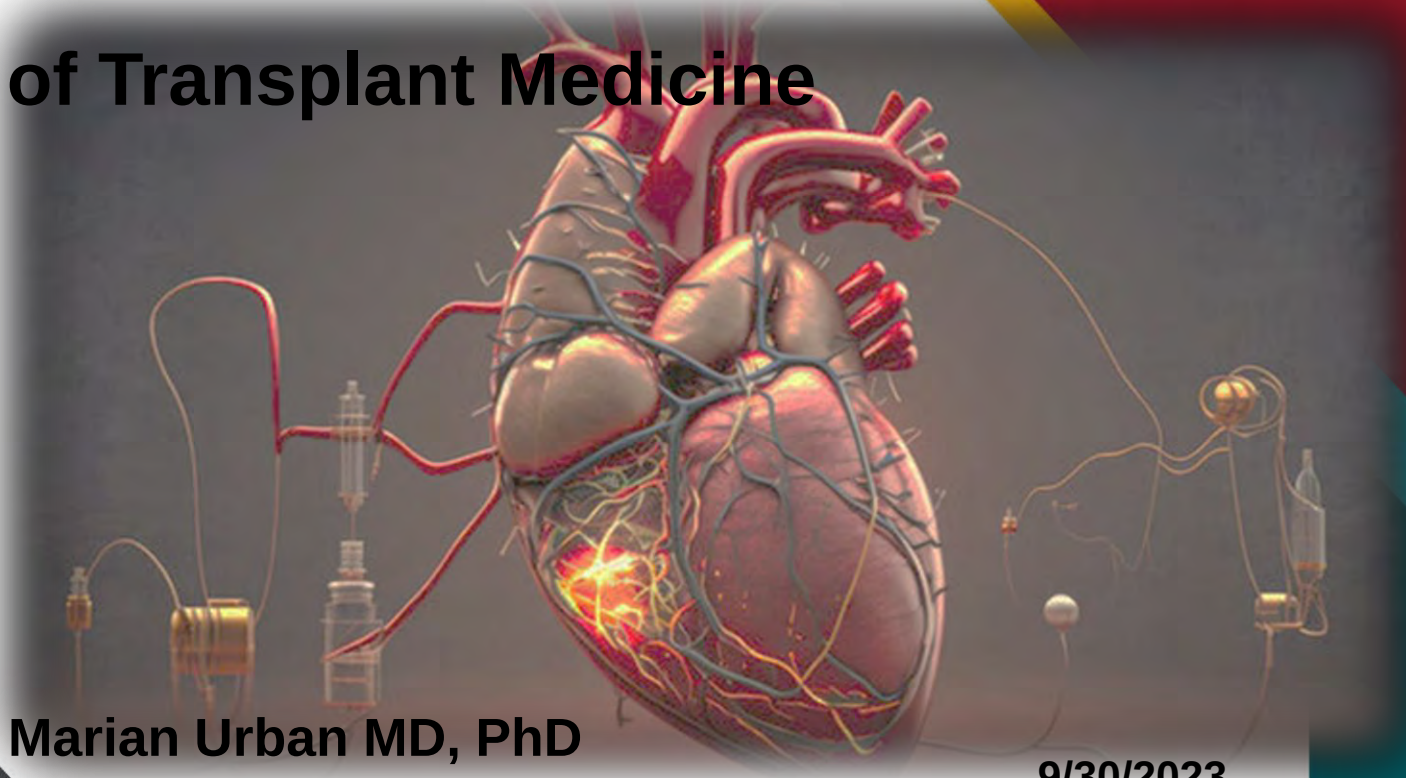
Updates in Cardiac Transplantation: Procuring the Future of Transplant Medicine

University of Nebraska Medical Center



Marian Urban MD, PhD

9/30/2023

Major Breakthroughs

Concept of brain death

Ischemic organ preservation

Ciclosporin

NDC# 0074-3109-32

First human heart transplantation

Donation after circulatory determined death

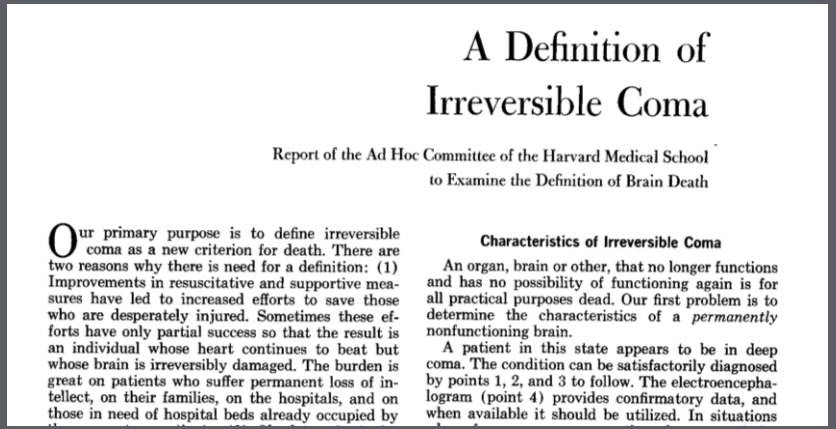
Donor and Recipient co-located

Definition of brain death

Individuals who sustained traumatic brain injury that caused them to be in irreversible coma, and had lost the ability to breathe spontaneously would be considered dead

Justification:

1. Allow for withdrawing life support from people who had sustained irreversible and devastating brain injury
2. Address obstacles to organ transplantation



A Definition of Irreversible Coma

Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death

Our primary purpose is to define irreversible coma as a new criterion for death. There are two reasons why there is need for a definition: (1) Improvements in resuscitative and supportive measures have led to increased efforts to save those who are desperately injured. Sometimes these efforts have only partial success so that the result is an individual whose heart continues to beat but whose brain is irreversibly damaged. The burden is great on patients who suffer permanent loss of intellect, on their families, on the hospitals, and on those in need of hospital beds already occupied by

Characteristics of Irreversible Coma

An organ, brain or other, that no longer functions and has no possibility of functioning again is for all practical purposes dead. Our first problem is to determine the characteristics of a *permanently* nonfunctioning brain.

