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Impact of Ex-Vivo Perfusion and DCD Donors: Expanding Access

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CUTTING EDGE OF TRANSPLANTATION

TRANSPLANT SUMMIT 2020
BALANCING EQUITY AND UTILITY IN THE FACE OF AN ORGAN SHORTAGE

Disclosure

I have no relevant disclosures

Learning Objectives

1) Describe the ex-vivo perfusion platform for procurement, maintenance and monitoring of the donor allograft and understand its potential role in expanding the donor pool in heart transplantation.

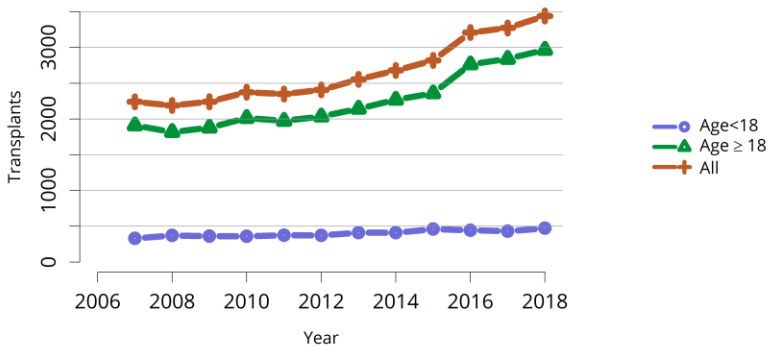
2) Learn the key concepts of DCD donation and understand its potential role in expanding the donor pool.

3) Understand the benefits and risks of ex-vivo perfusion and DCD donation.

4) Recognize the ethical issues surrounding DCD donation.

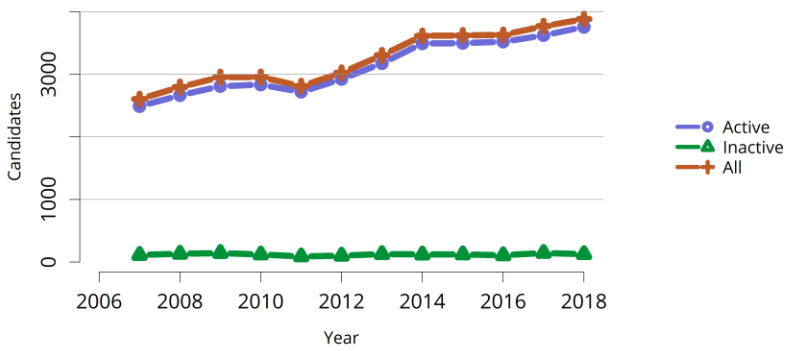
Heart Transplant Rates and Waitlist Volume

Figure HR 45. Total heart transplants



OPTN/SRTR 2018 Annual Data Report

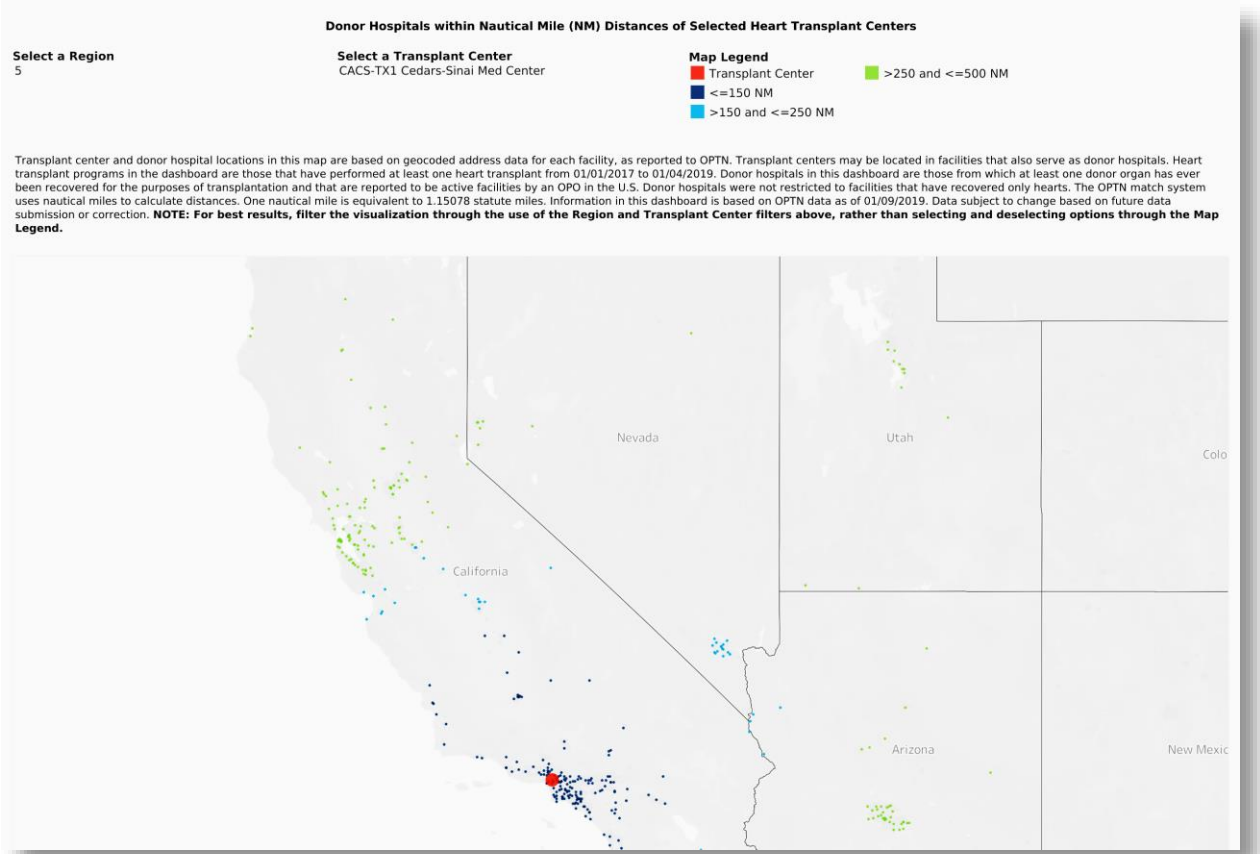
Figure HR 1. New adult candidates added to the heart transplant waiting list



