survival. (B) Death-censored graft survival.

487 renal TX patients,60 European centers,
124 dopamine
140 control
5 years follow up

Clin J Am Nephrol 12:493-501,2017.

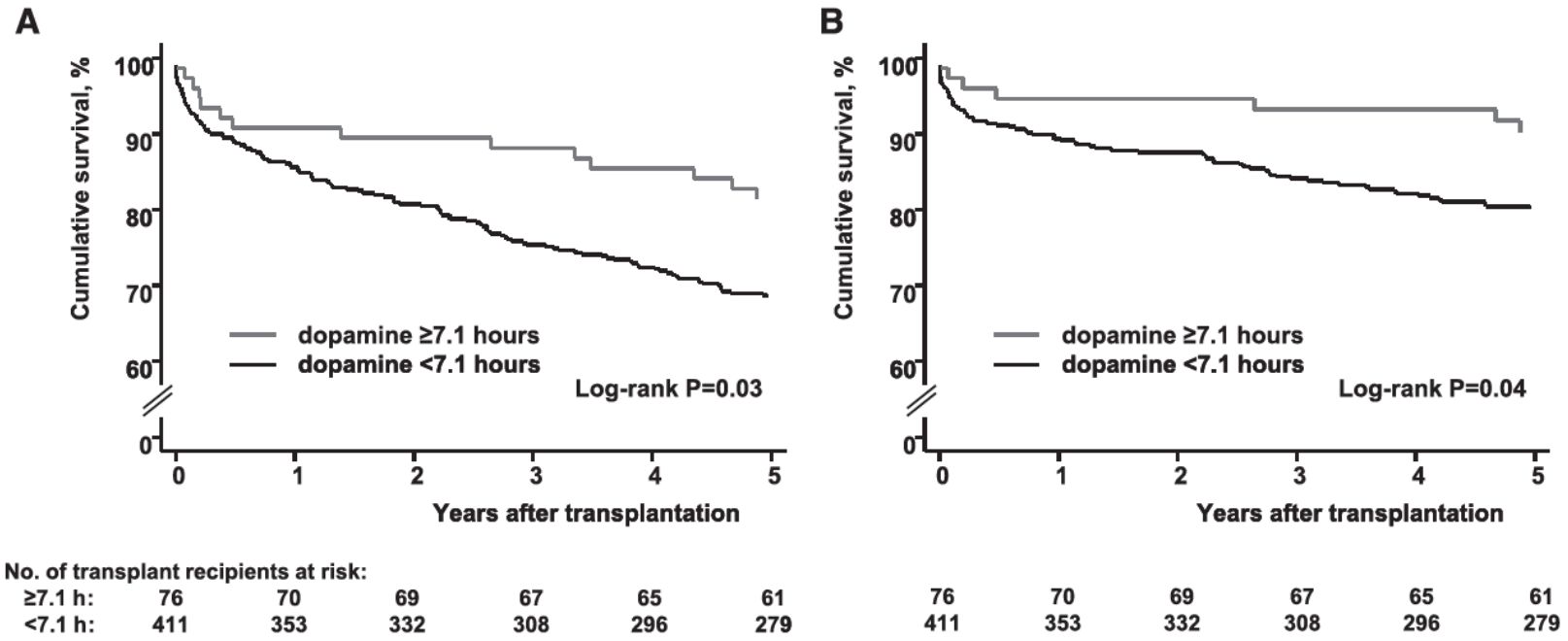


Figure 4. | Kaplan–Meier estimates of kidney graft survival until 5 years after transplantation according to dopamine infusion time ≥7.1 hours indicated a relevant benefit of dopamine. (A) Overall graft survival. (B) Death-censored graft survival.

J Trauma Acute Care Surg. 2020 June ; 88(6): 783–788. doi:10.1097/TA.0000000000002688.

Vasopressor Selection During Critical Care Management of Brain Dead Organ Donors and the Effects on Kidney Graft Function

Elizabeth A. Swanson, PhD[1], Madhukar S. Patel, MD MBA[2], Tahnee Groat, MPH[3], Nora E. Jameson, MS[3], Margaret K. M. Ellis, MD[3,4], Michael P. Hutchens, MD[3], Claus U. Niemann, MD[5], Darren J. Malinoski, MD[3,6], Mitchell B. Sally, MD[3,6]

- **Prospective observational data, 2012-2018**,

Analysis of **2,985 DBDs**
5,554 kidney transplant recipients from **nine OPTN regions.**
Increased phenylephrine dose during donor management is independently associated with the **risk of DGF** in kidney transplant recipients.

None of the other vasopressors nor total combined vasopressor dose were found to be independent predictors of recipient DGF.

Effects of Terlipressin on Management of Hypotensive Brain-Dead Patients Who are Potential Organ Donors: A Retrospective Study

Donghua Zheng[1†], Genglong Liu[2†], Li Chen[1], Wenfeng Xie[1], Jiaqi Sun[1], Siqi Wang[1] and Qiang Tai[1]*

- **A retrospective study** was conducted by using the ICU database of one hospital.
- **18 patients** in a **total of 294 brain-dead** cases were enrolled and administered **terlipressin intravenously.**
- Recruited brain-dead patients are **hemodynamically unstable (MAP < 65 mm Hg),** and require **high-dose norepinephrine (>0.5 µg/kg/min**) with **fluid resuscitation** to maintain MAP at 65~105 mm Hg.
- Frontiers 2021

- **Terlipressin** significantly increased **mean arterial pressure (MAP)** from **69.56** ± 10.68 mm Hg (baseline) to **101.82 ±** 19.27mm Hg.

- **Systolic blood pressure (SBP)** from **89.78** ± 8.53 mm Hg (baseline) to **133.42** ± 26.11 mm Hg (immediately before organ procurement) in all patients.

- which **resulted in the reduction of norepinephrine dose** over time **from 0.8** ± 0.2 **µg/kg/min** (baseline) **to 0.09 ± 0.02 µg/kg/min** (immediately before organ procurement).

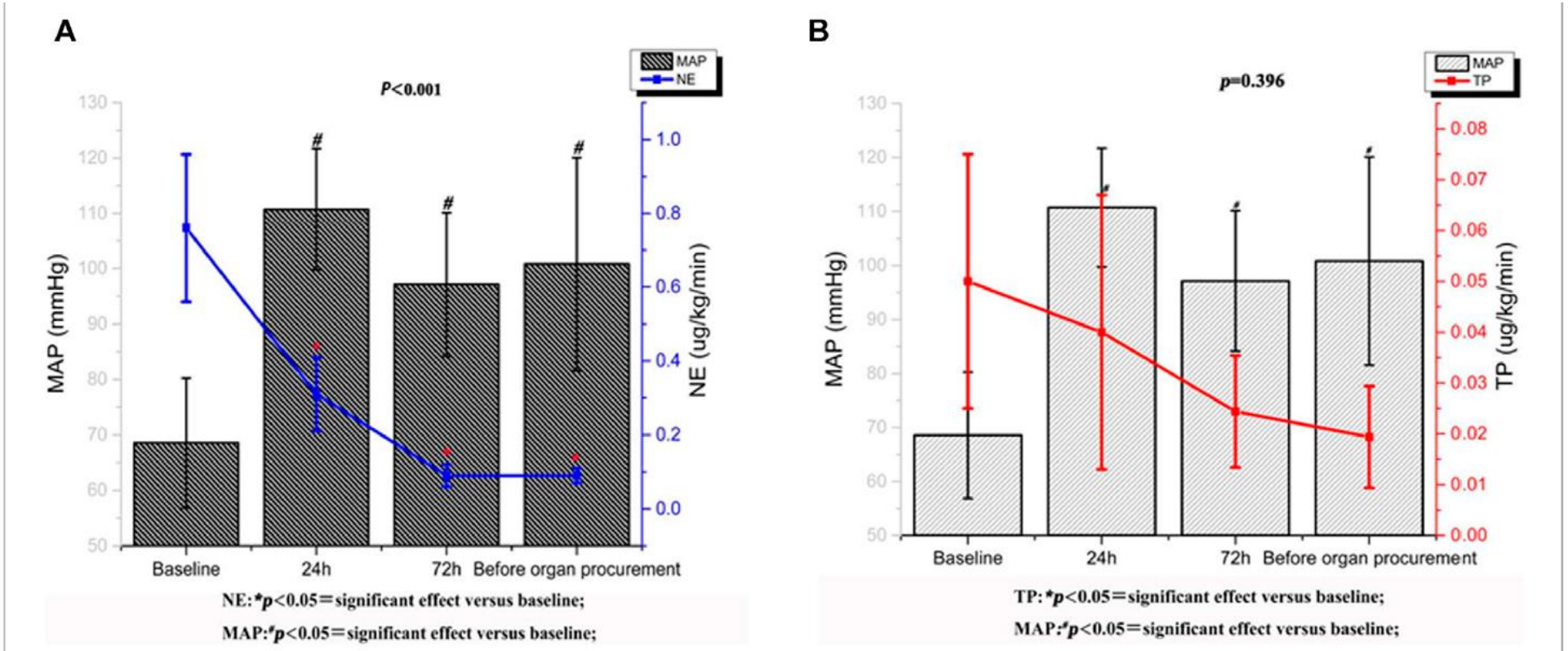


FIGURE 1 | Norepinephrine and terlipressin requirement variations and mean arterial pressure trend after treatment with terlipressin.

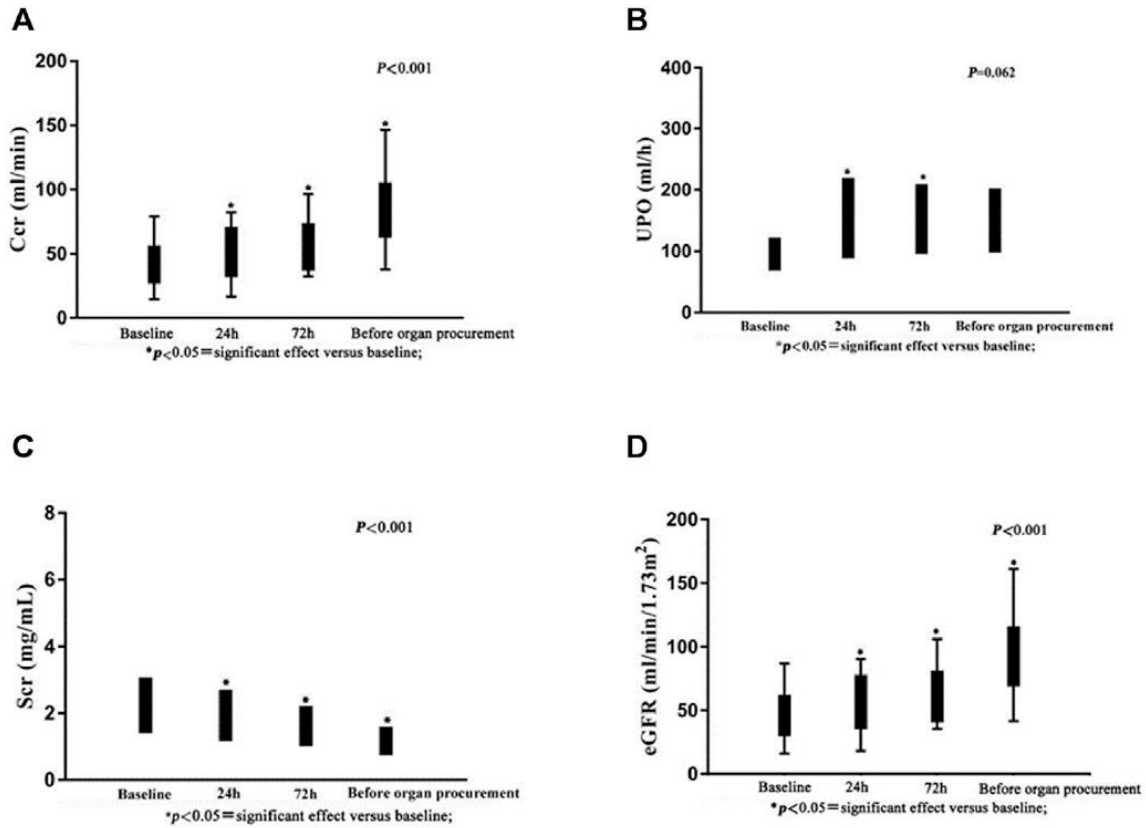


FIGURE 3 | Serum creatinine, urine output, creatinine clearance rate and estimated glomerular filtration rate after intravenous bolus dose of terlipressin.

Reduced myocardial function

- If the **left ventricular ejection fraction** is estimated at **less than 45%** , an **inotropic agent**, such as dopamine, dobutamine, or epinephrine, is used.
- The **response to treatment is assessed by serial echocardiography**, or placement of a **pulmonary artery catheter.**

- **Most heart transplant centers** prefer the **donor to be on minimal** or **no vasopressors or inotropes** during the **last echocardiogram** prior to a heart offer.

- Other frequent causes of hypotension in DBD patients include
- hypovolemia (through
- **diabetes insipidus**
- **mannitol-induced** osmotic diuresis
- **trauma-induced hamorrhage**)
- any exposed **ischemic heart disease**
- potentially, **central hypothyroidism**
- **adrenal insufficiency**
- *Intensive Care Med (2024) 50:964–967*

Endocrine treatment

- **Diabetes insipidus** occurs in **46–86% of DBD** patients, and manifests as polyuria and progressive hypernatremia, which may contribute to hemodynamic instability

  and (for hypernatremia ≥ 155 mmol/L) to poor liver graft function.

