



Blood, Cells and Organs Exploring Transfusion in Transplantation

21st November 2019

NHSBT

Stephen Large ma ms mrcp frcs(cth) frcs mba pae(rcp)

on behalf of the PIT

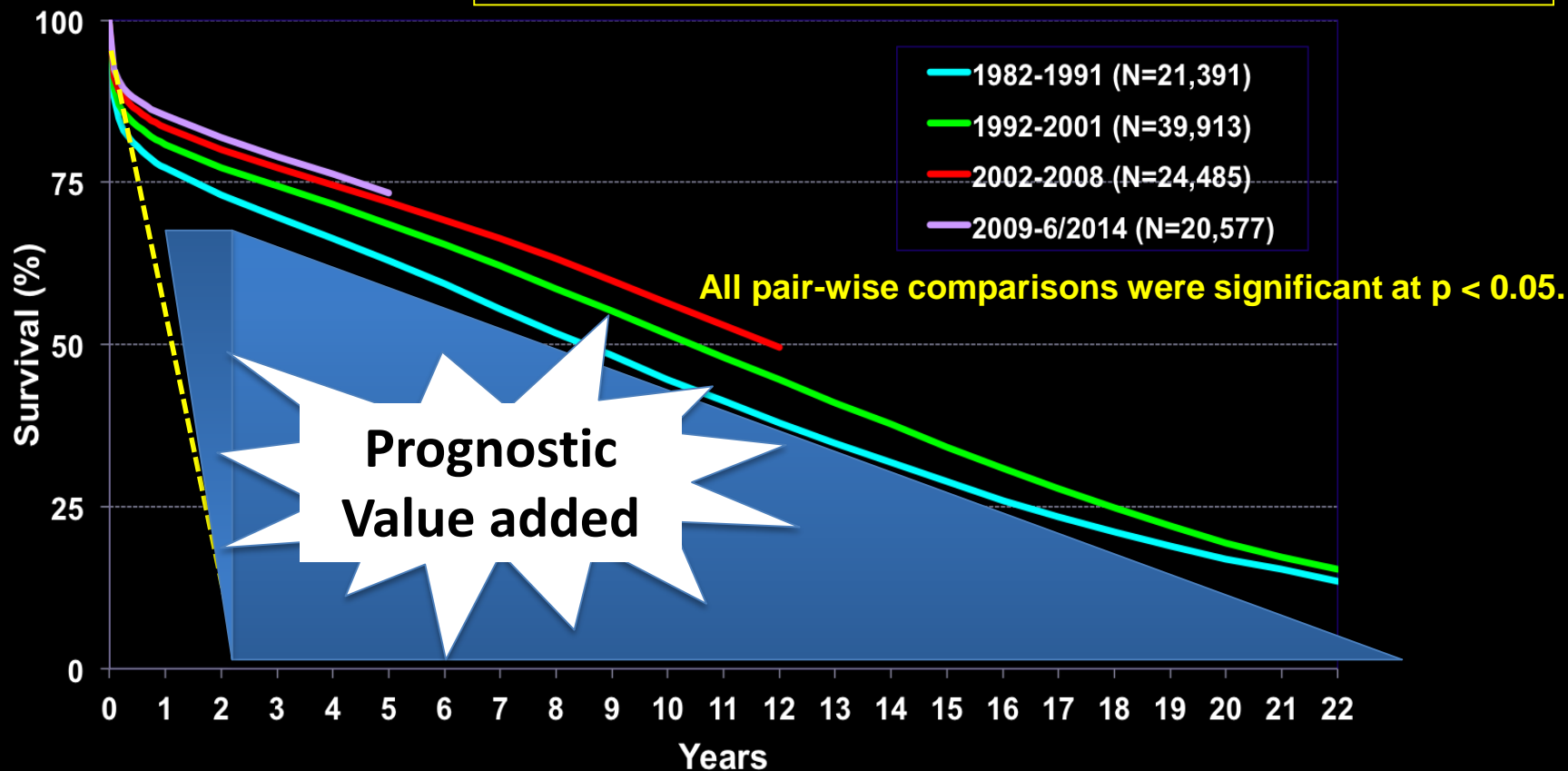
Papworth intra-thoracic transplant team

Adult Heart Transplants Kaplan-Meier Survival by Era

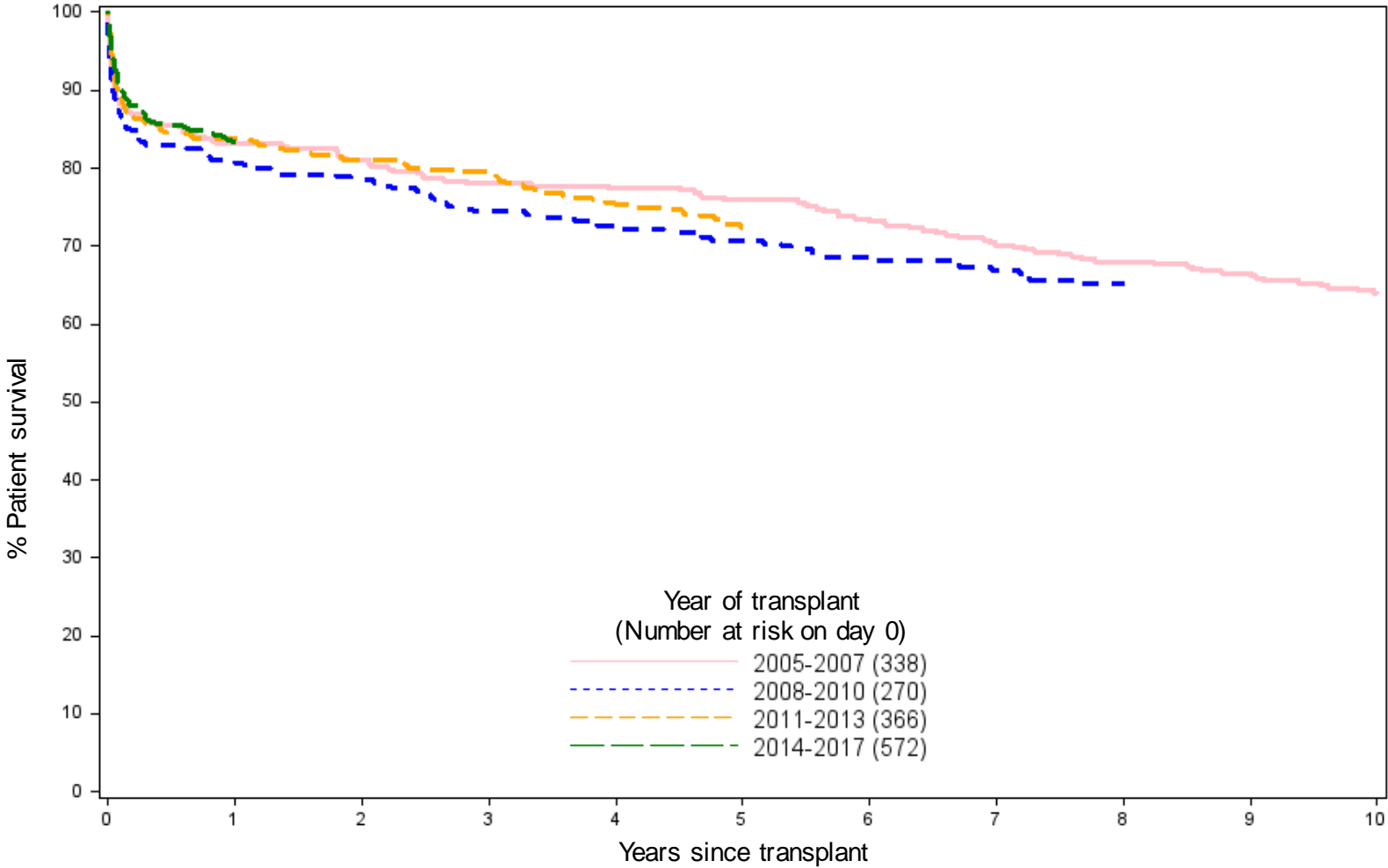
(Transplants: January 1982 – June 2014)

Median survival (years):

1982-1991=8.5; 1992-2001=10.4; 2002-2008=11.9; 2009-6/2014=NA



Long-term patient survival after first adult heart only transplant from donors after brain death, 1 January 2005 – 31 December 2017

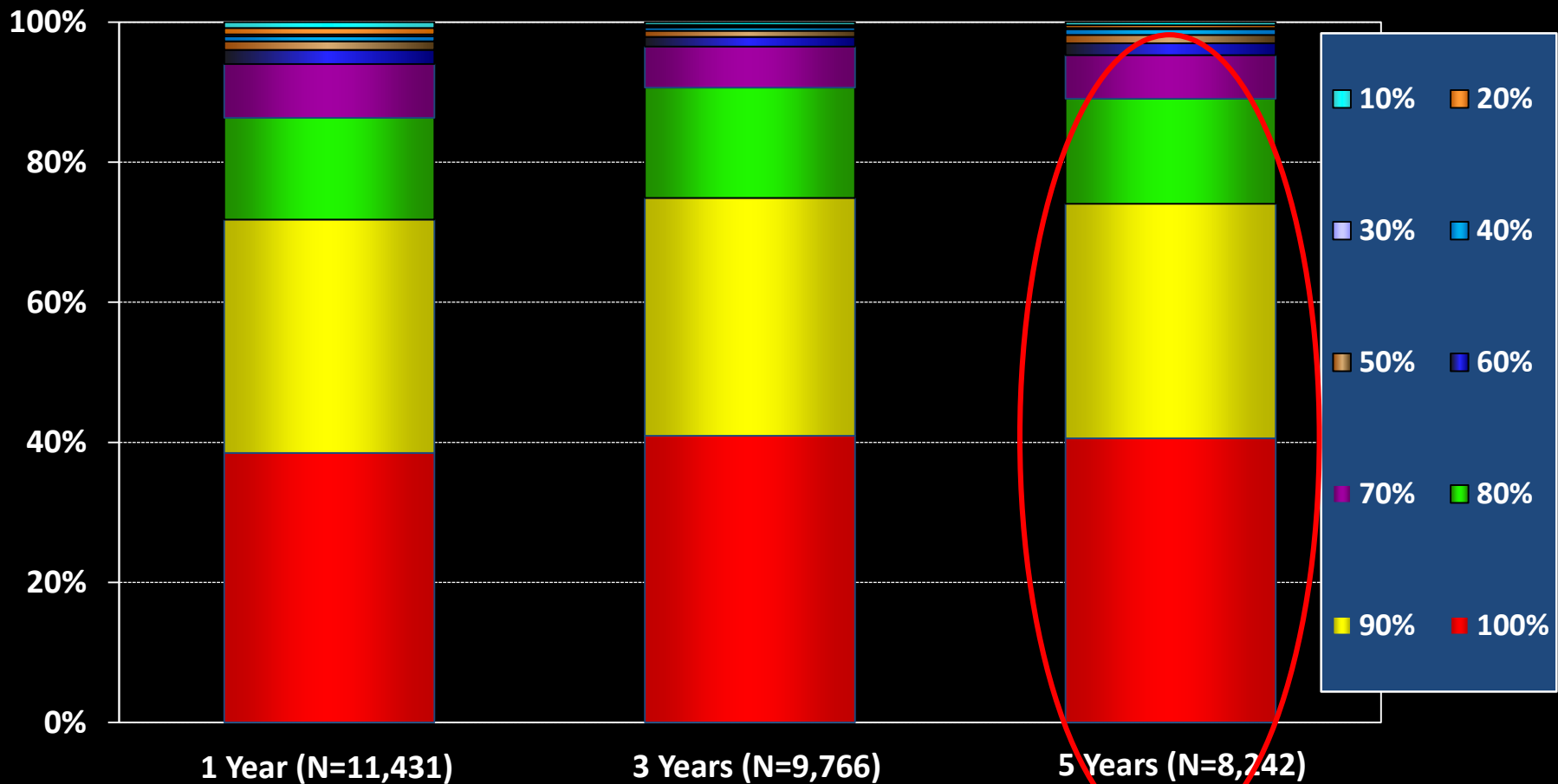


Source: Transplant activity in the UK, 2018-2019, NHS Blood and Transplant

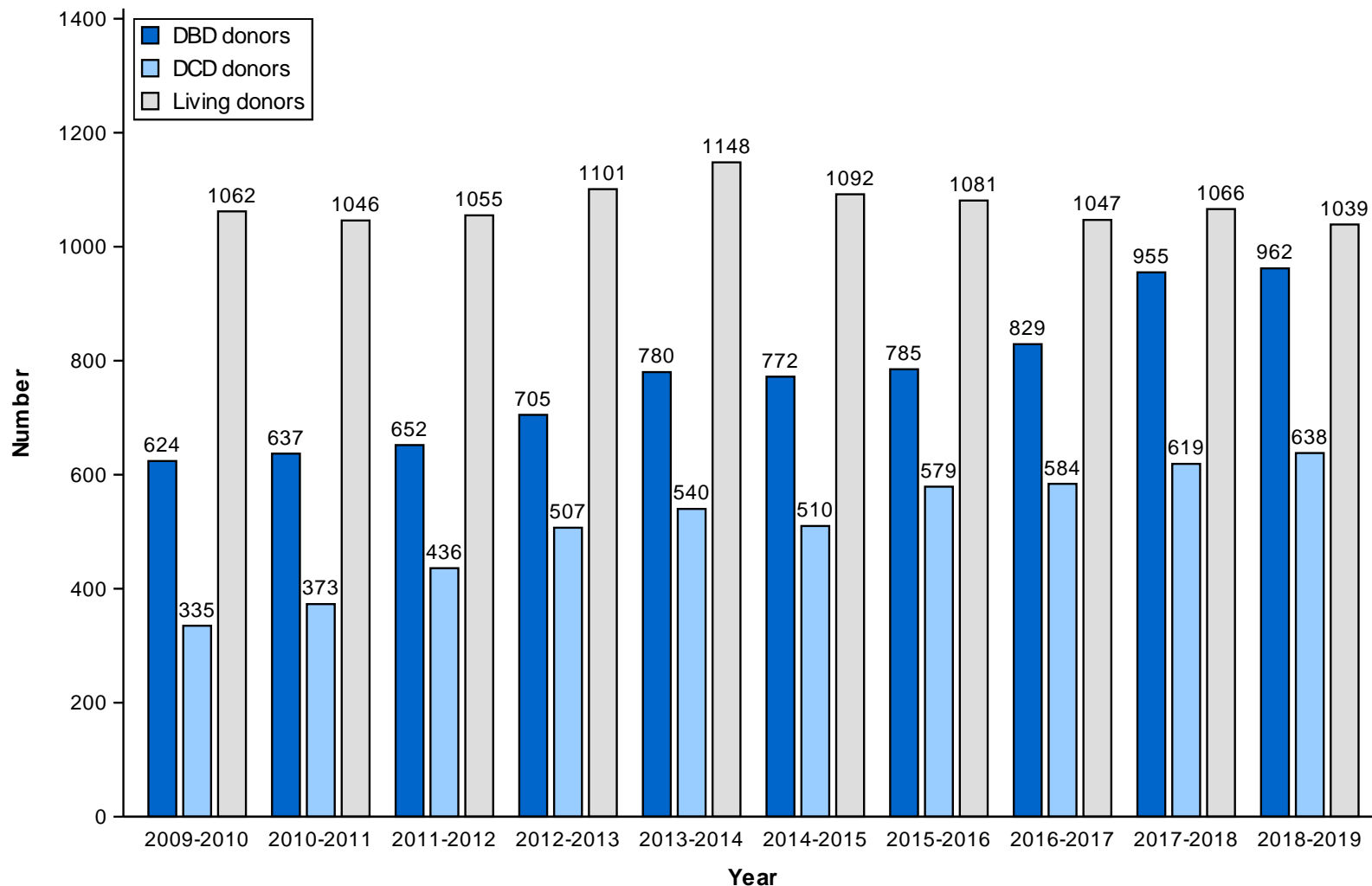


Adult Heart Transplants

Functional Status of Surviving Recipients by Karnofsky Score (Follow-ups: January 2009 – June 2015)