OPTN/SRTR 2018 Annual Data Report

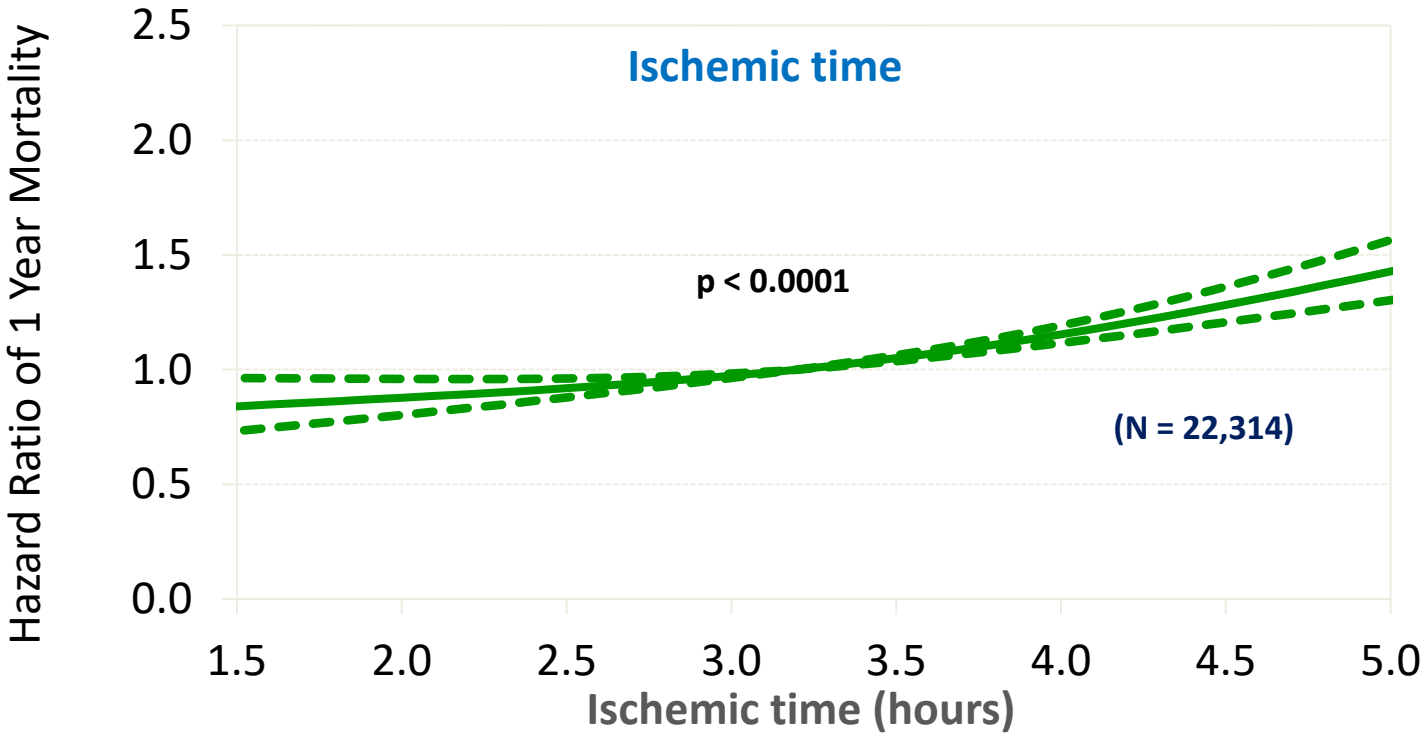
New UNOS Allocation Scheme - Goals

- Better stratify the most medically urgent heart transplant candidates
- Reflect the increased use of mechanical circulatory support devices (MCSD) and prevalence of MCSD complications
- Address geographic disparities in access to donors through broader sharing and elimination of donor service areas