A patient in this state appears to be in deep coma. The condition can be satisfactorily diagnosed by points 1, 2, and 3 to follow. The electroencephalogram (point 4) provides confirmatory data, and when available it should be utilized. In situations

Uniform Determination of Death Act (UDDA)

UDDA Overview

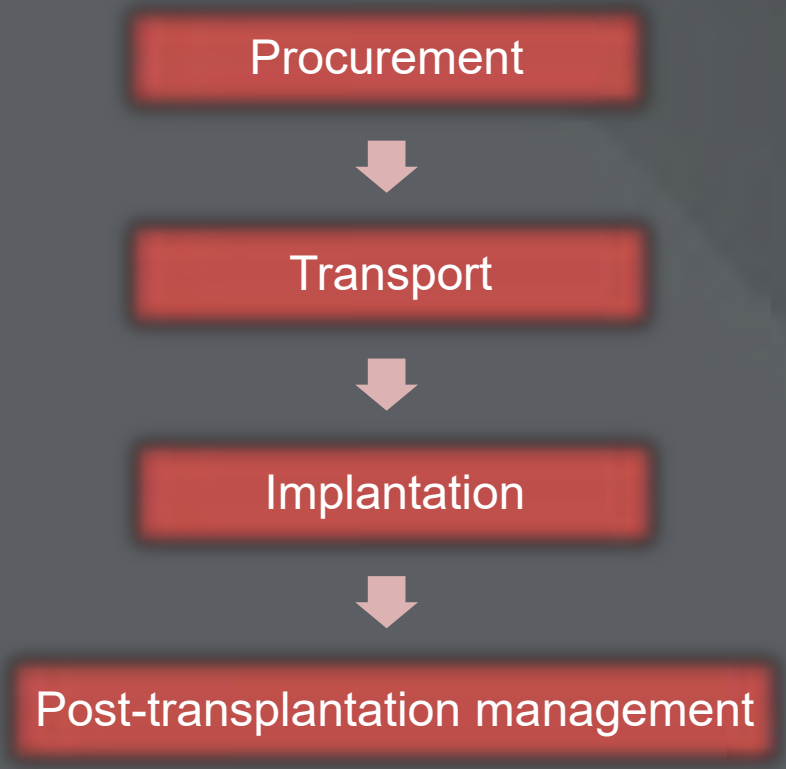
The Uniform Declaration of Death Act was drafted in 1981 by a President's Commission study on brain death. It was approved by both the American Medical Association (AMA) and the American Bar Association (ABA) shortly after its publication. Health care is primarily handled on a state-by-state basis, so the intent of the Act was to provide a model for states to emulate.

The UDDA offers two definitions for when an individual may legally be declared dead:

1. Irreversible cessation of circulatory and respiratory functions; or
2. Irreversible cessation of all functions of the entire brain, including the brain stem.

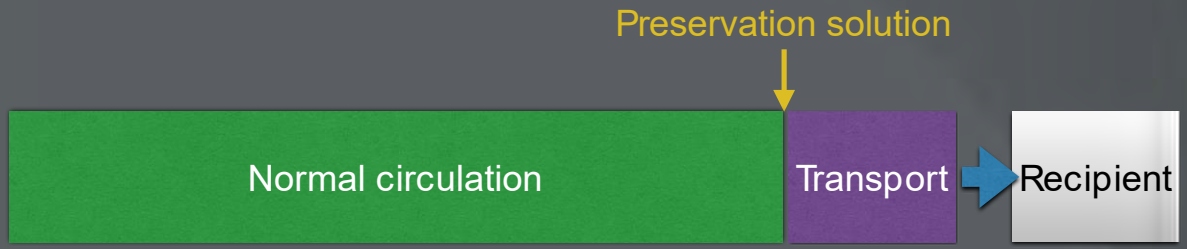
The most common type of death is the first one, in which the heart has stopped beating and/or the patient is no longer breathing (usually followed by brain death). But sometimes (as in the second definition), an individual may be kept "alive" through the use of ventilators and feeding tubes even though there is zero brain activity. Most states consider brain dead individuals legally dead and remove them from life support, although the body's other life functions may be maintained until organs are harvested for donation.