- Treatment consists of restoring fluid losses, and vasopressin or desmopressin.

- In case of **vasoplegia, vasopressin is usually preferred**, because desmopressin

  only acts on the renal V2 receptors.

- *Intensive Care Med (2024) 50:964–967*

- Careful attention should be paid to maintaining normal electrolyte levels.
- According to current guidelines, **serum sodium** should be maintained **below 155 mEq/dL** and **potassium** **between 4 and 5 mEq/dL**

Diabetes insipidus Management

- Desmopressin is an analog of vasopressin with a greater antidiuretic effect and substantially less vasopressor effect.

- This agent is used for patients with **DI who are not hypotensive**.
- Initial dose of **1 to 4 micrograms** is given intravenously.

- to achieve a **urine volume <4 mL/kg/hour**.
- A typical dose is **1 to 2 micrograms intravenously every six hours**.

DI and Hypotension

- **Vasopressin** is often used as part of hormonal therapy for deceased organ donors with **hypotension**, but without frank DI, although this is off-label.
- A typical dosing regimen is an initial bolus infusion of 1 unit, followed by a continuous infusion of **0.01 to 0.1 units/minute** (typical doses are 0.01 to 0.04 units/minute.
- **Doses >0.04 units/minute have been associated with adverse cardiac effects.**

The Southwestern Surgical Congress

Arginine vasopressin significantly increases the rate of successful organ procurement in potential donors

David S. Plurad M.D., Scott Bricker M.D., Angela Neville M.D., Frederic Bongard M.D., Brant Putnam M.D.

- A total of 10,431 donors were included.
- AVP was infused in 7,873 (75.5%)
- Increased rate of high-yield procurement (50.5% vs 35.6%, $P < .001$).

- The use of AVP with hormone replacement therapy is independently associated with an increased rate of organ recovery.

J Surg Res. 2014 Jan;186(1):452-7. doi: 10.1016/j.jss.2013.09.028. Epub 2013 Oct 7.

The effect of arginine vasopressin on organ donor procurement and lung function

Devon S Callahan [1], Angela Neville, Scott Bricker, Dennis Kim, Brant Putnam, Frederic Bongard, David S Plurad

- There were 12,322 donors included, of which 7686 received AVP (62.4%).
- There was a significant increase in high yield (≥4 organs) (51.0% versus 39.3%, <0.001).
- Rate of successful lung recovery (26.3% versus 20.5%, <0.001) with AVP.

RED Cell Transfusion

- **Intraoperative red cell transfusion** is often necessary in patients with prior abdominal surgery, in whom the dissection of the liver and kidneys for organ procurement might be difficult, or in patients whose blood vessels are difficult to cannulate.

- Guidelines suggest a target hemoglobin level >7 g/dL.

Clin Transplant. 2022 Sep;36(9):e14764. doi: 10.1111/ctr.14764. Epub 2022 Jul 14.

The benefits of initiating continuous renal replacement therapy after brain death in organ donors with oligoanuric acute kidney injury

Gary F Marklin [1], Laura Ewald [1], W Dean Klinkenberg [1], Christina M Joy [2], Steven J Bander [3], Marcos Rothstein [2]

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY
دوازدهمین سمینار سراسری انجمن علمی نفرولوژی ایران کلیه در شرایط کریتیکال
The 12th National Congress of the Iranian Society of Nephrology (NIrSN)
انجمن نفرولوژی ایران IRANIAN SOCIETY OF NEPHROLOGY

cohort groups: Historical oliguric cohort and CRRT group

	Historical oliguric cohort[a] (% or SD)	CRRT group[b] (% or SD)	Statistical test
Number of donors	($n = 14$)	($n = 27$)	
Total organs transplanted/ donor (mean)	1.4 (.6)	2.9	$P < .01$
Total kidneys transplanted/ donor(mean)	.2 (.6)	0.7	$P = .10$
Liver transplanted	12 (85.7%)	20 (74.1%)	$P = .69$
Lungs transplanted[c]	3 (21.4%)	13 8.1%)	$P = .18$
Heart transplanted	2 (14.3%)	12 (44.4%)	$P = .08$
Total thoracic organs trans- planted/donor (mean)[d]	.6 (.9)	1.4 1.2)	$P = .02$

TABLE 3B Number of organs transplanted from the CRRT and cohort groups: Contemporaneous nonoliguric cohort and CRRT group

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 30, 2023 VOL. 389 NO. 22

Intravenous Levothyroxine for Unstable Brain-Dead Heart Donors

Rajat Dhar, M.D., Gary F. Marklin, M.D., W. Dean Klinkenberg, Ph.D., Jinli Wang, M.S., Charles W. Goss, Ph.D., Abhijit V. Lele, M.D., M.S.C.R., Clark D. Kensinger, M.D., Paul A. Lange, M.D., and Daniel J. Lebovitz, M.D.

- RCT ,(**838** were included in the primary analysis:
- **419 in the levothyroxine group** 30 µg per hour for a minimum of 12 hours
- **419 in the saline group**.
- Hearts were transplanted from
- **230 donors (54.9%) in the levothyroxine group**
- **223 (53.2%) in the saline group** (adjusted risk ratio, 1.01; 95% confidence interval [CI], 0.97 to 1.07; P = 0.57).

- **Graft survival at 30 days occurred in 224 hearts (97.4%)** transplanted from donors assigned to receive levothyroxine
- **213 hearts (95.5%) transplanted from donors assigned to receive saline**

- Although brain-dead patients **usually develop low triiodothyronine levels**, this reflects increased conversion of thyroxin in to reverse T3

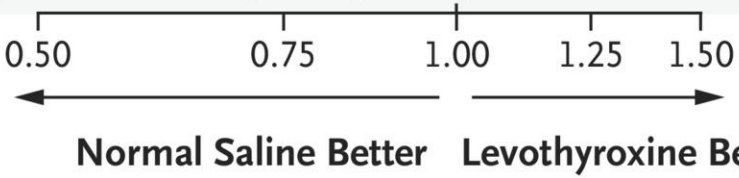
, typical of **euthyroid sick syndrome**.

- Nevertheless, **some DBD patients may develop central hypothyroidism**, which **could induce cardiac dysfunction**.

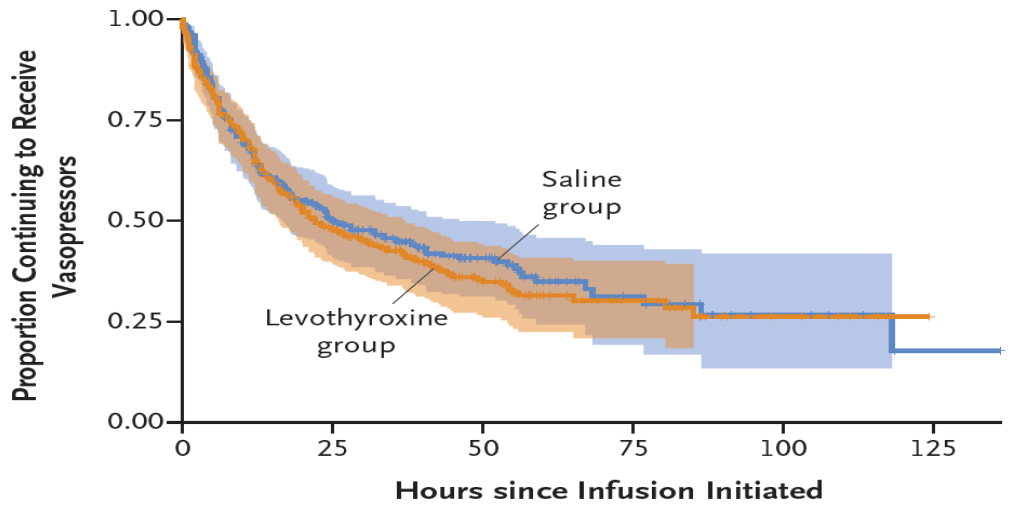
- *Intensive Care Med (2024) 50:964–967*

Subgroup Analysis of Hearts transplanted(Primary Outcome)

Subgroup	Levothyroxine	Normal Saline	Adjusted Risk Ratio (95% CI)
	no. of events/no. of donors (%)		
Overall	230/419 (55)	223/419 (53)	1.01 (0.97–1.07)
LVEF from first echocardiogram			
Abnormal: ≤50%	20/59 (34)	28/73 (38)	0.99 (0.75–1.31)
Normal: >50%	197/291 (68)	180/263 (68)	0.95 (0.88–1.04)
Time from brain death to trial infusion			
≤12 hr	178/315 (57)	163/304 (54)	1.02 (0.95–1.10)
>12 hr	47/96 (49)	46/80 (58)	0.85 (0.71–1.01)



Kaplan–Meier Estimates of the Proportion of Donors Continuing to Receive Vasopressors



No. at Risk

Saline group	385	141	59	16	6	1
Levothyroxine group	404	142	59	18	6	0

Figure 2. Kaplan–Meier Estimates of the Proportion of Donors Continuing to Receive Vasopressors.

Shown are survival curves in the intention-to-treat population for the time from initiation of levothyroxine or saline infusion until weaning from vasopressors and inotropes (excluding vasopressin at a dose of <1 unit per hour) in the two trial groups. The shaded bands represent 95% confidence intervals. The proportional-hazards assumption was satisfied.

- Hence, **routine supplementation is not indicated**, although it **could** be considered in selected DBD patients with severe cardiac **depression.**

T4 20µ IV+ 10µ/h

T3 4µ IV+ 3µ/h

Intensive Care Med (2024) 50:964–967

- **Central adrenal insufficiency** may develop after brain death, manifesting **as vasodilatation and hypovolemia**

.

- However, many DBD patients do not develop low cortisol Levels.

- Routine hydrocortisone treatment is consequently not indicated, but **may be considered in patients with severe vasoplegia**.

- *Intensive Care Med (2024) 50:964–967*

Comparison of high- and low-dose corticosteroid regimens for organ donor management

Rajat Dhar [1], Colleen Cotton, Jason Coleman, Diane Brockmeier, Dean Kappel, Gary Marklin, Robert Wright

Affiliations + expand

PMID: 22762934 DOI: 10.1016/j.jcrc.2012.04.015

- **132 consecutive brain-dead donors** managed before and after changing the **steroid protocol from 15 mg/kg methylprednisolone** (HD) to **300 mg hydrocortisone** (LD).

- Final **Pao2 remained higher (394 mm Hg LD vs 333** mm Hg HD, P=.03); but **improvement in oxygenation was comparable** (+37 mm Hg LD vs +28 mm Hg HD, P=.43), as was the proportion able to come off vasopressor support (39% LD vs 47% HD, P=.38).

- **Similar proportions of lungs (44% vs 33%) and hearts (31% vs 27%) were transplanted** in both groups.

Pinsard *et al. Critical Care* 2014, **18**:R158
http://ccforum.com/content/18/4/R158

CRITICAL CARE

RESEARCH Open Access

Interest of low-dose hydrocortisone therapy during brain-dead organ donor resuscitation: the CORTICOME study

Michel Pinsard[1], Stéphanie Ragot[2], Paul Michel Mertes[3], Jean Paul Bleichner[4], Samira Zitouni[5], Fabrice Cook[6], Marc Pierrot[7], Laurent Dube[8], Edgard Menguy[9], Laurent Martin Lefèvre[10], Laurence Escaravage[11], Pierre-François Dequin[12], Philippe Vignon[13] and Nicolas Pichon[14*]

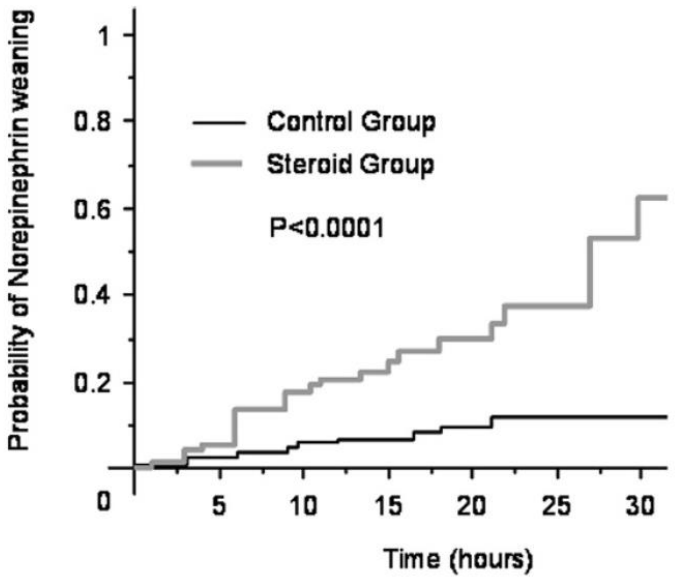
- In this **prospective multicenter cluster study**,
- **259** subjects were included.
- Administration of **low-dose steroids** **composed the steroid group (n = 102).**

- **Mean dose of vasopressor** administered after brain death was **significantly lower** than in the control group (**1.18** ± 0.92 mg/H vs. **1.49** ± 1.29 mg/H: P = 0.03),
- **duration of vasopressor** support use was **shorter**(874 min vs. 1160 min: P < 0.0001)
- **Organ procurement rate** and **post-transplant graft function were not improved.**

- The **ACTH stimulation test** was performed in the **80** patients in
- **the steroid group** and in **41 patients in the control** group;
- it revealed **adrenal insufficiency** in 94/121 brain-dead patients **(78%).**

- Patient then received a **50-mg injection of hydrocortisone** followed

by a continuous infusion of **10 mg/h** until the aortic clamping was performed in the operating room during organ retrieval.