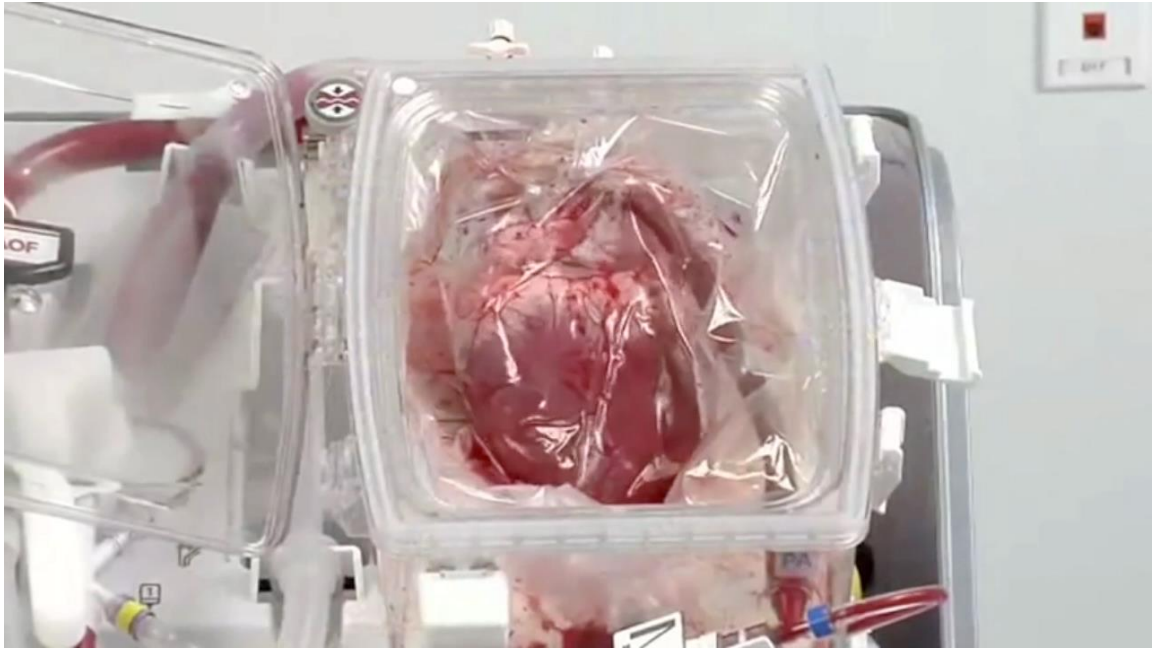
Adult Heart Transplants (2011-6/2016)

Risk Factors For 1 Year Mortality with 95% Confidence Limits



The Organ Care System (OCS™)

Donor heart placed into this protected box



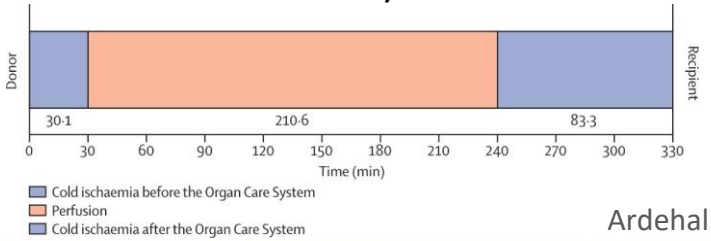
- Assessment is by means of arterial and venous lactate trends, hemodynamic pressures and visual inspection.

Results of the PROCEED Trial

- PROCEED was a prospective, multi-center, randomized trial comparing ex-vivo heart perfusion (n=65) to the standard cold storage (n=63) techniques to preserve human donor hearts for transplantation.

- The primary endpoint of 30-day post-transplant patient and graft survival was similar in the OCS and the control groups (93% vs 96%, respectively, p=NS).

- Total preservation time was significantly longer in the ex-vivo heart perfusion vs. control group, with a shorter cold ischemia time.
  - The longest preservation time in the study was 9.7 hours.