Background

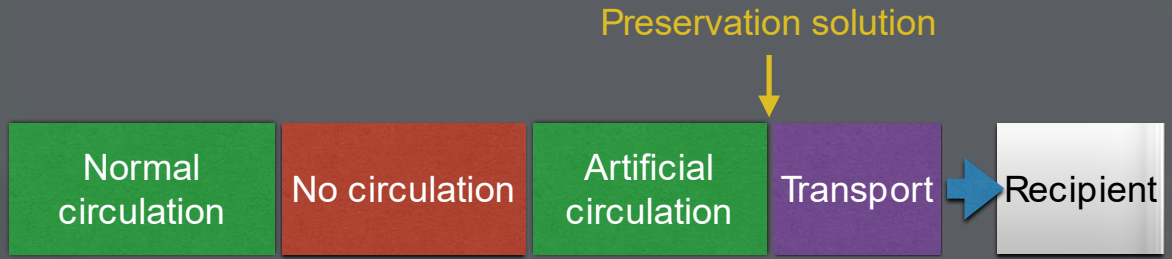

Procurement
Transport
Implantation
Post-transplantation management

DBD versus DCD

Donation After Brain Death



Donation After Circulatory Death



Clinical DCD

Unquantifiable injury due to warm ischemia

Inability to assess function of the asystolic heart

DBD versus DCD

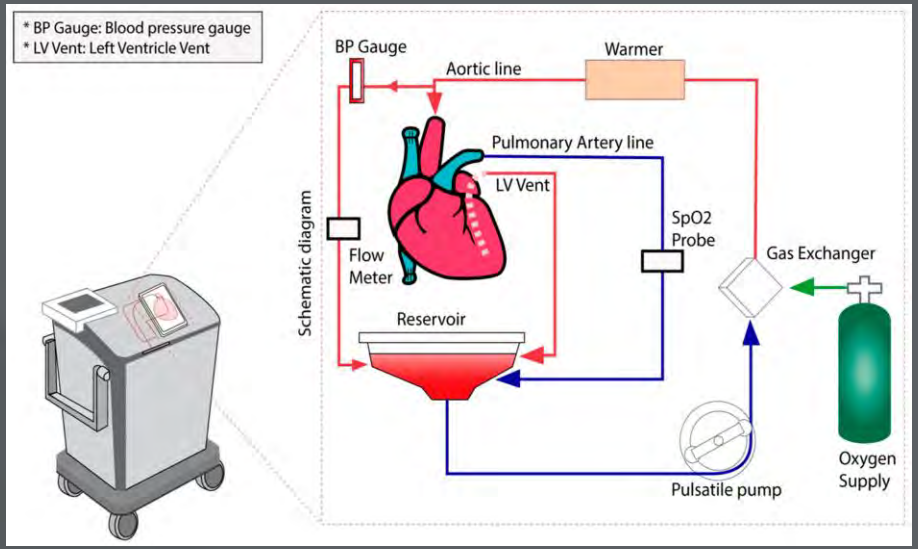
DBD related Injury

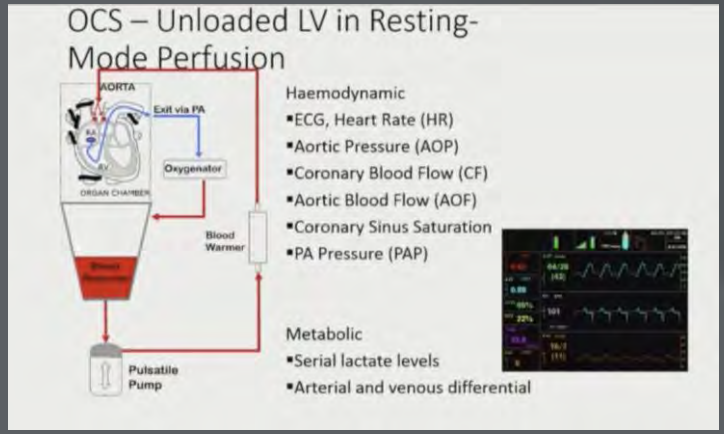
1. Brain death associated injury
2. Cold ischemia
3. Cold ischemia-reperfusion injury

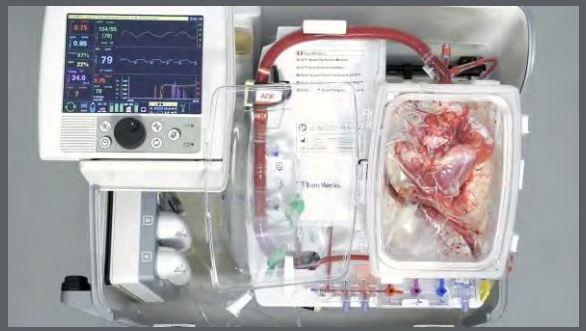
DCD related Injury

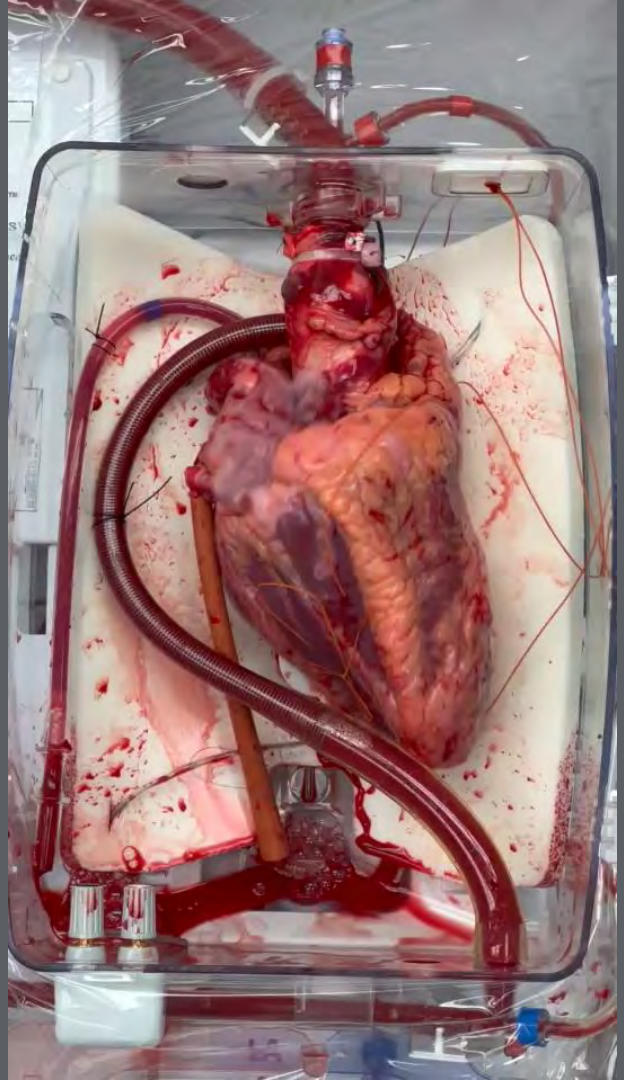
1. Warm ischemia
2. Warm ischemia-reperfusion injury
3. Cold ischemia
4. Cold ischemia-reperfusion injury

