

# STS/EACTS Latin America Cardiovascular Surgery Conference

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www.CardiovascularSurgeryConference.org

## Increasing Organ availability: From Machine Perfusion to Donors after Cardiac Death

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The Society  
of Thoracic  
Surgeons



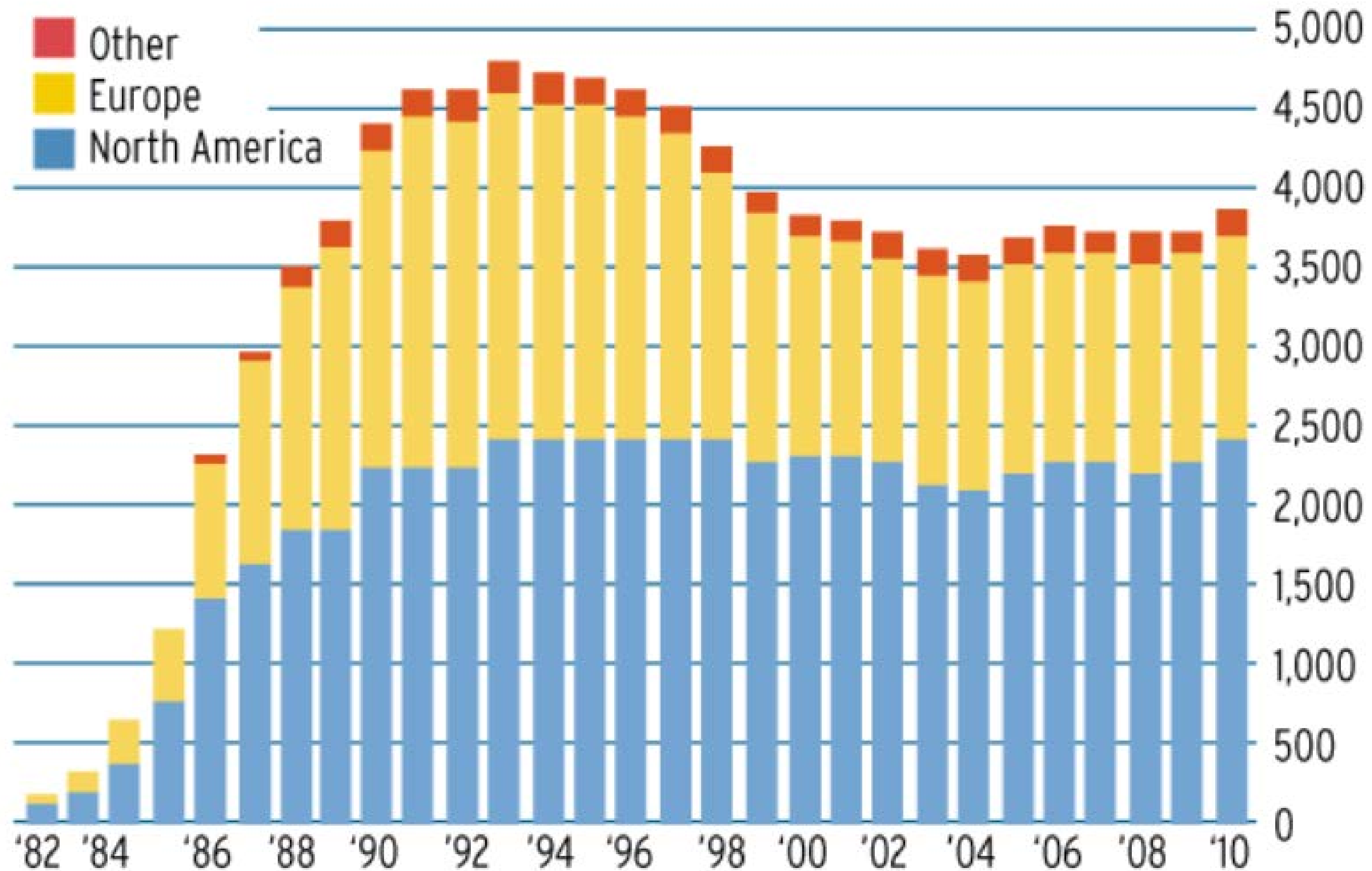
**EACTS**  
European Association For Cardio-Thoracic Surgery





No relevant financial disclosures

# Heart Transplantation - Activity



# Donor Heart Preservation

- Static preservation with cold storage
  - Cornerstone of organ preservation
  - Simplicity is major advantage
  - Organs can be preserved for only limited periods of time across defined distances
  - Substantial incidence of primary graft dysfunction

# Machine Perfusion of the Donor Heart

- First generation of devices approved for clinical use
  - Likely to have a prominent role in donor heart preservation in the future
  - Portable ex-vivo perfusion devices designed to perfuse the donor heart with normothermic blood
  - Aim to improve organ quality, validate organ viability and increase utilization of donor hearts
  - Maintenance of donor heart in a near-physiologic state outside of the human

# Transmedics Organ Care System

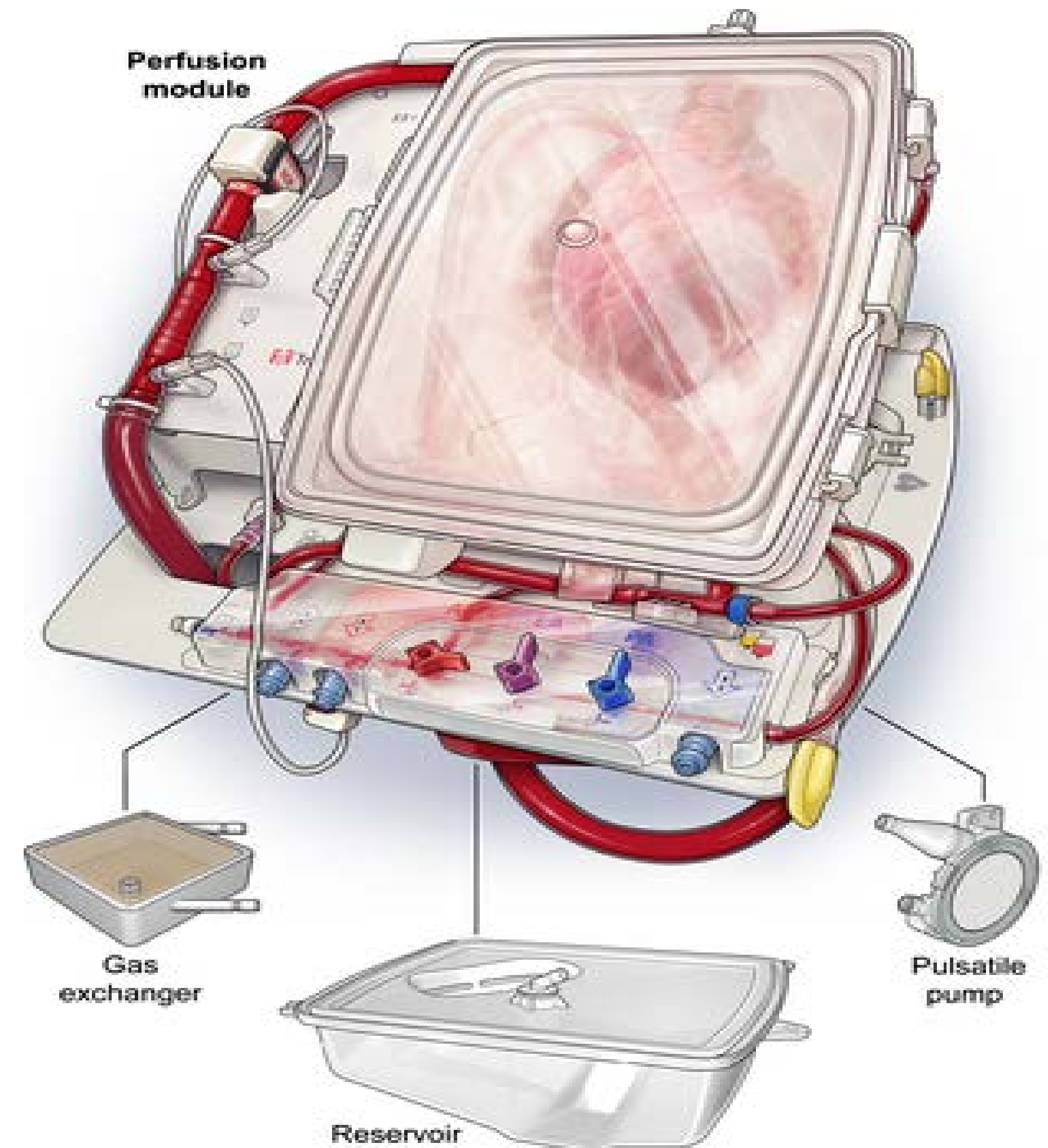
- Portable ex-vivo perfusion device
- Only current fully portable technology for ex-vivo donor heart perfusion
- In use in several transplant centers in Europe, Australia and Canada
- Being tested in clinical trials within the U.S.A.





# Transmedics Organ Care System

- 1.2 – 1.5 l of donor blood collected prior to aortic cross-clamping
- Donor heart retrieved in standard fashion followed by instrumentation onto device
- Oxygenated blood delivered into donor aortic root via pulsatile pump
  - Maintain aortic pressure 65-90 mm Hg and coronary flow rate of 650-850 l/min
- Wireless monitor controls perfusion rate of OCS and displays aortic pressure, coronary flow rate, hematocrit, temperature and oxygen saturation



# Clinical Evaluation

- PROTECT I

- First-in-man multicenter prospective single arm non-randomized safety and performance study conducted in UK and Germany
- Primary endpoint: 7-day survival
- Secondary endpoint: 30-day patient and graft survival
- 20 eligible hearts transplanted
- All 20 patients met primary endpoint and demonstrated 30-day survival

- PROCEED I

- Prospective multicenter single arm non-randomized FDA safety and performance study
- First U.S. clinical trial of OCS device
- 14 hearts instrumented onto OCS, 13 transplanted and one declined after assessment
- 11/13 recipients reached 7- and 30-day survival endpoints
- 2 patients suffered PGD with one re-transplanted and one death
- Based on combination of PROTECT I and PROCEED I FDA granted approval for PROCEED II



# Clinical Evaluation

- **PROCEED II**

- Prospective, randomized, international multicenter, non-inferiority trial
- Comparison of safety and efficacy of OCS to cold storage
- Primary endpoint: 30-day patient and graft survival
- Completion of recruitment in September 2013
- 128 recipients transplanted
- Primary outcome of 30-day patient survival achieved in 93% of patients randomized to OCS device vs. 96% in cold storage group