Ardehali, Kobashigawa et al Lancet 2015; 385: 2577–84

Ex-vivo perfusion can expand the donor pool

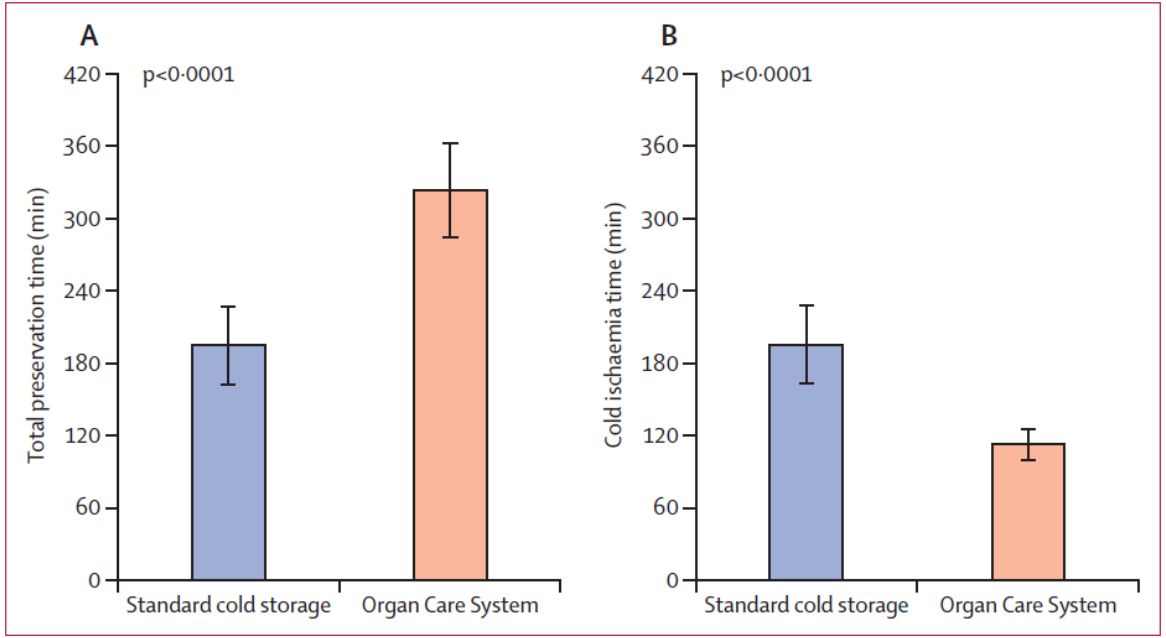


Figure 5: **Mean total preservation (out-of-body) time (A) and total cold ischaemia time (B) in the Organ Care System group versus the standard cold storage group**
Error bars show SDs.

Ardehali, Kobashigawa et al, Lancet 2015; 385: 2577–84

PROCEED II: Results

Cardiac-related serious adverse events (as-treated population)

	Organ Care System group (n=62)	Standard cold storage group (n=66)	p value
Left ventricular dysfunction	5 (8%)	4 (6%)	0·657
Right ventricular dysfunction	2 (3%)	6 (9%)	0·170
Graft failure	1 (2%)	0	0·330

Ardehali, Kobashigawa et al. 2015; 385: 2577–84

Organ Care System For Recruiting, Preserving and Assessing Expanded Criteria Donor Hearts for Transplantation (EXPAND Trial)

- International prospective single-arm trial including 20 worldwide centers
- Inclusion criteria:
  - Expected total cross-clamp time of ≥4 hrs
  - Expected total cross-clamp time of ≥2 hrs plus one or more risk factors
- Primary composite endpoint of 30-day patient survival and absence of primary graft dysfunction within 24 hours of transplant.
- Safety endpoints:
  - incidence of serious adverse events
  - moderate to severe primary graft dysfunction

- Clinical implications have potential to improve donor heart utilization for transplant as many are currently discarded due to strict selection criteria

Donation After Circulatory Death (DCD) - Definitions

- **Donation After Brain Death (DBD)**
  - Death defined as *irreversible cessation of all functions of the entire brain, including the brain stem*
    - adapted from Harvard Ad Hoc Committee (1968)[1] and codified into law in the Uniform Determination of Death Act (1981)
  - *The heart does not need to stop for a valid declaration of death*
- **Donation After Circulatory Death (DCD)**
  - retrieval of organs for the purpose of transplantation from patients whose death is diagnosed and confirmed using cardio-respiratory criteria.
  - *Asystole must be confirmed for at least 5 mins*

[1]Beecher HK et al. JAMA. 1968;205:337–40

Maastricht Classification of DCD

	Definition	**Where**
I	Dead on arrival	Spain, France, Italy
II	Unsuccessful resuscitation	
III	Cardiac arrest awaited after withdrawal of life support in patients who are not brain dead	Belgium, United Kingdom, Netherlands, Australia, **USA**, New Zealand
IV	Cardiac arrest after brain death	