DPP + ex-situ machine perfusion





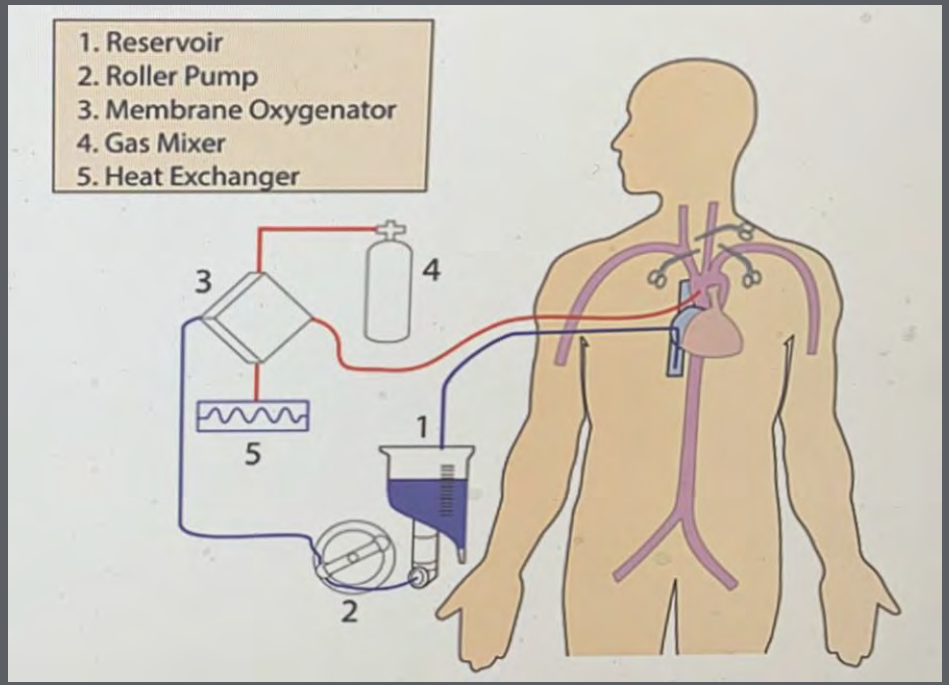


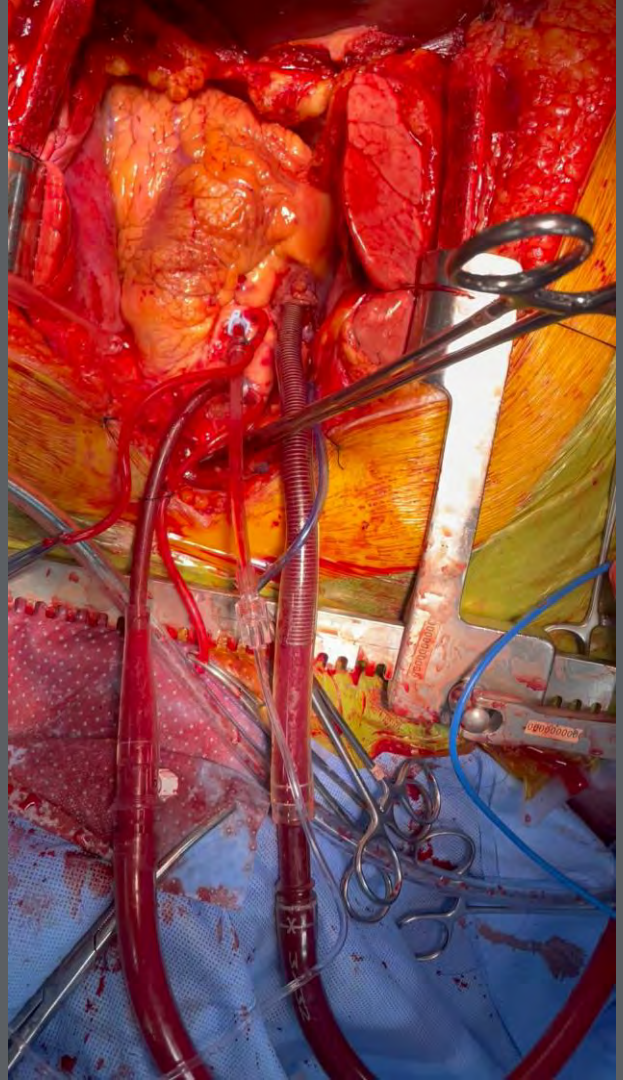


Caveats to using OCS for DCD

1) Limited scope for functional evaluation
2) Relatively high incidence of PGD3 (25-30%)
3) Technical issues
4) Function deteriorating with time
5) Cost