- **EXPAND**

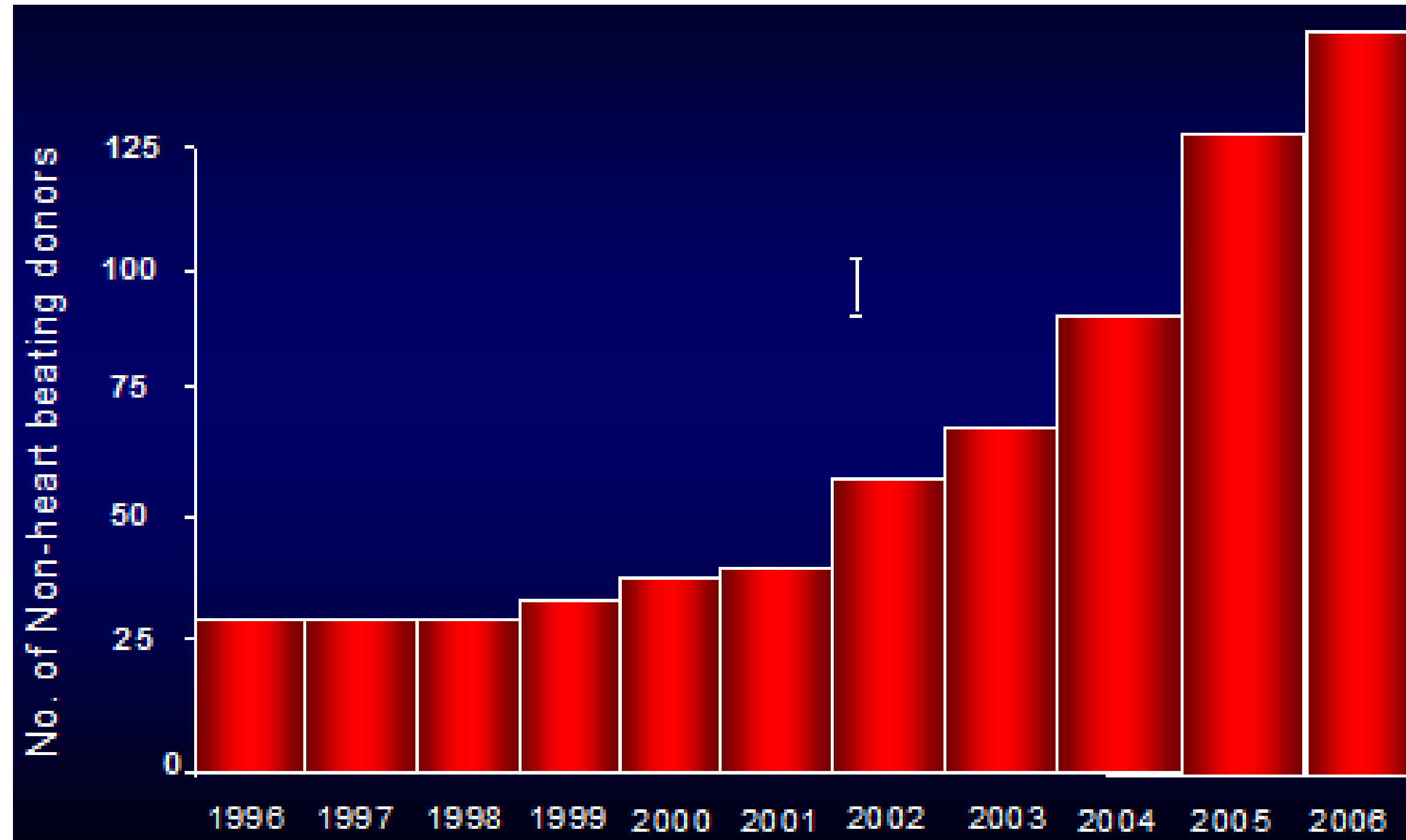
- Prospective multicenter international single arm study to evaluate safety and outcome of heart transplantation using extended criteria donor hearts preserved with the OCS
- Phase 3 clinical trial to assess ability to recover donor hearts which do not meet standard acceptance criteria for transplantation
- Study commenced in eight participating centers in September 2015 and due to conclude in November 2017, aim to enroll 75 patients

# PROCEED II

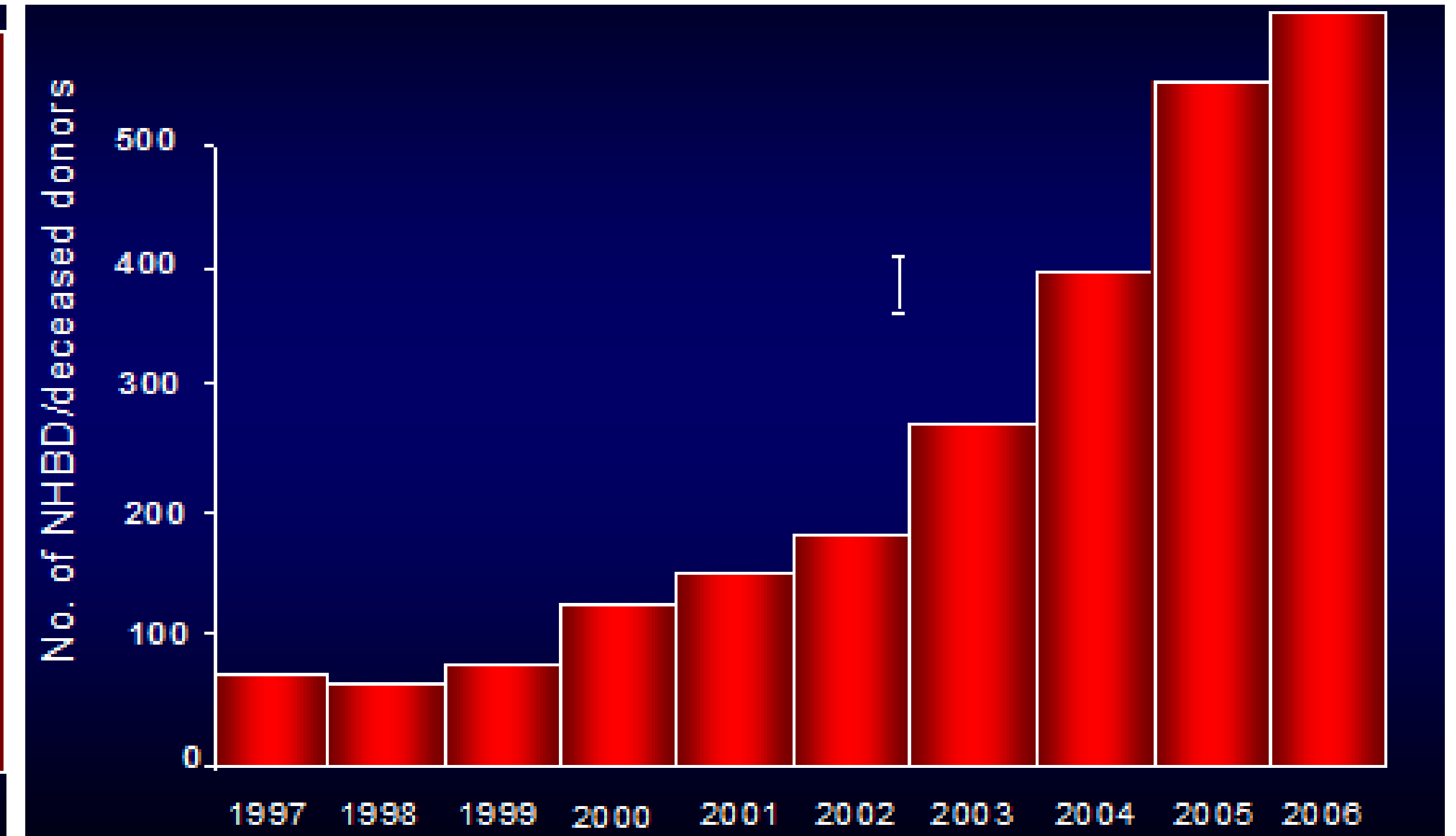
- Interim analysis
  - Ischemic time and clinical results

	OCS ( <i>n</i> = 43)	SOC ( <i>n</i> = 49)	<i>P</i> -value
OCS, Organ Care System; SOC, standard of care.			
Total cross-clamp time (mins)			
Mean ± SD	324 ± 84	204 ± 66	<0.0001
Range	156–546	72–462	
Total ischaemic time (mins)			
Mean ± SD	108 ± 24	204 ± 66	<0.0001
Range	60–168	72–462	
30-day recipient survival	93%	96%	0.66
30-day graft survival	93%	96%	0.66
Cardiac SAE	5	9	–
Early graft dysfunction	5	7	–
Grade 2 rejection	5	4	–