MC I, II, uncontrolled

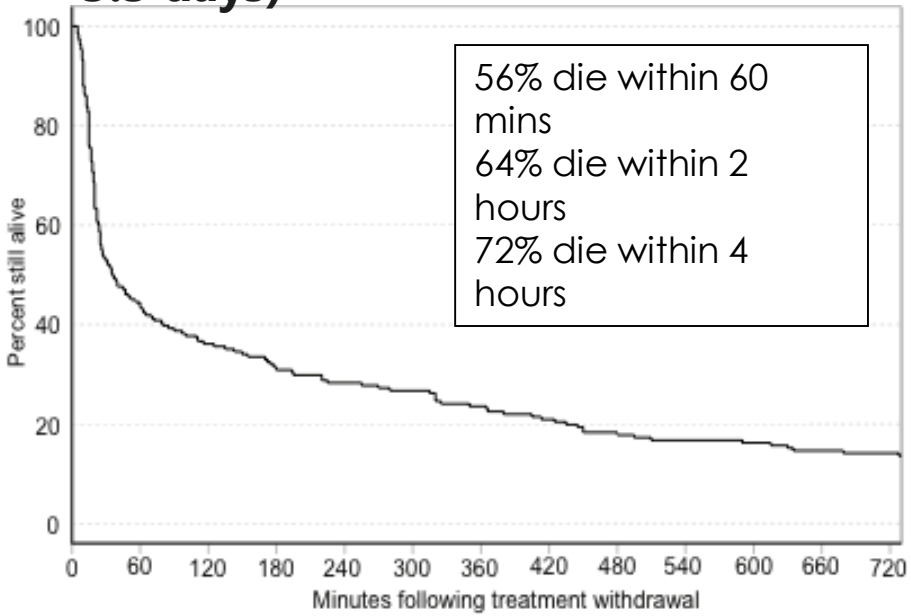
MC III, IV: controlled

Donation after Cardiac Death (DCD)

- Usually involves younger ventilated patients with extensive brain damage not qualifying for brain death whose family/doctors agree to withdraw care.
- These patients can donate organs after the heart ceases to beat with a 5 minute stand-off time.
- It is predicted that organ donation might increase by up to 30% with these cases.

Time to Asystole after Withdrawal of Life-sustaining Support

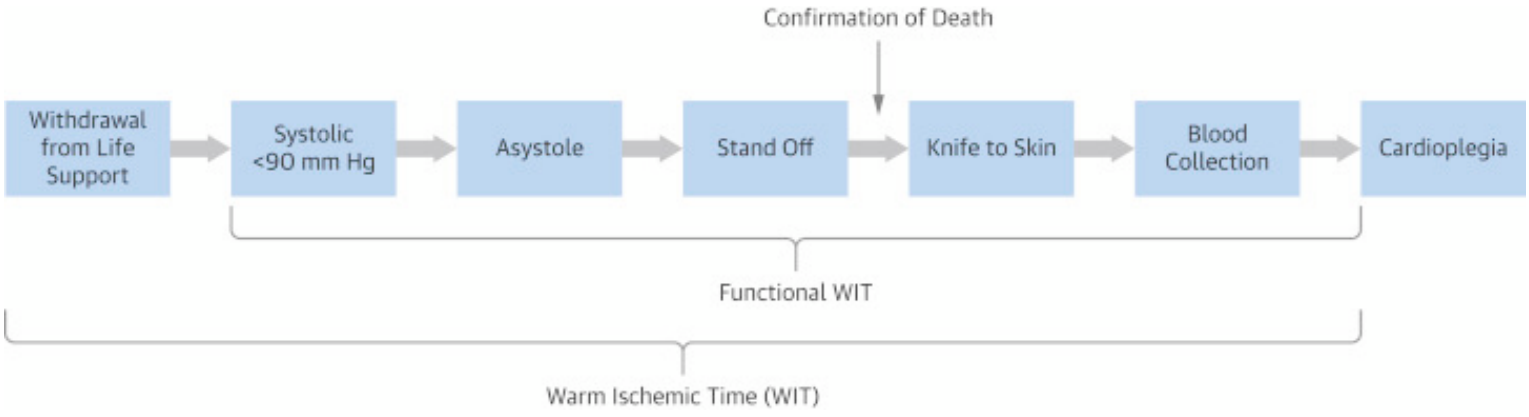
median time to death of 36 min (range 5 min to 3.3 days)



- Younger age
- High respiratory support
  - High FiO_2
  - PEEP > 10 cmH_2O
  - IPPV
- Inotropes
- GCS 3
- BMI > 30