Thoracoabdominal Normothermic Regional Perfusion



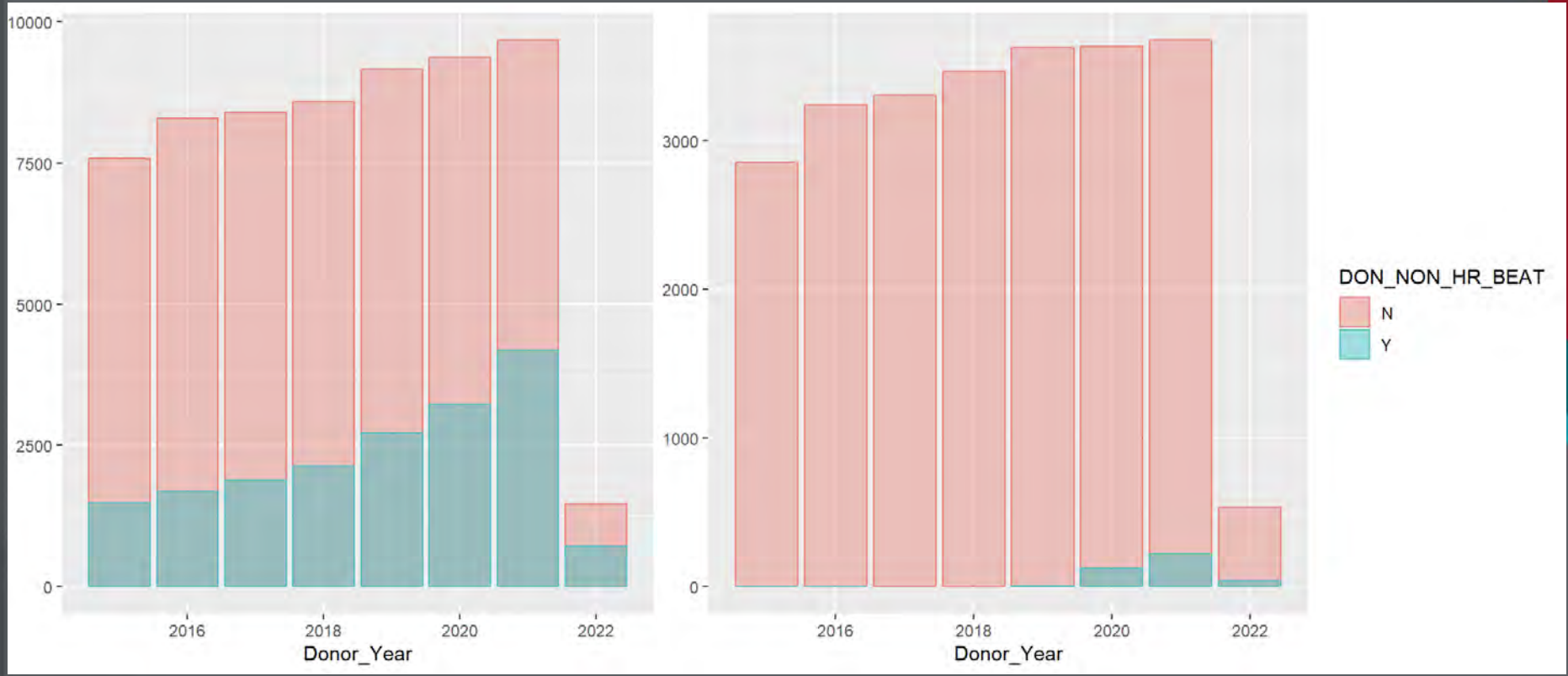


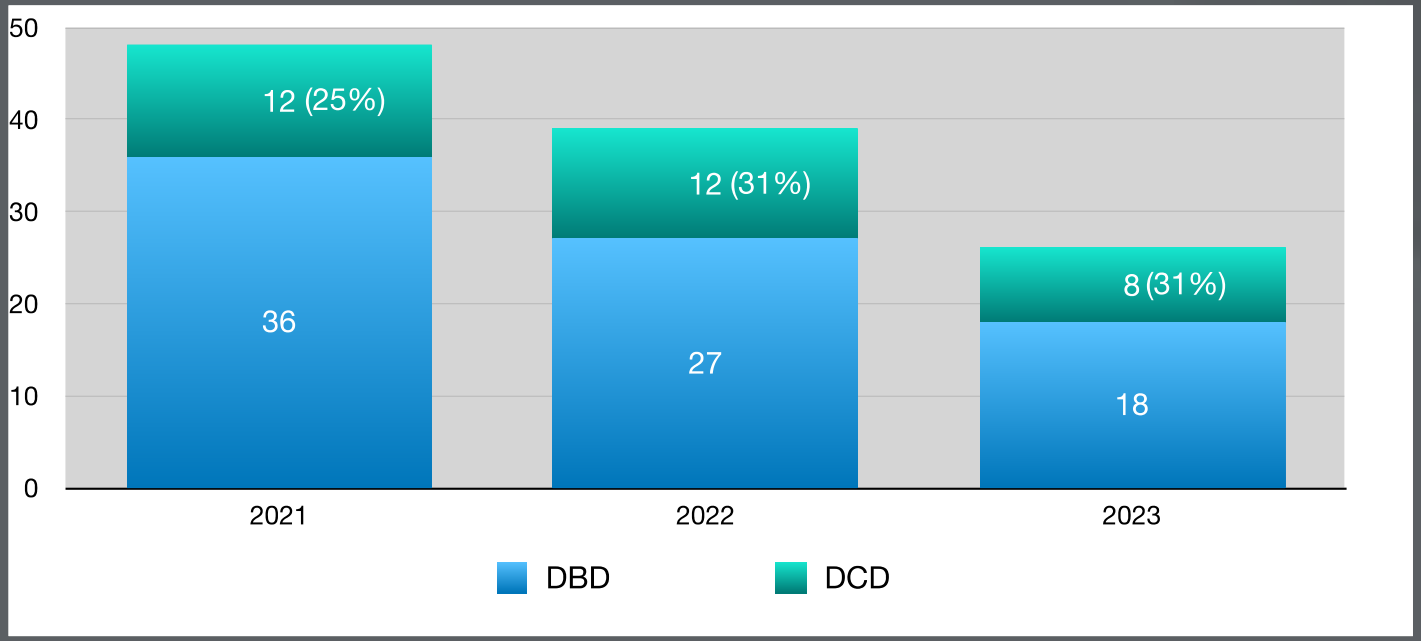
TA-NRP versus DP-NMP

- Evaluation
- Increased utilization and better outcome for other organs
- Cost
- No weight limit
- Heart transplantation outcome?

Caveats to using TA-NRP

- Ethical objections
- Resource consuming


10000
7500
5000
2500
0
2016
2018
2020
2022
Donor_Year
3000
2000
1000
0
2016
2018
2020
2022
Donor_Year
DON_NON_HR_BEAT
N
Y


50
40
30
20
10
0
12 (25%)
36
12 (31%)
27
8 (31%)
18
2021
2022
2023
DBD
DCD

Transport/ Storage

Preserve the organ during transport from a recovery hospital to an implant center

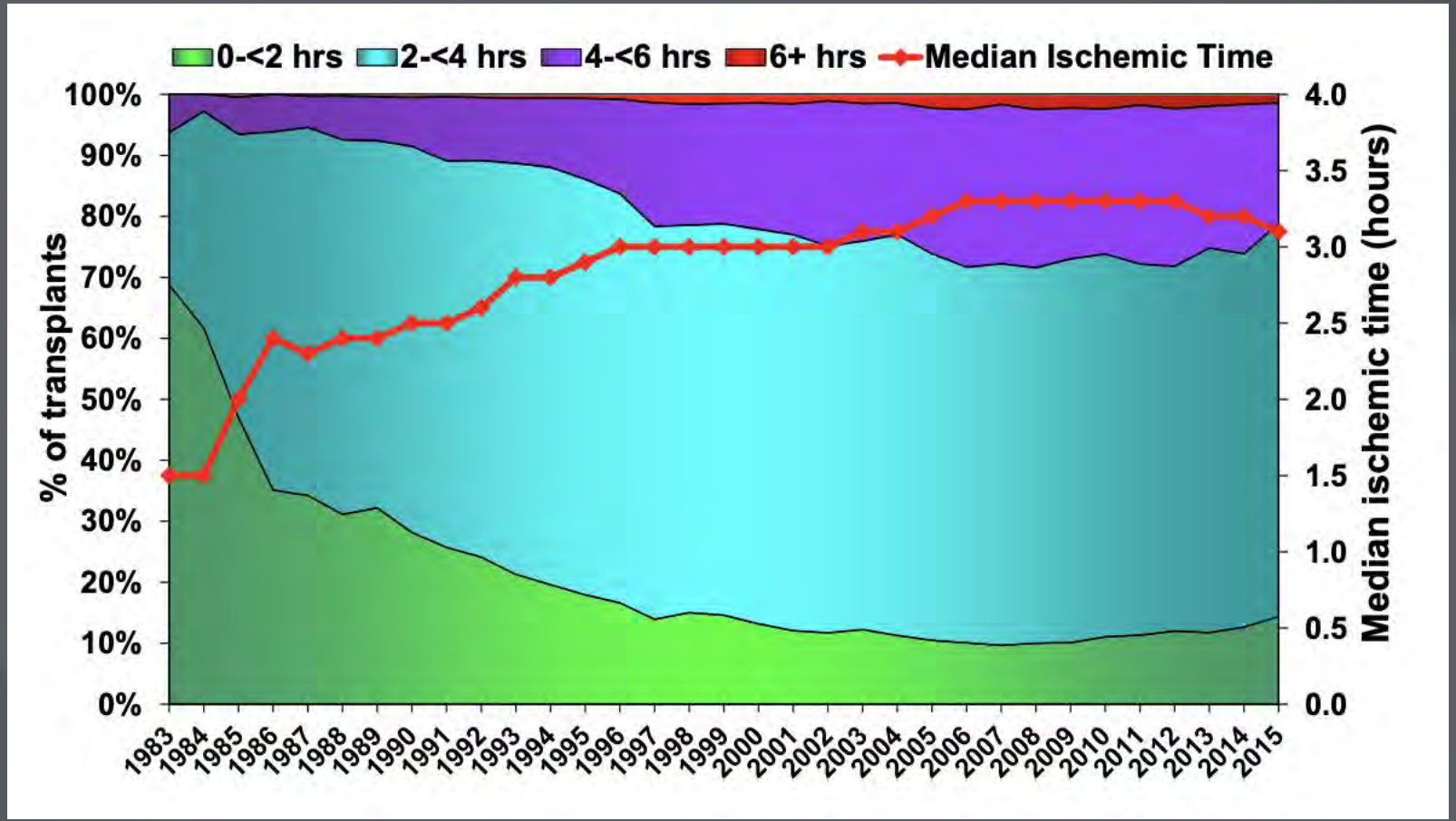
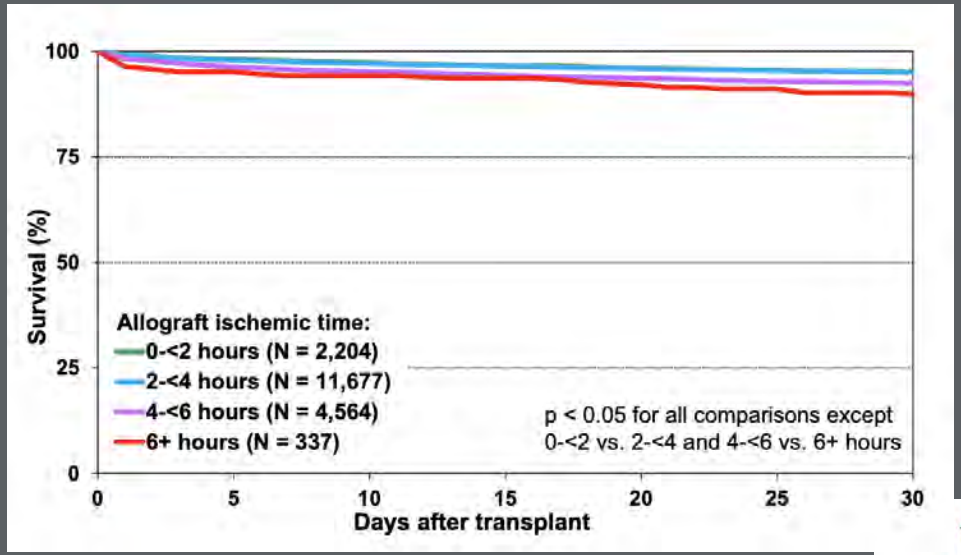
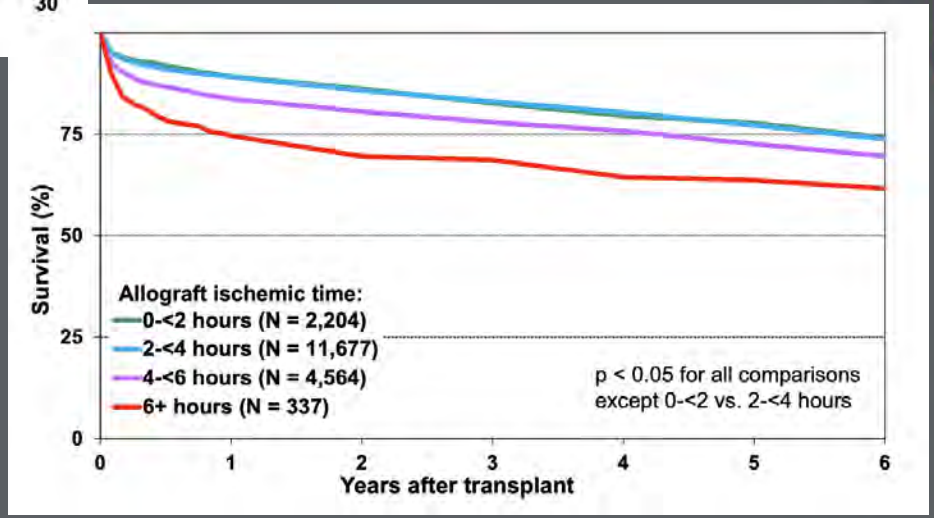