N° at risk							
Control Group	103	98	91	77	44	27	13
Steroid Group	76	71	56	33	22	9	3

Figure 2 Kaplan-Meier curves for the probability of continuation of norepinephrine.

Table 4 Organs recovered/organs recoverable (%)

Organs	All patients (n = 208)	Control group (n = 128)	Steroid group (n = 80)	*P*-value
Kidney	394/403 (97.7)	243/248 (98)	151/155 (97.4)	0.65
Liver	162/172 (94.2)	99/105 (94.3)	63/67 (94)	0.61
Heart	66/80 (82.5)	47/56 (83.9)	19/24 (79.1)	0.74
Lung	71/93 (73.9)	44/62 (70.9)	27/34 (79.4)	0.36
Pancreas	21/47 (44.6)	16/39 (41)	5/8 (62.5)	0.43
Total	714/798 (89.5)	449/510 (88)	265/288 (92)	0.07
Organs/donors, n (SD)	3.43 (1.37)	3.51 (1.39)	3.31 (1.36)	0.23

Results presented as number/total number (%) unless stated otherwise.

- **Hyperglycemia,** common in DBD patients, **is associated with poorer post-transplant graft function** .

- However, large RCTs studying blood glucose management in DBD patients are lacking.

Intensive Care Med (2024) 50:964–967

Ventilation and oxygenation

- The goal of mechanical ventilation is to
- **maintain tissue oxygenation**
- **protect the lungs for transplantation**.

- **Venous thromboembolism and stress ulcer prophylaxis** — Deceased organ donors are at high risk for venous thromboembolism.
- As with critically ill patients, we generally use thromboprophylaxis rather than mechanical methods and prefer **low molecular weight** heparin (eg, enoxaparin 40 mg every 12 hours) for patients with **normal kidney function**.
- Unfractionated heparin is an alternative for those with kidney failure or in whom cost is an issue.
- We follow guidance for **stress ulcer prophylaxis** in critically ill patients.

- **Empiric antibiotics** — Empiric antibiotics may be administered based on the organ(s) being transplanted.

- For lung donors, who typically have lower respiratory tract colonization with nosocomial pathogens, the regimen is designed to cover methicillin-resistant *S. aureus* (MRSA) and gram-negative pathogens with adjustment, as needed, based on microbiology data

Hypothermia versus Normothermia

- **Mild therapeutic hypothermia** versus **maintenance of Normothermia**.
- Normothermia may be maintained **passively with blankets** or with **active rewarming** (eg, forced air blankets) if necessary.
- With the **loss of hypothalamic temperature regulation**, the brain-dead donor tends to be hypothermic.
- A target temperature range of **36.5 to 37.5°C** is reasonable unless therapeutic hypothermia **(34 to 35°C) is used to reduce delayed graft** function of **the kidneys.**

- **Therapeutic hypothermia** — Mild donor therapeutic hypothermia is under investigation as a method to improve subsequent **kidney allograft function, but the data are mixed.**
- Traditionally, **a normothermic body temperature (36.5 to 37.5°C),** which may require active warming, has been used for organ donors. A few studies have suggested benefit to kidney allograft function after mild donor hypothermia, but others have not .

The NEW ENGLAND JOURNAL of MEDICINE

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Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function

- (**180 in the hypothermia** group **34 to 35°C**
- **190 in the normothermia group**) **36.5 to 37.5°C**
- 572 patients received a kidney transplant (**285 kidneys** from donors in the **hypothermia** group and **287 kidneys** from donors in the normothermia group).

- **Delayed graft function** developed in
- 79 recipients of kidneys from donors in the **hypothermia group (28%)**
- and in 112 recipients of kidneys from donors in the **normothermia group (39%)**
- (**odds ratio, 0.62**; 95% confidence interval, 0.43 to 0.92; P = 0.02).

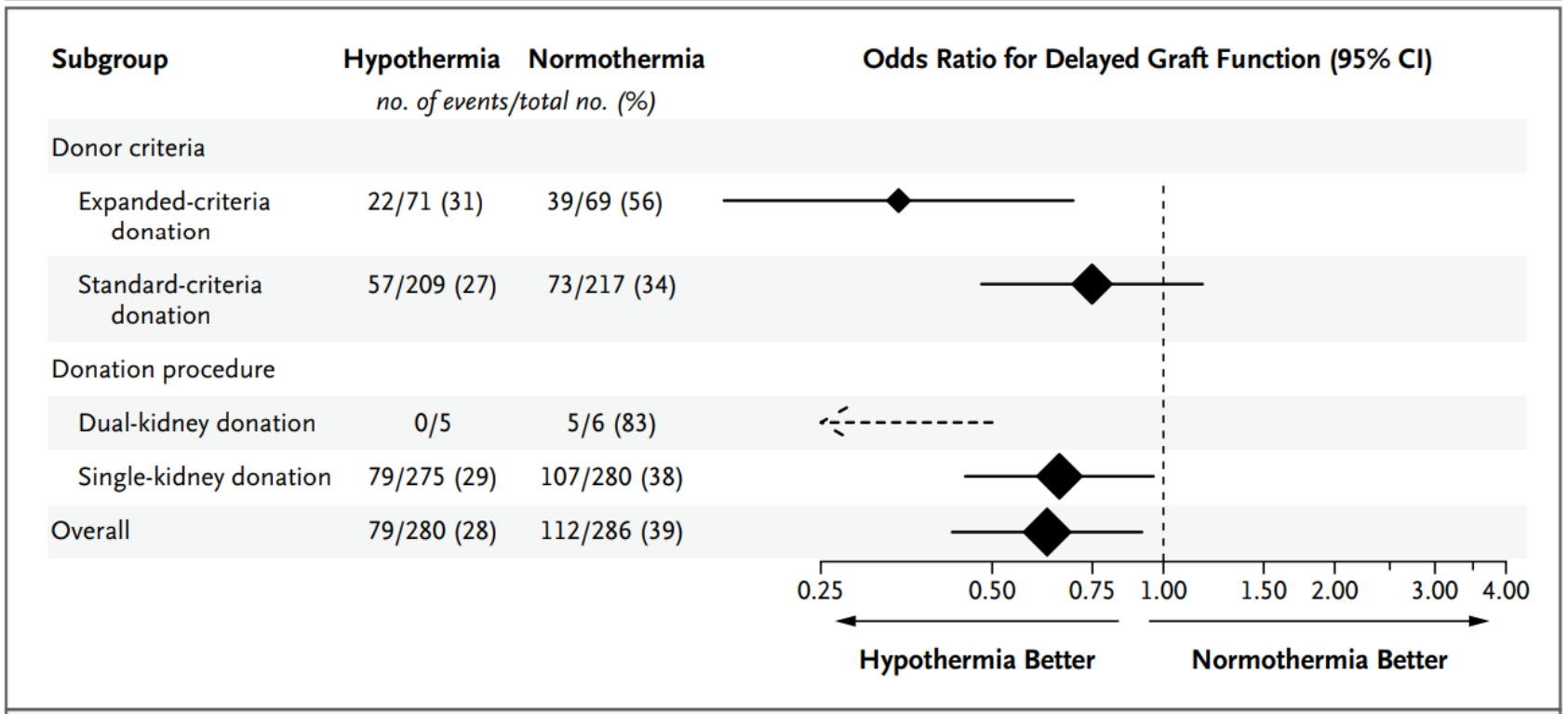

Figure 2. Odds Ratio for the Development of Delayed Graft Function.

Delayed graft function was defined as the requirement for dialysis in the recipient within 7 days after renal transplantation. Dual-kidney recipients received two kidneys from the same donor. In the dual-kidney subgroup, odds ratios could not be estimated because there were no instances of delayed graft function in the hypothermia group. Horizontal bars represent the 95% confidence intervals for the odds ratio. The size of the diamonds is proportional to the number of patients in the subgroup.

JAMA Network Open

Original Investigation | Nephrology

Therapeutic Hypothermia in Low-Risk Nonpumped Brain-Dead Kidney Donors
A Randomized Clinical Trial

Madhukar S. Patel, MD, MBA, ScM; Juan D. Salcedo-Betancourt, MD; Christina Saunders, PhD; Kristine Broglio, MS; Darren Malinoski, MD; Claus U. Niemann, MD

- **509 low-risk donors (age <60 years; mean kidney donor profile index of 29**)
- **No difference** was seen between the **hypothermic and normothermic donors (17 versus 18** percent **incidence of DGF**, respectively).
- Based on these data, **hypothermia is of uncertain efficacy** at preventing DGF, particularly in **low-risk donors.**
- Hypothermia **may reduce DGF in high-risk donors**; however, **ex vivo pulsatile organ perfusion is likely a more effective intervention** for this group.
- JAMA Network Open. 2024;7(2):e2353785

Table 3. Results of the Primary Analysis of DGF[a]

Variable	AOR for DGF (95% CI)	*P* value
Hypothermia vs normothermia	0.92 (0.64-1.33)	.66
Enrollment creatinine, mg/dL	1.69 (1.19-2.4)	.004
Donor age, y	1.03 (1.02-1.05)	<.001
Donor type: ECD vs SCD	0.11 (0.03-0.45)	.002
Kidney cold ischemia time, h	1.03 (1.01-1.06)	.003
OPO 2 vs 34	2.59 (1.68-3.99)	<.001
OPO 29 vs 34	0.64 (0.33-1.26)	.20
OPO 40 vs 34	0.79 (0.41-1.49)	.46

Abbreviations: AOR, adjusted odds ratio; DGF, delayed graft function; ECD, Extended Criteria Donor; OPO, Organ Procurement Organization; SCD, Standard Criteria Donor.

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DOI: 10.1111/ajt.16580

MINIREVIEW

"Time is tissue"—A minireview on the importance of donor nephrectomy, donor hepatectomy, and implantation times in kidney and liver transplantation

Line Heylen[1,2] | Jacques Pirenne[3,4] | Maarten Naesens[1,5] | Ben Sprangers[5,6] | Ina Jochmans[3,4]

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دوازدهمین سمینار سراسری انجمن علمی نفرولوژی ایران کلیه در شرایط کریتیکال

The 12th National Congress of the Iranian Society of Nephrology (NIrSN)

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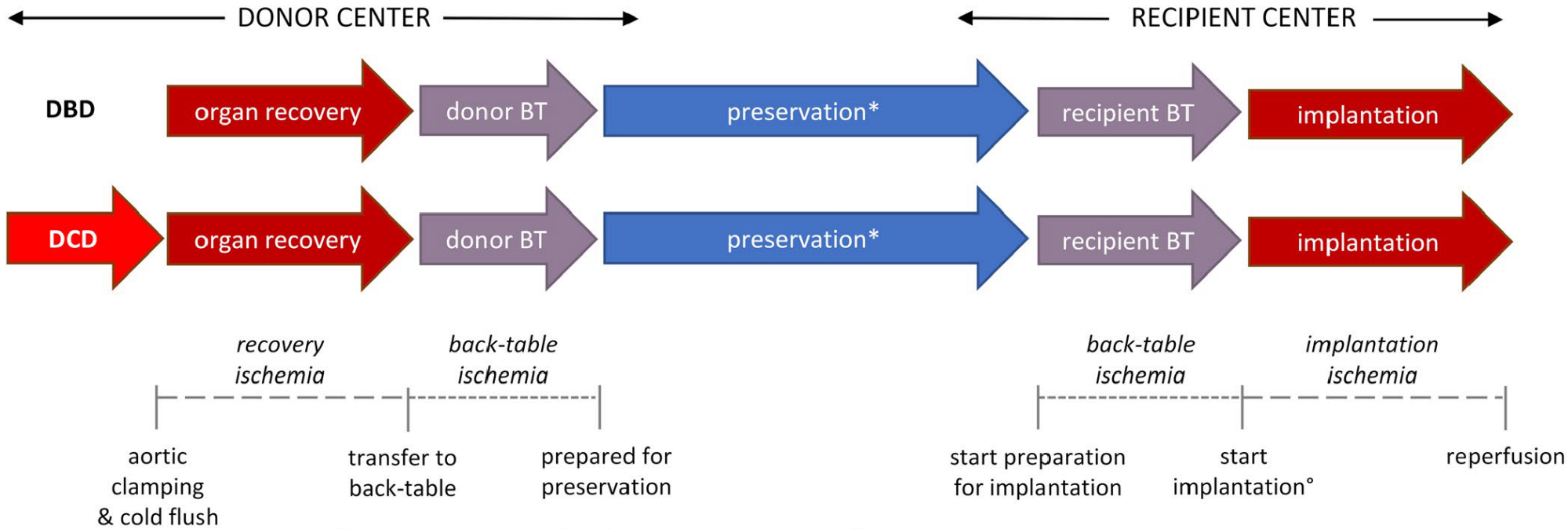

** preservation by static cold storage or any form of organ perfusion*

° grafts might be repackaged or reconnected to the perfusion device, marking the end of recipient back-table (BT) time