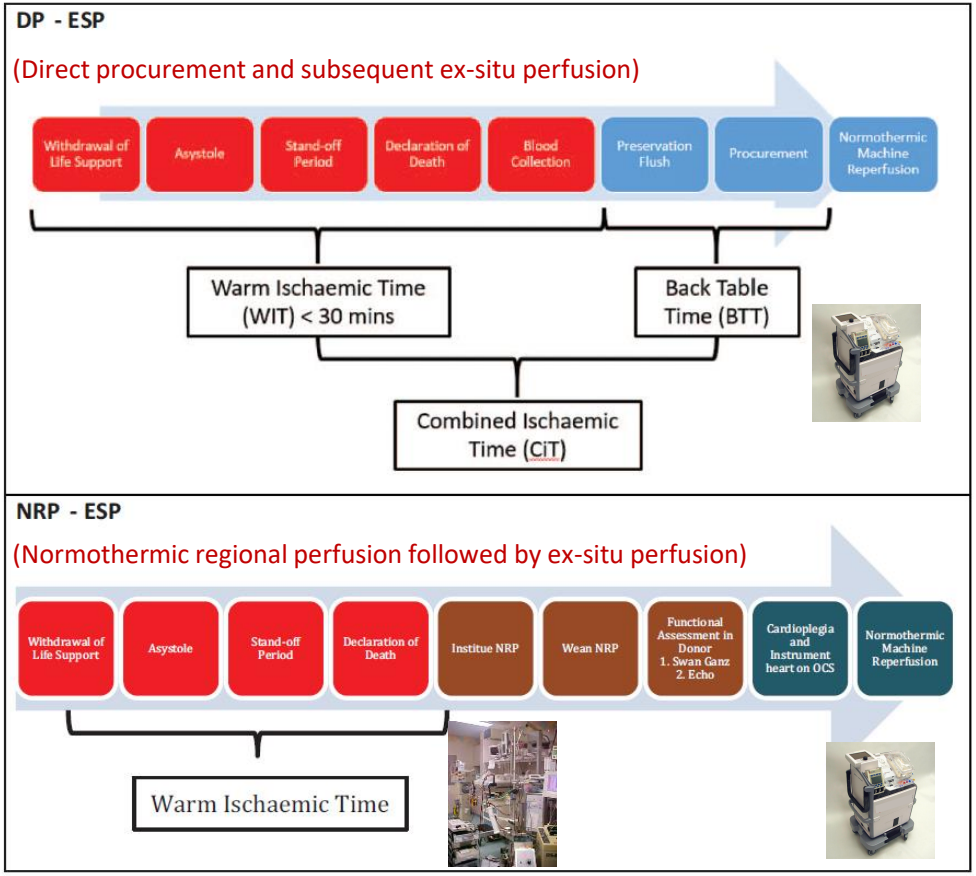
Suntharalingam et al. AJT 2009;9:2157

Definitions



Chew et al. JACC 2019

DCD Protocols

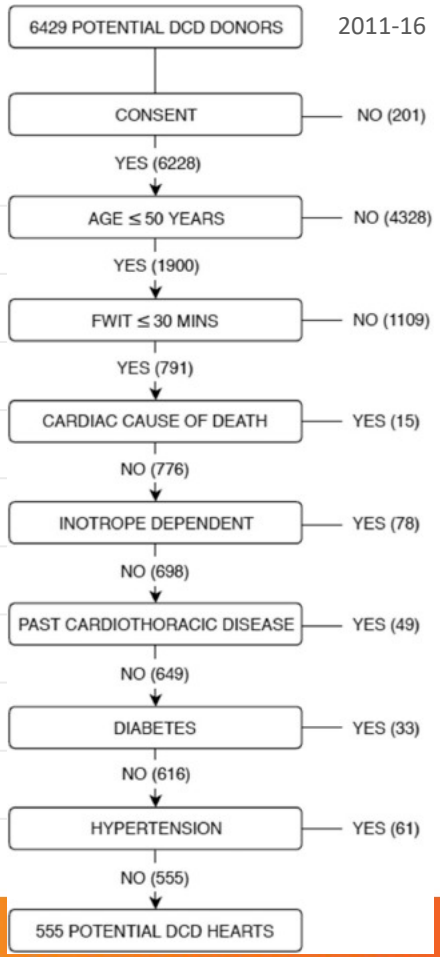


Normothermic reperfusion serves to restore aerobic conditions prior to cold perfusion and allow functional assessment

Macdonald P et al. Curr Opin Organ Transplant 2017

Criteria for Potential Donation after DCD Heart Donation in UK

Inclusion criteria	Exclusion criteria
Consent present for donation	Cardiac-related cause of death
Maastricht type III/IV donors	Past medical history of cardiac disease
Donor age ≤ 50 years old	Diabetic
Proceeded to donate ≥ 1 organ	History of hypertension
FWIT ≤ 30 minutes	On inotrope support
Complete donor demographics	Adrenaline
	Dobutamine
	Dopamine