# DCD Donors



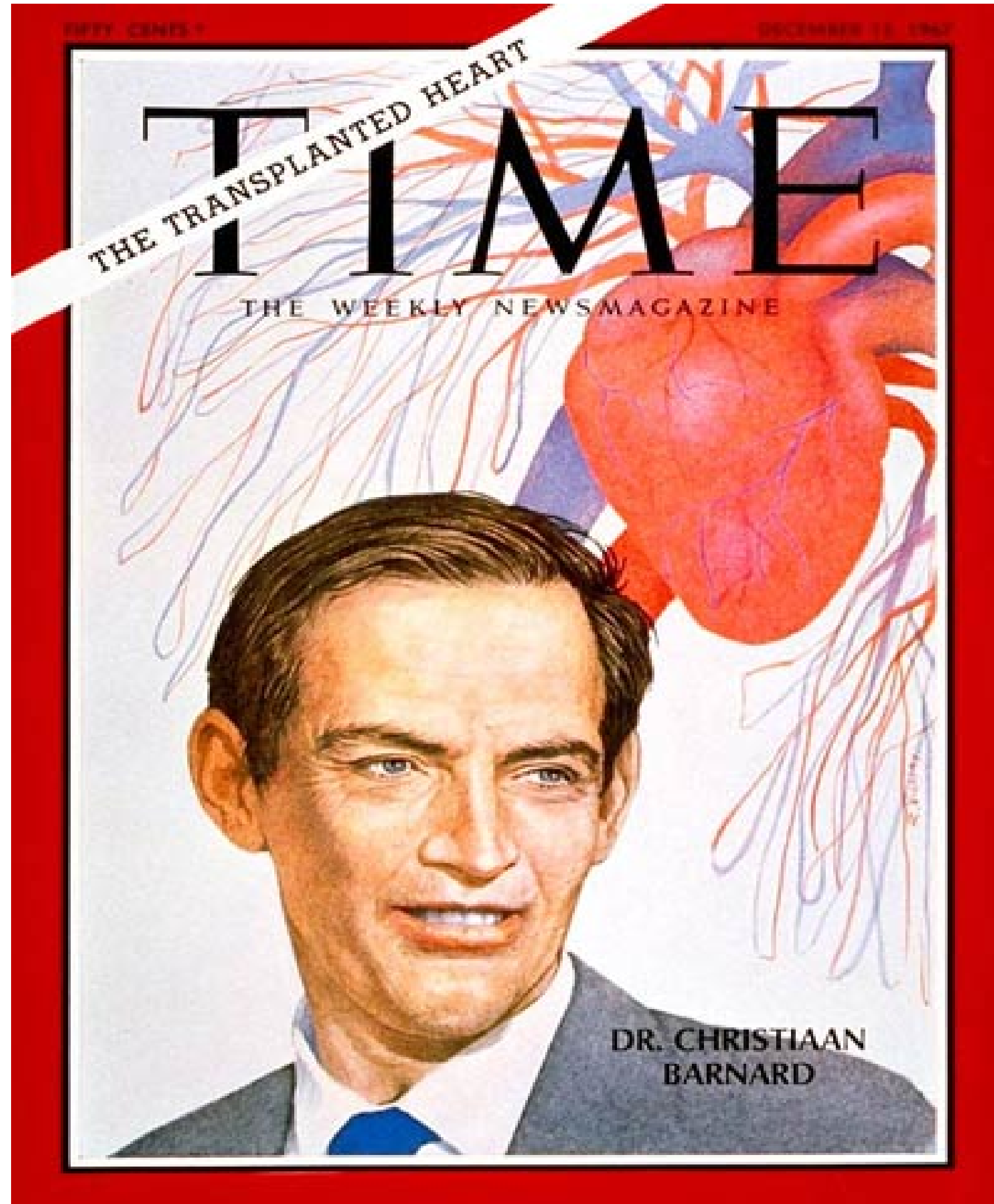
DCD donors UK



DCD donors UNOS



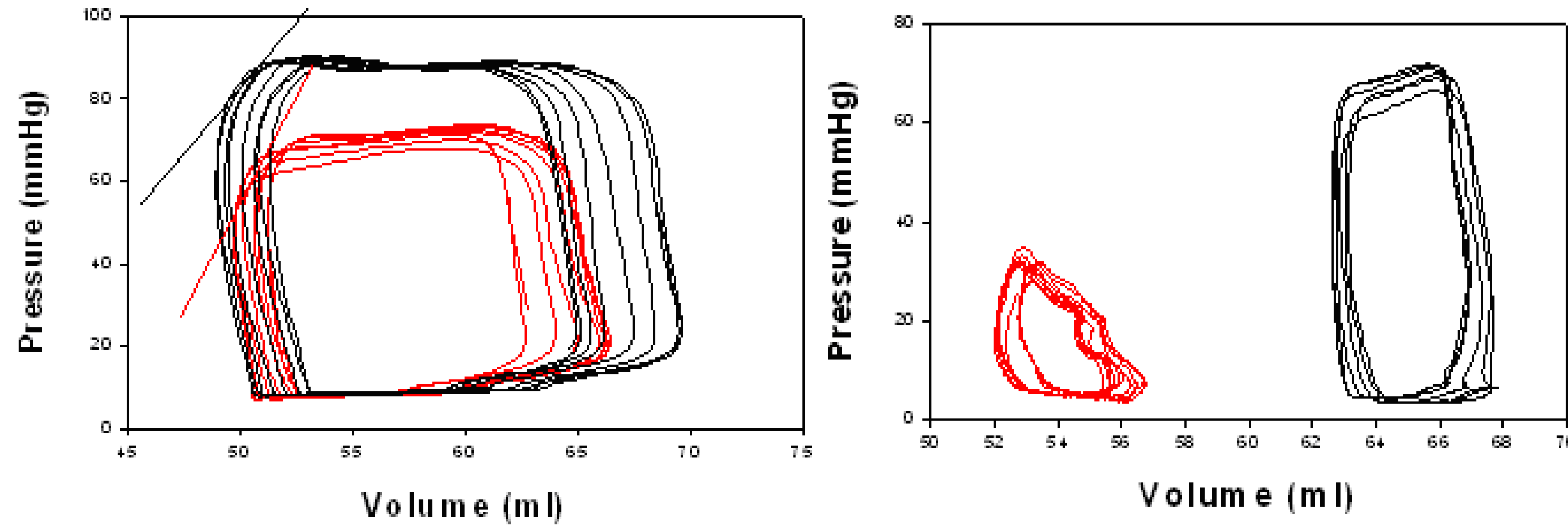
# DCD Heart Transplantation





# 2006

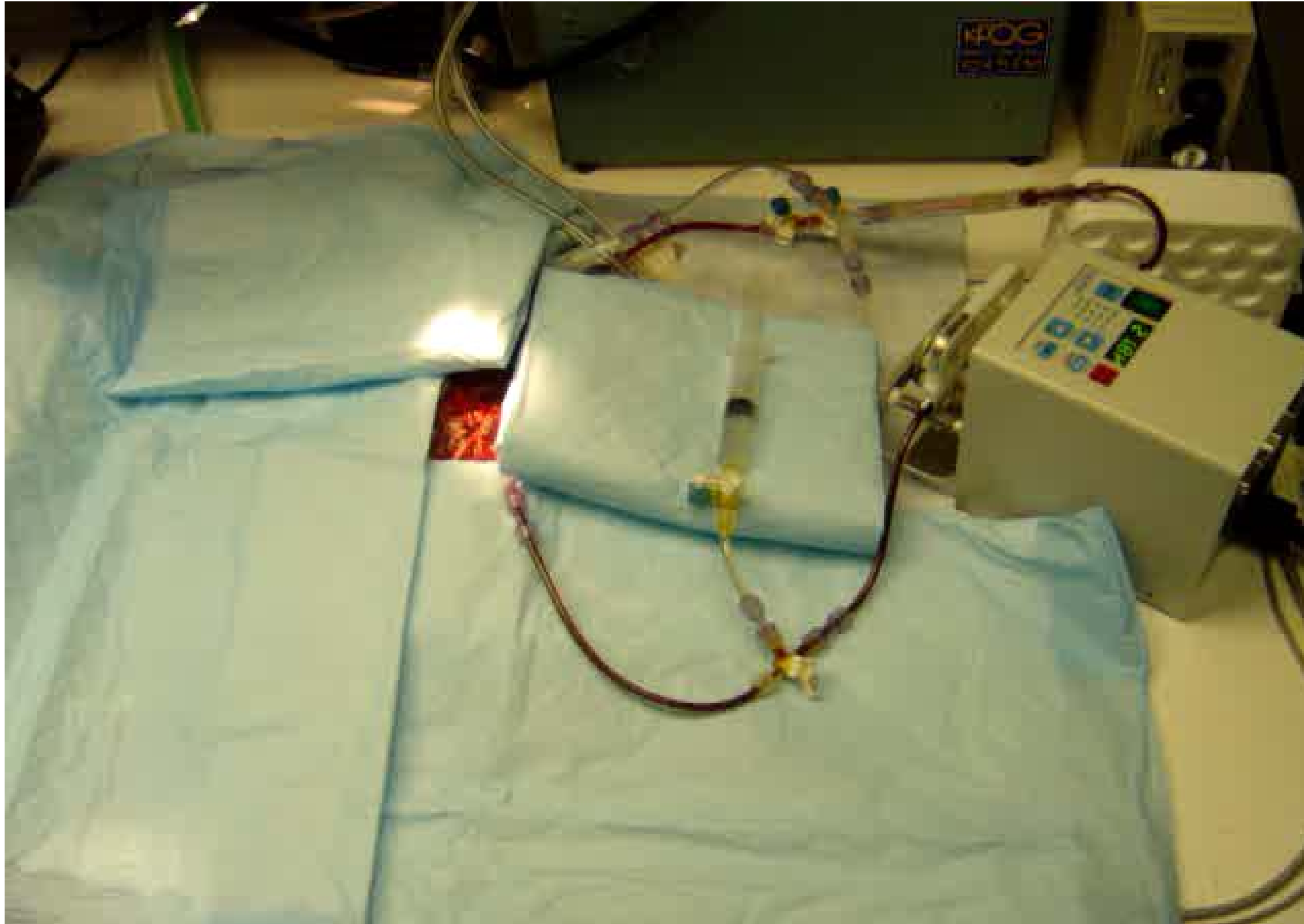
## Successful resuscitation of human DCD heart following ECMO reperfusion



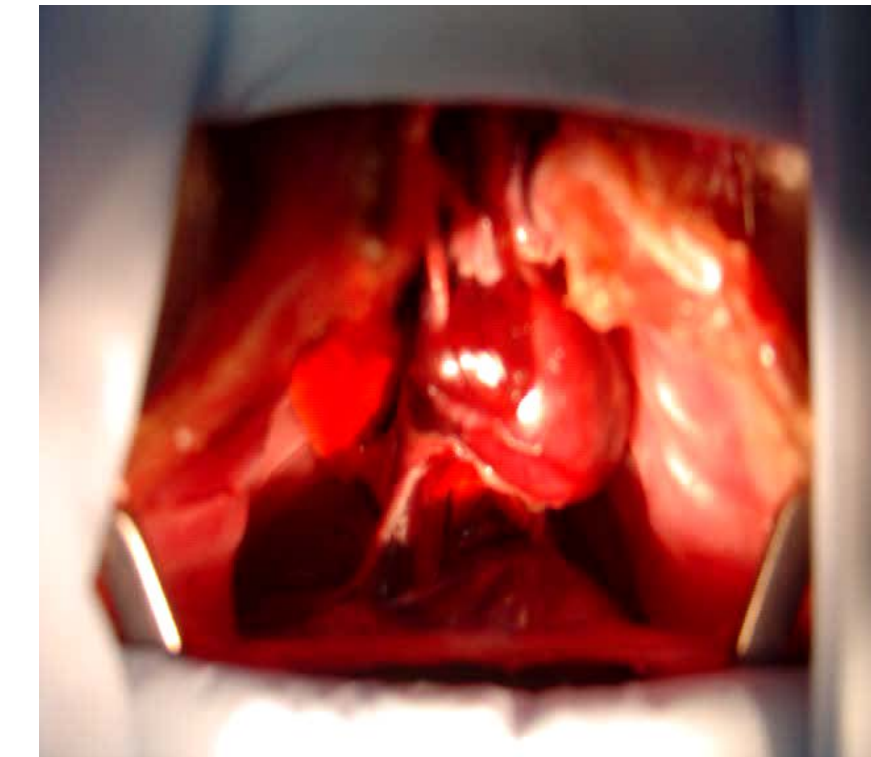
Time	Flow (L/min)	Mean arterial Pressure (mm HG)	H <sup>+</sup> (mmol/L)	pCO <sub>2</sub> (mm Hg)	pO <sub>2</sub> (mm Hg)	Hb (g/dl)	SvO <sub>2</sub> (%)	K <sup>+</sup> (mmol/L)	ACT (s)
15:54	4.0	40	<b>81.4</b>	61	232	6.4	64	<b>6.1</b>	407
16:45	5.8	53	41.6	37	195	6.5	53	4.6	442
17:15	6.0	65	35.4	34	273	6.7	61	4.5	
17:45	5.8	68	35.8	39	241	6.9	58	4.7	430
18:15	4.6	63	33.4	38	263	5.6	55	4.5	
18:45	5.3	69	34.2	37	210	5.9	57	4.5	407
19:00	4.8	69	44.5	48.1	163	7.7	56	4.8	

