

Improving transplant outcomes:

The use of new technologies

Colin Wilson

20:20 Vision

The Future of Transfusion

Wednesday 13th October 2021

Introduction

- Organ perfusion
 - Defatting livers, repairing bile ducts
 - Identifying organs for transplant (6 gene signature)
- Artificial Intelligence
- Novel communication tools
- Advanced therapeutics
- Novel blood substitutes

- (Stem cells)

Organs are not being transplanted

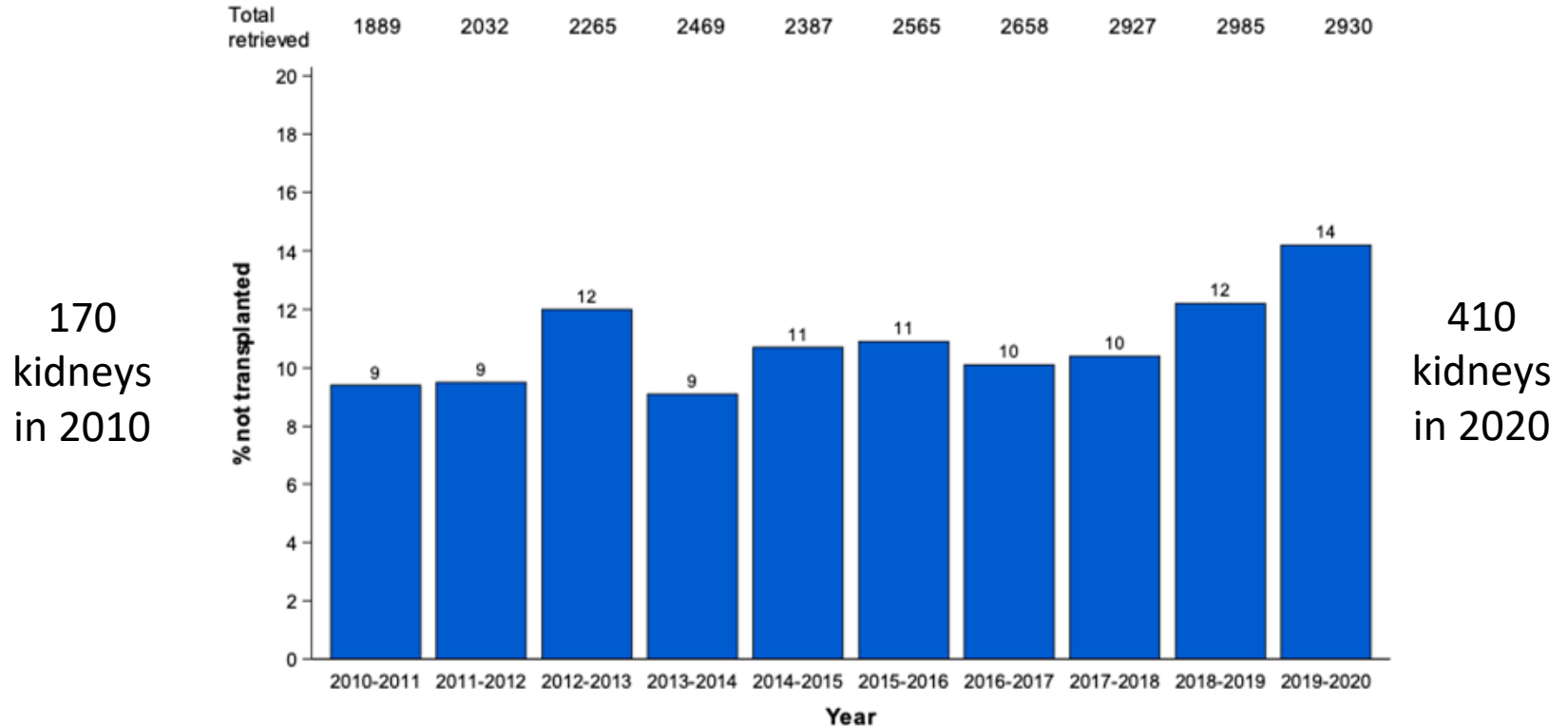
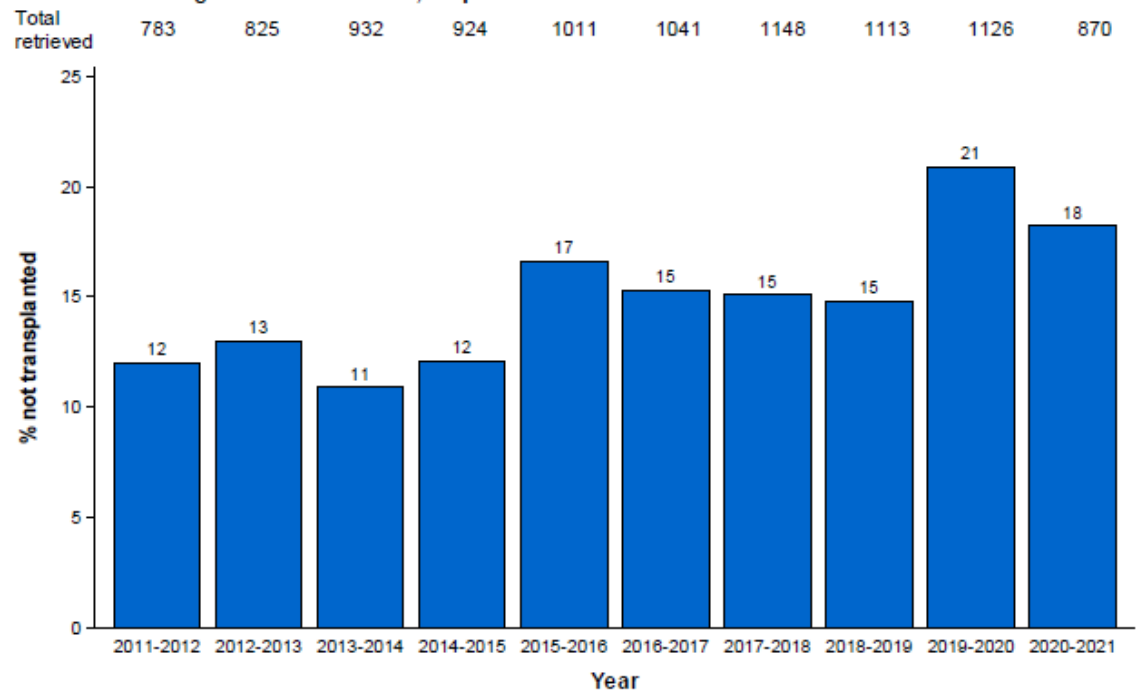