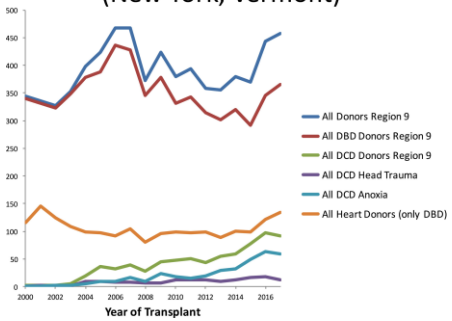
Messer et al. JHLT Aug 2019

Potentially increase HTx activity by 56%

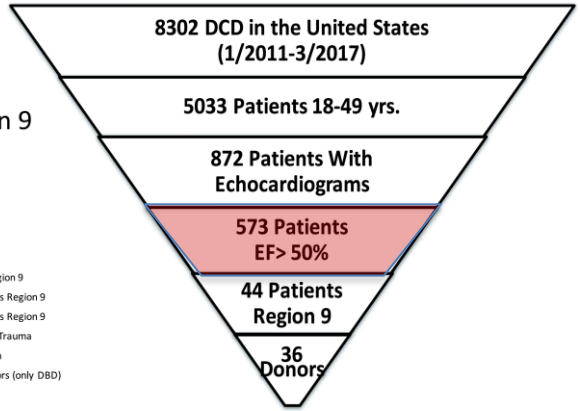
Increasing the US Heart Transplant Donor Pool with DCD

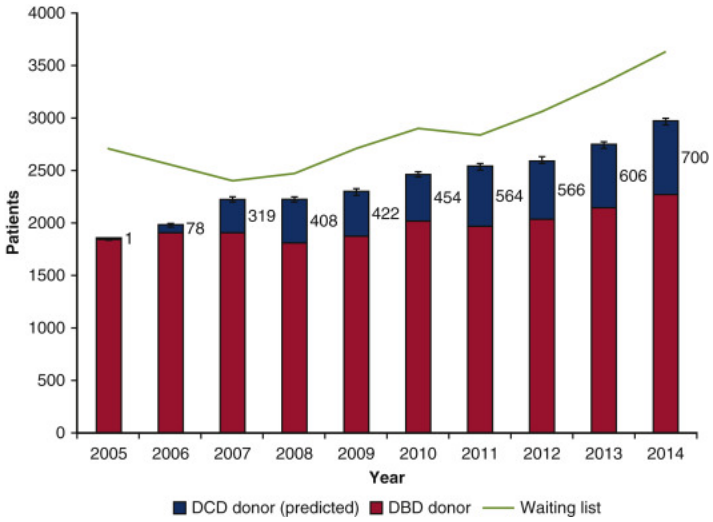
After application of the criteria of Messer to the 2005 to 2014 pool of US DCD donors, a total of 4118 potential DCD heart transplant donors were identified, representing a 30% increase in potential donors

Trends in Transplantation Region 9
(New York, Vermont)



Potential DCD Heart Donors





Farr et al. AJT Feb 2020

Jawitz et al J Thorac Cardiovasc Surg. 2019 Sep 30.

DCD Outcomes in Heart

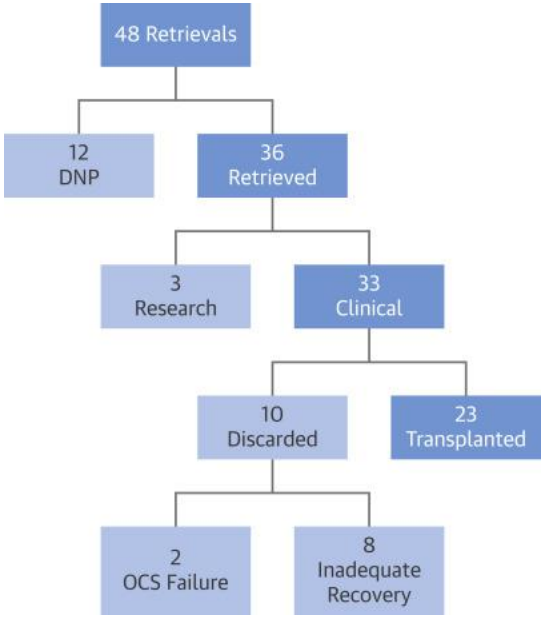
Table 5. Donation after circulatory death heart transplant outcomes

	Procurement strategy	No DCD heart transplants	30-Day survival (%)	6-Month survival	1-Year survival
St Vincent's Hospital, Sydney, Australia	DP-ESP	14	100	100	100
Harefield Hospital, London, UK[a]	DP-ESP	4	75	75	75
Papworth Hospital, Cambridge, UK[a]	DP-ESP	14	100	85.7	78.6
	NRP-ESP	13	100	100	100
Total		45	97.8	93.3	91.1

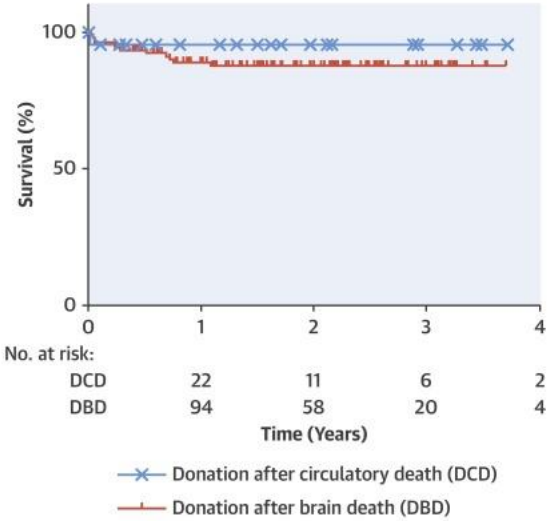
DCD, donation after circulatory death; DP-ESP, direct procurement and ex-situ perfusion; NRP-ESP, normothermic regional perfusion in the donor followed by ex-situ perfusion.
[a]Personal communication.