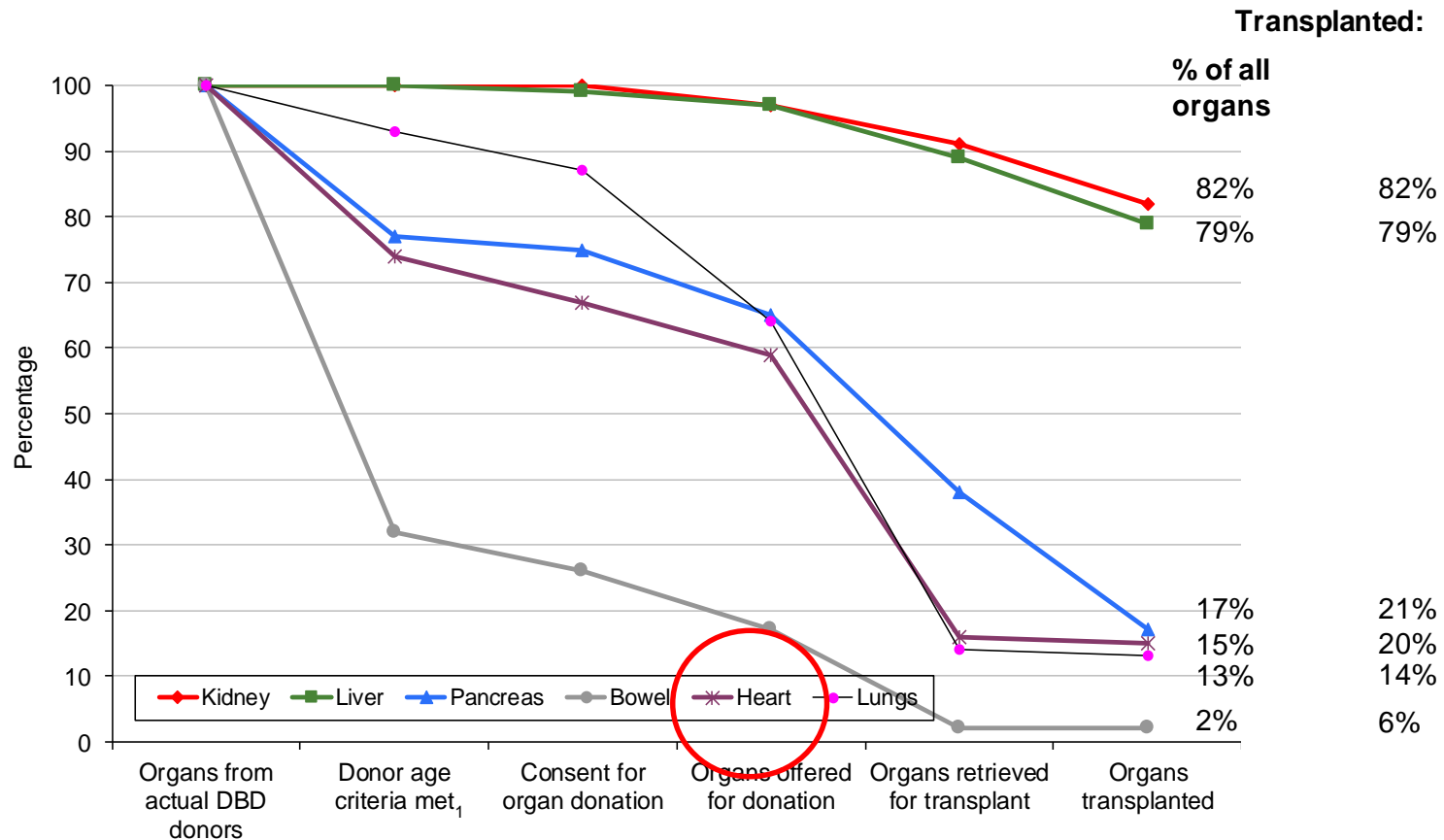


Number of deceased and living donors in the UK, 1 April 2009 - 31 March 2019



Source: Transplant activity in the UK, 2018-2019, NHS Blood and Transplant

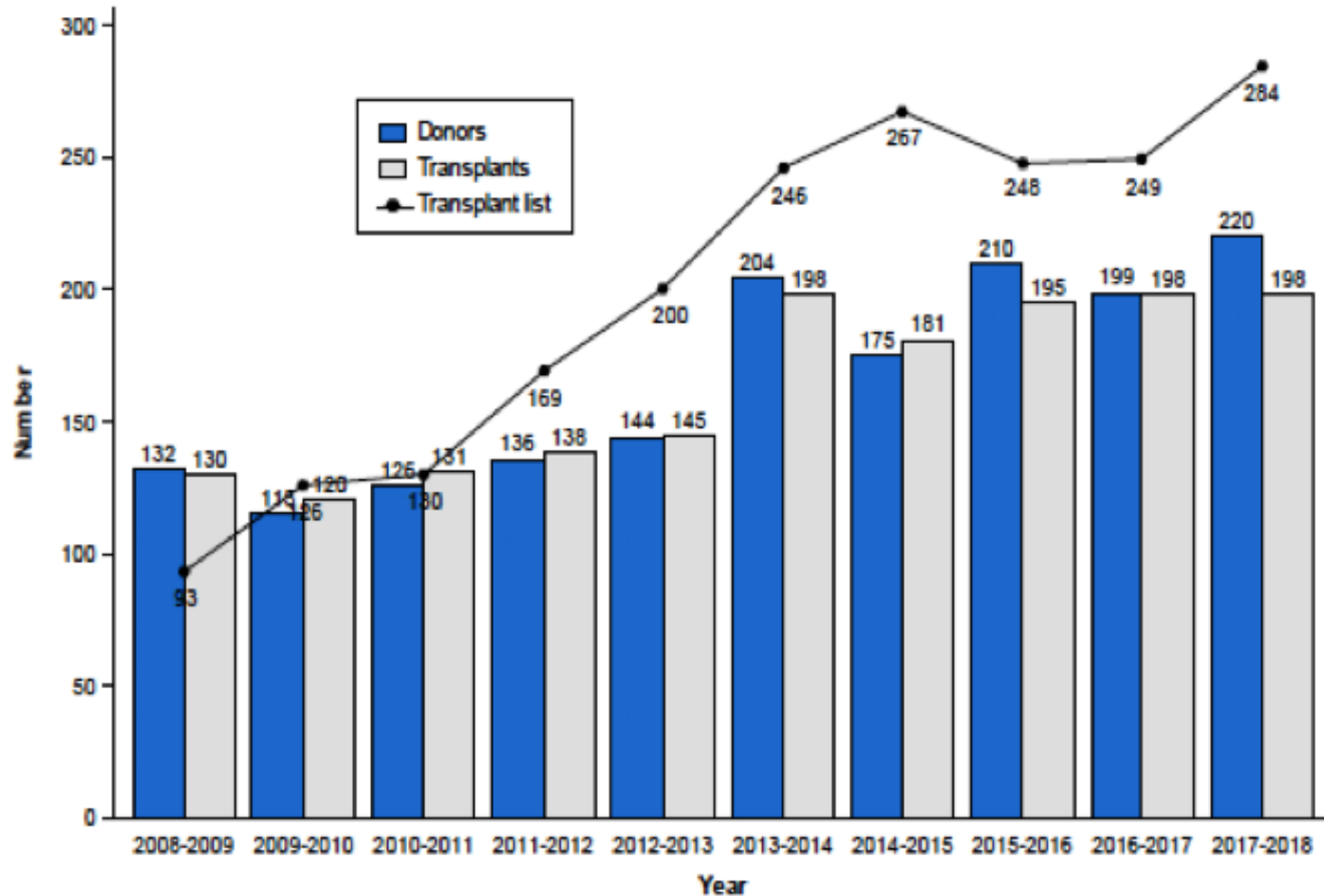
Donation and transplantation rates of organs from DBD organ donors in the UK, 1 April 2018 – 31 March 2019



¹Hearts – in addition to age criteria, donors who died due to myocardial infarction are excluded
 Bowels – in addition to age criteria, donors who weigh >=80kg are excluded

Heart Transplantation in UK: Demand vs Supply

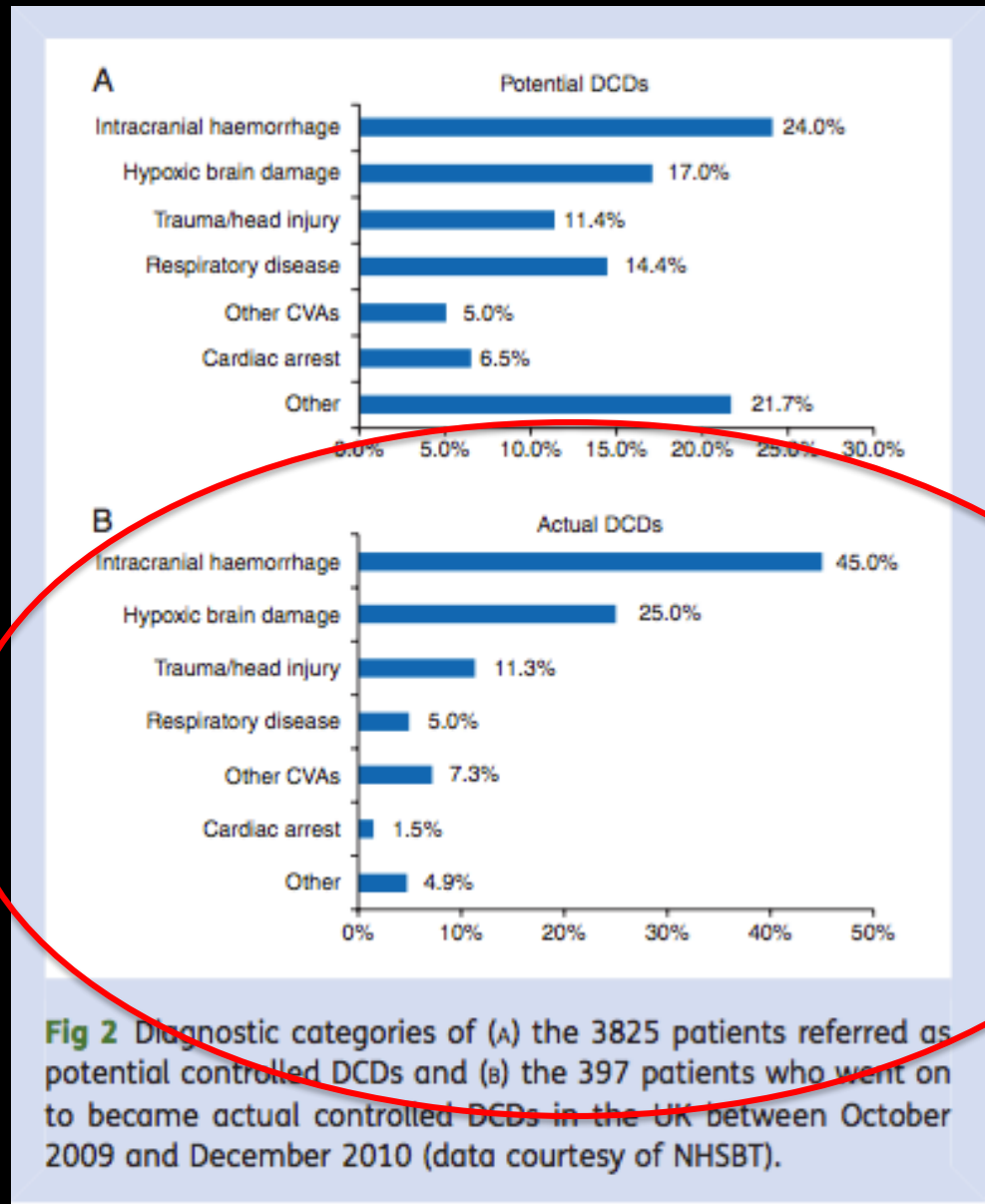
Figure 7.1 Deceased donor heart programme in the UK, 1 April 2008 - 31 March 2018, Number of donors, transplants and patients on the active transplant list at 31 March