# 2009

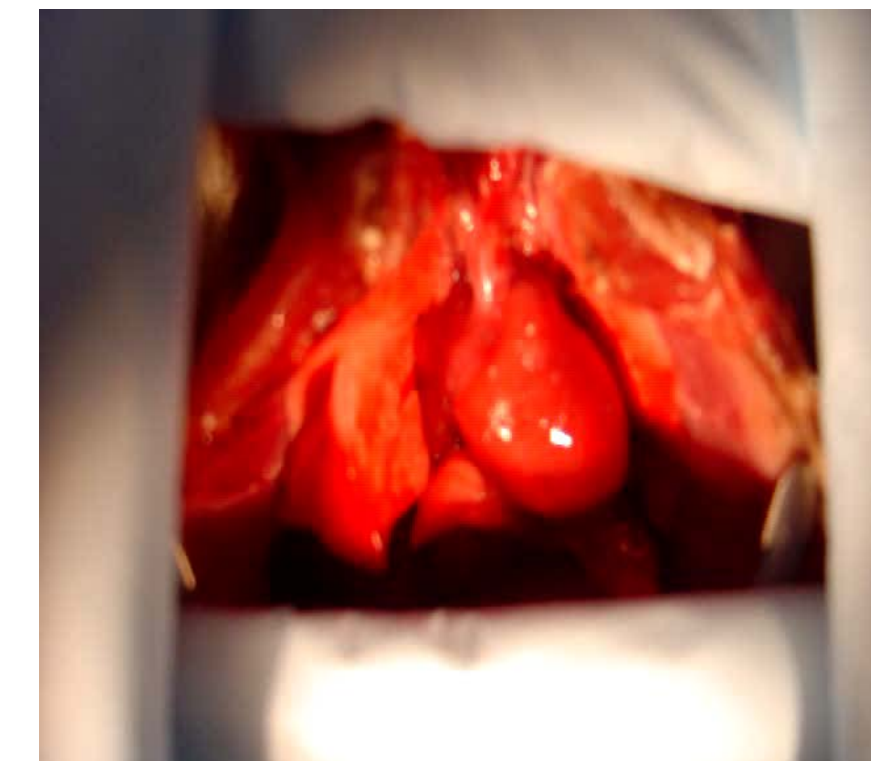
## Cardiac resuscitation in a rodent DCD model



Baseline



Circulatory arrest

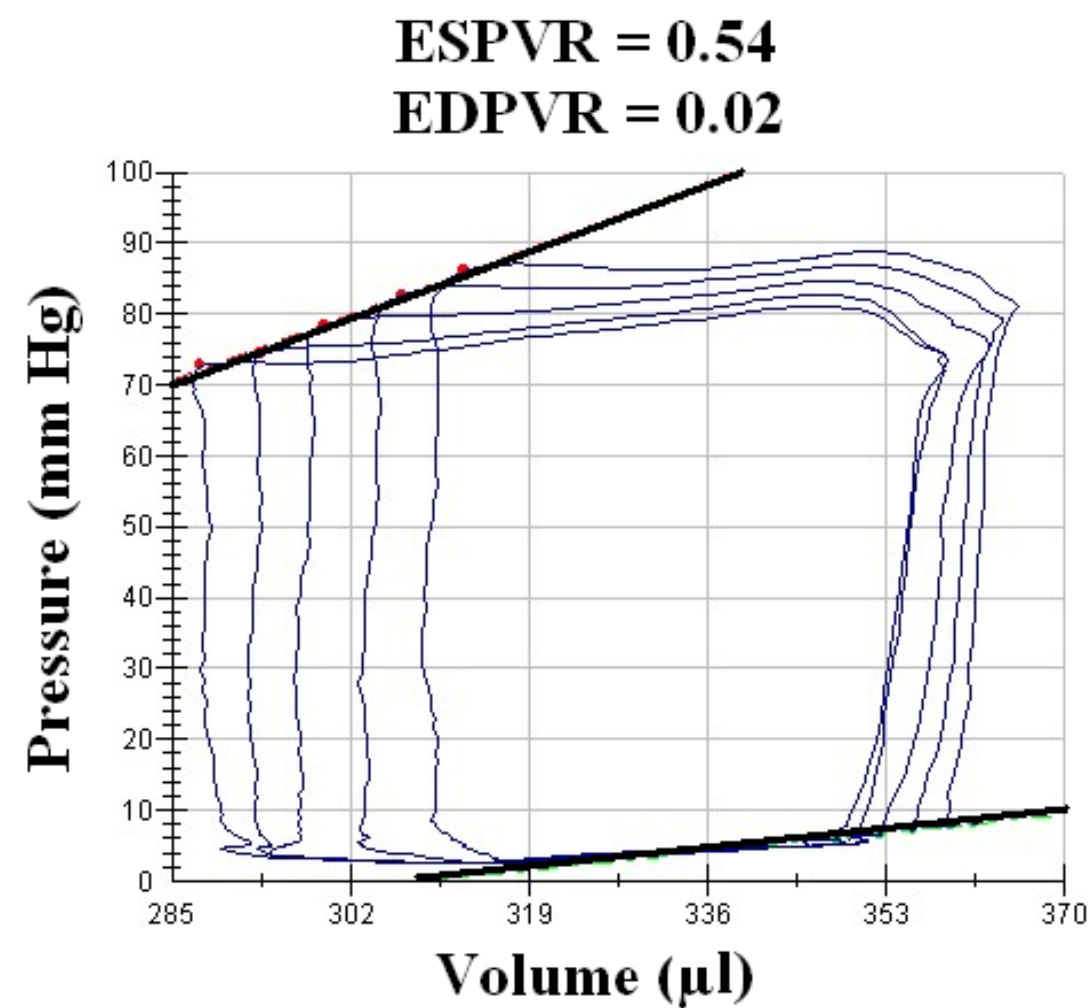


Cardiac resuscitation

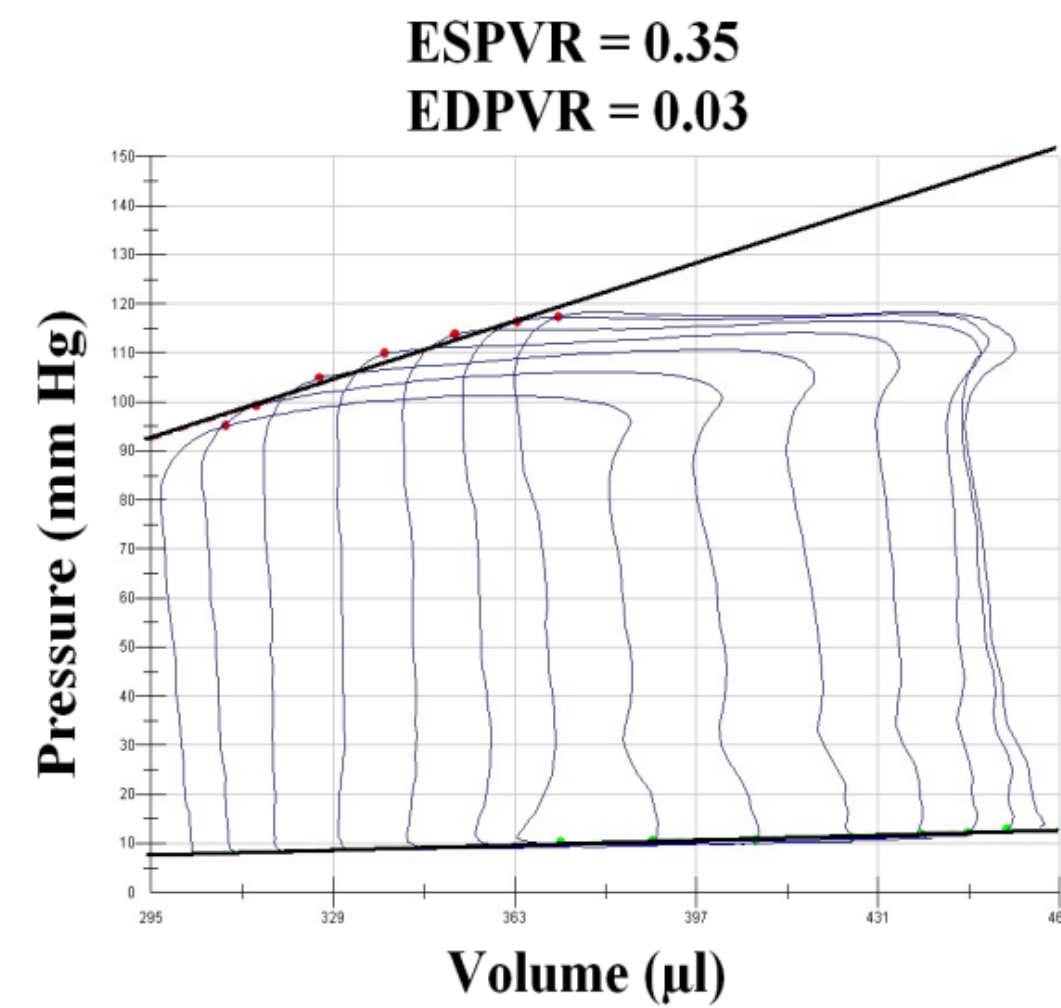


# 2009

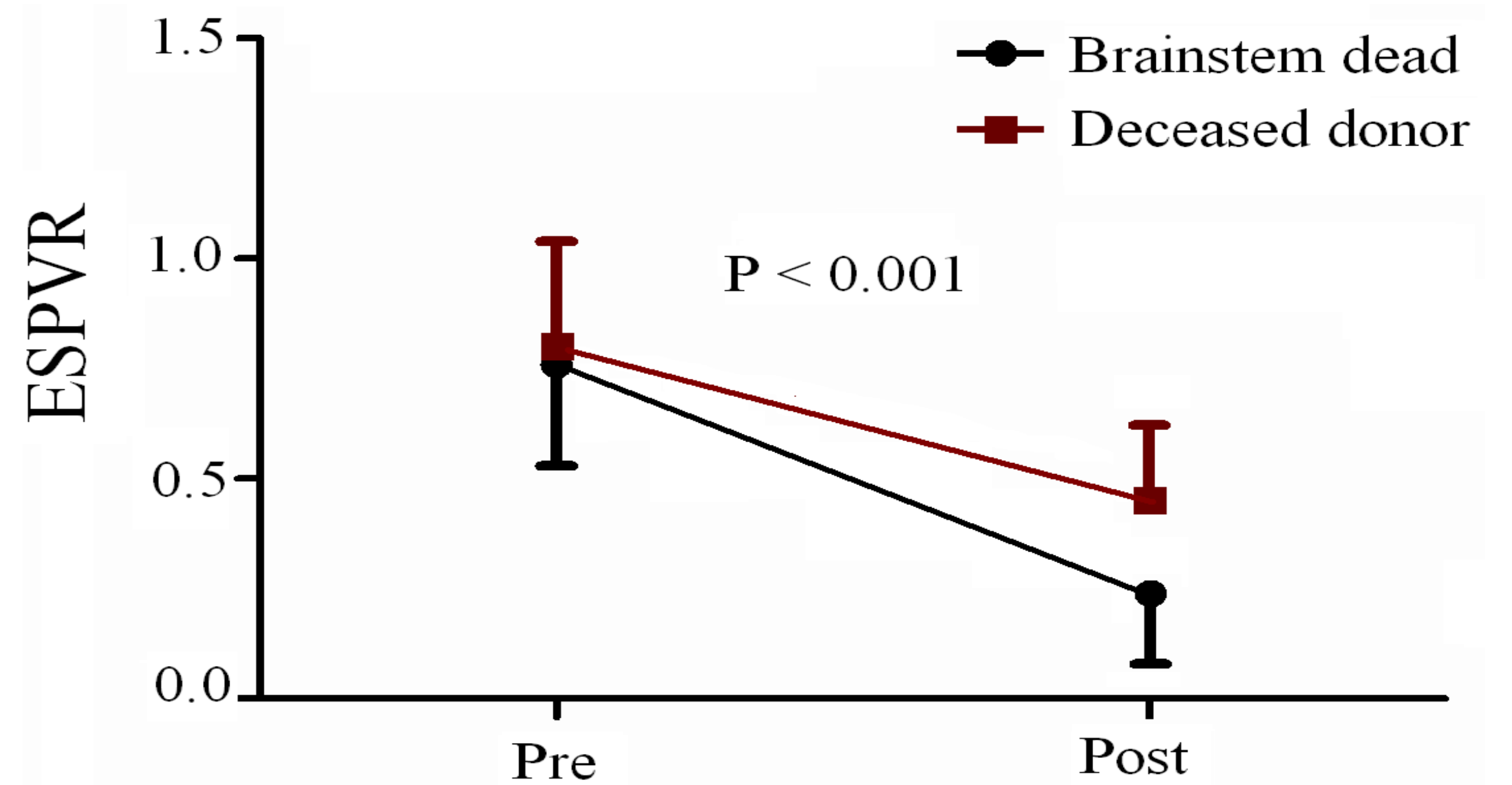
## Cardiac resuscitation in a rodent DCD model