0-<2 hrs
2-<4 hrs
4-<6 hrs
6+ hrs
Median Ischemic Time
% of transplants
Median ischemic time (hours)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015

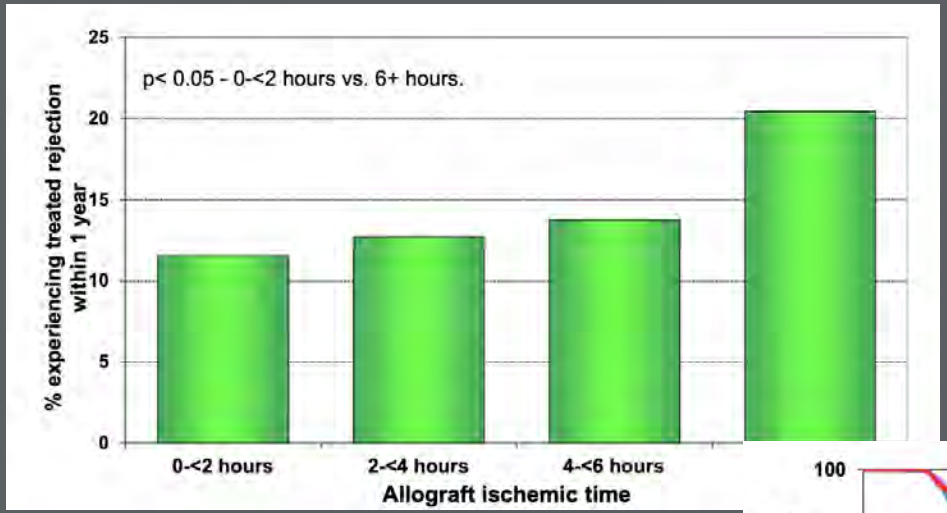
Table 5 Donor-recipient Matching and Transplant-related Characteristics of LVAD-Bridged Patients Transplanted Within Each Allocation Policy Era

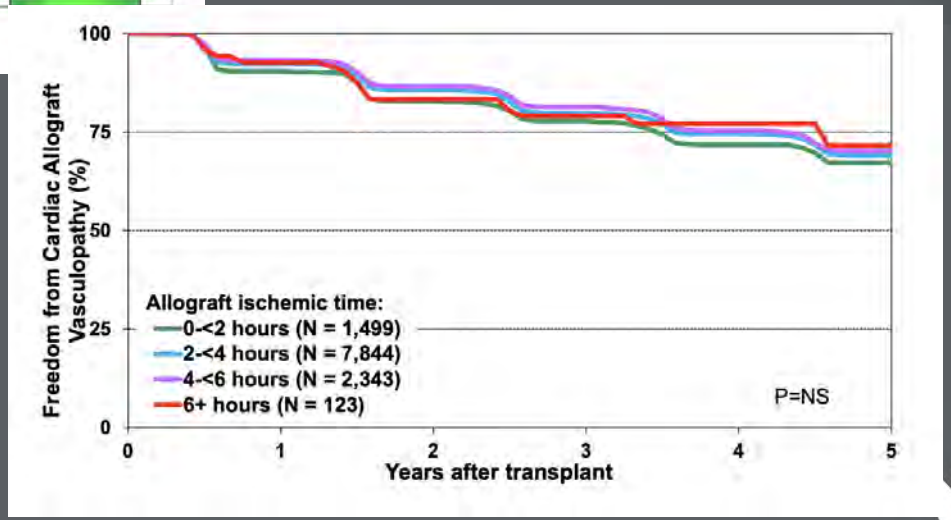
	Old policy *N* = 1,418	New policy *N* = 1,142	*p*-value
Donor-recipient matched			
Sex	1,123 (79.2%)	930 (81.4%)	0.16
Race	736 (51.9%)	597 (52.3%)	0.85
HLA (≤3 loci mismatch)	192 (13.5%)	155 (13.6%)	0.98
Blood type	1,241 (87.5%)	1,043 (91.3%)	0.002
CMV serology	761 (53.8%)	615 (54.0%)	0.90
Transplant Details			
Waitlist time, days	245 (110-522)	220 (54-529)	<0.001
Donor distance from transplanting center, nautical miles	57 (8-207)	186 (50-379)	<0.001
Cold ischemic time, hours	3.1 (2.3-3.8)	3.4 (2.7-4.0)	<0.001