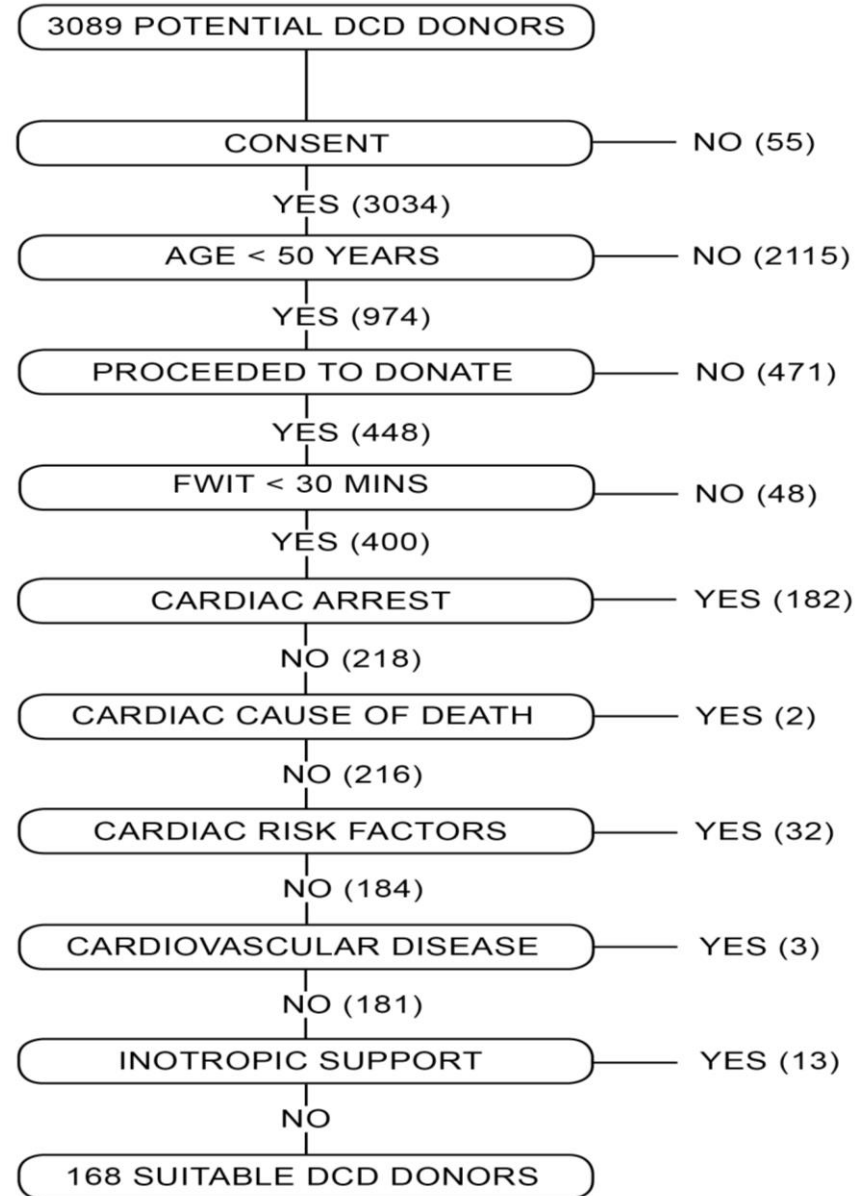
Is DCD heart transplantation possible?

*Recent NHSBT update:
probably 135 more donor /year*

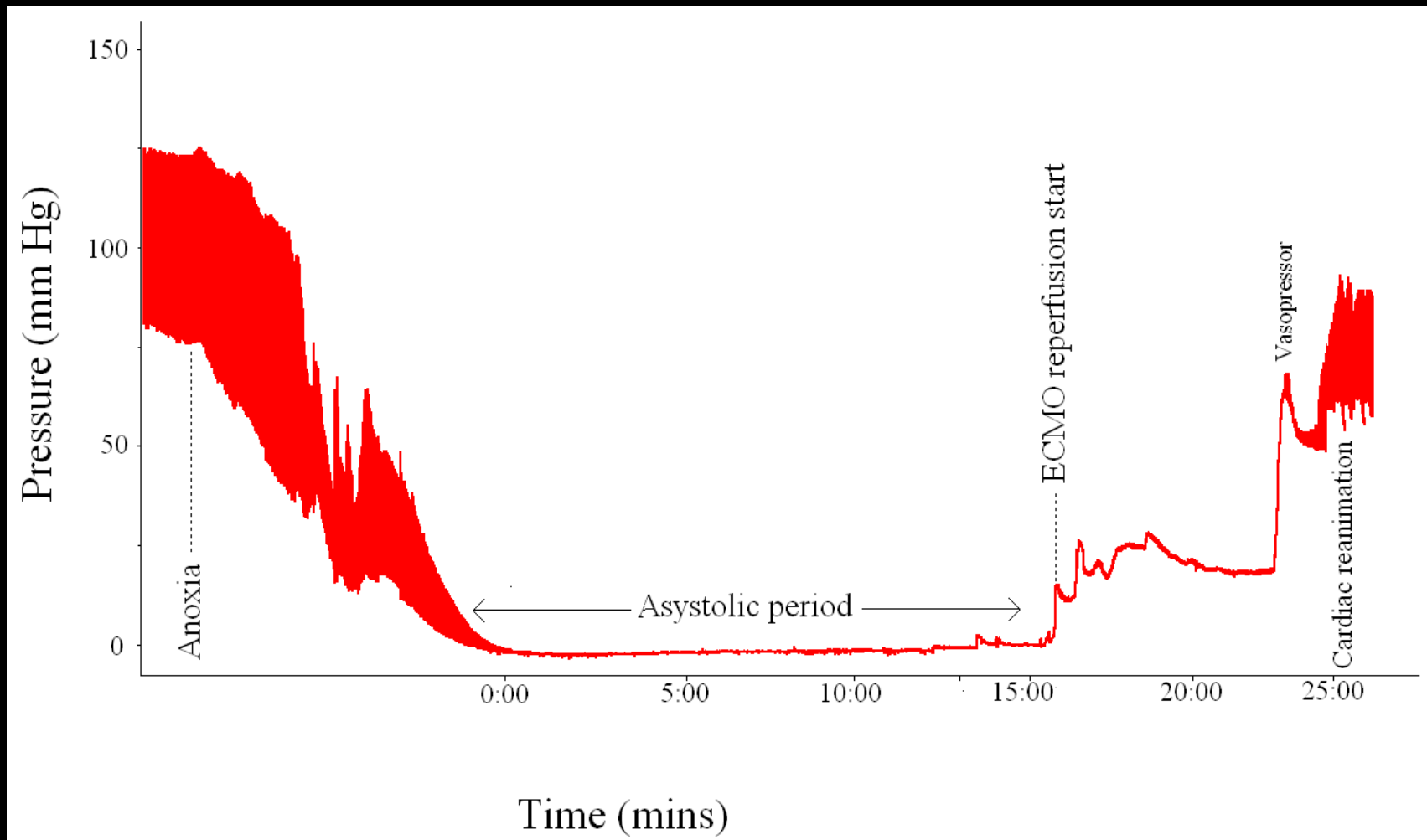
*British Journal of Anaesthesia 108 (S1):
i108–i121 (2012) Donation
after circulatory death A. R. Manara 1*,
P. G. Murphy 2 and G. O'Callaghan 3*



The size of the pool:



Method for modelling DCD (rat and pig): Circulatory determined brain death DCD

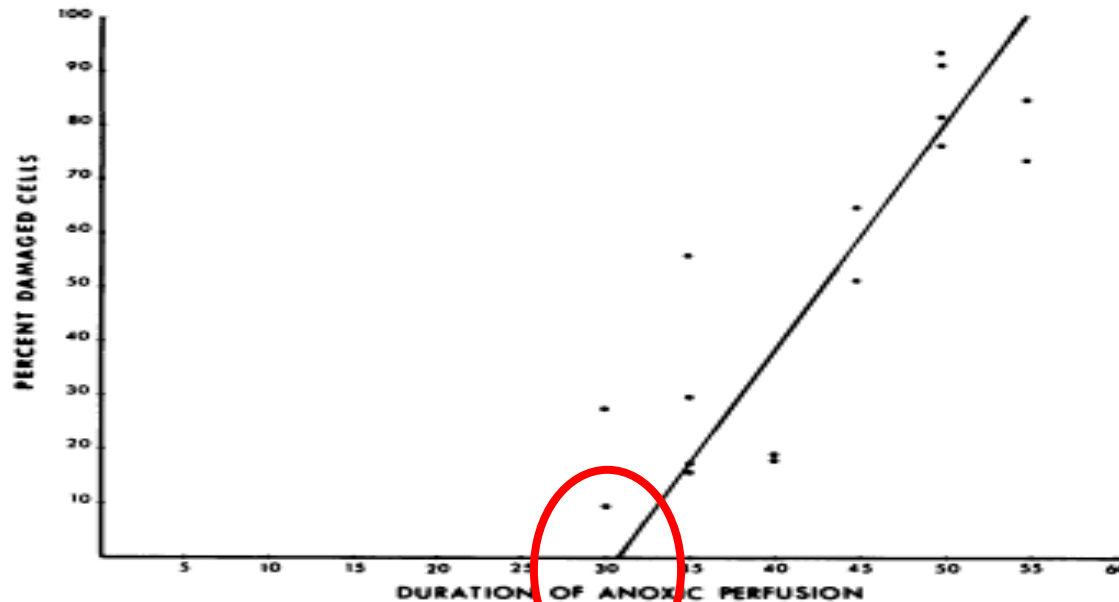


Tolerance of ischaemia (*rat*):

426

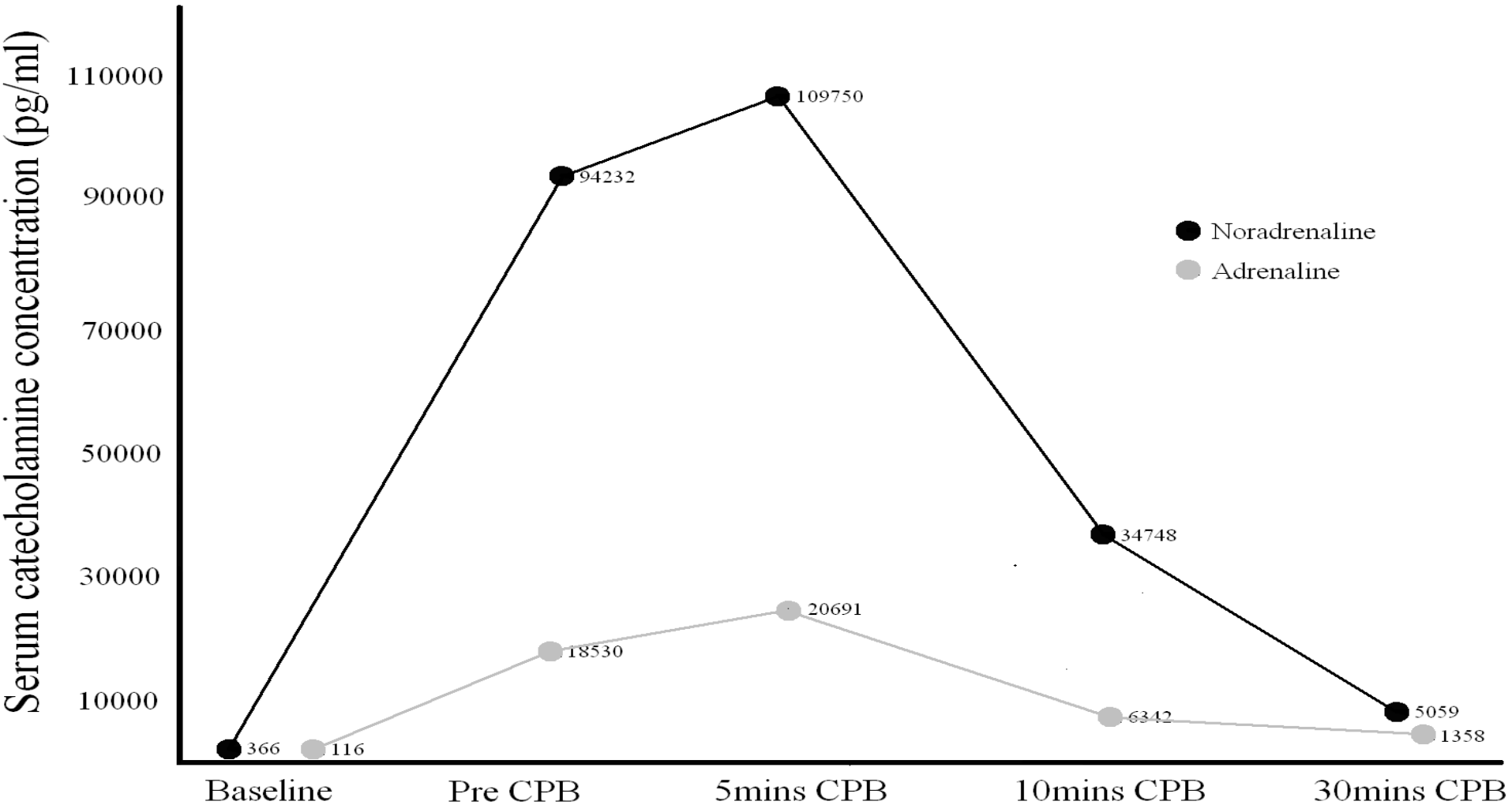
GANOTE ET AL

American Journal
of Pathology



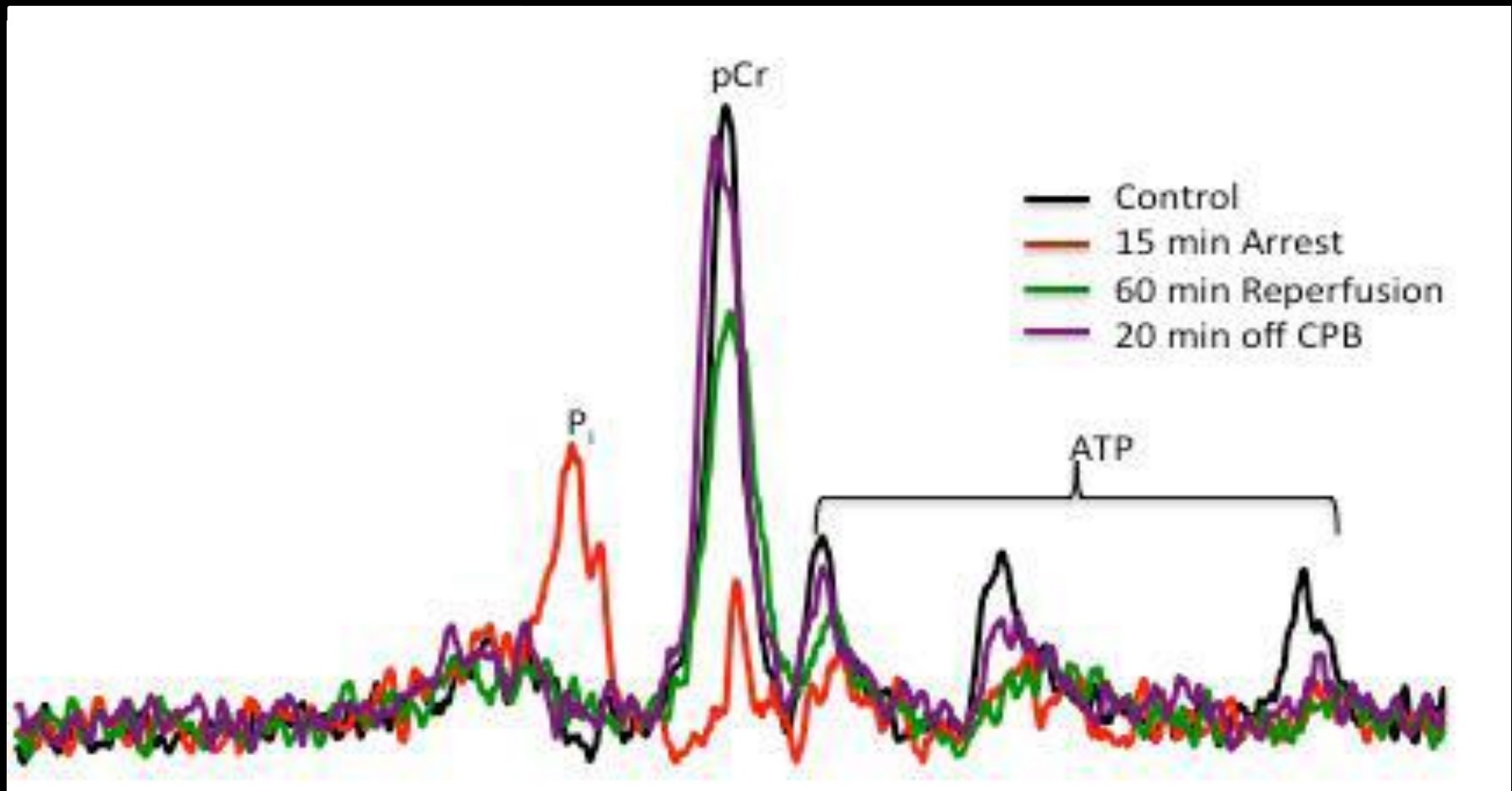
TEXT-FIGURE 4—The percent of severely damaged cells in hearts subjected to 30 to 55 minutes of anoxia and then reoxygenated for a total of 120 minutes of perfusion was estimated by direct counts from four equally spaced light microscopic sections of each heart. The percent of damaged cells correlated linearly by regression analysis ($r = 0.861$, $P < 0.001$) with duration of anoxic perfusion between 30 and 55 minutes.