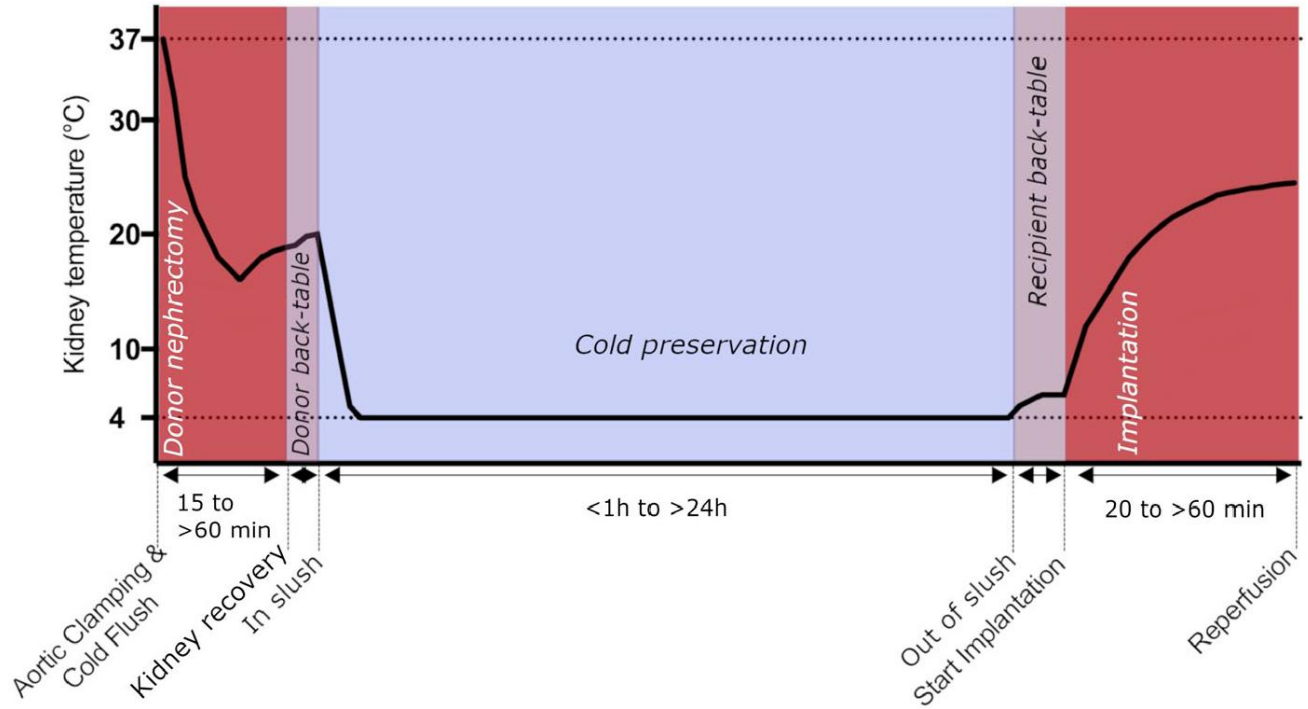

FIGURE 2 Temperature changes of the kidney graft from graft procurement to implantation. Temperature estimates are based on studies that measured kidney graft temperature during the donor procedure, cold preservation, and transplantation[2,7,45]

TABLE 1 Overview of studies investigating the independent effect of donor nephrectomy time on short- and long-term outcomes after kidney transplantation, organized by donor type and publication date

Author and study details	Donor nephrectomy time	Independent effect short-term	Independent effect long-term outcome
Deceased donor kidneys			
Osband et al.[21] Single center, n = 576 (520 DBD, 56 DCD)	44. <6(>6(	*For times>60 min; per 5-min increase* PNF: aOR: 1.19 (95% CI 0.96–1.49) DGF: aOR: 1.19 (95% CI 1.02–1.39)	*For times>60 min; per 5-min increase* Death-censored graft failure: aHR: 0.66 (95% CI 0.32–1.38) Graft failure, per 10-min increase: *in DBD*: aHR: 1.01 (95% CI 0.98–1.04) *in DCD*: aHR: 1.05 (95% CI 1.01–1.09)
Heylen et al.[9] Registry, n = 13,914 (12,855 DBD, 1059 DCD)	51 DB DCD: 57 (43–78)		

Am JTransplant. 2021;21:2653–2661.

TABLE 2 Overview of studies investigating the independent effect of implantation time on short- and long-term outcomes after kidney transplantation, organized by donor type and publication date

Author and study details	Kidney implantation time: Length (min)	Independent effect short-term outcome	Independent effect long-term outcome
Deceased donor kidneys			
Halloran et al.[13] Multicenter, n = 207 (DBD)	*PNF* *DGF* *EGF:*	*Versus EGF, per 1-min increase* DGF: MVRC −0.049 (SE 0.018) PNF: MVRC −0.053 (SE 0.019)	-
Marzouk et al.[14] Single center, n = 298	30 (2		eGFR 1y: MVRC −0.09 eGFR 2y: MVRC −0.11 eGFR 3y: MVRC −0.09
Heylen et al.[15] Single center, n = 699 (DBD)	34 (3	*per 1-min increase* DGF: aOR 1.04 (95% CI 1.02–1.06)	Interstitial fibrosis 1y: aOR 1.05 (1.02–1.08) Interstitial fibrosis 2y: aOR 1.06 (1.02–1.12)
Tennankore et al.[16] Registry, n = 131,677 (71,891 DBD, 9199 DCD, 50, 587 living donors)	35 (2 p	*per 1-min increase* DGF: aOR 1.05 (95% CI 1.02–1.07) eGFR (90 days): MVRC −0.11	*Versus reference category (10 to <20 min)* Death-censored graft failure, DBD and DCD: *30 to <40 min*: aHR: 1.23 (95% CI 1.08–1.39) *40 to <50 min*: aHR: 1.23 (95% CI 1.08–1.39) *50 to <60 min*: aHR: 1.28 (95% CI 1.12–1.46) *≥60 min*: aHR:1.34 (95% CI 1.18–1.52) Death-censored graft failure, DCD only: *50 to <60 min*: aHR: 1.49 (95% CI 1.07–2.08) *≥60 min*: aHR: 1.40 (95% CI 1.01–1.93)
Heylen et al.[17] Registry, n = 13,964 (12,806 DBD, 1158 DCD)	36 (29–45)	-	*per 10-min increase* Death-censored graft failure aHR 1.10 5% CI 1.06–1.14) Patient death: aHR 1.00 CI 0.97–1.02)

Received: 20 December 2019 | Revised: 25 March 2020 | Accepted: 22 April 2020

DOI: 10.1111/ajt.15995

ORIGINAL ARTICLE

AJT

Effect of preservation solutions for static cold storage on kidney transplantation outcomes: A National Registry Study

Camille Legeai | Louise Durand | Emilie Savoye | Marie-Alice Macher | Olivier Bastien

- The effects of each preservation solution on delayed graft function (DGF) and 1-year transplant failure were evaluated with hierarchical multivariable logistic regression models.

	UW	CE	HTK	IGL-1	Euro-Collins
Osmolarity (mOsm/L)	320	320	310	320	375
pH	7.4	7.3	7.2	7.4	7.1
Viscosity (cp)	5.70	1.15	1.8	1.28	N/A
Na^+ (mmol/L)	25–30	100	15	120	10
K^+ (mmol/L)	125–130	15	10	30	115
Mg^{2+} (mmol/L)	5	13	4	5	–
Ca^{2+} (mmol/L)	–	0.25	0.015	–	–
Cl^- (mmol/L)	–	41.5	50	20	15
PO_3^- (mmol/L)	25	–	–	25	47.5
SO_4^- (mmol/L)	5	–	–	5	30

Composition of cold storage solutions for organ preservation.

- The **DGF risk was significantly lower with IGL-1** than with all other solutions (odds ratio [OR] 0.55, 95% confidence interval[CI] 0.48-0.64).

- Conversely, **SCOT was associated with a DGF risk significantly higher**
- than the other solutions (OR 2.69, 95% CI 2.21-3.27) and **triple** that of **IGL-1** (OR 3.37, 95% CI 2.72-4.16).

- **One year after transplantation**, the **transplant failure rate did not**
- **differ significantly** by preservation solution.

- The study finally included 7640 transplanted kidneys:
- 3473 (45.5%) preserved with **Institut Georges Lopez-1 solution(IGL-1**),
- 773 (10.1%) with **University of Wisconsin** solution,
- 731 (9.6%) with Solution de Conservation des Organes et Tissus (**SCOT,** organ and tissue preservation solution),

- 2215 (29.0%) with **Celsior**,
- and 448 (5.9%) with **histidine–tryptophan–ketoglutarate**.

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TABLE 2.

Characteristics and compositions of current and future solutions for static and hypothermic perfusion preservation of abdominal organs

	UW SCS[28]	HTK[29]	Celsior[30]	IGL-1[31]	UW MPS[32,33]	Vasosol[34]	Polysol[35]	HTK-N[36]	IGL-2[37]	LS-A
pH	7.4	7.02–7.2	7.3	7.4	7.4	7.4		7.0	7.4	6.75
Osmolarity, mOsm/L	320	310	320–360	320	300	300	320	305	360	340
Viscosity, cP[a]	5.70	1.8	1.15	1.28	2.40		1.8		1.7	1.1
Colloids										
HES, g/L	50	–	–	–	50	50	–	–	–	–
PEG, g/L	–	–	–	0.03	–	–	10	–	5	20
Impermeants										
Gluconate, mmol/L	–	–	–	–	90	90	10	–	–	–
Glucose, mmol/L	–	–	–	–	10	10	16	–	–	–
Lactobionate, mmol/L	100	–	80	100	–	–	–	–	100	50
Mannitol, mmol/L	–	30	60	–	–	30	–	–	60	–
Raffinose, mmol/L	30	–	–	30	30	–	–	–	–	–
Sucrose, mmol/L	–	–	–	–	–	–	–	33	–	100
Buffers	Phosphate Sulfate	Histidine	Bicarbonate Histidine	Phos-phate	HEPES Phosphate	HEPES Phosphate	Bicarbonate HEPES Phosphate Sulfate	Histidine N-acetylhisti-dine	HEPES Histidine Phosphate Sulfate	Bicarbonate Phosphate
Electrolytes										
Calcium, mmol/L	–	0.015	0.25	–	0.5	0.5	2	0.02	–	–
Chloride, mmol/L	–	50	41.5	20	1	1	109	30.04	–	–
Magnesium, mmol/L	5	4	13	5	5	5	14	8	5	–
Potassium, mmol/L	120	10	15	30	25	28	5	10	25	5
Sodium, mmol/L	25	15	100	120	100	110	135	16	125	45
Zinc, mmol/L	–	–	–	–	–	–	–	–	0.091	–
Metabolic precursors	Adenosine	α-ketoglutarate	–	Adenosine	Adenine Adenosine Ribose	Adenine L-arginine α-ketoglutarate Ribose	Adenine Adenosine Amino acids Pyruvate Vitamins	Alanine Arginine Aspartate Glycine α-ketoglutarate	Adenosine Sodium nitrite	–
Antioxidants and free-radical scavengers	Allopurinol Glutathione	Tryptophan	Glutamic acid Glutathione	Allopurinol Glu-tathione	Allopurinol Glutathione	NAC	Allopurinol Glutathione	Deferoxamine LK-614 Tryptophan	Glutathione	Allopurinol Glutamic acid Glutathione Salicylic acid
Other additives	Dexamethasone Insulin Penicillin G	–	–	–	–	NTG PGE_1	Phenol red	–	–	Diltiazem

[a]Viscosity at 4 to 5 °C.

HES, hydroxyethyl starch; HTK, histidine-trytophan-ketoglutarate; IGL, Institut Georges Lopez; LS-A, Leeds Solution for Abdomen; MPS, machine perfusion solution; NAC, N-acetylcysteine; NTG, nitroglycerin; PEG, polyethylene glycol; PGE_1, prostaglandin E_1; SCS, static cold storage; UW, University of Wisconsin.