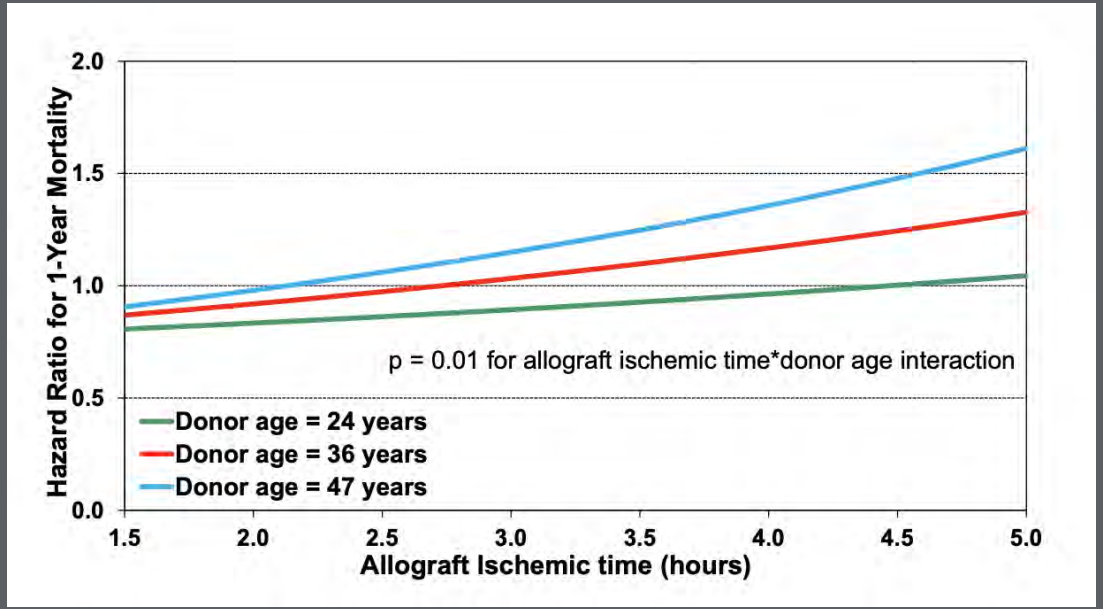
Abbreviations: CMV, cytomegalovirus; HLA, human leukocyte antigen.


100
75
50
25
0
Survival (%)
Allograft ischemic time:
0-<2 hours (N = 2,204)
2-<4 hours (N = 11,677)
4-<6 hours (N = 4,564)
6+ hours (N = 337)
p < 0.05 for all comparisons except
0-<2 vs. 2-<4 and 4-<6 vs. 6+ hours
0
5
10
15
20
25
30
Days after transplant


75
50
25
0
Survival (%)
Allograft ischemic time:
0-<2 hours (N = 2,204)
2-<4 hours (N = 11,677)
4-<6 hours (N = 4,564)
6+ hours (N = 337)
p < 0.05 for all comparisons
except 0-<2 vs. 2-<4 hours
0
1
2
3
4
5
6
Years after transplant


p< 0.05 - 0-<2 hours vs. 6+ hours.
% experiencing treated rejection within 1 year
25
20
15
10
5
0
0-<2 hours
2-<4 hours
4-<6 hours
Allograft ischemic time

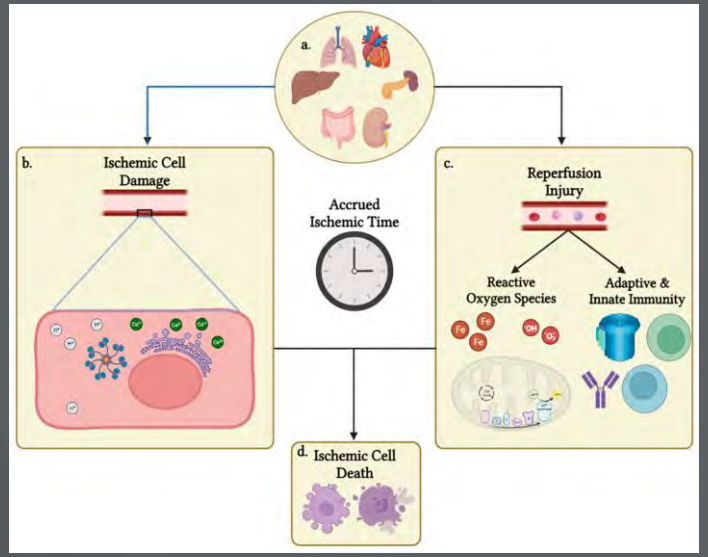

Freedom from Cardiac Allograft Vasculopathy (%)
100
75
50
25
0
Allograft ischemic time:
0-<2 hours (N = 1,499)
2-<4 hours (N = 7,844)
4-<6 hours (N = 2,343)
6+ hours (N = 123)
P=NS
0
1
2
3
4
5
Years after transplant


Hazard Ratio for 1-Year Mortality
2.0
1.5
1.0
0.5
0.0
p = 0.01 for allograft ischemic time*donor age interaction
Donor age = 24 years
Donor age = 36 years
Donor age = 47 years
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Allograft Ischemic time (hours)

Ischemic heart preservation

Static cold storage with ice

Limitations of static cold storage with ice



Ischemia + Ischemia/reperfusion

Freezing injury

Static Cold Storage with Ice

- Multi-center clinical study found that average organ temperature during transportation (n=186) was below 2°C, and after 6 hours below 0°C
- < 1°C: Irreversible suppression of diastolic function
- < 0°C: Proteins denature

Ischemic heart preservation

Uncontrolled cold storage

Controlled cold static storage

GUARDIAN Clinical Results

US Multi-Center Analysis Of The Global Utilization And Registry Database For Improved Heart Preservation (GUARDIAN) Registry: 1-year Transplant Survival Analysis M.