Catecholamine concentrations after brainstem death and in the NHBD donor



*Hearts from DCD donors display acceptable biventricular function after heart transplantation.
Am J Transplant 2011 11(8) 1621-32 Ali A et al.*

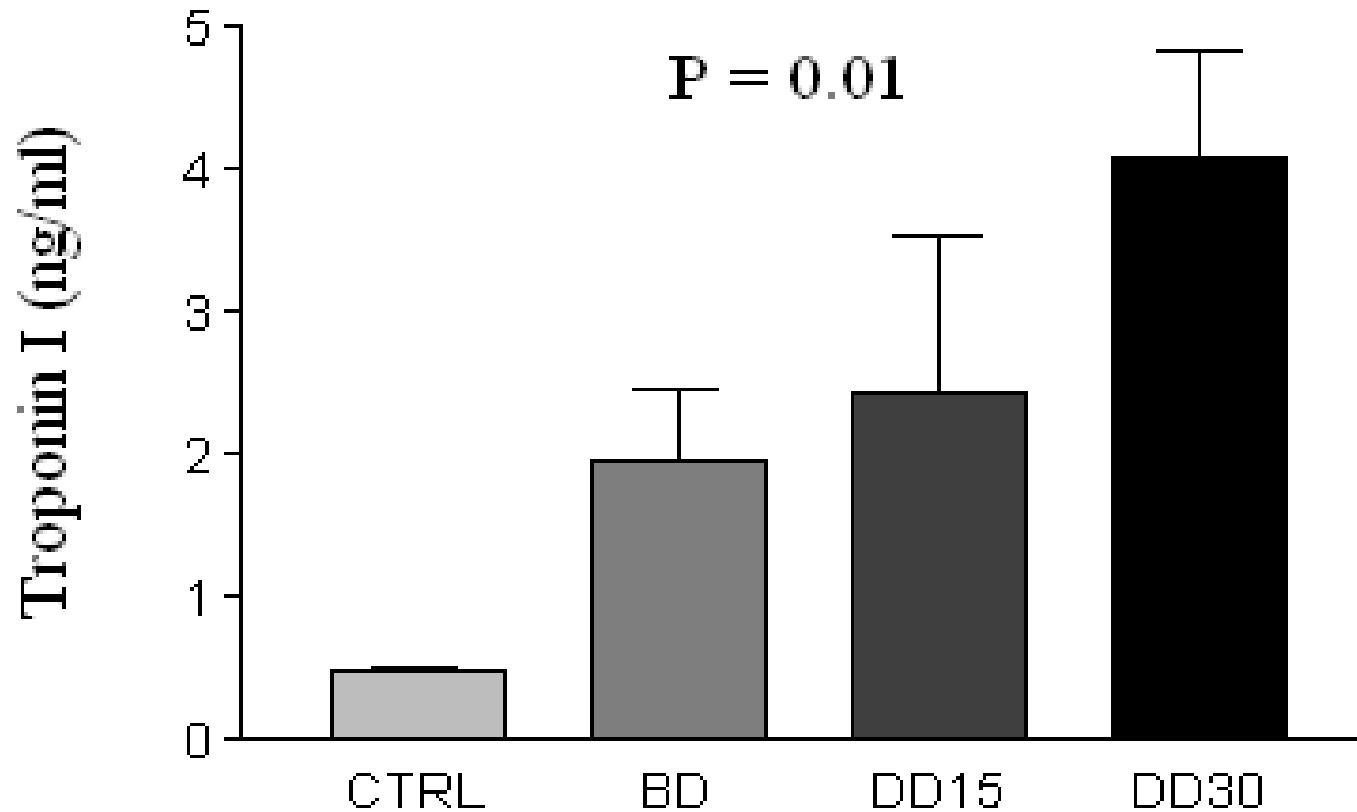
DCD heart transplantation: How tolerant the heart to normothermic ischaemia?



Looks to be largely an ischaemic insult

Am J Transplant 2011 11(8) 1621-32 Ali A et al.

Is the heart damaged?



Hearts from DCD donors display acceptable biventricular function after heart transplantation.
Am J Transplant 2011 11(8) 1621-32 Ali A et al.

OK! So clinically?



Is it Possible?

- First Successful human heart transplant Barnard December 3rd 1967
- Survived for 18 days succumbing to pneumonia

The Code Of Practice For The Diagnosis & Confirmation Of Death

- After 5 minutes of continued cardiorespiratory arrest, the absence of pupillary responses to light, of corneal reflexes, and of motor response to supra-orbital pressure is confirmed
- Diagnosing death in this situation requires confirmation that there has been irreversible damage to the vital centres in the brain-stem due to the length of time in which the circulation to the brain has been absent.
- Cerebral perfusion should not be restored after death has been confirmed

www.odt.nhs.uk/pdf/code-of-practice-for-the-diagnosis-and-confirmation-of-death.pdf

ACADEMY OF
MEDICAL ROYAL
COLLEGES

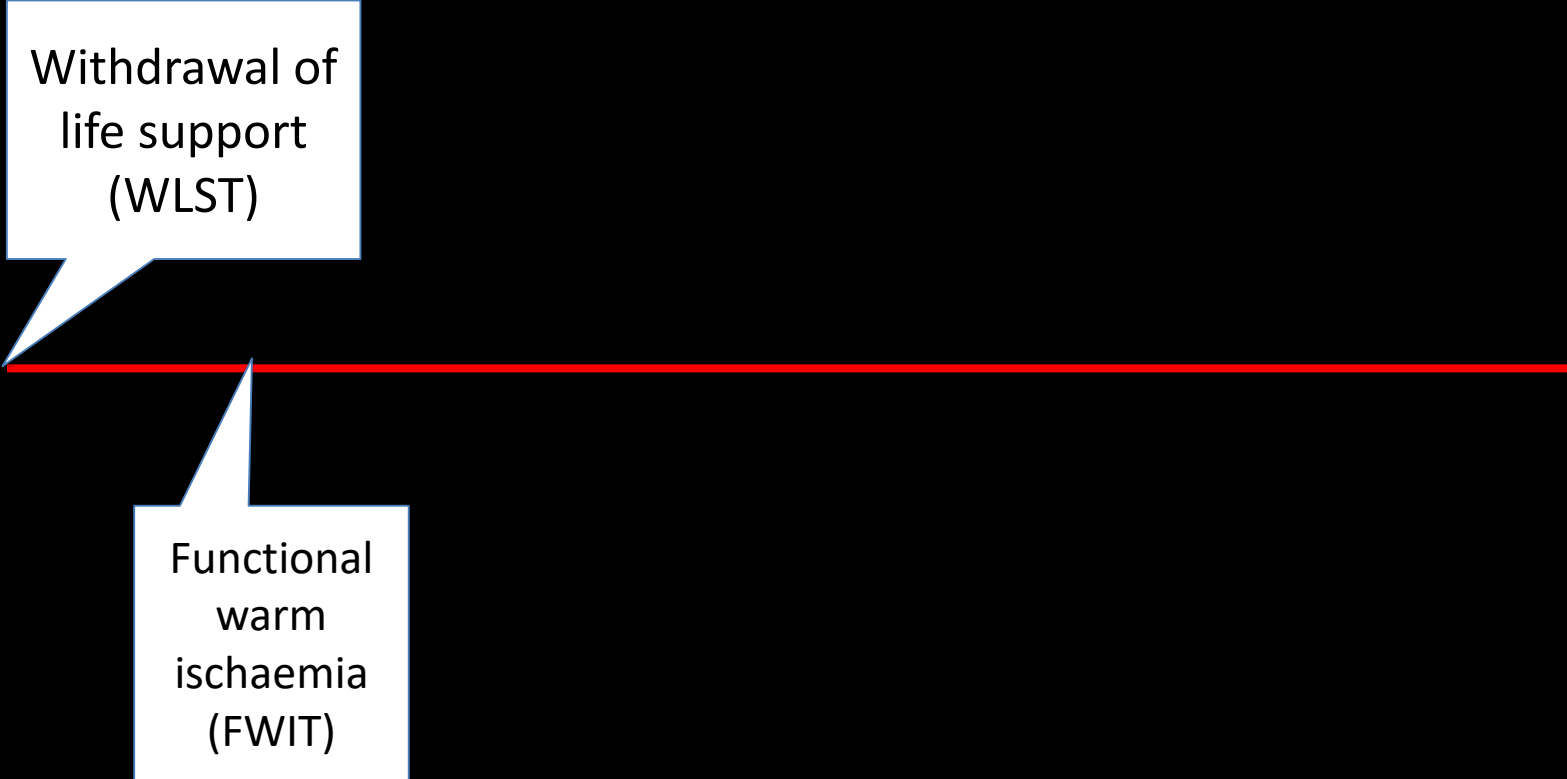
A CODE OF PRACTICE FOR
THE DIAGNOSIS AND
CONFIRMATION OF DEATH

Timings following identification of futile treatment & consent for DCD organ donation:

Withdrawal of
life support
(WLST)

Timings following identification of futile treatment & consent for DCD organ donation:

Withdrawal of
life support
(WLST)



The diagram features a horizontal red line. A white speech bubble containing the text 'Withdrawal of life support (WLST)' is positioned above the line, with its tail pointing to the line. A second white speech bubble containing the text 'Functional warm ischaemia (FWIT)' is positioned below the line, with its tail also pointing to the line. This visualizes the temporal relationship between these two events.

Functional
warm
ischaemia
(FWIT)

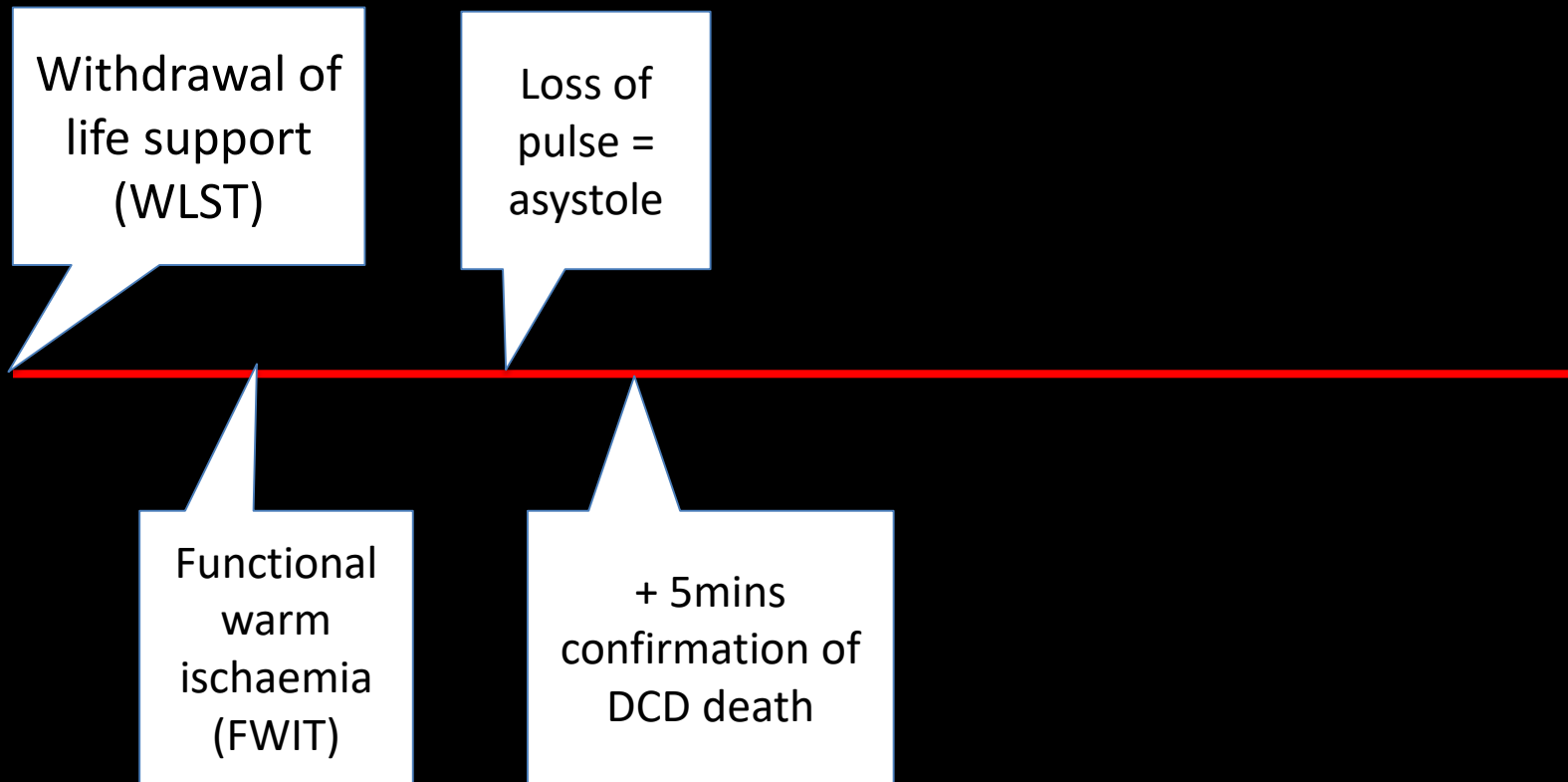
Timings following identification of futile treatment & consent for DCD organ donation:

Withdrawal of
life support
(WLST)

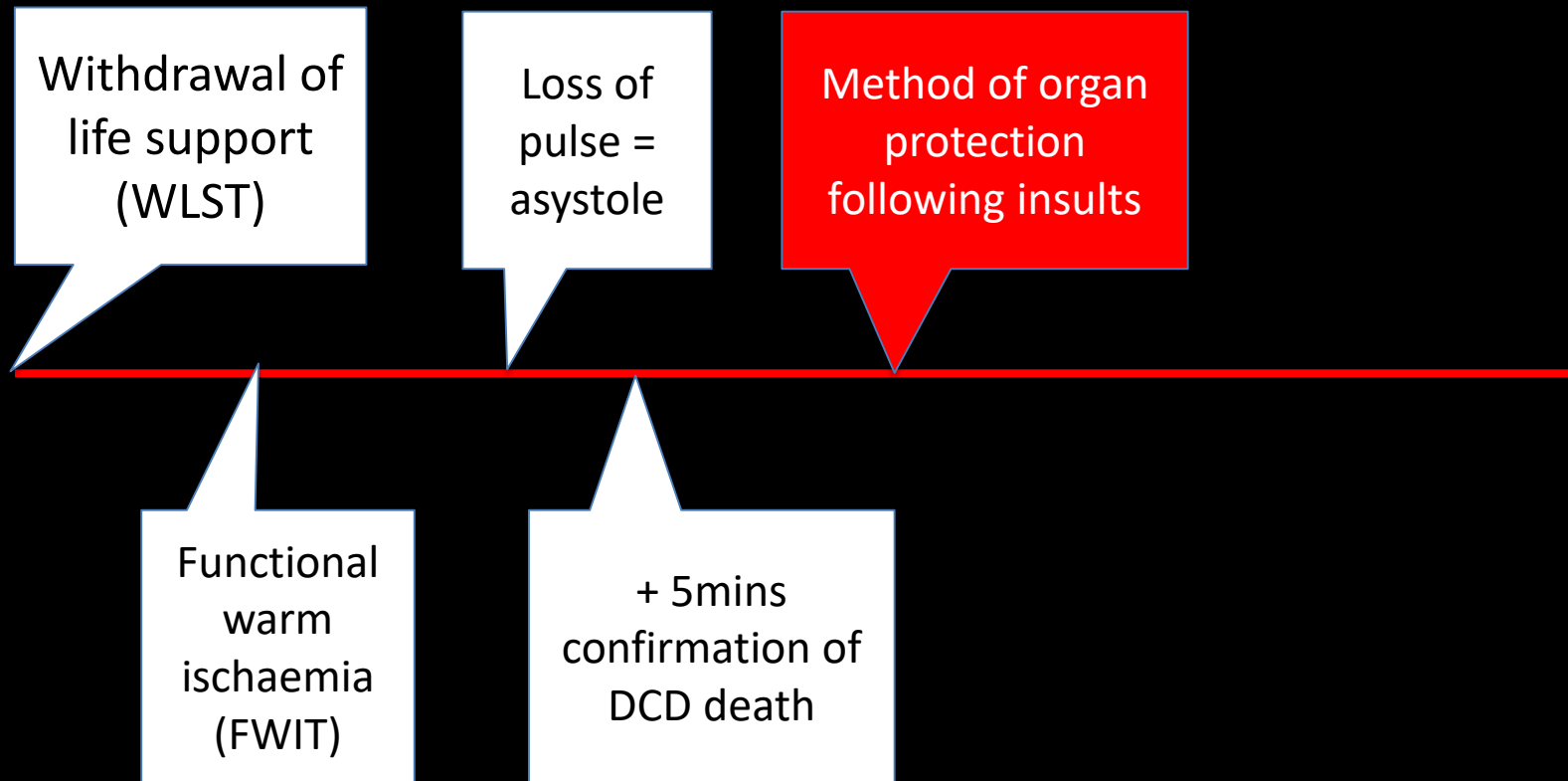
Loss of
pulse =
asystole

Functional
warm
ischaemia
(FWIT)

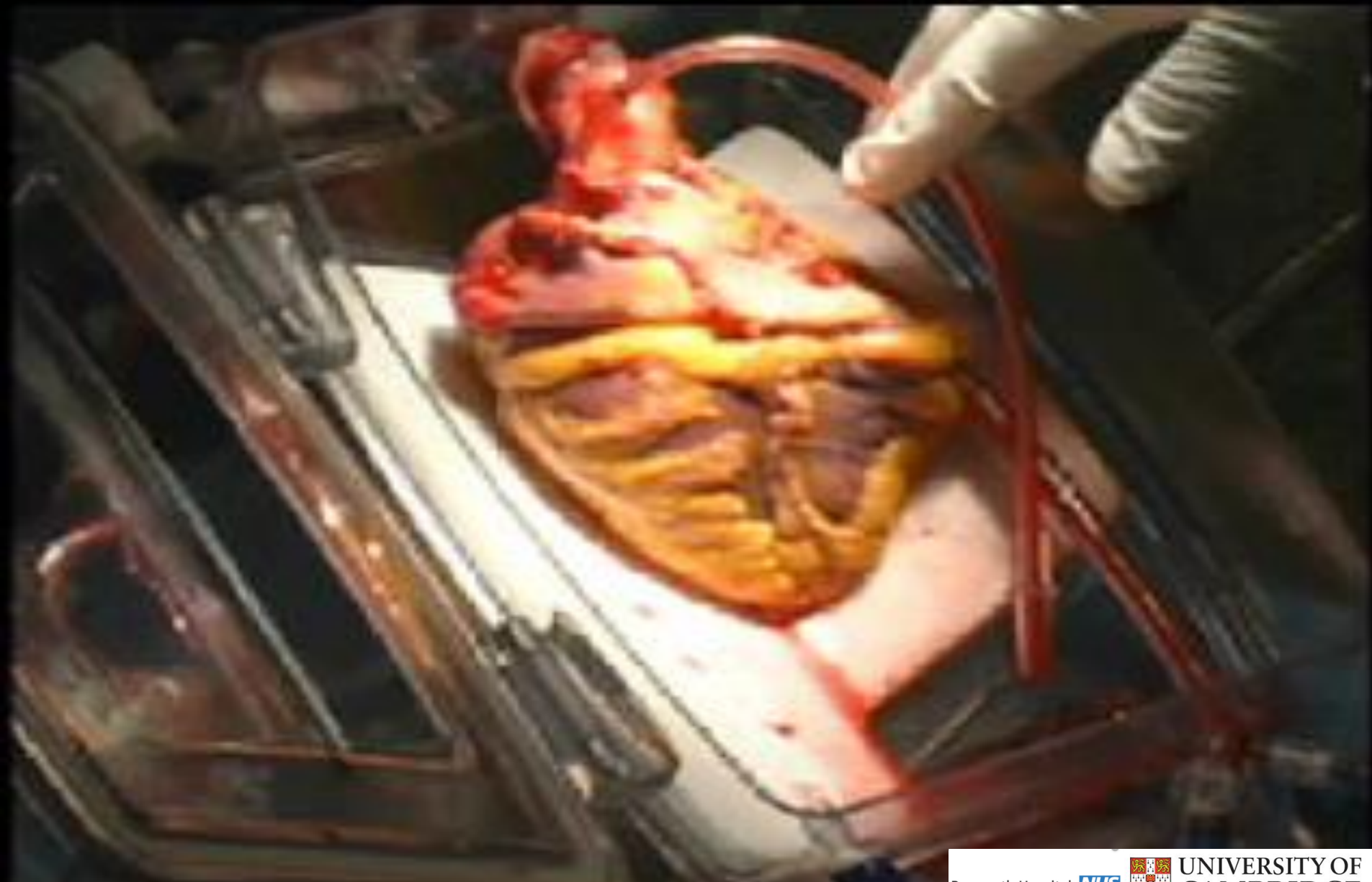
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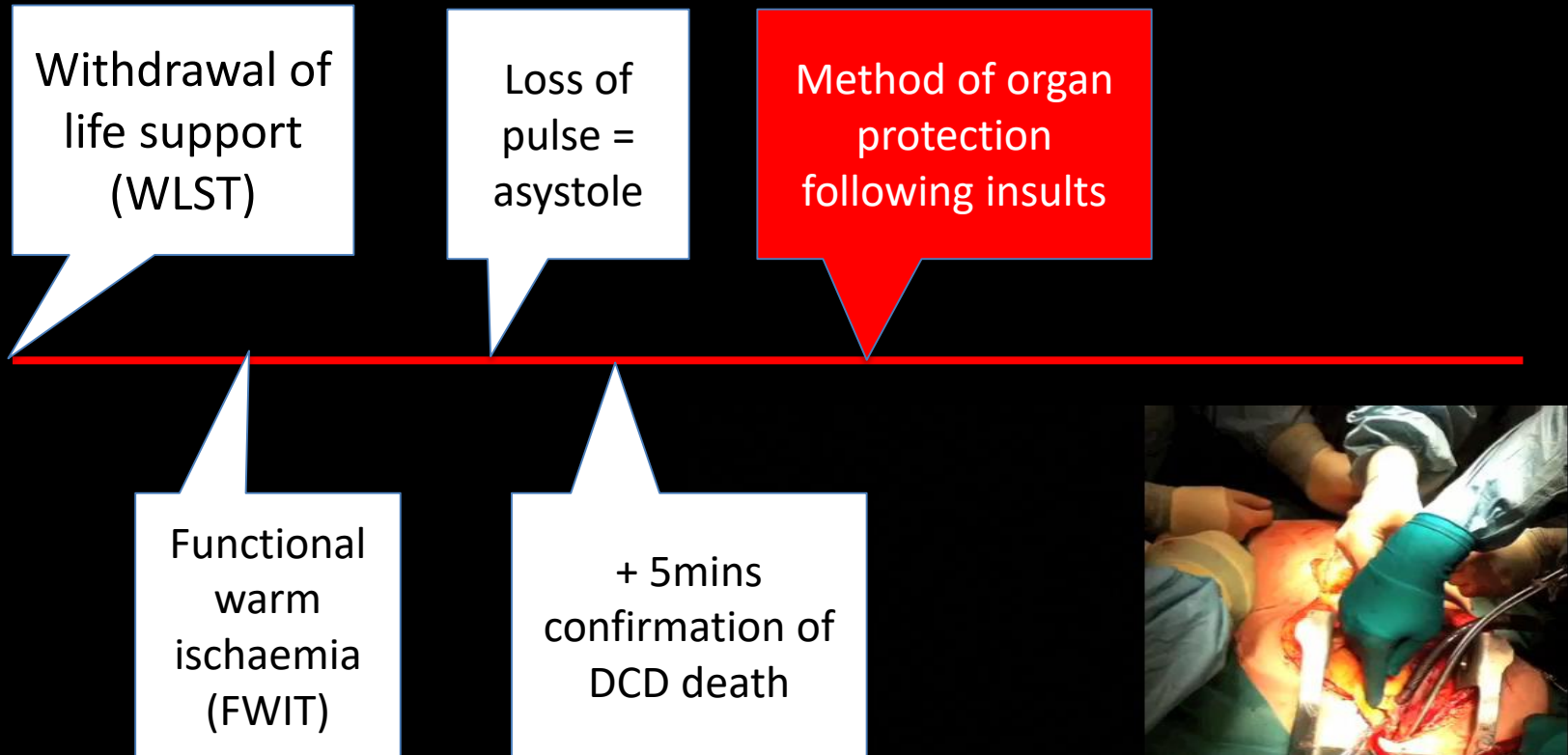
Timings following identification of futile treatment & consent for DCD organ donation:



Direct Procurement



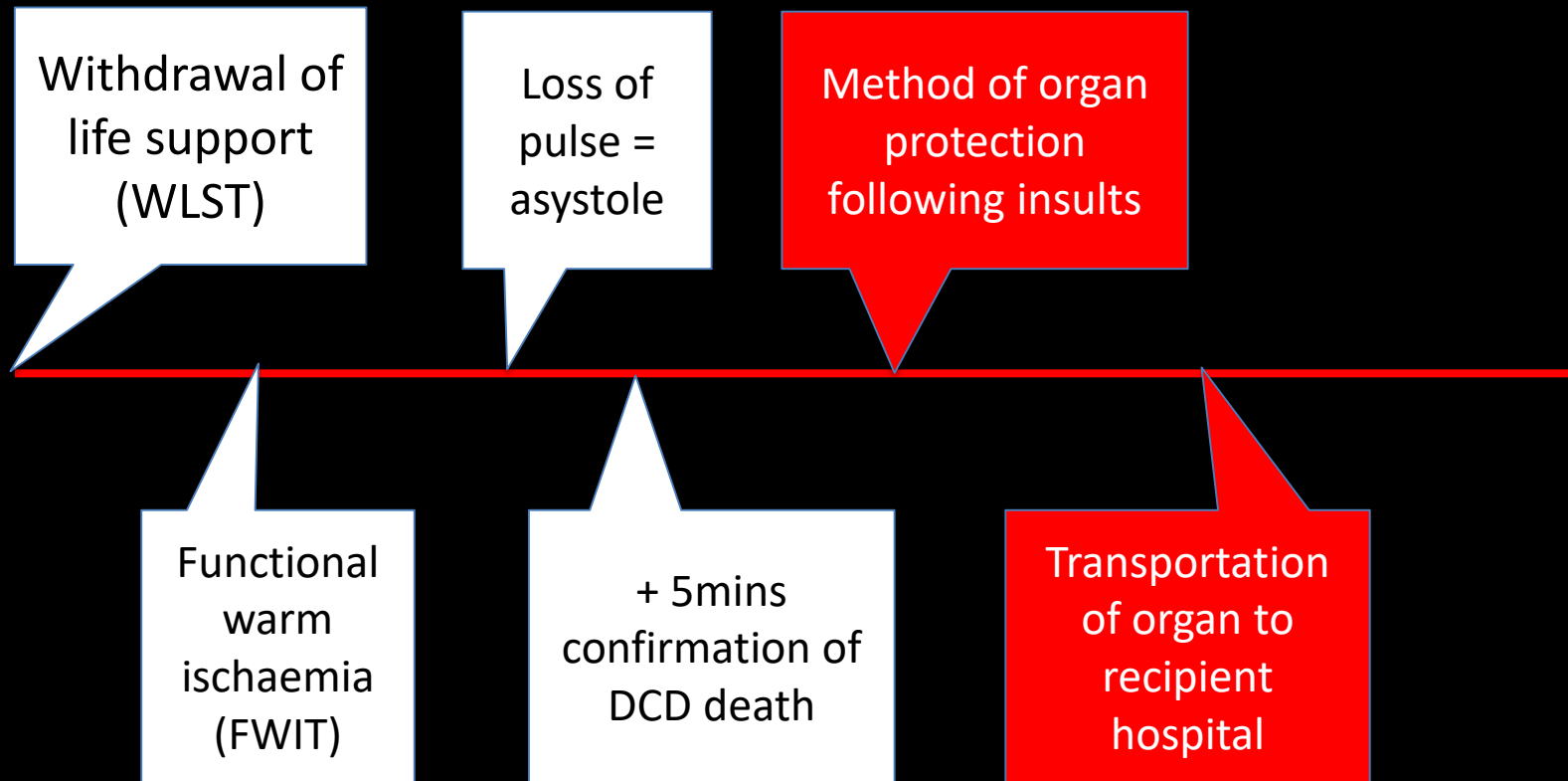
Timings following identification of futile treatment & consent for DCD organ donation:



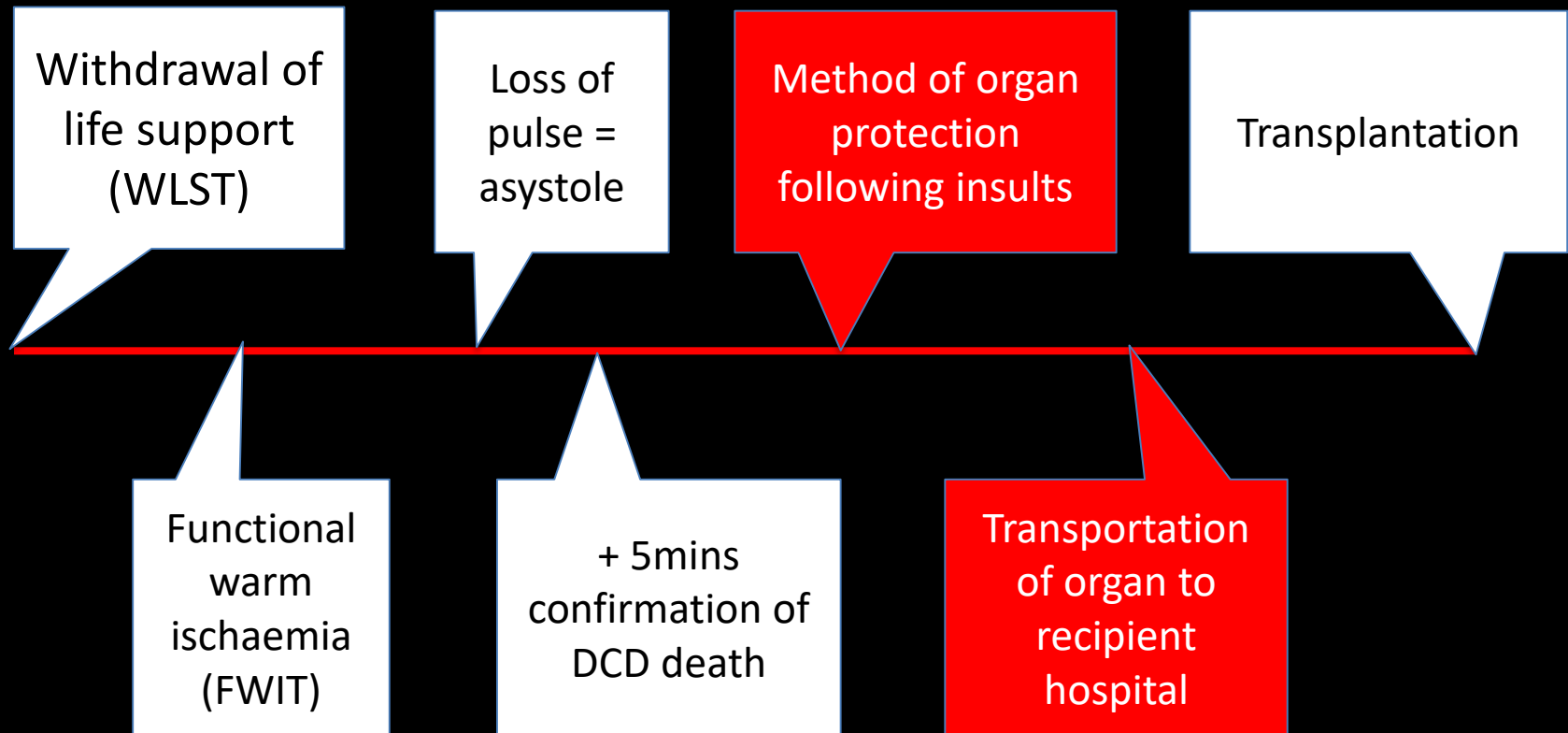
Normo-thermic Regional Perfusion (NRP)



Timings following identification of futile treatment & consent for DCD organ donation:



Timings following identification of futile treatment & consent for DCD organ donation:



Donor Demographics

	DCD n=75
Age Med(IQR)	36 (30-43)
Male n (%)	61 (82)
Height cm	175 (171-180)
NRP/DPP	23/52
OCS/CS	73/2
Cause of Death	
HBI n (%)	42%
ICH n (%)	22%
TBI n (%)	18%
Other n (%)	18%

Outcomes

	DCD n=75
Survival	
30 day survival n (%)	100%
90 Day survival n (%)	95%
1 year survival	89%
Mechanical Support	
IABP n (%)	20%
VA-ECMO n (%)	10%
VAD n (%)	4%

DBD v DCD survival

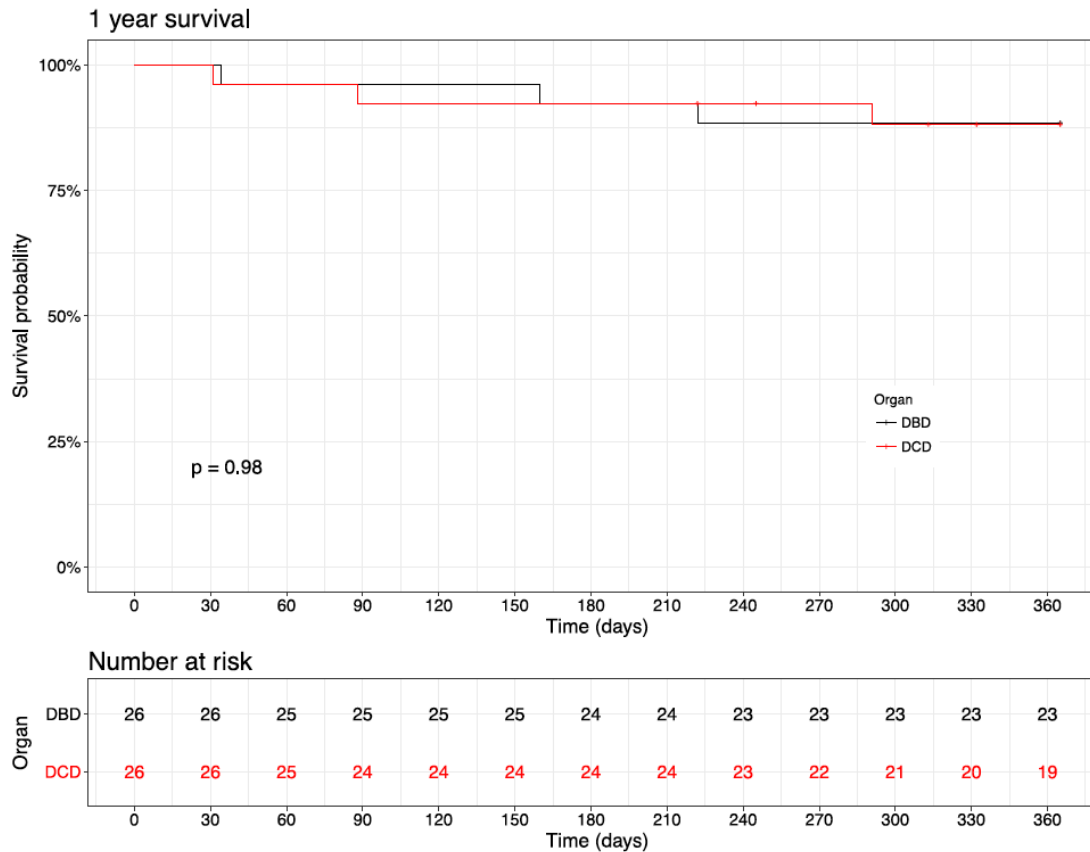


Figure 2 Kaplan-Meier survival of donation after circulatory-determined death (DCD) and donation after brain death (DBD) heart transplantation.

Ischaemic Timings NRP/DPP

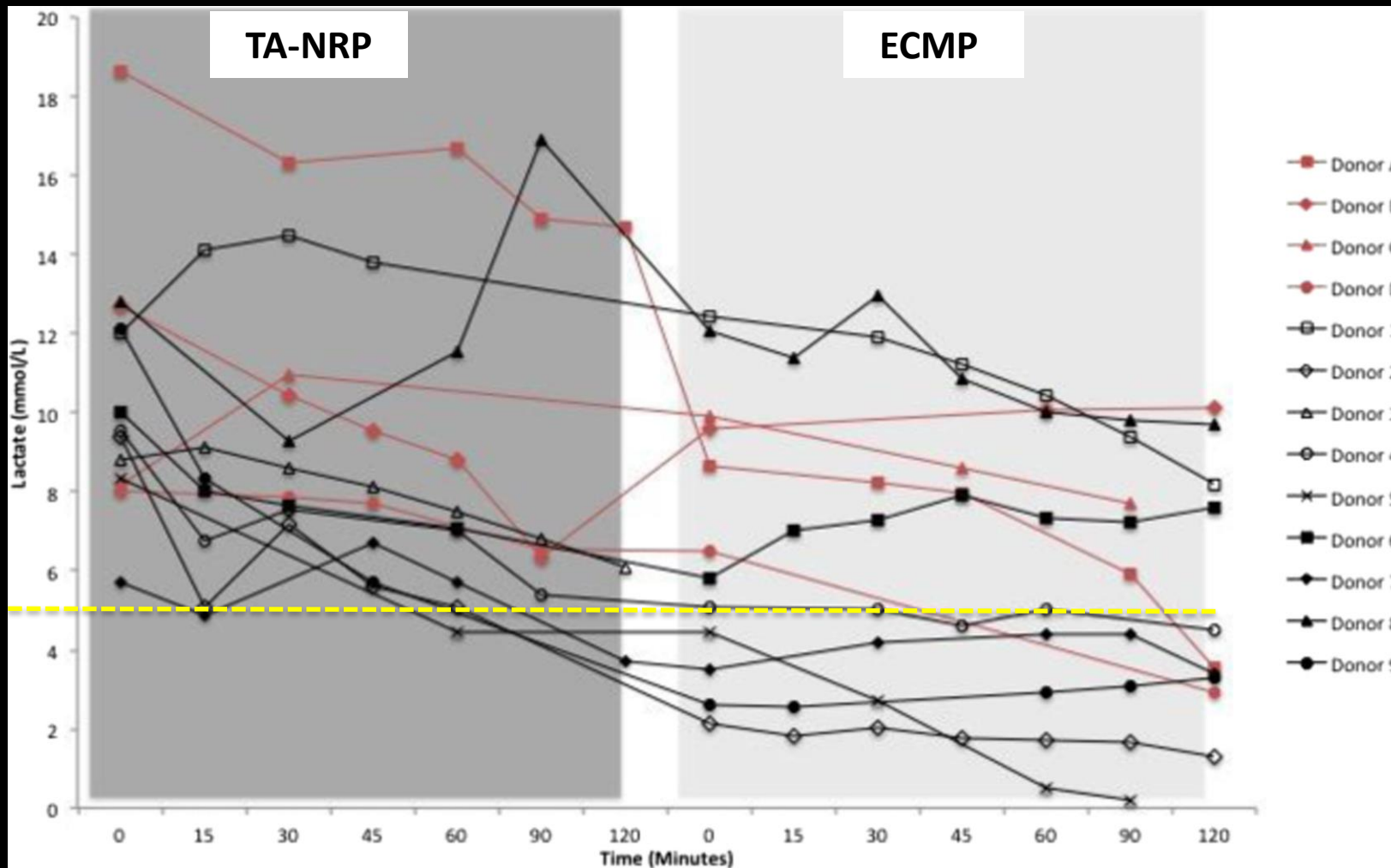
Time	NRP n=17	DPP n=27	P value
Withdrawal to death (mins) Med(IQR)	17 (13-21)	18 (14-25)	ns
Donation Withdrawal Ischaemic Time (mins)	24 (21-28)	36 (30-41)	0.005
Functional Warm Ischaemic Time (mins)	18 (16-22)	25 (23-30)	0.003
NRP Duration (mins)	39 (32-52)	-	-
OCS Perfusion Time (mins)	173 (140-186)	243(210-280)	0.003
Starting A lactate (mmol/L)	6.34 (3.49-6.83)	7.33 (6.39-9.25)	ns
Final A lactate (mmol/L)	4.25 (3.48-6.98)	5.5 (4.05-6.7)	ns
Implant Duration (mins)	32 (31-39)	42 (35-51)	0.03