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The 12th National Congress of the Iranian Society of Nephrology (NIrSN)
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Abdominal Organ Preservation Solutions in the Age of Machine Perfusion

Pedro Ramos, MD,[1] Paul Williams, MD,[2] Javier Salinas, MD, PhD,[1,3] Jordi Vengohechea, BS,[3,4] J. Peter A. Lodge, MD, PhD,[2] Constantino Fondevila, MD, PhD,[1,3,5] and Amelia J. Hessheimer, MD, PhD[1,3,5]

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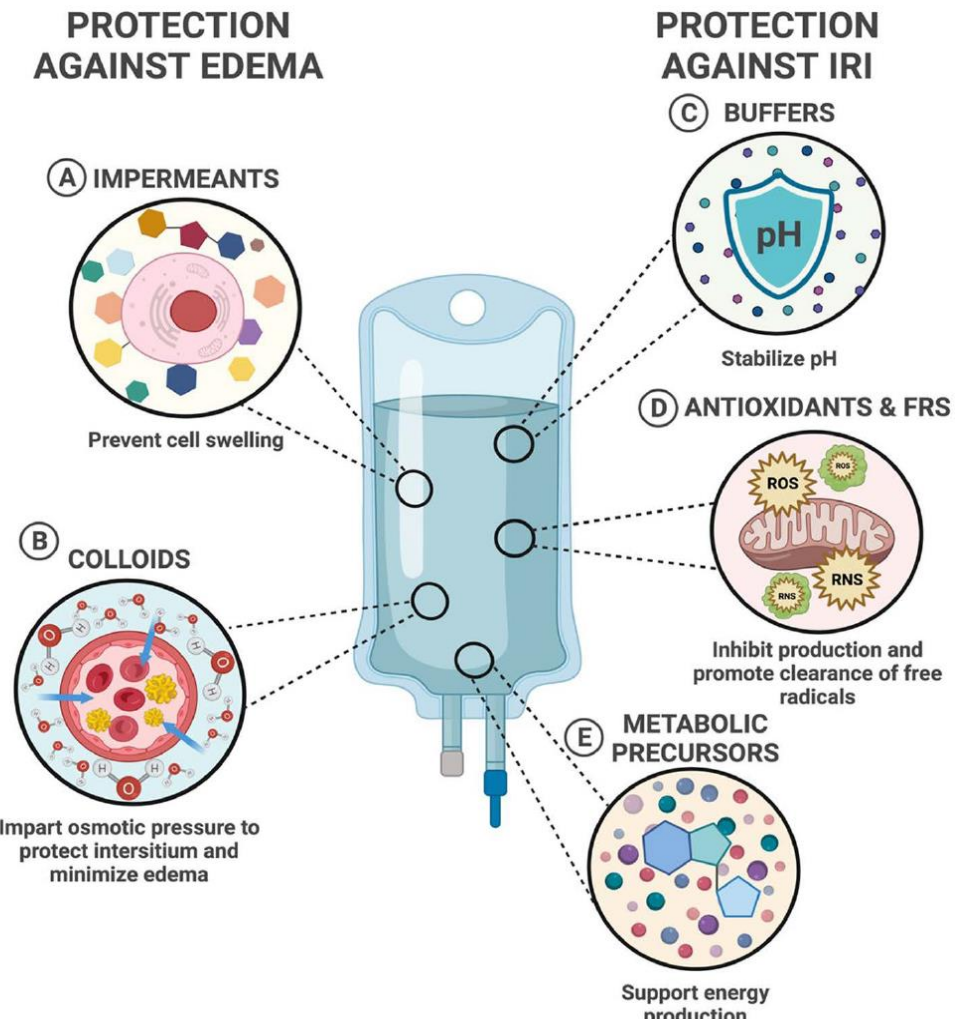

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TABLE 1.
Key components of modern static preservation solutions

Component	Role	Common examples
Impermeants	Anions that remain extracellular and help maintain transmembrane osmotic balance and avoid cellular edema	Monosaccharides (eg, glucose, mannitol) Disaccharides (eg, sucrose) Trisaccharides (eg, raffinose) Nonsaccharides (eg, gluconate, citrate, and lactobionate)
Colloids	High-weight molecules that largely remain intravascular and impart colloid osmotic pressure to help avoid progressive edema developing during prolonged static cold preservation and counterbalance hydrostatic pressure during perfusion preservation	Hydroxyethyl starch Polyethylene glycol (20–35 kDa)
Buffers	Prevent progressive acidosis and subsequent activation of phospholipases and proteases, lysosomal damage, and cellular death	Bicarbonate HEPES Histidine Phosphate Sulfate
Antioxidants and free-radical scavengers	Inhibit production and aid removal of reactive oxygen species arising before and during graft reperfusion	Allopurinol Glutathione
Metabolic precursors	Support energy production occurring during and immediately following the preservation period	Adenine Adenosine Amino acids Keto acids

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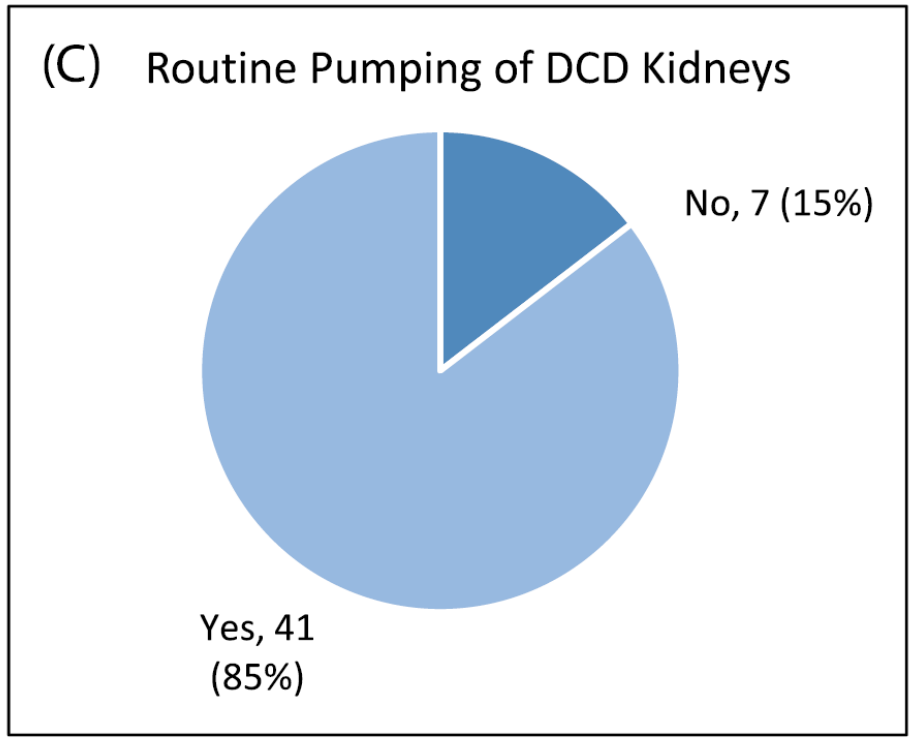
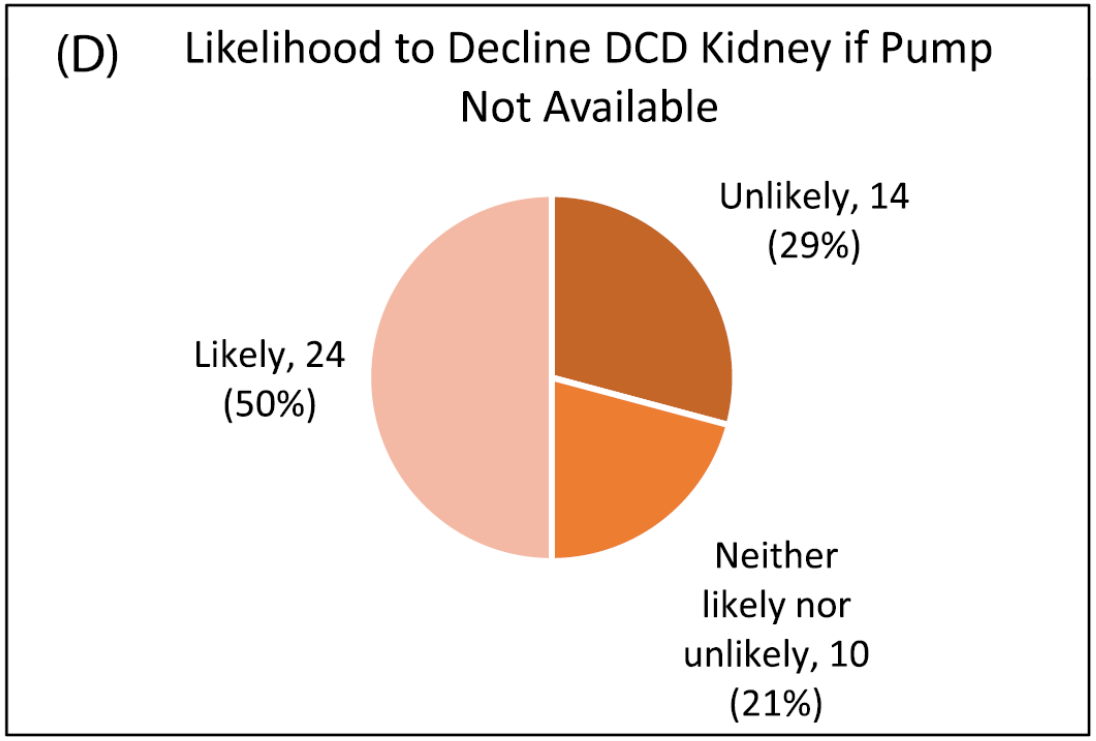
A Survey of United States Transplant Center Donation After Circulatory Death Kidney Transplant Practices in the Modern Era

Karima Alghannam[a], Brian Howard[b], Jennifer Loza[a], Naeem Goussous[a], Junichiro Sageshima[a], Neal M. Mineyev[a], Aileen Wang[c], Richard V. Perez[a], and Peter A. Than[d*]

- 



MANAGEMENT DURING ORGAN PROCUREMENT

- **Preparation** — The **supportive measures** (eg, monitoring, central venous access, arterial line, mechanical ventilation, vasopressors/inotropic agents) should be continued when the donor is brought to the operating room, or instituted as necessary in the operating room. Antibiotics that were initiated in the intensive care unit (ICU) should be continued as scheduled up until procurement. In anticipation of organ procurement, the following issues should be discussed between the surgical team and the clinicians who will be monitoring and supporting the donor during the procedure:
- ●The **amount of cross-matched blood** that should be available
- ●The **required doses of heparin and glucocorticoids**
- ●For lung procurement, the need to **change/upsize the existing endotracheal tube, typically to size 8.0 or 8.5 mm**

- **Control of spinal reflexes** — The brain-dead organ donor usually has a functioning spinal cord, and thus may exhibit unregulated sympathetic and motor spinal reflexes in response to stimulation.
- ●**Motor reflexes** – **Neuromuscular blocking agents (NMBAs)** are typically administered to **prevent uninhibited motor responses to surgery**. NMBAs should be administered in doses that **result in deep neuromuscular blockade** (ie, zero twitches using a train of four peripheral nerve stimulation monitor).
- ●**Sympathetic reflexes** – Reflex sympathetic responses (ie, hypertension and tachycardia) can be controlled with vasoactive drugs, or with **inhaled anesthetics (eg, isoflurane, desflurane, sevoflurane)** if available.

DONATION AFTER CIRCULATORY DEATH

- . Donation after circulatory death (DCD, can be considered when organ donation is desired for a patient who **does not meet** neurologic criteria for **brain death** but has (**no hope of viable recovery** and the decision has been made to **withdraw life-sustaining treatment**.

- The longer the time between withdrawal of life support and declaration of death, the greater the warm ischemic injury to the organs to be procured.
- **Warm ischemic time** can be calculated from the time of onset of hypotension or hypoxemia until the time the organs have been cooled, although some centers advocate calculating the time from when the support is withdrawn until the time the organs are cooled.

- Ideally, **warm ischemic time should be no longer than 30 minutes for livers** and **60 minutes for kidneys and lungs**.
- If the patient does not expire after 60 minutes, the patient may be returned to the intensive care unit (ICU).
- .

Role of normothermic regional perfusion (NRP) in DCD

- Normothermic regional perfusion involves perfusing organs in situ using **extracorporeal membrane oxygenation after circulatory de**ath is declared in order to improve organ viability and transplant outcomes.
- Once the donor is declared dead by circulatory criteria, cessation of circulation to the brain is ensured via clamping, ligation, or division of the cerebral vessels from the aortic arch.

- Subsequently **abdominal and/or thoracic organs** are perfused using **ECMO**.
- NRP allows for **assessment of organ viability** prior to procurement and has potential to increase the number of transplantable organs.

- **NRP** has been associated with **improved graft function** and **reduced rates of delayed graft function for kidneys, livers, and pancreas**.

EJT European Journal of Transplantation
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DOI: 10.57603/EJT-013

Invited review

ABDOMINAL NORMOTHERMIC REGIONAL PERFUSION IN DONATION AFTER CIRCULATORY DEATH: ORGAN VIABILITY OR ORGAN PRESERVATION?