Dhital et al. Curr Opin Organ Transplant 2017

Outcomes of Donation After Circulatory Death Heart Transplantation in Australia



CENTRAL ILLUSTRATION: Recipient Survival After Cardiac Transplantation Using Donation After Circulatory Death Versus Donation After Brain Death



Chew, H.C. et al. J Am Coll Cardiol. 2019;73(12):1447-59.

Duke University doctors perform first-of-its-kind heart transplant

December 04, 2019 03:20 PM

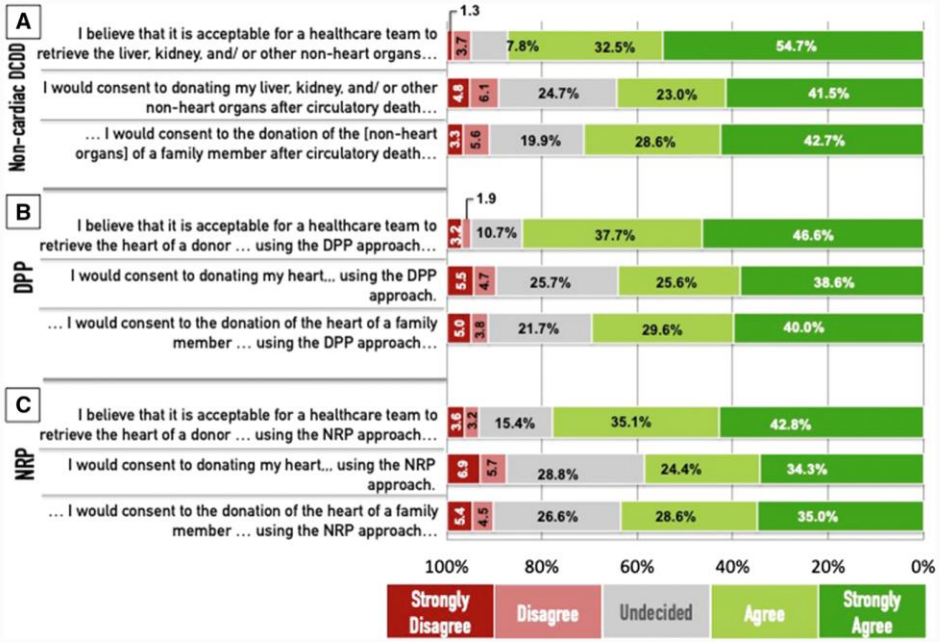
Doctors at Duke University performing an adult heart transplant through a process known as donation after circulatory death, or DCD, on Sunday, Dec. 1, 2019 Shawn Rocco *Duke Health*

DURHAM

Ethical Issues

- Definition of death
- Conflict between donor death and preserving organs
- Maintaining the “Hands Off” period - acceptable length of observation between cessation of circulation to declaration of death
- Clamping cerebral vessels to prevent restoration of brain circulation in NRP
- Acceptance of pre-mortem interventions to protect organ function

Acceptability of cardiac donation after circulatory determination of death: a survey of the Canadian public



Respondents' attitudes towards A) non-cardiac donation after circulatory determination of death (DCDD), B) cardiac DCDD using the direct procurement and perfusion (DPP) protocol, and C) cardiac DCDD using the normothermic regional perfusion (NRP) protocol

Honarmand, K.,. *et al. Can J Anesth* **67,** 292–300 (2020)

Organ Donation after Ethanasia (ODE)

ELSEVIER

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

PERSPECTIVE

Euthanasia through living organ donation: Ethical, legal, and medical challenges

CrossMark

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J Heart Lung Transplant 2019;38:111

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Organ Donation after Medical Assistance in Dying — Canada's First Cases

Ball et al. NEJM Feb 2020

Perspective

FEBRUARY 6, 2020

Altruism *in Extremis* — The Evolving Ethics of Organ Donation

Lisa Rosenbaum, M.D.

Summary

- The demand for heart transplantation continues to outstrip available organs
- The increased demand has prompted efforts to expand the donor pool
- Ex-vivo perfusion allows organs to be procured from greater geographical distances and is non-inferior to standard procurement

  EXPAND trial will determine if technology feasible for marginal donors
- DCD organs in conjunction with ex vivo perfusion provide comparable short-term survival to DBD donors and may represent a significant source of viable organs
- Ethical concerns surrounding DCD donation remain but do not appear to be insurmountable