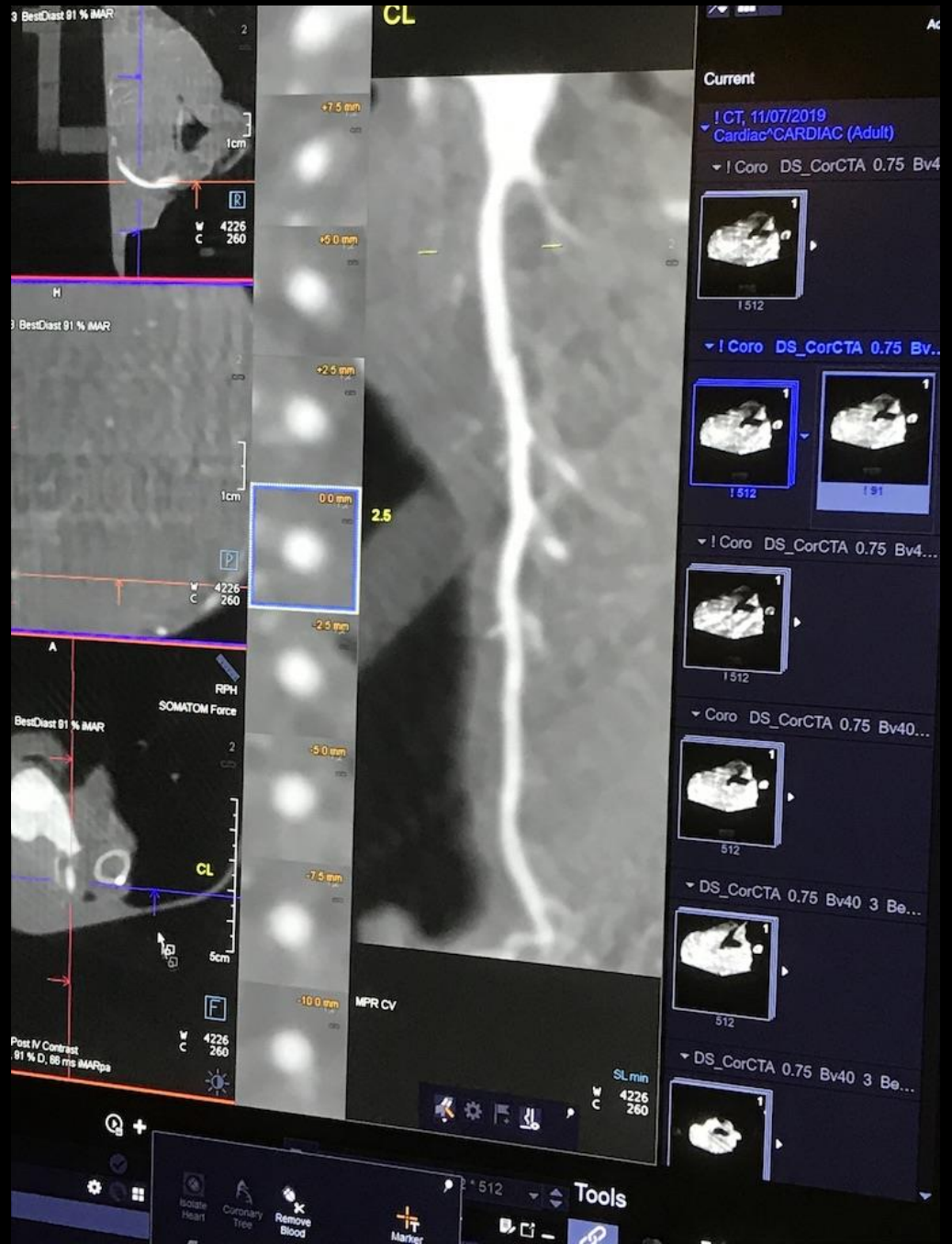
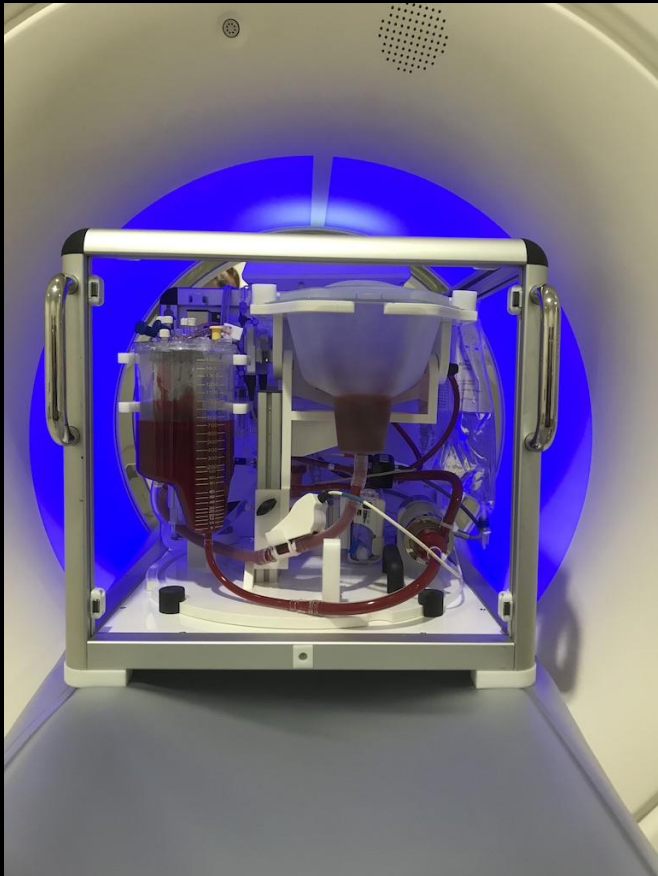
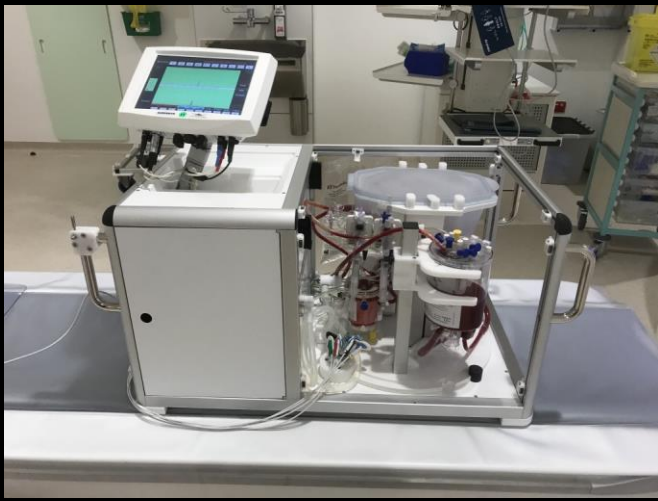
Issues with NRP/DPP

- Organ assessment

Serum lactate levels in the blood based perfusate of the DCD donor heart on donor NRP and OCS or ECMS (extra corporeal machine perfusion)

(Messer S 2016 by kind permission)





Issues with NRP/DPP

- Organ assessment
- Organ usage

Figure 3.3 Number of adult patients on the heart transplant list at 31 March each year for the last 10 years, by centre

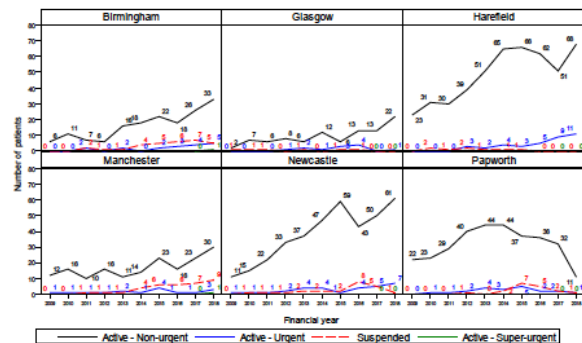


Figure 6.3 Risk-adjusted five year patient survival rates for adult heart transplants, by centre, 1 April 2009 to 31 March 2013

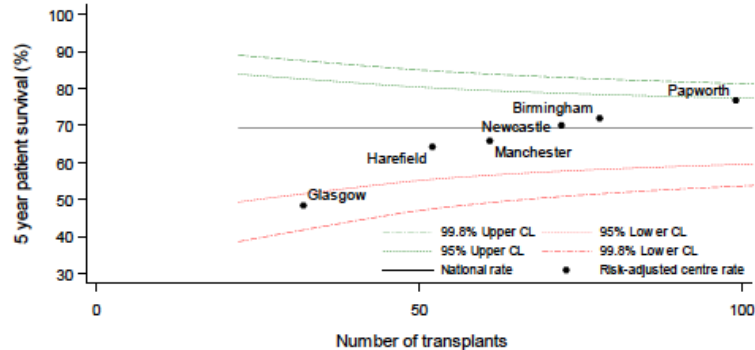


Figure 4.1 UK adult DBD donor heart offer decline rates by centre, 1 April 2015 to 31 March 2018

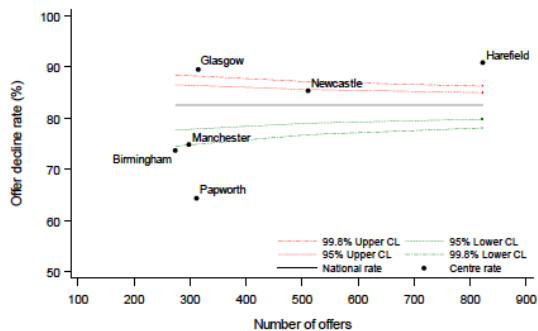
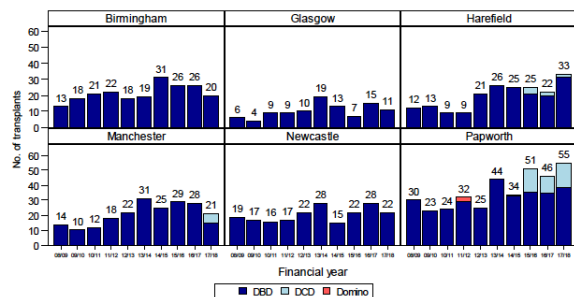


Figure 5.2 Number of adult heart transplants in the UK, by financial year, centre and donor type, 1 April 2008 to 31 March 2018



DCD Clinical Program

Early Outcomes after Heart Transplantation from DCD donors

- Set up February 2015
- Early Outcomes
 - Comparable allograft function, hospital stay, treated rejection episodes.
 - 90 day survival DCD 92% DBD 96% (p= 1.0)

	DCD (n=26)	DBD (n=26)	p value
<i>Cardiac output L/min</i>	4.9 (4.0-5.2)	3.9 (3.2-4.4)	0.006
<i>Cardiac index L/min/m²</i>	2.5 (2.1-2.7)	2.0 (1.8-2.4)	0.04
<i>Ejection fraction %</i>	63 (58-63)	63 (62-63)	1.00
<i>Length of stay, days</i>	20 (17-28)	27 (21-34)	0.09
<i>Treated rejection</i>	9 (35)	15 (58)	0.15
<i>90 day survival %</i>	92 (24)	96 (25)	1.00

Messer S et al (Dec 2017). Outcome after heart transplantation from donation after circulatory-determined death donors. J Heart Lung Transplant. 36 (3), 1311-1318.

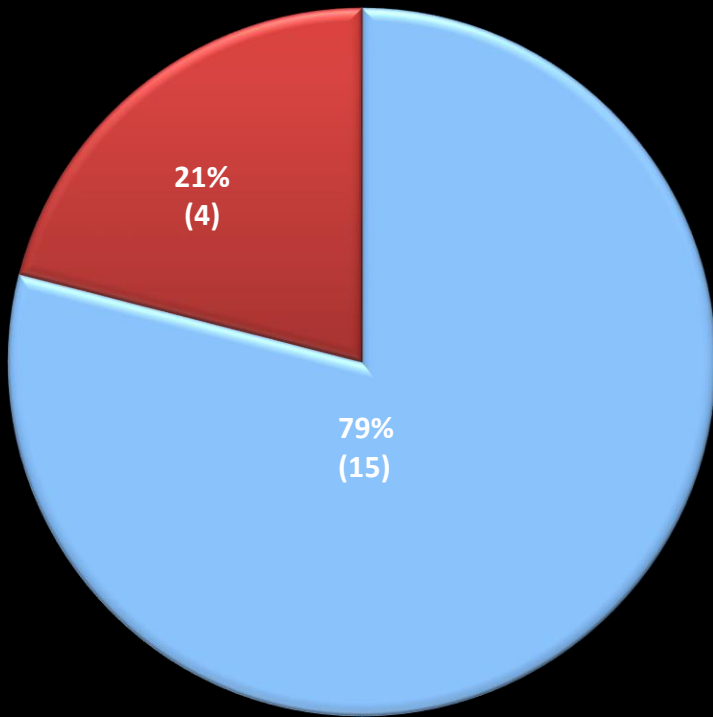
Renal Function at One Year

No patients on renal replacement therapy

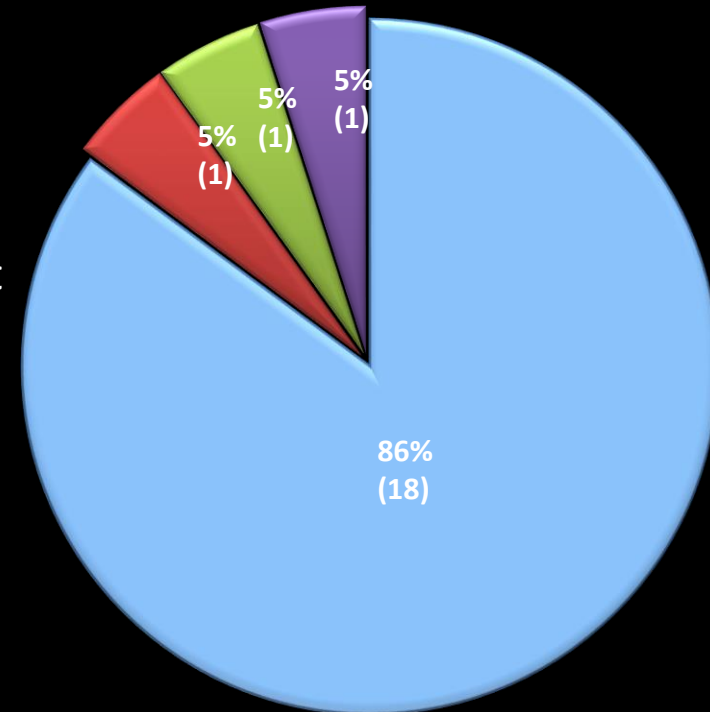
eGFR (mL/min/1.73m²)	DCD	DBD	P value
>60	53%	58%	0.59
30-60	47%	38%	
<30	0%	14%	

Cardiac Performance. Echocardiography

DCD



DBD



- Normal EF (>55%)
- Mild impairment (EF 45-54%)
- Moderate impairment (EF 36-44%)
- Severe impairment (EF <35%)

p value= 0.2

Issues with NRP/DPP

- Organ assessment
- Organ usage
- Does NRP upset other organ procurement?