DCD

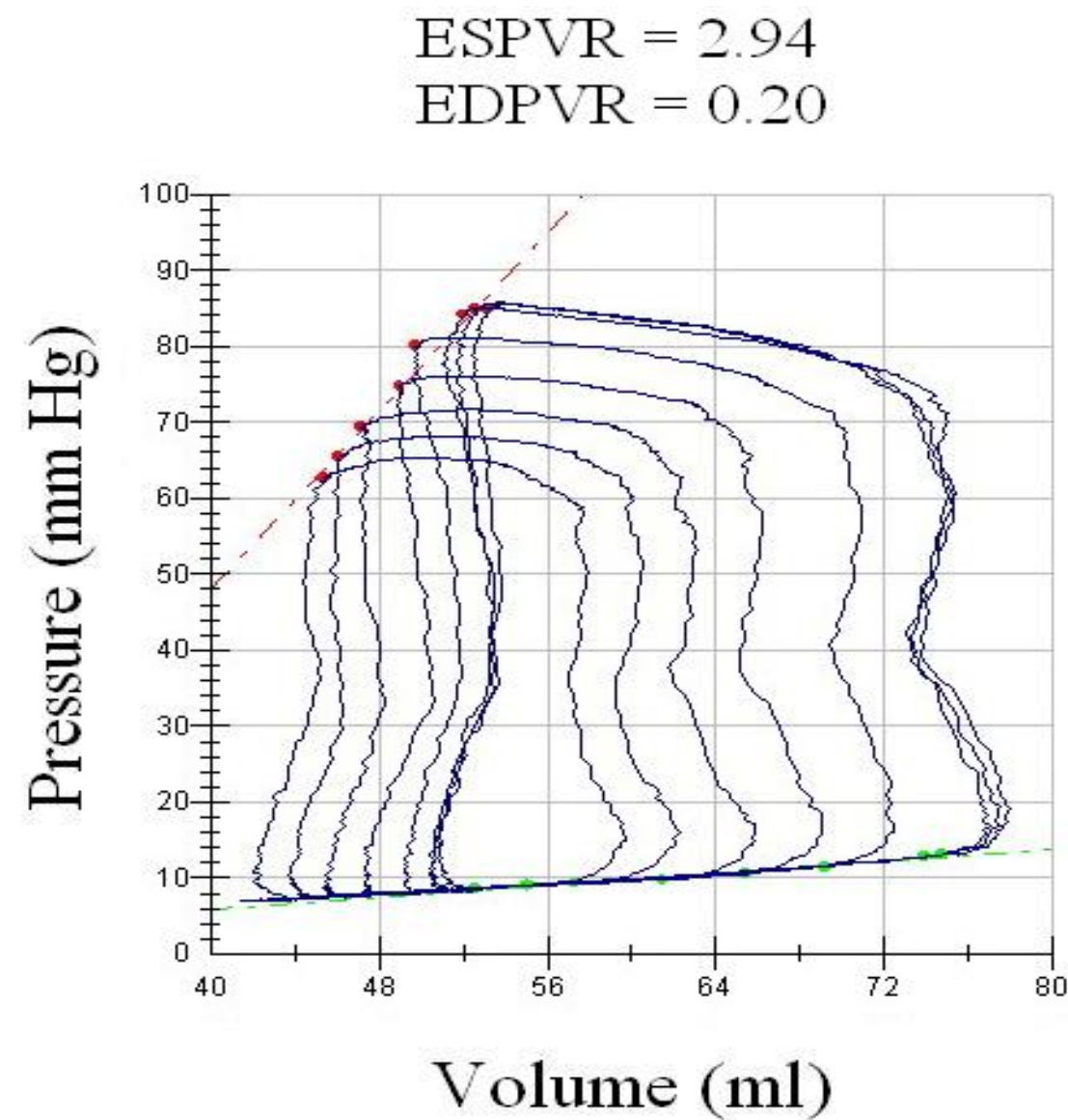


Brainstem death

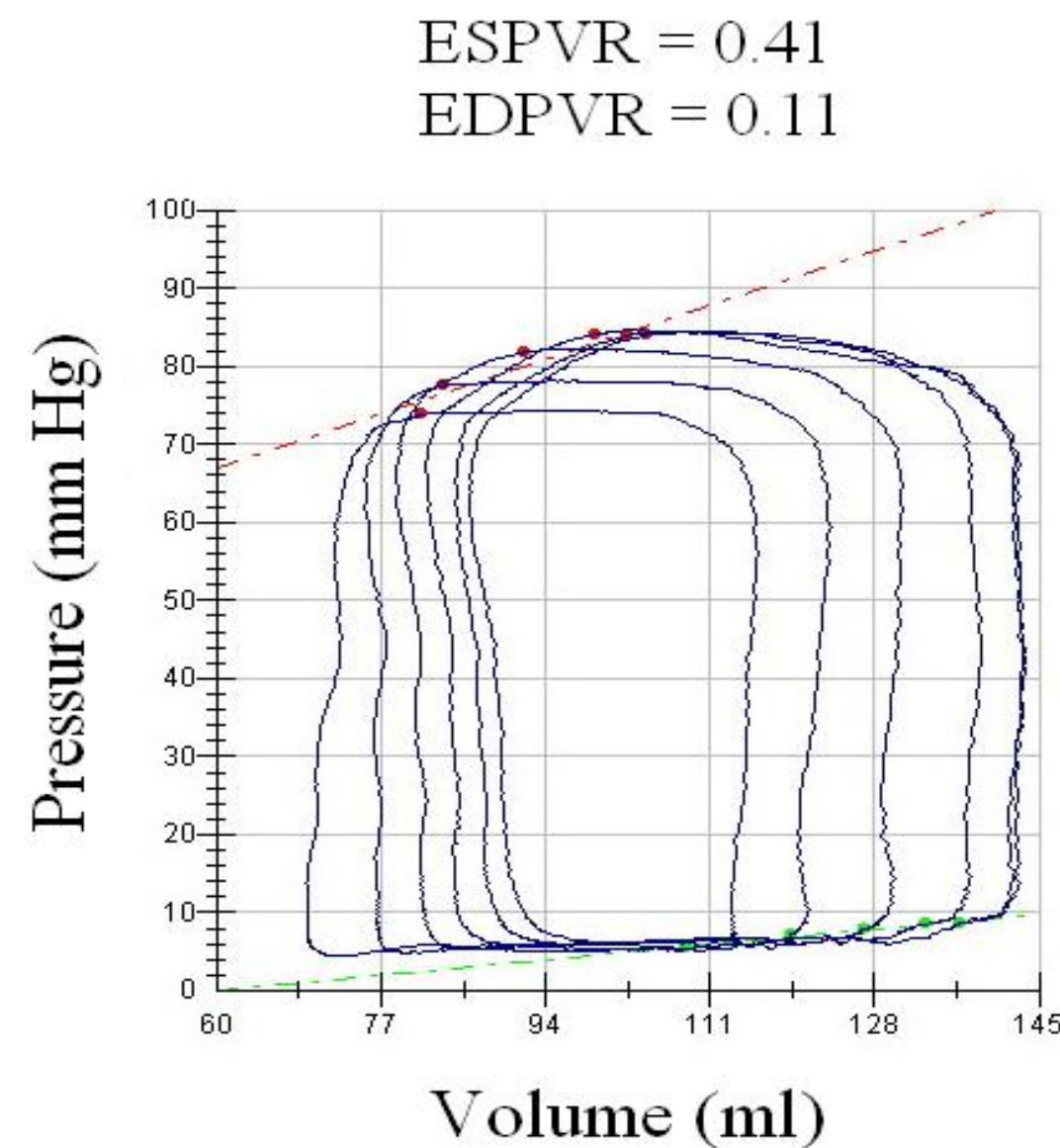


# 2010

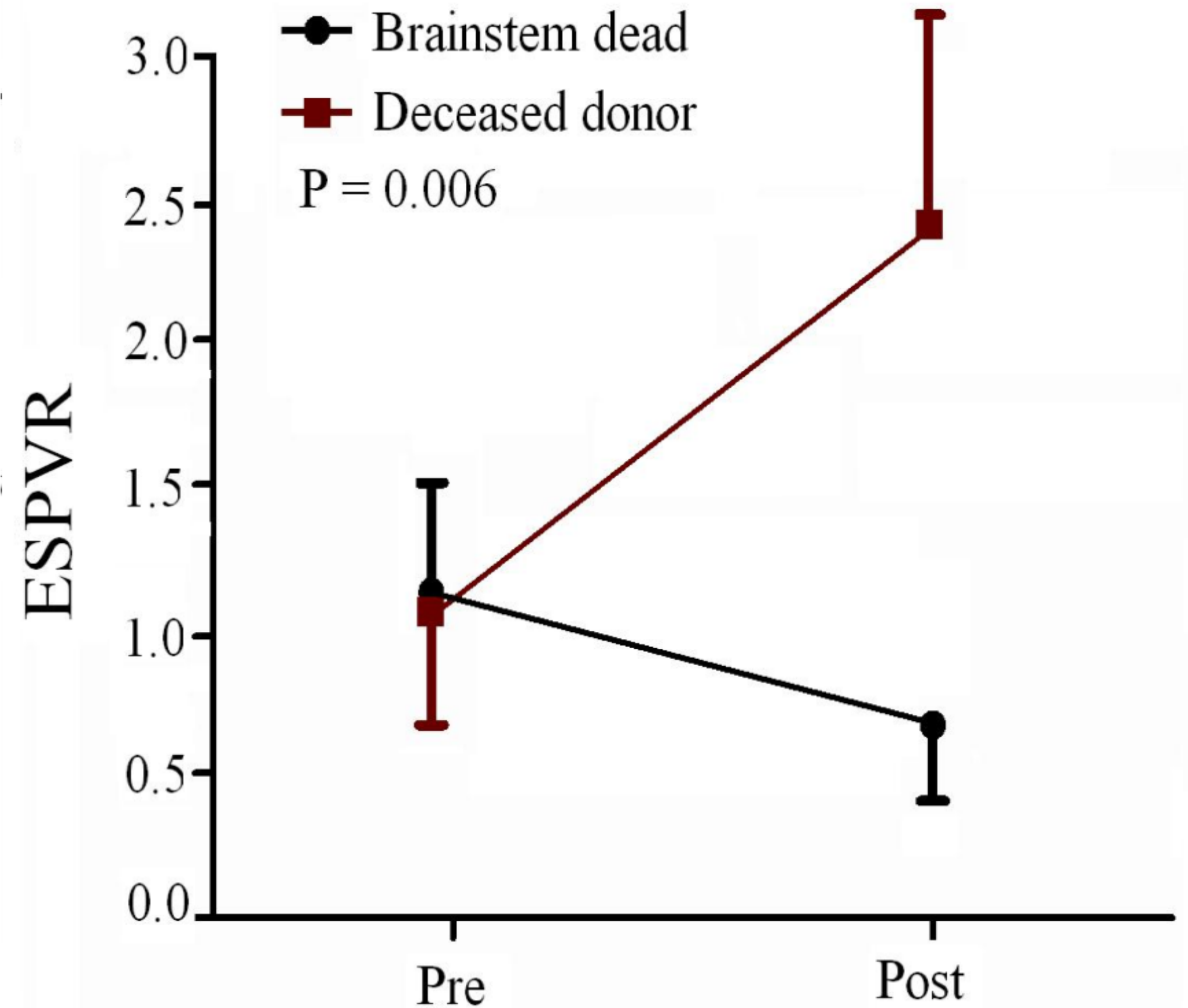
## Cardiac resuscitation in a porcine DCD model