Riccardo De Carlis[1], Leonardo Centonze[1], Michele Migliorini[1,2], Ludovica Pitoni[1,3], Raffaele Cerchione[1,4], Andrea Lauterio[1,3], Luciano De Carlis[1,3]

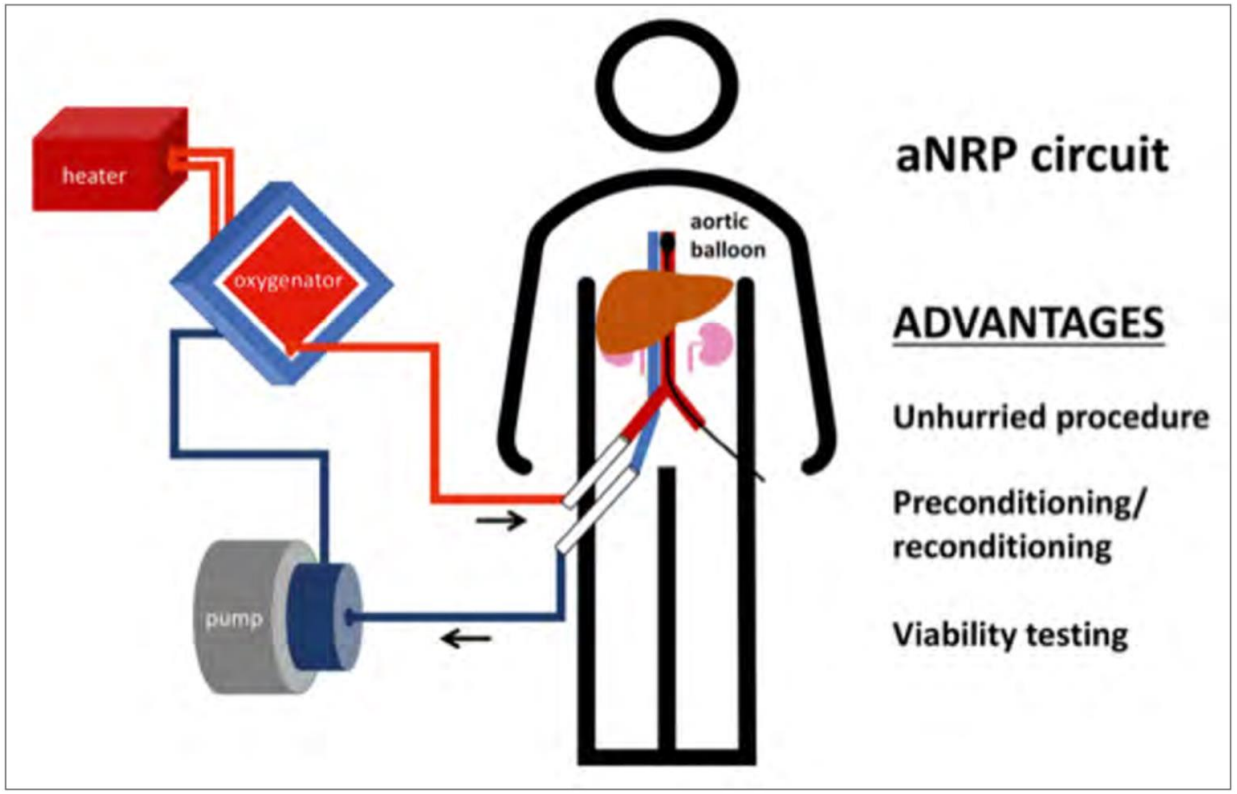


Figure 1. NRP circuit and advantages. The abdominal NRP circuit relies on extracorporeal membrane oxygenation technology and includes a pump, an oxygenator, and a heater. The blood is pumped through arterial and venous cannulae in the femoral vessels. Supraceliac aortic balloon occlusion prevents cerebral reperfusion. aNRP: abdominal normothermic regional perfusion.

Table III. Clinical series of KTs from cDCD with NRP.

Author, year	Study type	n	Donor fWIT (min)	MP	PNF	DGF	Graft survival (follow-up)	Patient survival (follow-up)
Foss, 2018 [25]	Single-centre, retrospective, observational	NRP: 14 DBD: 163	NRP: 26.5 (20-49)	No	NRP: 0% DBD: 0%	NRP:7.1% DBD: 4.9%	NRP: 93% DBD: 95% (1y)	N/A
Miñambres, 2017 [26]	Single-centre, retrospective, observational	NRP: 37 DBD: 36	NRP: 12 (10-19)	No	NRP: 5% DBD: 0%	NRP: 27% DBD: 33.3%	NRP: 91.8% DBD: 97.2% (18mo.)	N/A
Ravaioli, 2018 [30]	Single-centre, retrospective, observational	NRP: 5	NRP: 151.2 (40-325)	HOPE	NRP: 0%	NRP: 30%	NRP: 100% (6mo.)	NRP: 100% (6mo)
Padilla, 2020 [28]	Nation-wide, retrospective, observational	NRP: 865 SRR: 1437	NRP: 13 (10-17) SRR: 18 (13-3)	NRP: 15.9% SRR: 7.3%	NRP: 4.8% SRR: 4.4%	NRP: 30.3% SRR: 48.4%	NRP: 93.1% SRR: 91.5% (1y)	NRP: 97.6% SRR: 95.6% (1y)
Ramirez, 2021 [27]	Single-centre, retrospective, observational	NRP: 22 SRR: 62 DBD: 98	NRP: 10 (10-35) SRR: 15 (11-28)	No	NRP: 4,55% SRR: 6,45% DBD: 10,20%	NRP: 36.36% SRR: 46.77% DBD: 20.41%	NRP: 91% SRR: 87% DBD: 84,4% (15mo.)	NRP: 77.27% SRR: 88.71% DBD: 85.71% (1y)

DBD: donation after brain death; DGF: delayed graft function; MP: machine perfusion; NRP: normothermic regional perfusion; PNF: primary nonfunction; SRR: super-rapid recovery

Abdominal Normothermic Regional Perfusion in Donation after Circulatory Death: A systematic review and critical appraisal.

[1,2]Fenna E.M. van de Leemkolk, MD; [3]Ivo J. Schurink; [4]Olaf M. Dekkers, MD, PhD; [5]Gabriel C. Oniscu, MD, PhD; [1,2]Ian P.J. Alwayn, MD, PhD; [2,6]Rutger J. Ploeg, MD, PhD; [3]Jeroen de Jonge, MD, PhD; [1,2]Volkert A.L. Huurman, MD, PhD.

- T IDCD and cDCD.
- All available studies demonstrated successful implementation of the technique into clinical practice.
- **Function and outcomes after kidney and liver transplantation using aNRP** appear **superior** to **non-aNRP DCD donors**, when comparing data to large cohorts described elsewhere.

- **Some studies found increased survival and lower complication rates.**
- . *Transplantation* 104.9 (2020): 1776-1791

- . During **aNRP, the cellular energy status was found to increase** due to partial

restoration of ATP content, which suggests that the ischemic injury obtained during the warm ischemia time can be partially reversed prior to transplantation

- Therefore, an ‘ischemic preconditioning’ effect can be observed, when using aNRP.
- Not only **intracellular adenosine levels rise,** but also a significant **decrease in**

xanthine levels, as an important nucleotide degradation product, has been observed.

- Overall, the flow for **aNRP was targeted at>1.7L/min.**
- The majority of studies used normothermic perfusion (36-37°C) during aNRP.
- .

- . **After aNRP** and procurement, **preservation of grafts during Cold Ischemia** Time (CIT) has been managed differently per country.

- In France, ex-situ **Hypothermic MachinePerfusion (HMP)** is systematically used for kidney-grafts.

- Del Rio et al.described that **33% of kidneys analysed in their Spanish** National registry cohort, were subjected to **HMP.**

OPEN

Randomized Trial of Machine Perfusion Versus Cold Storage in Recipients of Deceased Donor Kidney Transplants With High Incidence of Delayed Graft Function

Helio Tedesco-Silva, Junior, MD,[1] Juliano Chrystian Mello Offerni,[2] Vanessa Ayres Carneiro,[2] Mayara Ivani de Paula,[1] Elias David Neto,[3] Francine Brambate Carvalhinho Lemos,[3] Lúcio Roberto Requião Moura,[4]

- In this **national**, **multicenter**, and **controlled trial, 80 pairs of kidneys** recovered from **brain-dead deceased donors** were randomized to **cold storage** or machine perfusion, transplanted, and followed up for **12 months**.
- The **primary endpoint** was the **incidence of DGF**.
- **Secondary endpoints** included the **duration of DGF**, **hospital stay**, **primary nonfunction**, **estimated glomerular filtration ra**te, acute **rejection**, and **allograft and patient survivals**
- .

Transplantation Direct 2017;3

- . The incidence of **DGF was lower in the machine perfusion** compared with cold storage group (61% vs. 45%, P = 0.031).
- **Machine perfusion was independently** associated with a **reduced risk** of **DGF (odds ratio, 0.49**; 95% confidence interval, 0.26-0.95).
- **Mean estimated glomerular filtration rate** tended to be **higher at day 28** (40.6 ± 19.9 mL/min per 1.73 m2 vs 49.0 ± 26.9 mL/min per 1.73 m2 ; P = 0.262) and **1 year** (48.3 ± 19.8 mL/min per 1.73 m2 vs 54.4 ± 28.6 mL/min per 1.73 m2 ; P = 0.201) in the **machine perfusion group**.
- **No differences in the incidence of acute rejection**, **primary nonfunction** (0% vs 2.5%), **graft loss** (7.5% vs 10%), or **death** (8.8% vs 6.3%) were observed.

- Conclusions. In this cohort of recipients of deceased donor kidneys with high mean cold ischemia time and high incidence of DGF, the use of **continuous machine perfusion** was associated with a **reduced risk of DGF** compared with the traditional cold storage preservation method.

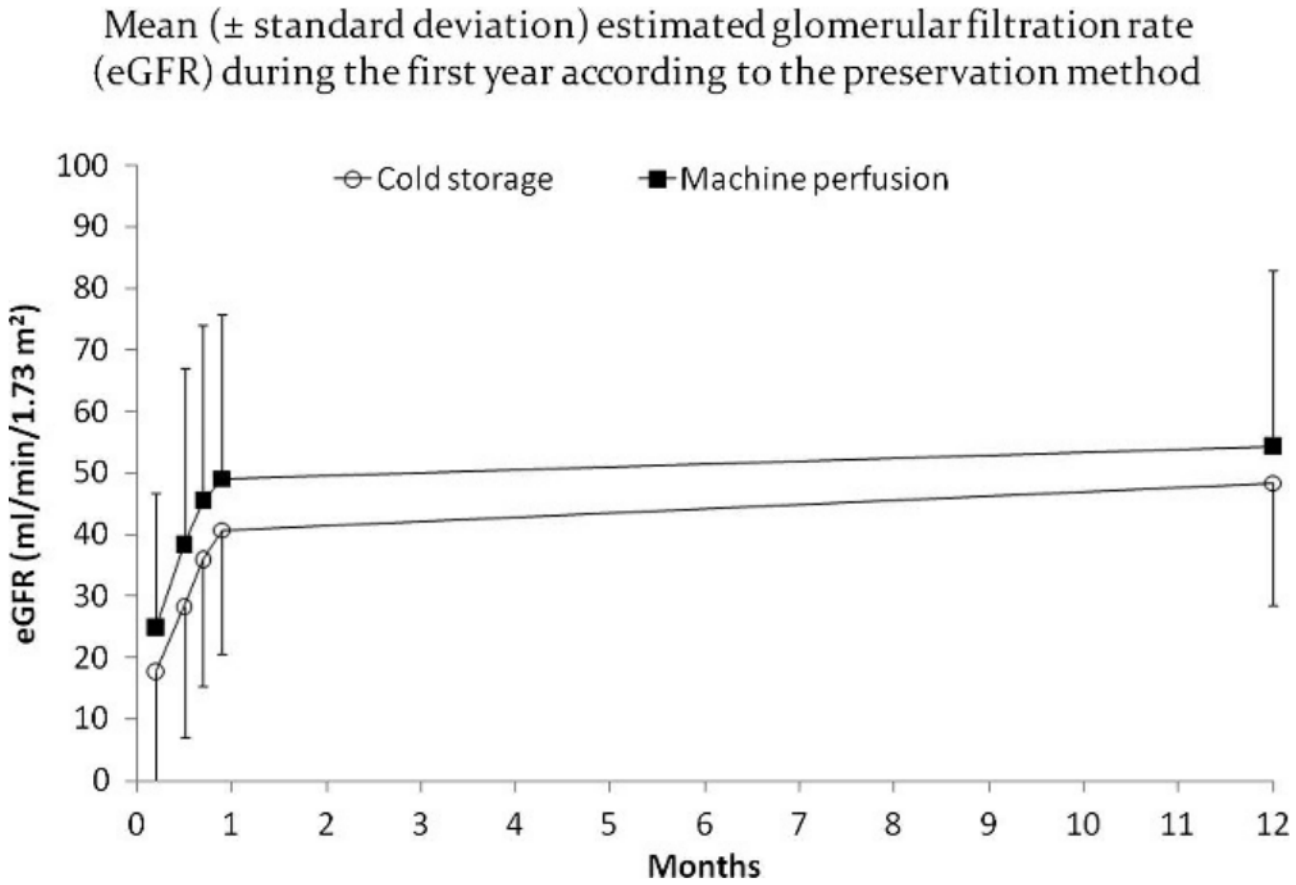


FIGURE 2. Mean (± SD) eGFR during the first year according to the preservation method.

- . **Eighteen studies** met the inclusion criteria, including **seven RCTs** (1475 kidneys) and **11 non-RCTs** (728 kidneys).
- The **overall risk of delayed graft function was lower with hypothermic machine** perfusion than static cold storage (RR 0·81, 95 per cent c.i. 0·71 to 0·92; P = 0·002).
- There was **no difference in the rate of primary non-function** (RR 1·15, 0·46 to 2·90; P = 0·767). There was a faster initial fall in the level of serum creatinine with hypothermic machine perfusion in two RCTs, but not in another. There was no relationship between rates of acute rejection or patient survival and the method of preservation.
- **Conclusion:** Data from the included studies suggest that **hypothermic machine perfusion reduces delayed graft function** compared **with static cold storage**.
- There was **no difference in primary non-function, acute rejection**, **long-term renal function or patient survival**. A difference in renal graft survival is uncertain.