Other solid organ usage with DCD heart Tx:

Organ	Donor organ utilisation	
	<i>National DCD donors (excluding heart donors)</i>	<i><u>Papworth DCD heart donors</u></i>
Heart	N/A	83 %
Lung	7 %	15 %
Kidney	84 %	78 %
Liver	36 %	47 %
Pancreas	22 %	26 %

Normothermic Regional Perfusion of Donors Following Circulatory Death Improves Outcomes in Liver Transplantation.

E. Mowlem,¹ L. Randle,² C. Fear,¹ K. Crick,¹ S. Messer,⁴ S. Large,⁴ A. Butler,³ C. Watson.³

¹Cambridge Transplant Unit, Addenbrookes Hospital, Cambridge, United Kingdom

²OrganOx Ltd, Oxford, United Kingdom

³Dept of Surgery, University of Cambridge, Cambridge, United Kingdom

⁴Papworth Hospital, Cambridge, United Kingdom

Meeting: 2017 American Transplant Congress

	NRP livers (n=20)	non-NRP livers (n=40)
1y actuarial graft survival (censored for death)	100%	87%
1 year actuarial patient survival	93%	94%
1y actuarial graft survival (not death censored)	93%	81%
Peak ALT (iu/L) in week one (median (IQR))	480 (349-1016)	840 (437-1443)
Biliary anastomotic leaks	6% (n=17)	5%
Biliary anastomotic strictures	12% (n=17)	5%
Ischaemic cholangiopathy	0 (n=17)	15%

Issues with NRP/DPP

- Organ assessment
- Organ usage
- Does NRP upset other organ procurement?
- Concerns about intra-cranial blood flow

Concerns about intra-cranial blood flow

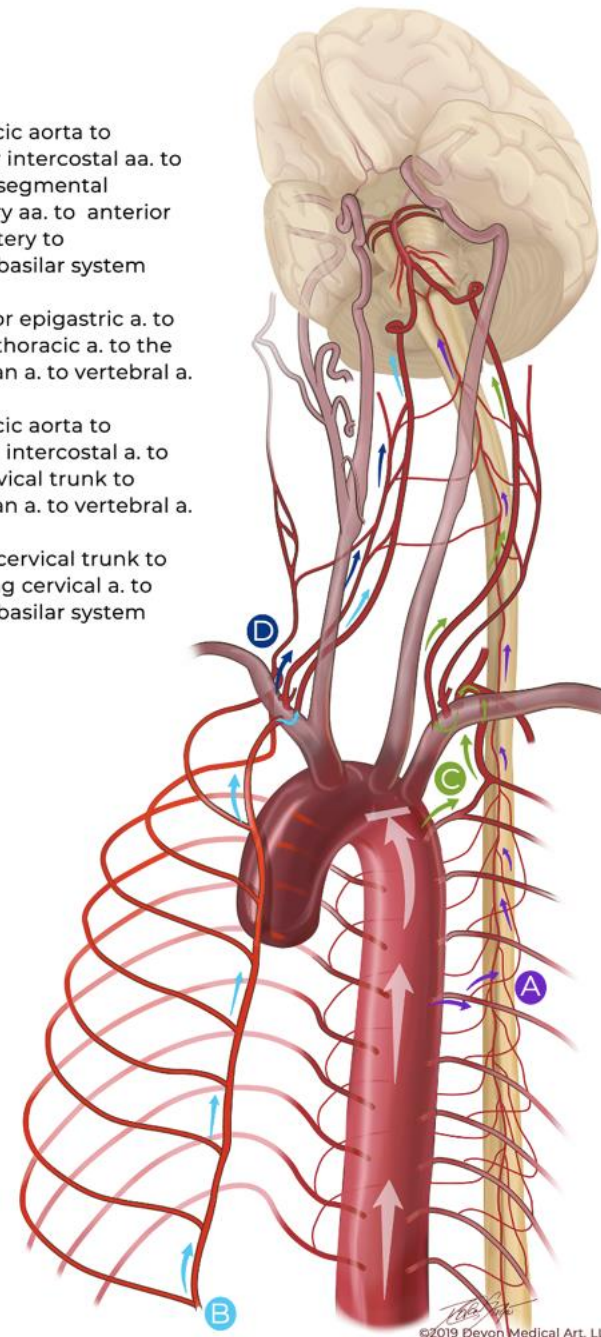
- Canadian DCD summit 2018
- What risk: intra-cranial blood flow?

A thoracic aorta to posterior intercostal aa. to anterior segmental medullary aa. to anterior spinal artery to vertebrobasilar system

B inferior epigastric a. to internal thoracic a. to the subclavian a. to vertebral a.

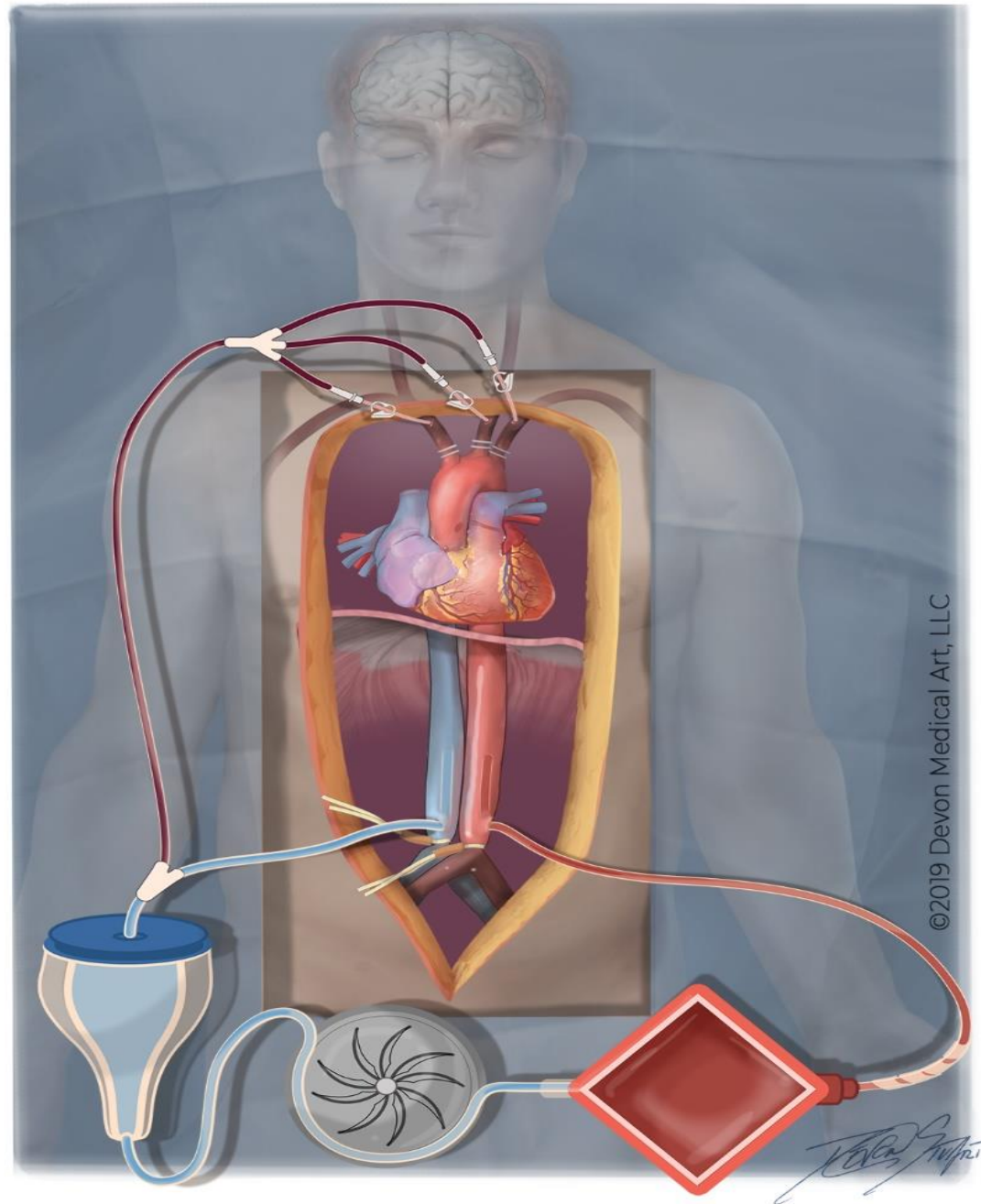
C thoracic aorta to supreme intercostal a. to costocervical trunk to subclavian a. to vertebral a.

D thyrocervical trunk to ascending cervical a. to vertebrobasilar system



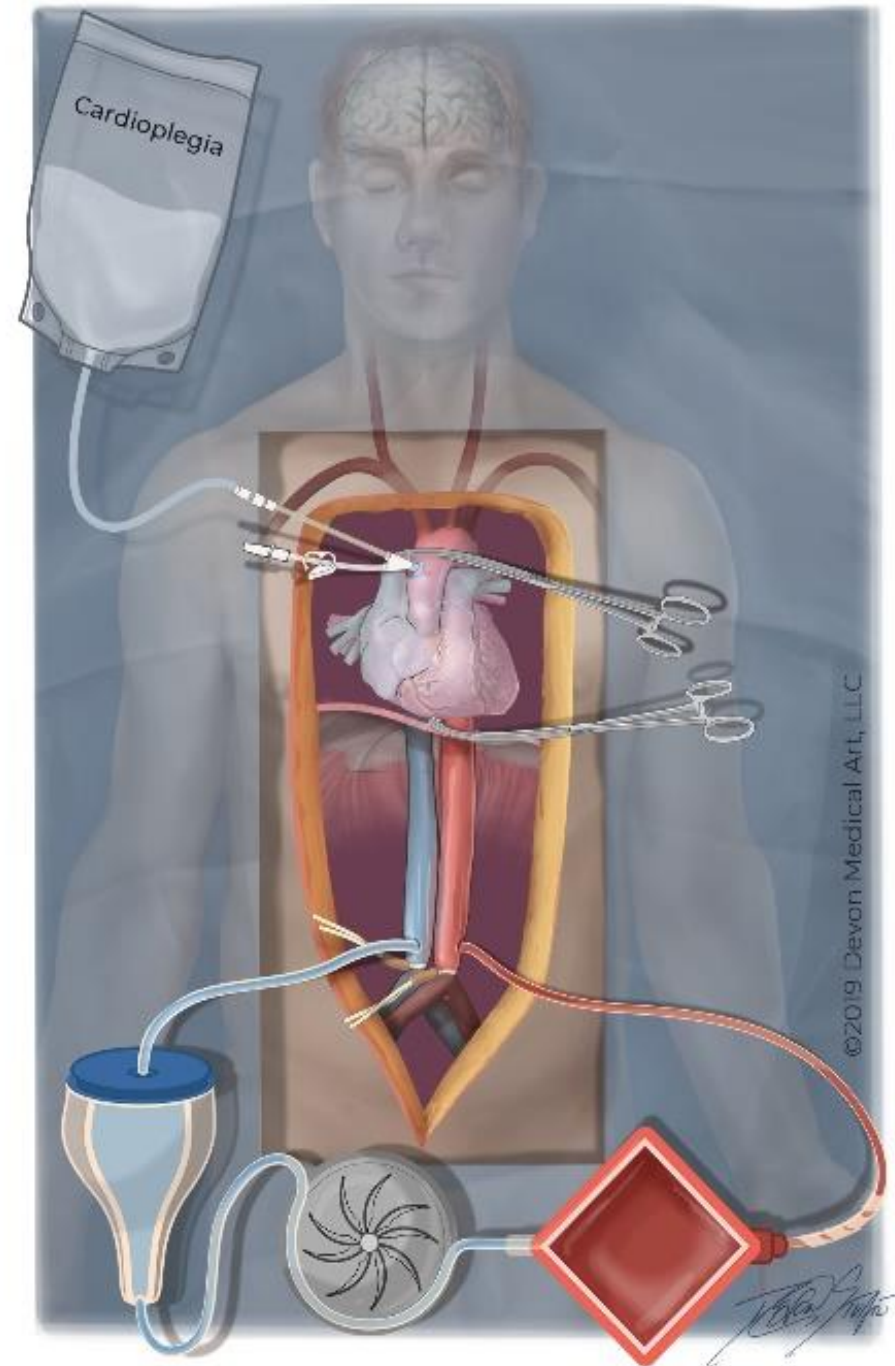
Concerns about intra-cranial blood flow

- Ligation of arch vessels
- and drainage of blood within arch vessels
- but concerns over ischaemic insult



Concerns about intra-cranial blood flow

- Ligation of arch vessels
- and drainage of blood within arch vessels
- but concerns over ischaemic insult
- Leading to the speediest solution: *Messer technique*



8 take home points

1. NRP probably offers earliest replenishment of energy stores within all organs

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2. a chance to assess cardiac function after death.

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3. a chance to review the heart in terms of coronary disease and

8 take home points

1. NRP probably offers earliest replenishment of energy stores within all organs,
2. a chance to assess cardiac function after death.
3. a chance to review the heart in terms of coronary disease and
4. a chance to assess the donor to exclude malignancy

8 take home points

5. We believe that the size of this new donor group may be as high as 100 patients/year for our 65million population (1.54donors pmp. which has the potential to raise our transplant activity by 50%).

8 take home points

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6. A chance to transport with cold storage as the Barnard brothers did in 1967.

8 take home points

5. We believe that the size of this new donor group may be as high as 100 patients/year for our 65million population (1.54donors pmp. which has the potential to raise our transplant activity by 50%).
6. A chance to transport with cold storage as the Barnard brothers did in 1967.
7. Heart donation from individuals dying of circulatory determined death (DCD) has led to heart transplantation in some 120pts world-wide 75 of which procured by by RPH 29% using NRP and 74 Tx by RPH (2 as nrp-cold storage and 1 as a DCD heart & lung Tx).

8+ take home points

8. DCD heart transplantation has delivered the same early and midterm outcomes as heart transplantation from heart donors after brain death

8+ take home points

8. DCD heart transplantation has delivered the same early and midterm outcomes as heart transplantation from heart donors after brain death
9. although NRP has 100% survival of recipients
 - i. We believe that the size of this new donor group may be as high as 100 patients/year for our 65million population (extra **1.54donors pmp**. So far 75 lives saved at RPH since 2015 = **16 lives/yr**
 - ii. which has the potential to raise our transplant activity by 40%)....with a technique now has international acceptance.

8+ take home points

10. I believe we can support a heart for an extended period (72hrs) opening opportunity for “repair in perfusion” on ex-situ perfusion:

- i. An increased use of DBD hearts perhaps:
through recovery of function
- ii. Through “pumping to perfection” organ banking on ex-situ machines



just may be?

"Picked one you like yet?"