Leacche, J. Philpott, S. Pham, Y. Shudo, M. Kawabori, J. Jacobs, S. Silvestry, J. Schroder, E. Molina, D. Meyer, D. D'Alessandro

KEY FINDINGS

The use of SherpaPak is superior to ice transport in 1-year post transplant survival in matched cohorts (from 89% to 96%, p=0.03)

•Survival benefit is potentially due to reduced incidence of severe PGD (from 12% vs 3%, p=0.005) and reduced post transplant circulatory support

Total Ischemic Time > 4 hours			
	ICE	CTS	
	N = 70	N = 132	*p-value*
Donor Age (years)	32.4 ± 10.9	34.9 ± 11.3	0.11
Donor BMI (kg/m^2)	27.6 ± 6.3	27.8 ± 6.8	0.82
Donor LVEF (%)	60.4 ± 7.1	61.9 ± 8.3	0.20
Distance to Organ (nautical miles)	**554.3 ± 295.2**	**746.1 ± 328.0**	**<0.001**
Total Ischemic Time (minutes)	273.7 ± 37.0	278.1 ± 31.9	0.14
F/M Mismatch	9 / 70 (12.9%)	23 / 132 (17.4%)	0.40
PHM Mismatch	0.0 ± 0.2	0.0 ± 0.2	0.78
Most undersized (<-15%)	16 / 70 (22.9%)	23 / 132 (17.4%)	0.35
Era (% Post Change)	**63 / 70 (90.0%)**	**131 / 132 (99.2%)**	**0.001**
Recipient Age (years)	55.8 ± 10.6	56.5 ± 13.4	0.65
Recipient BMI (kg/m^2)	27.2 ± 4.8	27.4 ± 4.7	0.77
Wait List Days	114.5 ± 226.2	111.8 ± 306.2	0.95
LVEF at Baseline (%)	23.2 ± 13.2	21.6 ± 11.2	0.41
Implantable VAD	**31 / 70 (44.3%)**	**34 / 132 (25.8%)**	**0.007**
Temporary IABP	17 / 70 (24.3%)	30 / 132 (22.7%)	0.80
Temporary ECMO/VAD	7 / 70 (10.0%)	22 / 132 (16.7%)	0.20
IMPACT Score	7.0 ± 5.2	8.0 ± 5.5	0.28
POST TRANSPLANT OUTCOMES			
LVEF at 24hrs	**53.0 ± 14.1**	**57.2 ± 13.7**	**0.062**
All Post Tx MCS	**26 / 70 (37.1%)**	**24 / 132 (18.2%)**	**0.003**
New IABP Post Tx	9 / 70 (12.9%)	11 / 132 (8.3%)	0.31
New ECMO/VAD Post Tx	**13 / 70 (18.6%)**	**12 / 132 (9.1%)**	**0.052**
CVP at Discharge	**8.6 ± 4.5**	**10.2 ± 6.2**	**0.043**
Cardioversion	12 / 70 (17.1%)	15 / 132 (11.4%)	0.25
PGD	15 / 70 (21.4%)	23 / 132 (17.4%)	0.49
PGD Severe	11 / 70 (15.7%)	11 / 132 (8.3%)	0.109
30-Day Survival	67 / 70 (95.7%)	129 / 132 (97.7%)	0.42
In-hospital Survival	66 / 70 (94.3%)	128 / 132 (97.0%)	0.35

Ischemic to non - ischemic heart preservation

Graft preservation

Hypothermia – limits energy demands – Cold injury

Higher temperatures require oxygen – oxygen delivery

Hypothermic oxygenation (no blood)

Normothermic oxygenation with blood

Hypothermic/Normothermic Oxygenated Perfusion

- Evidence demonstrating switching from anaerobic metabolism to aerobic metabolism during preservation
- Tissue biopsies that indicate significantly lower inflammatory and cellular death markers when compared to the standard of care
- Significantly higher contractility than hearts preserved with the standard of care, as tested in vitro using an isolated heart Langendorff device.

Non - Ischemic heart preservation

Normothermic

Trans-medics

Hypothermic

XVIVO

XVIVO Heart Preservation System

with Supplemented XVIVO Heart Solution

For hypothermic oxygenated perfusion (HOPE)

Portable

Compact design and integrated battery. Fits in standard aircrafts and ground vehicles.

Temperature controlled

Insulated container and a cooling unit that holds 8°C. Cold storage as back-up for safety.

Continuous oxygenation

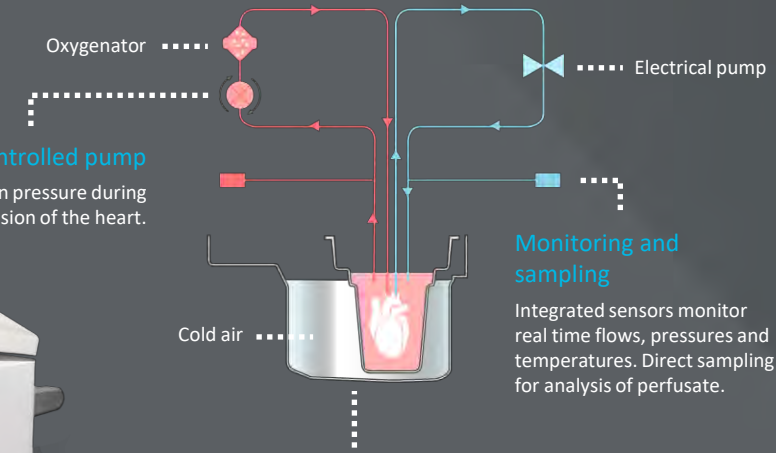
Cylinder with a carbogen gas mix (95% oxygen and 5% carbon dioxide) and regulator for oxygenation during perfusion.

Automated perfusion

Once perfusion has been established there is no need to adjust pressure, flow or temperature.

Pressure controlled pump

To control the perfusion pressure during perfusion of the heart.



Monitoring and sampling

Integrated sensors monitor real time flows, pressures and temperatures. Direct sampling option for analysis of perfusate.

Protective reservoir

The heart is submerged in the cold oxygenated perfusion solution in a reservoir.

Ease of use

User interface for easy operation and software with guiding instructions.

XVIVO

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