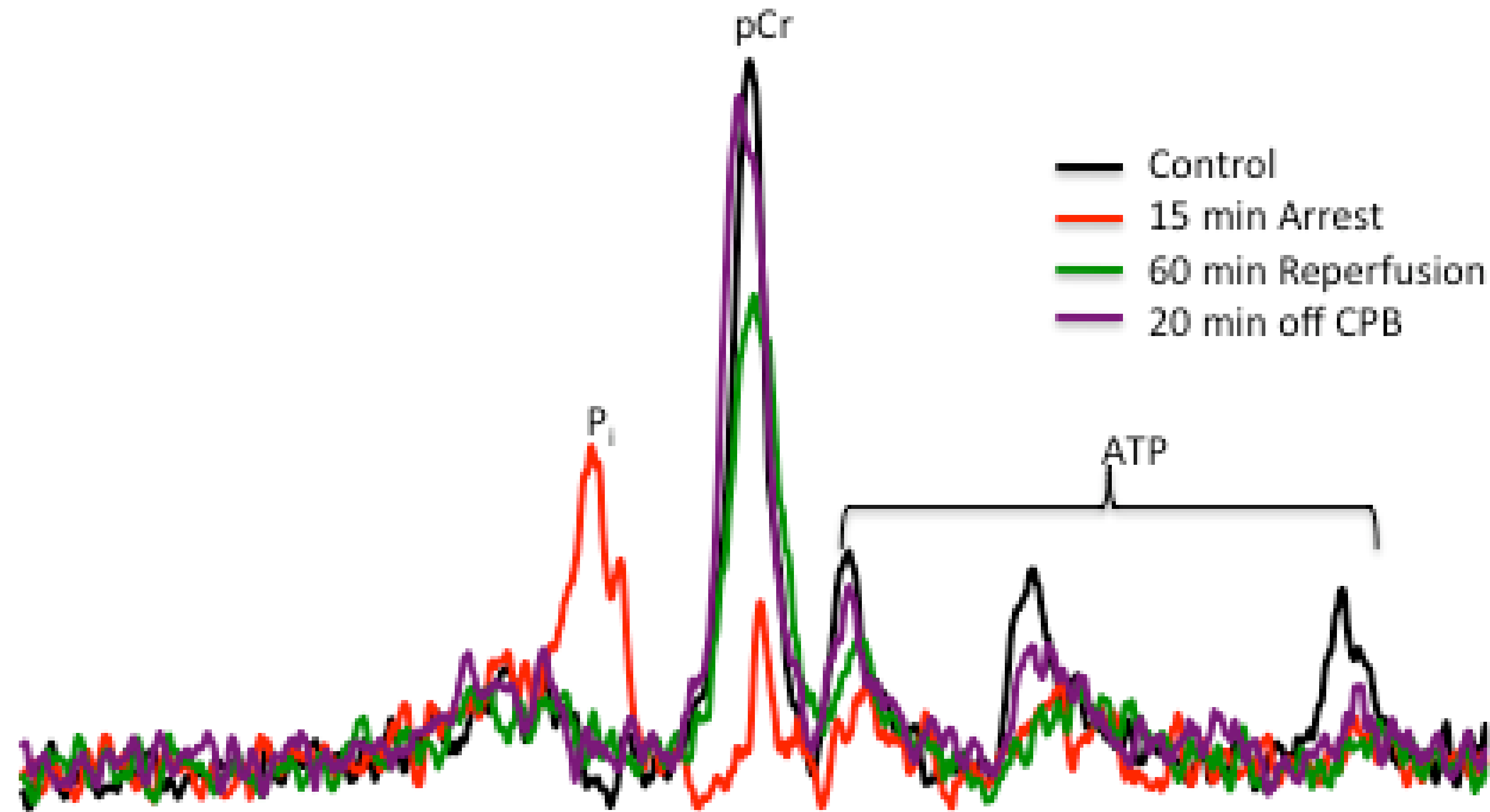
DCD



Brainstem death

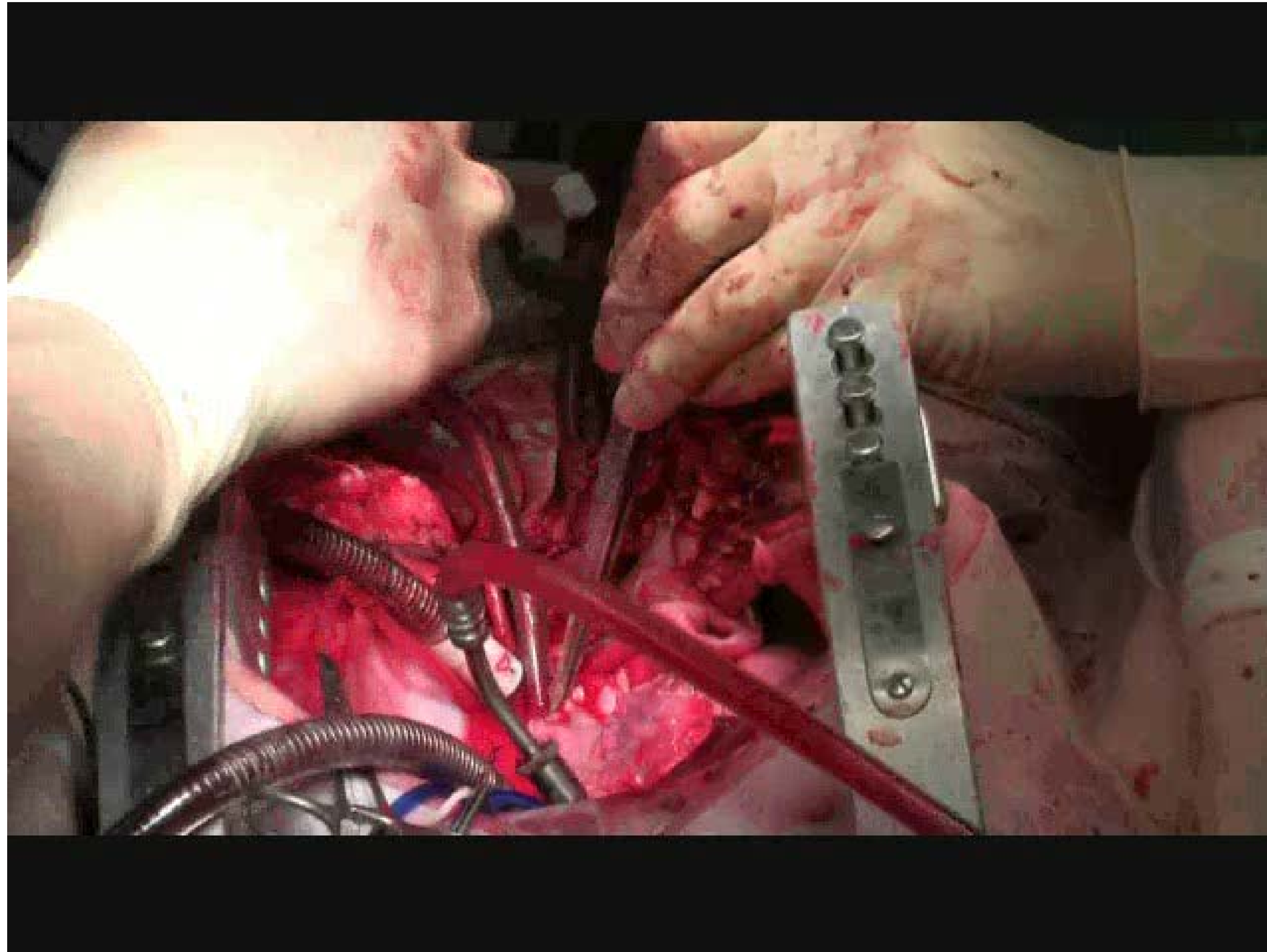


# Myocardial energetics





# Porcine Orthotopic DCD heart transplantation

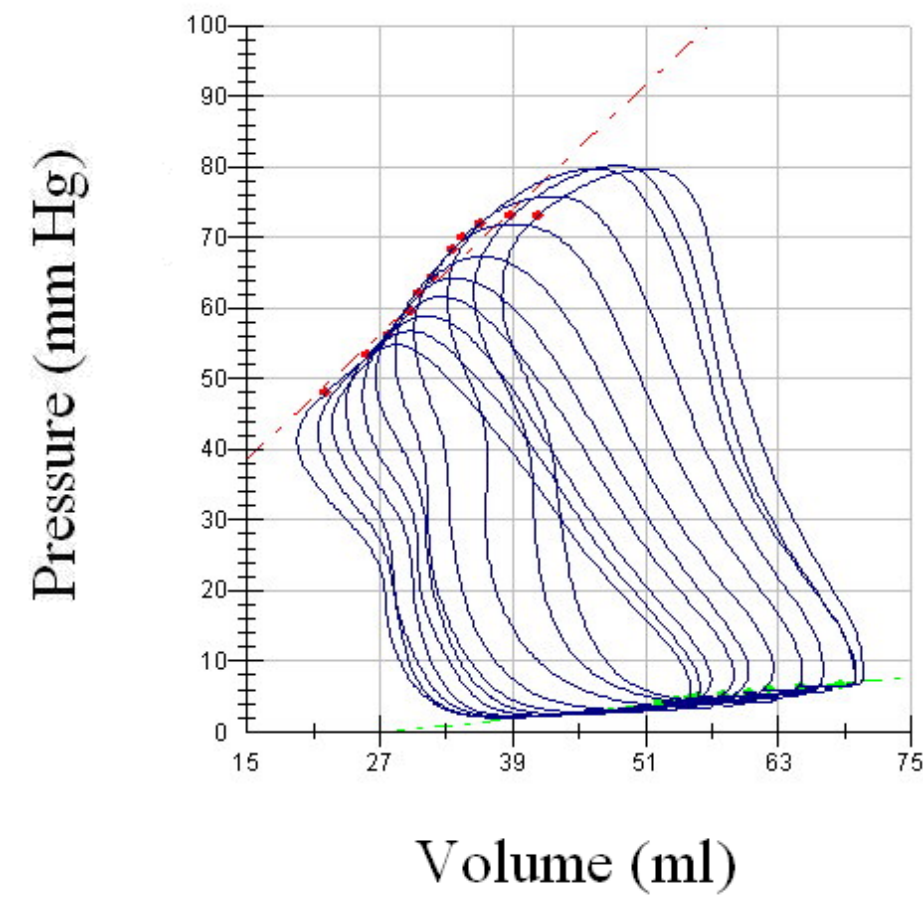


# Porcine Orthotopic DCD heart transplantation

LV

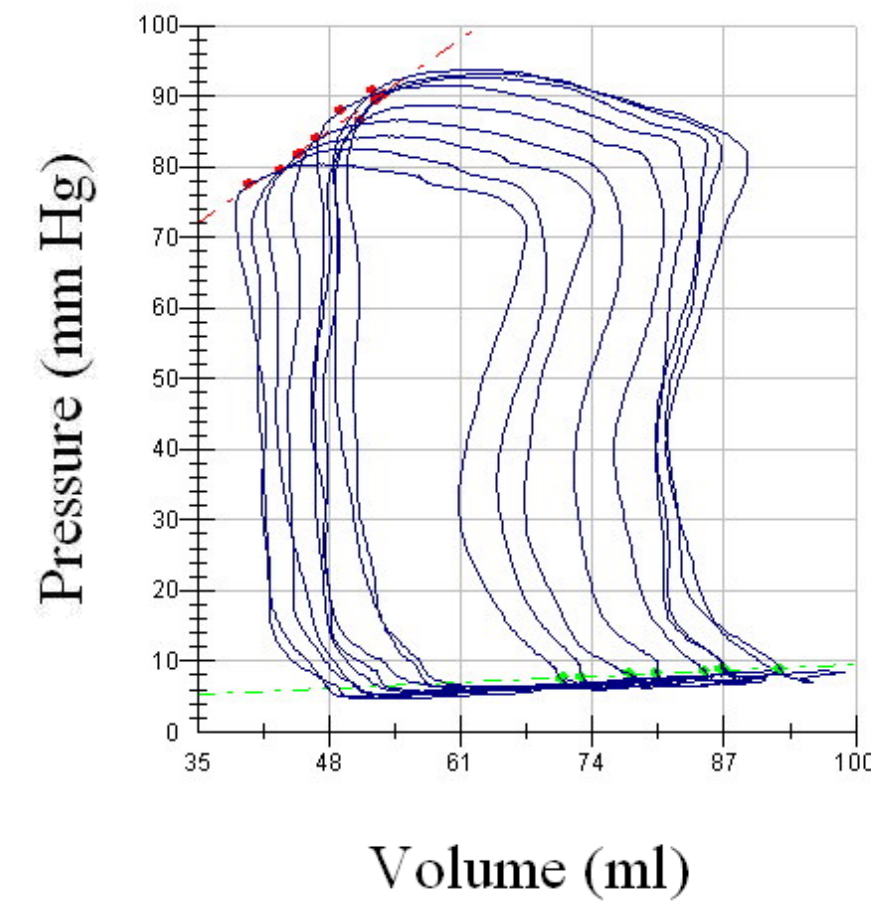
DCD

ESPVR = 1.48



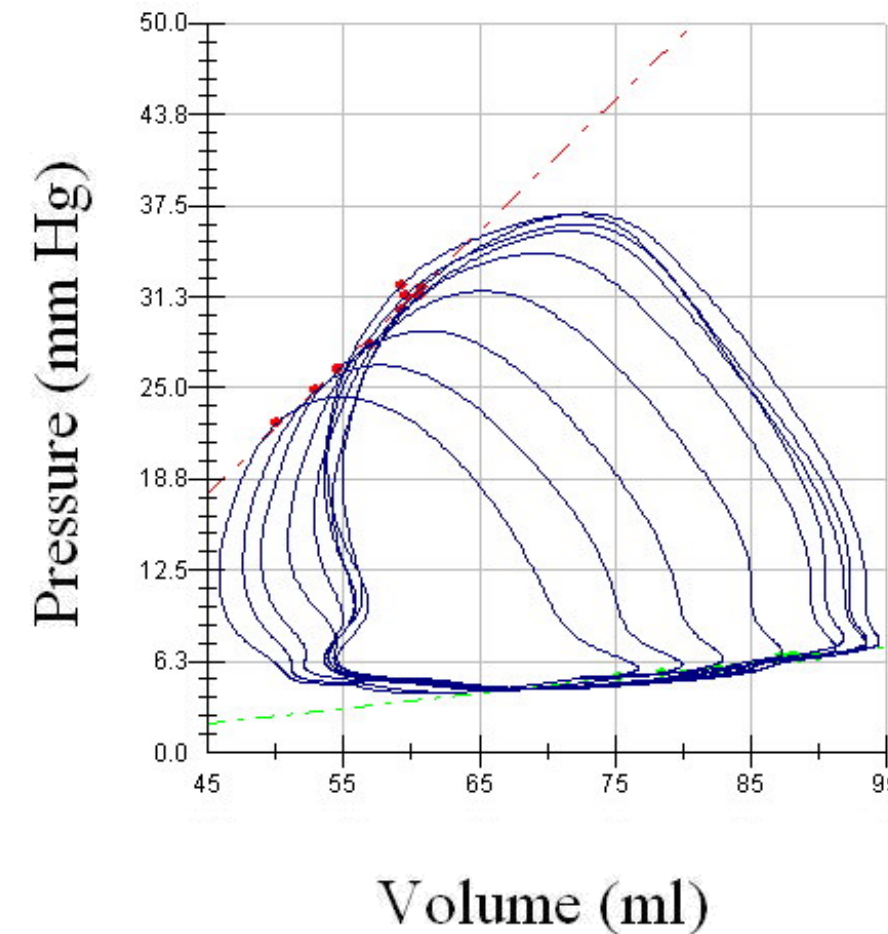
Brainstem death

ESPVR = 1.01

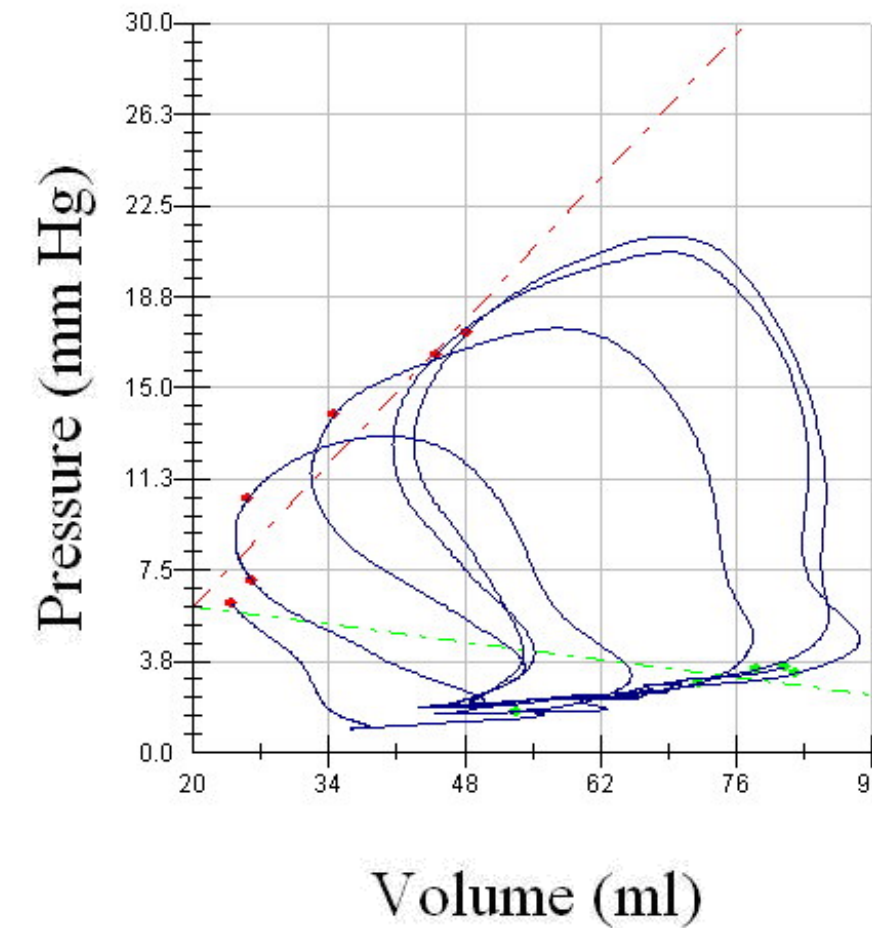


RV