General treatment principles for DBD patient ≈ general ICU patient

Hemodynamic management[1]

- Crystalloids first choice
- Avoid overhydration
- Vasopressor – inotrope as clinically indicated

Lung-protective ventilation

- Prevention of barotrauma and derecruitment
- Prone positioning if poor gas exchange despite optimizaton of ventilatory settings

Prevention of complications

- Infections
- Deep venous thrombosis:
  LMWH unless bleeding risk

Maintain normothermia

Metabolic control

- Glucose control as in general ICU patients

Endocrine therapy: tailored

Diabetes insipidus
Treat polyuria (hypovolemia) + progressive hypernatremia[2]

Thyroid hormone
Consider in case of severe cardiac depression (unresponsive to inotropes)[3]

Hydrocortisone
Consider in case of severe vasoplegia (unresponsive to pressors)[4]

International Journal of
Molecular Sciences

MDPI

Review

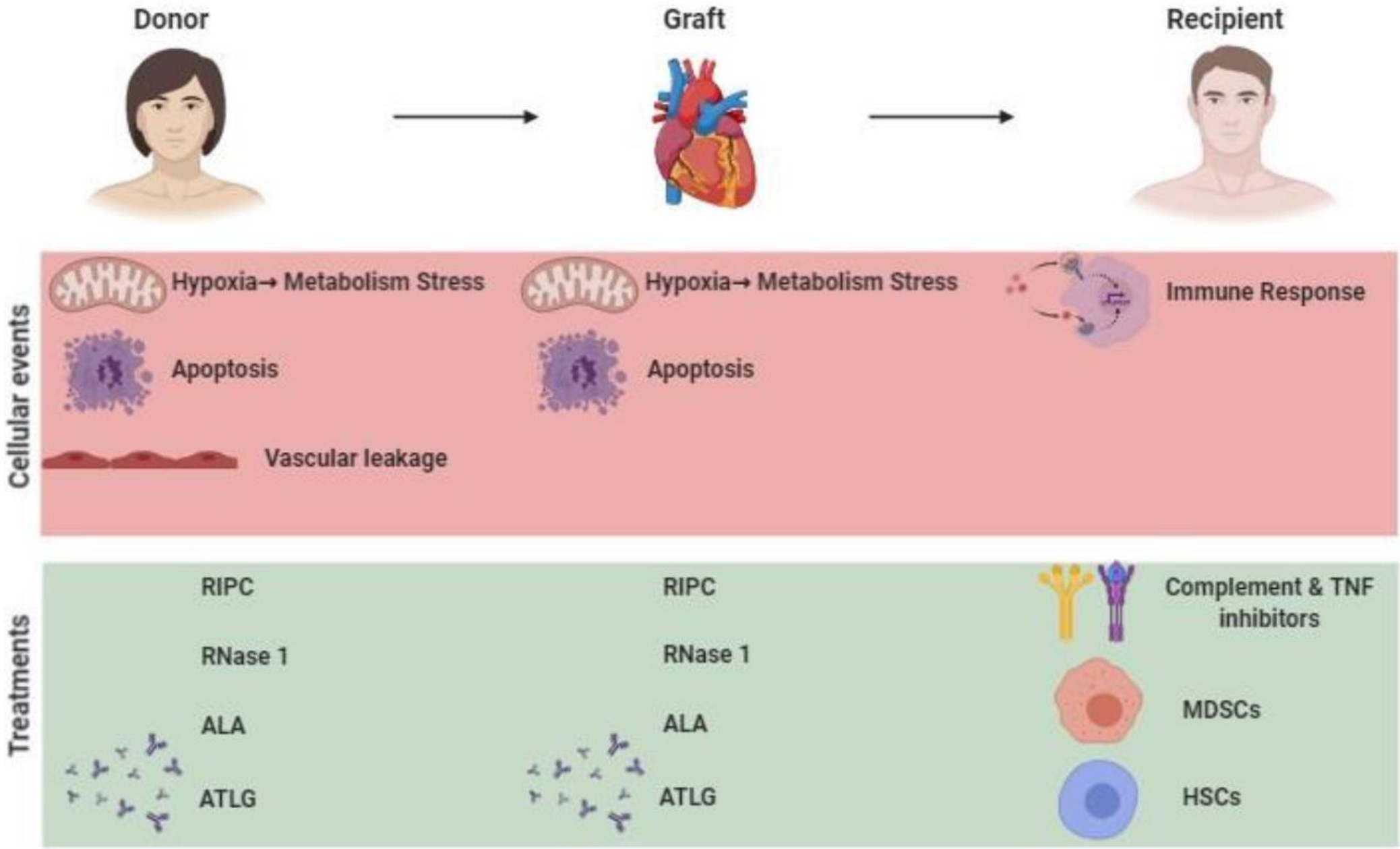
Review: Ischemia Reperfusion Injury—A Translational Perspective in Organ Transplantation

André Renaldo Fernández [1], Rodrigo Sánchez-Tarjuelo [2,3], Paolo Cravedi [4], Jordi Ochando [2,3] and Marcos López-Hoyos [1,5,*]

- In kidney transplantation, ischemia/reperfusion injury (IRI) is known to underlie the clinical entity of delayed graft function (DGF).

- IRI is a **multifactorial inflammatory condition** with underlying factors that include
- **hypoxia,**
- **metabolic stress, leukocyte extravasation,**
- **cellular death pathways,**
- **activation of the immune response**.

- .


Donor
Graft
Recipient
Cellular events
Hypoxia→ Metabolism Stress
Apoptosis
Vascular leakage
Hypoxia→ Metabolism Stress
Apoptosis
Immune Response
Treatments
RIPC
RNase 1
ALA
ATLG
RIPC
RNase 1
ALA
ATLG
Complement & TNF inhibitors
MDSCs
HSCs

Received: 23 July 2019 | Revised: 5 December 2019 | Accepted: 22 December 2019

DOI: 10.1111/ajt.15777

ORIGINAL ARTICLE

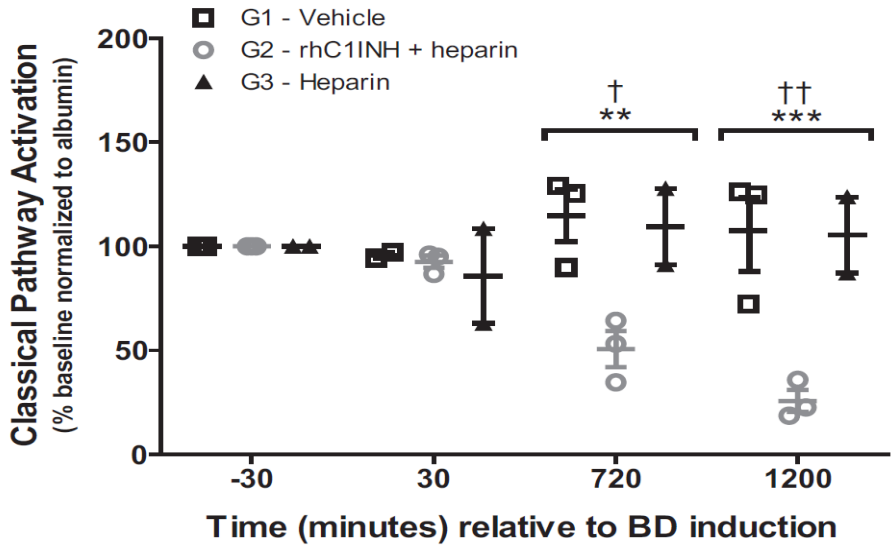
AJT

Targeted donor complement blockade after brain death prevents delayed graft function in a nonhuman primate model of kidney transplantation

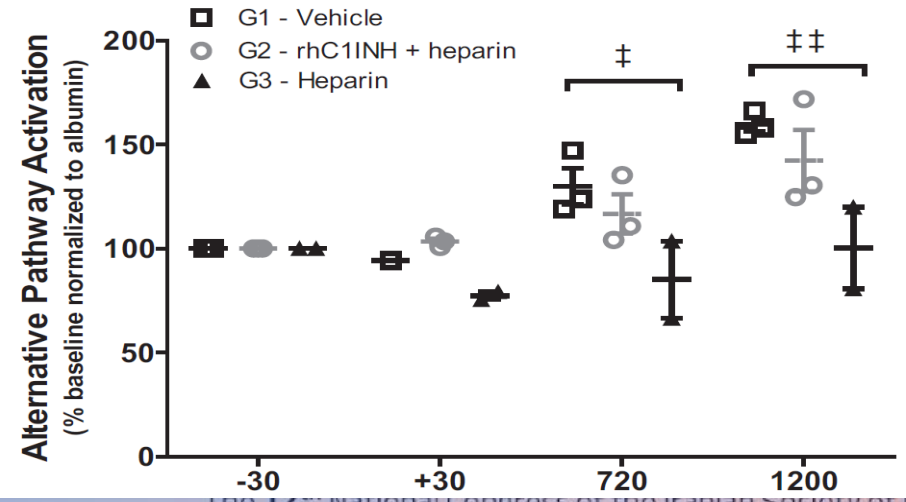
Juan S. Danobeitia[1] | Tiffany J. Zens[1] | Peter J. Chlebeck[1] | Laura J. Zitur[1] | Jose A. Reyes[1] | Michael J. Eerhart[1] | Jennifer Coonen[2] | Saverio Capuano[2] | Anthony M. D'Alessandro[1] | Jose R. Torrealba[3] | Daniel Burguete[3] | Kevin Brunner[2] | Edwin Van Amersfoort[4] | Yolanda Ponstein[4] | Cees Van Kooten[5] | Ewa Jankowska-Gan[1] | William Burlingham[1] | Jeremy Sullivan[1] | Arjang Djamali[6] | Myron Pozniak[7] | Yucel Yankol[1] | Luis A. Fernandez[1]

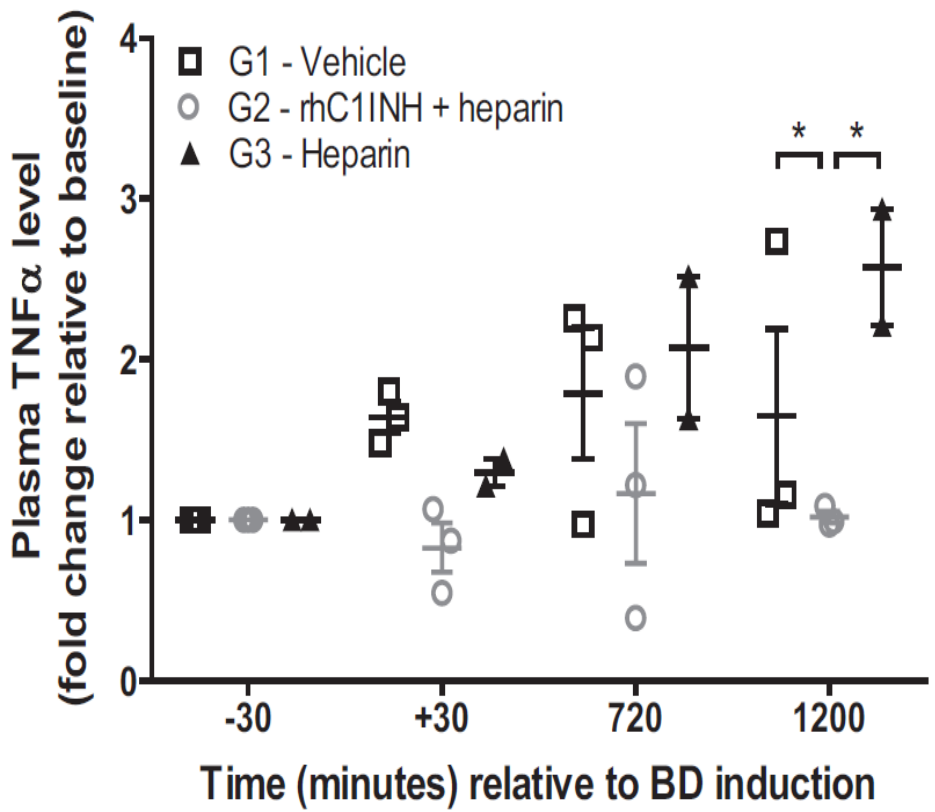
- . Animals were divided into 3 donor-treatment groups:
- **G1 - vehicle**, **G2 - rhC1INH+heparin**, **G3 - heparin**.

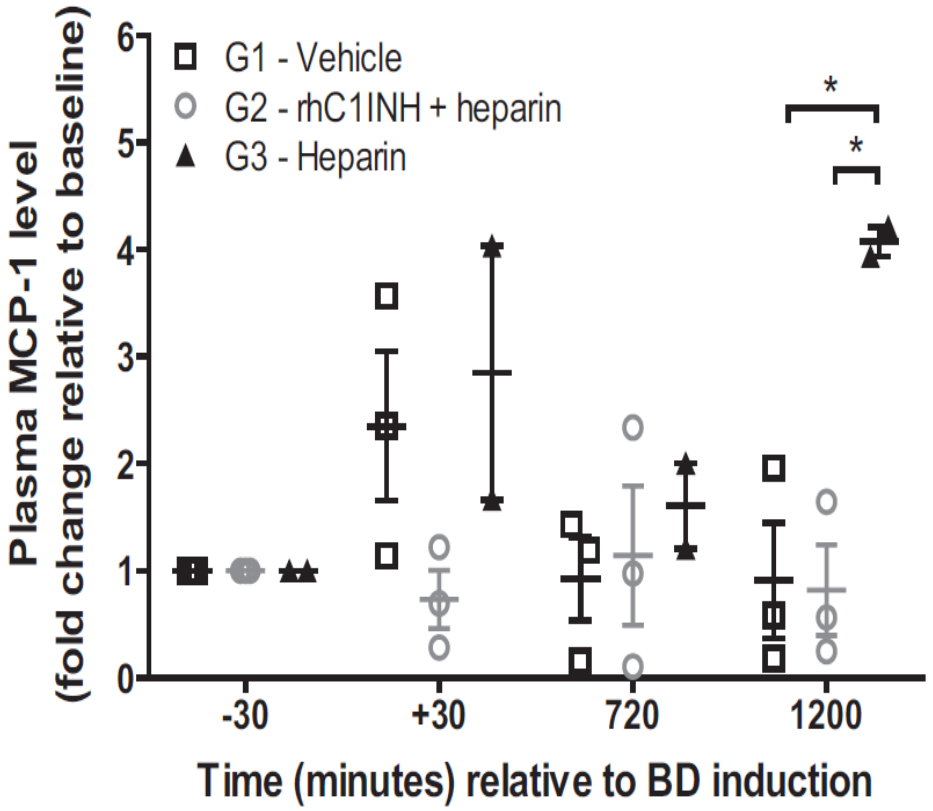
- G2 donors showed **significant reduction** in classical complement pathway activation and **decreased levels of TNFα and MCP1**.