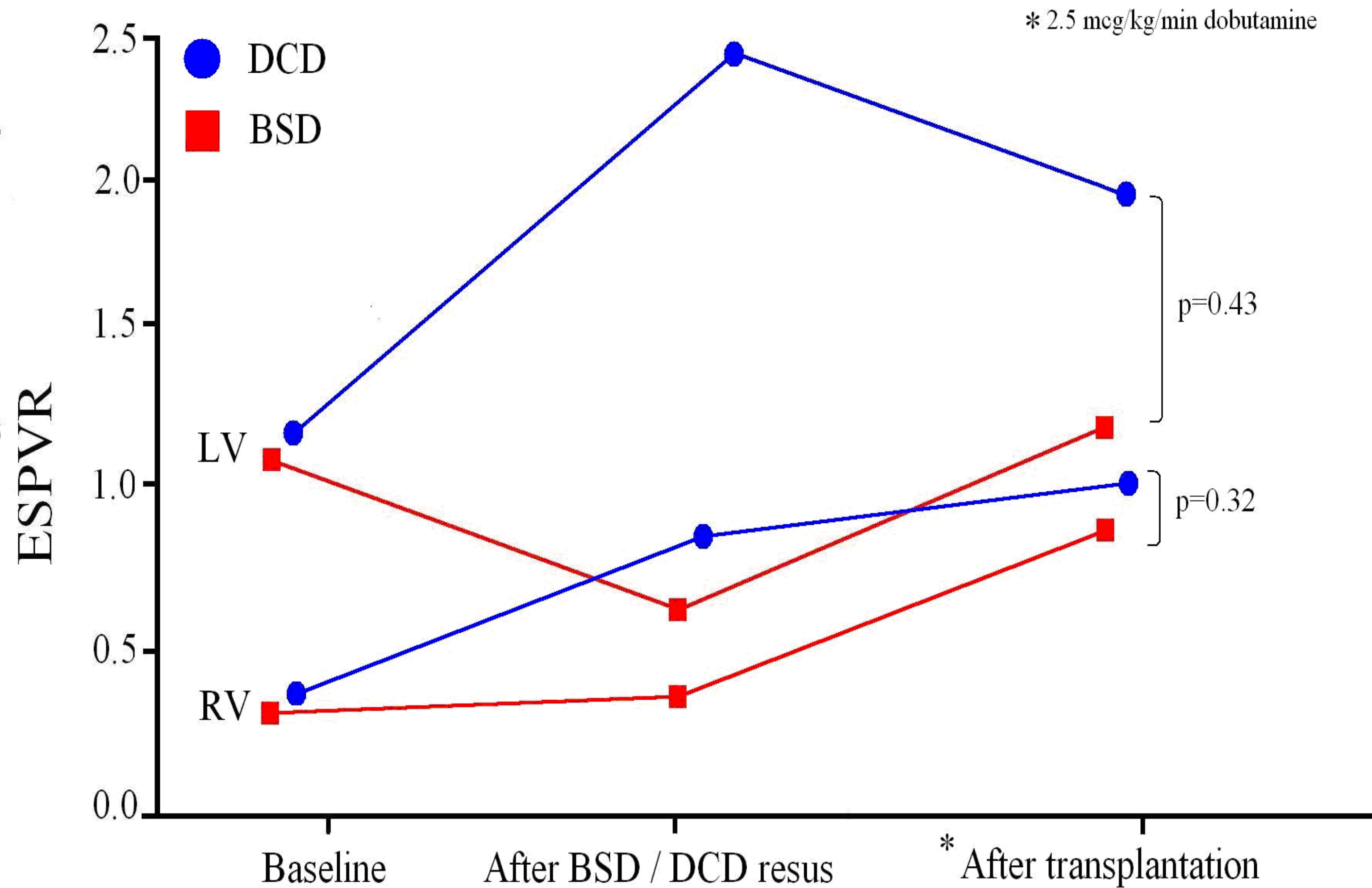
ESPVR = 0.90



ESPVR = 0.42



# Porcine Orthotopic DCD heart transplantation





# Human DCD Heart Resuscitation



# Clinical DCD Heart Transplantation

- 29 DCD heart transplants at Papworth Hospital since introduction of clinical program in March 2015
- 30-day survival: 100%
- 90-day survival: 96%
- Has resulted in 39% increase in heart transplantation at our institution
- 2 procurement methods
  - NRP/ECMO
  - Direct procurement