G1 - Vehicle
G2 - rhC1INH + heparin
G3 - Heparin
Classical Pathway Activation
(% baseline normalized to albumin)
200
150
100
50
0
†
**
††
***
-30
30
720
1200
Time (minutes) relative to BD induction

D


G1 - Vehicle
G2 - rhC1INH + heparin
G3 - Heparin
Alternative Pathway Activation
(% baseline normalized to albumin)
200
150
100
50
0
‡
‡‡
-30
+30
720
1200


G1 - Vehicle
G2 - rhC1INH + heparin
G3 - Heparin
Plasma TNFα level
(fold change relative to baseline)
0
1
2
3
4
-30
+30
720
1200
*
*
Time (minutes) relative to BD induction


G1 - Vehicle
G2 - rhC1INH + heparin
G3 - Heparin
Plasma MCP-1 level
(fold change relative to baseline)
0
1
2
3
4
5
6
-30
+30
720
1200
*
*
Time (minutes) relative to BD induction

- DGF was diagnosedin 4/6 **(67%) G1** recipients, 3/3 (100%) G3 recipients, and 0/6 (**0%) G2** recipients (*P* = .008).

- In addition, **G2 recipients showed superior renal function**, **reduced**
- **sC5b-9**, and **reduced urinary NGAL** in the first week posttransplant.

- We observed **no differences** in incidence or severity of **graft rejection between groups**.

- Collectively, the data indicate that donor-management targeting complement activation **prevents the development of DGF.**
- .

Clin J Am Soc Nephrol. 2012 Sep 7; 7(9): 1498–1506.
Published online 2012 Jun 28. doi: 10.2215/CJN.01360212
PMCID: PMC3430945
PMID: 22745272

Effect of High-Dose Erythropoietin on Graft Function after Kidney Transplantation: A Randomized, Double-Blind Clinical Trial

Kalathil K. Sureshkumar,* Sabiha M. Hussain,* Tina Y. Ko,* Ngoc L. Thai,† and Richard J. Marcus*

prospective, randomized, double-blind, placebo-controlled clinical trial

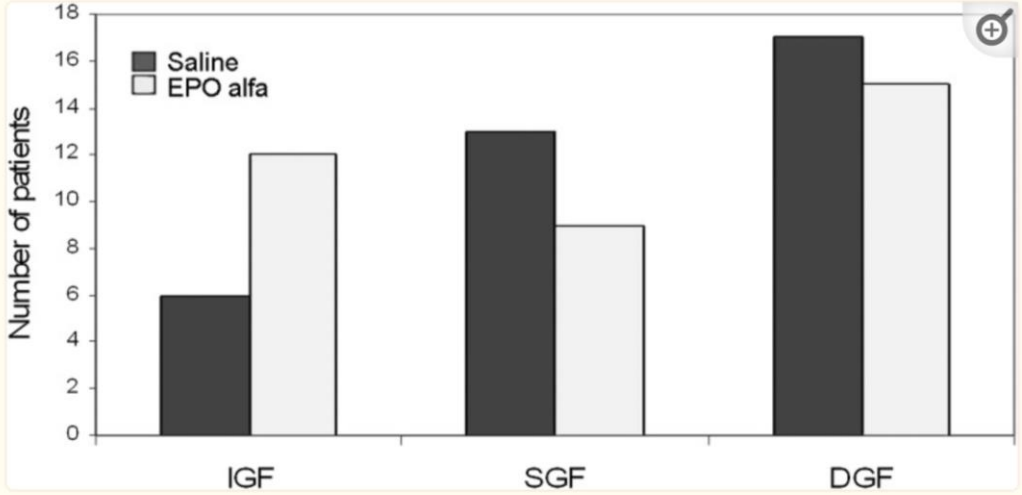


Figure 2.

Incidences of delayed graft function (DGF), slow graft function (SGF), and immediate graft function (IGF) between the groups. There were no significant differences between the groups (P=0.24). EPO, erythropoietin.

influence of EPO-α administered intraoperatively on the outcomes

- **EPO-α (*n*=36)** or placebo (*n*=36) The **incidences of DGF, slow graft function, and immediate graft** function **did not significantly differ** between the treatment and control groups.
- The groups had **similar levels of urinary biomarkers**

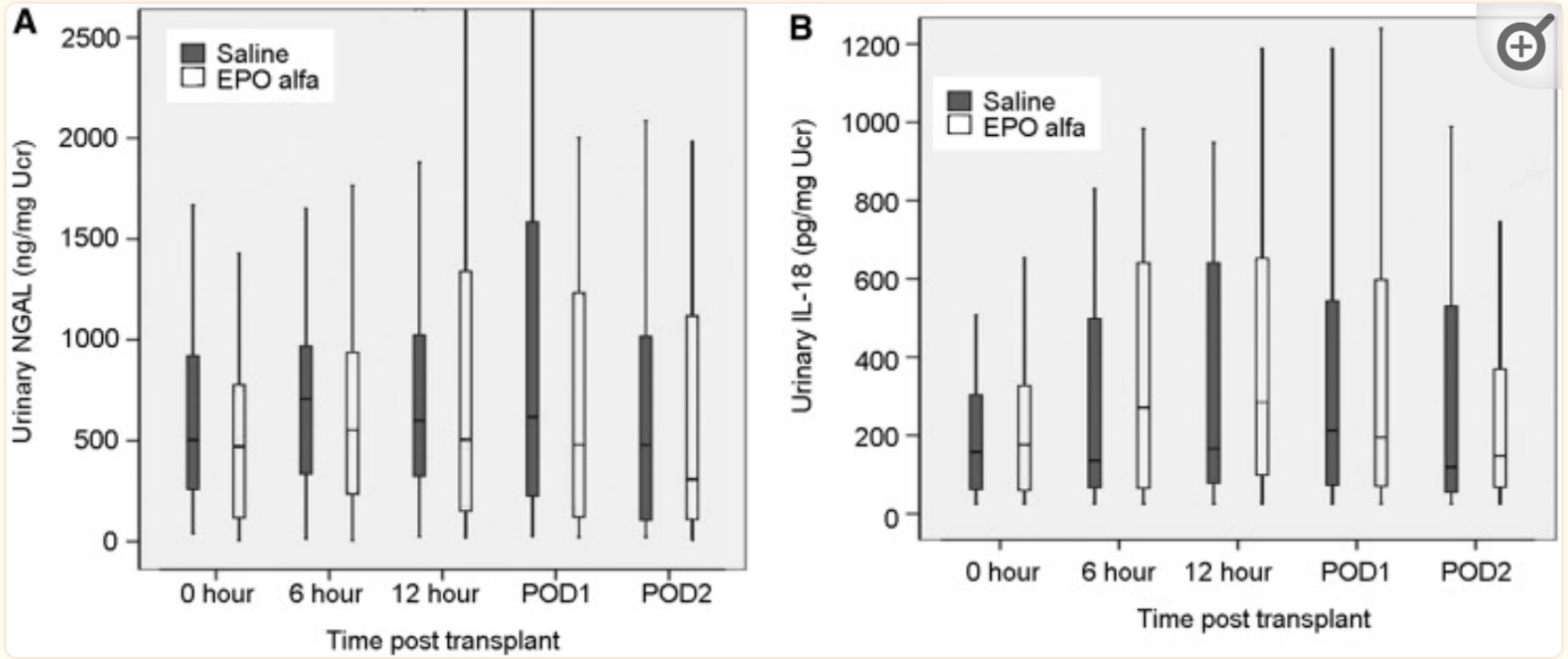


Figure 3.

Comparison of urinary neutrophil gelatin-associated lipocalin (NGAL) and IL-18 levels between the groups at various time points in the early post-transplant period. The differences in NGAL (A) and IL-18 (B) were not statistically significant (P=0.35 and 0.53, respectively). EPO, erythropoietin.

YSPSL (rPSGL-Ig) for improvement of early renal allograft function: a double-blind, placebo-controlled, multi-center Phase IIa study†

A. Osama Gaber, Shamkant Mulgaonkar, Barry D. Kahan, E. Steve Woodle, Rita Alloway, Iman Bajjoka, Stephen Jensik, Goran B. Klintmalm, Pamela R. Patton, Alexander Wiseman, Gerald Lipshutz, Jerzy Kupiec-Weglinski, Lilian W. Gaber, Eliezer Katz, William Irish, Elizabeth C. Squiers, Stefan Hemmerich ... See fewer authors

First published: 16 August 2011 | https://doi.org/10.1111/j.1399-0012.2010.01295.x |

- . **Abstract: Introduction:** Recombinant **P-selectin glycoprotein ligand IgG fusion protein**, rPSGL-Ig (YSPSL), a fusion protein of human P-selectin ligand and IgG1-Fc, **blocks leukocyte adhesion** and **protects against ischemia reperfusion injury (IRI) in animal models.**
- **Patients and Methods:** This **randomized 15-center, double-blind**, **59-patient Ph2a study** assessed YSPSL's safety in recipients of deceased-donor kidney allografts and its potential efficacy in improving early graft function. Two doses and two dosing modalities were evaluated.

Patient management for thoracic organ donor candidates: the lung transplantation team's view

Hye Ju Yeo[1,2]

[1]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, Korea
[2]Transplantation Research Center and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Korea

Clin Transplant Res 2024;38:18-22

Table 2. Lung donor-management protocol at University Hospital Marqués de Valdecilla

No.	Protocol
1	Apnea test performed with a ventilator (continuous positive pressure mode)
2	Mechanical ventilation with positive end-expiratory pressure of 8–10 cmH_2O and tidal volume of 6–8 mL/kg
3	Recruitment maneuvers once per hour and after any disconnection from the ventilator
4	Bronchoscopy with bilateral bronchoalveolar lavage
5	Hemodynamics are closely monitored with the PICCO System (PULSION Medical Systems SE), with the goal of extravascular lung water <10 mL/kg (administering diuretics if necessary) and a central venous pressure objective <8 mmHg
6	Methylprednisolone (15 mg/kg) after brain death declaration
7	Alveolar recruitment involved controlled ventilation (peak pressure limit of 35 mmHg) with positive end-expiratory pressure of 18–20 cmH_2O for 1 minute and a 2 cmH_2O decrease each minute, followed by increasing the tidal volume by 50% for 10 breaths
8	In lung donors with PaO_2/FIO_2 <300 mmHg, semi-lateral decubitus position plus recruitment maneuvers are carried out.

PICCO, pulse index continuous cardiac output.

Clin Transplant Res2024;38:18-22

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PICCO, pulse index continuous cardiac output.

Additional interventions to improve lung function

- . **Donor management protocol** – A comprehensive **lung-protective donor management protocol** at one OPO's organ recovery center demonstrated a significant increase in lung procurement rate (lungs donors/all brain-dead donors) from 19.8 percent (prior to 2008) to 33.9 percent (after the protocol was started, 2009 to 2016) [33].
- The national average of **lungs procured/brain-dead donor** is **22 percent**.
- The protocol included
- **low tidal volume (6 to 8 mL/kg ideal body weight), low flow rates (25 to 30 L/min**), **inspiratory:expiratory ratio (I:E) 1:1**,
- **peak pressures <30 mmHg**,
- and **PEEP 8 to 10 cm H_2O**.
- It also included
- **intrapulmonary percussive ventilation every four hours**,
- **frequent bronchoscopy to remove secretions,**
- **recruitment maneuvers (PEEP up to 15 cm H_2O**),
- and **pulmonary ultrasound** to evaluate for pulmonary edema. Further study is needed to confirm these results

- **Prone ventilation –**
- **Basilar opacities and/or atelectasis was present in 75 percent of the donors, and significantly decreased in the donors after prone ventilation .**
- Prone ventilation should be considered in the **hypoxemic donor with basilar opacities on a chest radiograph or CT scan**.
- .

- **Ex-vivo lung perfusion (EVLP)** – If the arterial oxygen tension/fraction of inspired oxygen (PaO_2/FiO_2) ratio remains below 300 after intensive lung donor management, EVLP may be an option after lung procurement to recondition lungs, improve oxygenation, and increase pulmonary compliance, thus improving acceptability of otherwise unacceptable lung allografts, as discussed separately.