# Inclusion & Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Category III DCD Donor	Previous cardiac surgery
Donor hospital in South East of England	Previous midline sternotomy
Age $\geq 18 \leq 50$ yrs old	Known coronary heart disease
Consent for donation from next of kin	Known congenital heart disease
Expected death within 4 hours of WLST	Previous myocardial infarct
WLST in <u>anaesthetic</u> room or ICU	Insulin- <u>dependant</u> Diabetes
Ejection fraction $>50\%$ prior to WLST	Massive inotropic or vasopressor support
No <u>valvular</u> abnormalities on echocardiogram	Active malignancy
	Hepatitis B antigen-positive
	Hepatitis C antibody-positive
	Malignant melanoma
	All secondary intracerebral <u>tumours</u>
	Human Immunodeficiency Virus
	Primary intra-cerebral lymphoma
	<u>Creutzfeldt</u> -Jacob disease



# Donor Demographics

	DCD Procurement Method			P-value
	DCD n=21	NRP n=12	DPP n=9	
<b>Donor Demographics</b>				
Age, yr	35 (32-38)	37 (33-39)	34 (30-36)	0.17
Sex male, n(%)	18(86)	9 (75)	9 (100)	0.23
Blood Group				
O, n (%)	14(67)	7 (58)	7 (78)	0.67
A, n (%)	6 (29)	5 (42)	1 (11)	
B, n (%)	1 (5)	0 (0)	1 (11)	
Cause of Death				
HBI, n (%)	9(42)	2 (17)	7 (78)	0.01
IH, n (%)	6 (29)	6 (50)	0 (0)	
TBI, n (%)	5 (24)	3 (25)	2 (22)	
Other, n (%)	1 (5)	1 (8)	0 (22)	
Height, cm	175 (172-181)	175 (169-180)	175 (172-181)	0.50
Noradrenaline, µg/kg/min	0.04(0.00-0.15)	0.04 (0.00-0.14)	0.07 (0.00-0.18)	0.97

# Recipient Demographics

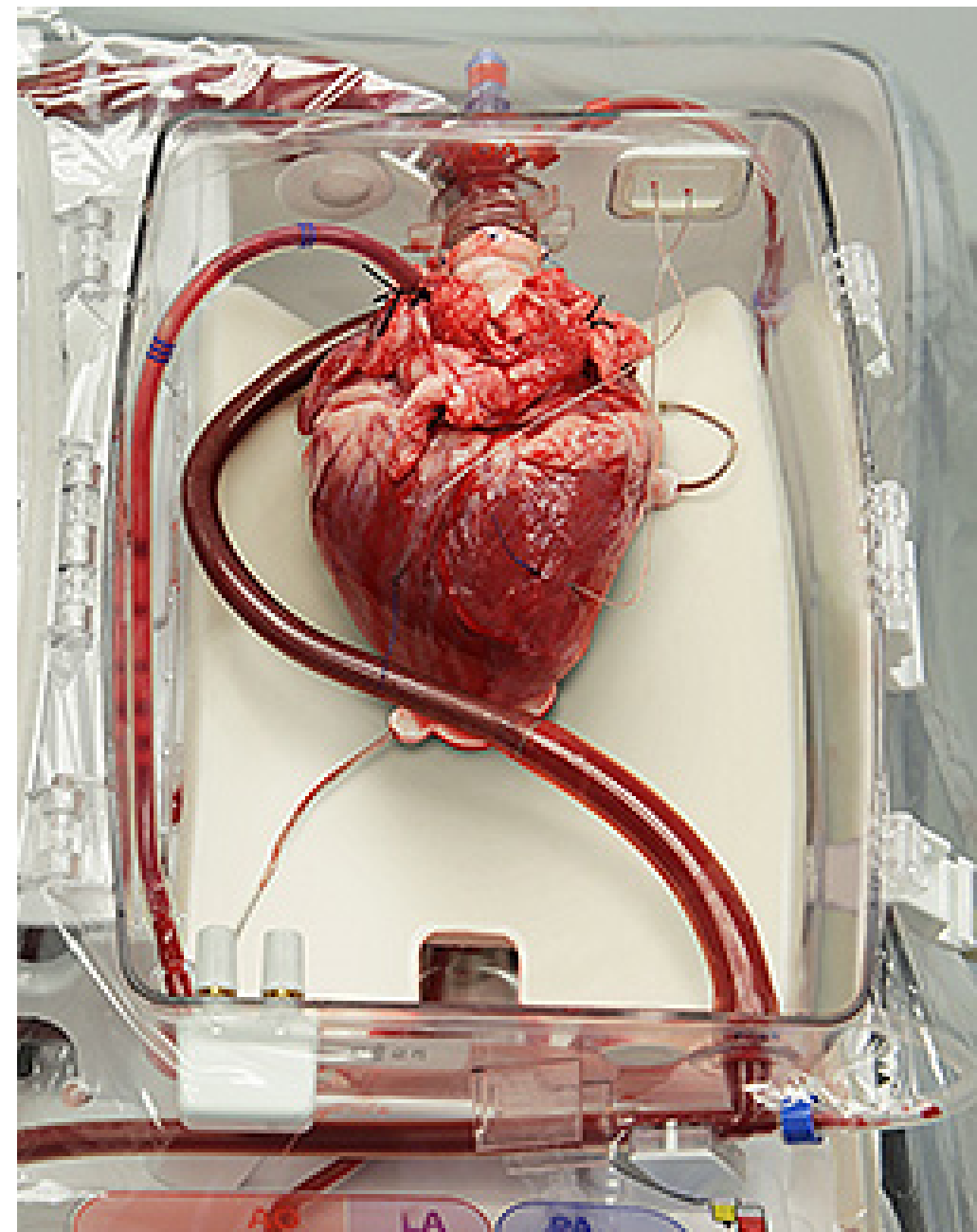
	<b>DCD n=21</b>	<b>NRP n=12</b>	<b>DPP n=9</b>	<b>P- value</b>
<b>Recipient Demographics</b>				
Age, yr	58(49-61)	59 (54-62)	50 (42-60)	0.28
Sex male, n(%)	18 (86)	10 (83)	8 (89)	0.23
<b>Blood Group</b>				
O, n (%)	9 (43)	4 (33)	5 (56)	0.30
A, n (%)	10 (48)	7 (58)	3 (33)	
B, n (%)	2 (10)	1 (8)	1 (11)	
AB, n (%)	0 (0)			
Height, cm	174 (171-178)	174 (169-175)	176 (172-181)	0.30
TPG, mmHg	7 (5-8)	8 (7-8)	6 (4-6)	0.05
PVR, Wood Units	1.9 (1.4-2.2)	2 (1.7-2.2)	1.5 (1.3-2.1)	0.24
<b>Diagnosis</b>				
DC, n (%)	12 (57)	9 (75)	3 (33)	0.10
HC, n (%)	5 (23)	2 (17)	3 (33)	
RC, n (%)	0 (0)	0 (0)	0 (0)	
IHD, n (%)	2 (10)	0 (0)	2 (22)	
VHD, n (%)	1 (5)	1 (8)	0 (0)	
ARVC, n(%)	1 (5)	0 (0)	1 (11)	
Pre Transplant VAD n (%)	4 (19)	(8)	3 (33)	

# DCD Heart: Ischemia & reperfusion

	<b>NRP n=12</b>	<b>DPP n=9</b>	<b>P-value</b>
Withdrawal to Death, mins	18 (13-21)	19 (15-23)	0.50
DWIT, mins	24 (21-28)	38 (32-43)	<b>0.005</b>
FWIT, mins	18 (15-20)	26 (23-31)	<b>0.002</b>
OCS Perfusion Time, mins	170 (140-179)	280 (206-308)	<b>0.02</b>
Implant Duration, mins	32 (31-38)	36 (33-44)	0.15

Values are Median (IQR). P-values are displayed between groups. □

DWIT = donation withdrawal ischaemic time; FWIT = functional warm ischaemic time; OCS = Organ Care System





# DCD Heart Transplant Outcomes

	DCD Procurement Method			P-value
	DCD n=21	NRP n=12	DPP n=9	
<b>Cardiac Performance</b>				
Cardiac Index, L/min/m <sup>2</sup>	2.5 (2.3-2.7)	2.5 (2.3-2.7)	2.5 (1.7-2.7)	0.66
Cardiac Output, L/min	4.7 (4.2-5.2)	4.9 (4.3-5.1)	4.6 (3.6-5.5)	0.92
MAP, mmHg	72 (64-81)	72 (64-81)	74 (66-79)	0.84
CVP, mmHg	9 (8-10)	10 (8-11)	9 (7-10)	0.44
PA Diastolic, mmHg	14 (13-17)	14 (13-16)	16 (13-18)	0.39
<b>Heart Transplant Outcome</b>				
Mechanical Support				
IABP, n (%)	5 (24)	2 (17)	3 (33)	0.61
ECMO, n (%)	2 (10)	1 (8)	1 (11)	1.00
VAD, n (%)	1 (5)	0 (0)	1 (11)	0.43
Pharmacological Support				
Dopamine, µg/kg/min	4.2	4.7	3.2	0.09
Adrenaline, µg/kg/min	0.05	0.04	0.05	0.73
Noradrenaline, µg/kg/min	0.00	0.00	0.01	0.41
Ventilation Duration, days	0.6 (0.5-1.5)	0.6 (0.4-1.1)	0.6 (0.5-4.0)	0.41
Intensive Care Duration, days	5 (3-5)	5 (4-5)	3 (3-7)	0.54
Hospital Duration, days	19 (17-26)	19.5 (18-27)	19 (16-23)	0.95
90-Day Mortality, n (%)	1(5)	0 (0)	1 (11)	0.43
Rejection, n (%)	9 (43)	4 (33)	5 (56)	0.36

# Conclusion

- Machine perfusion of the donor heart is likely to have a major role in the future of heart transplantation
- This technology is expected to aid in the recovery and resuscitation of extended criteria donor hearts
- Early results of DCD heart transplantation suggest that results are comparable to heart transplantation from BSD cadaveric donors



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# Thank You



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