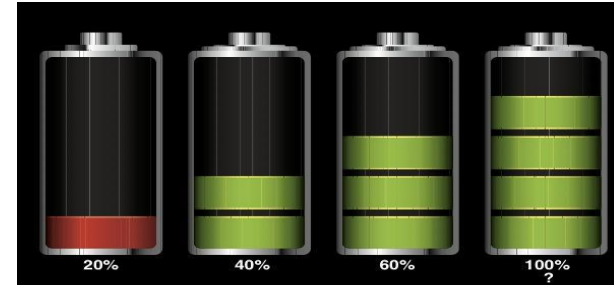
Figure 4.4 Percentage of livers retrieved that were not transplanted from deceased organ donors in the UK, 1 April 2011 - 31 March 2021



Normothermic perfusion (EVNP)



- Red cells
- Nutrients
- Oxygen



Ex vivo normothermic perfusion (EVNP) of deceased donor kidneys – current studies

Colin Wilson, Chris Callaghan, Gabi Oniscu,
Sarah Hosgood, Mike Nicholson

KRUK-funded studies (1)

- RCT comparing EVNP with standard treatment (SCS) in DCD kidney transplantation (ISRCTN 15821205)
 - Open label
 - 4 sites (Cambridge, Guy's, Newcastle, Edinburgh)
 - Aim: determine if EVNP improves initial graft function in DCD kidney transplantation
 - Primary outcome: DGF (any dialysis in first week)
 - Secondary outcomes: PNF, DGF duration, fDGF, LOS, BPAR, 12m eGFR, PS, DCGS

KRUK-funded studies (1)

- RCT comparing EVNP with standard treatment (SCS) in DCD kidney transplantation (ISRCTN 15821205)
 - Duration of follow-up: one and 5 years
 - Sample size: 400 patients (30% relative reduction in DGF, from 50% to 35%, with a power of 80% and significance of 0.05)
 - Interim analyses (ITT) at 125 patients enrolled (7 days), and 250 patients enrolled (7 days)
 - Recruitment terminated at 306- Covid awaiting results

KRUK-funded studies (2)

- Quality Assessment Study (QAS)
 - Open label, non-randomised
 - 3 sites (Cambridge, Newcastle, Guy's)
 - Aim: to increase the number of kidneys for transplantation by using EVNP to assess quality of organs declined by other centres that would otherwise have been discarded

KRUK-funded studies (2)

- Quality Assessment Study (QAS)
 - Scoring system

Table 1 *Ex vivo* normothermic perfusion assessment score

	Score
Macroscopic assessment	
Grade I: excellent perfusion (global pink appearance)	1
Grade II: moderate perfusion (patchy appearance)	2
Grade III: poor perfusion (global mottled and purple/black appearance)	3
Renal blood flow (ml per min per 100 g)	
Threshold \geq 50	0
Threshold $<$ 50	1
Total urine output	
Threshold \geq 43	0
Threshold $<$ 43	1

1 – Best
5 – Worst

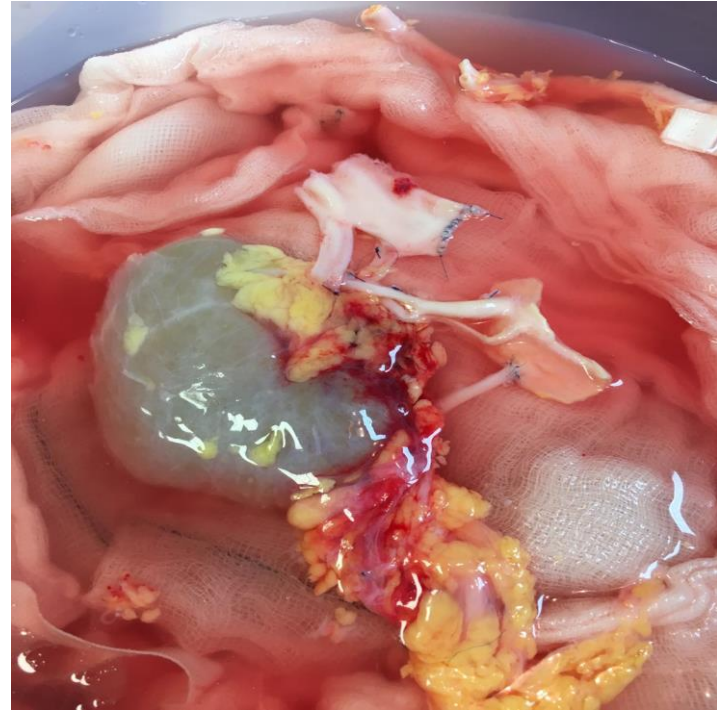
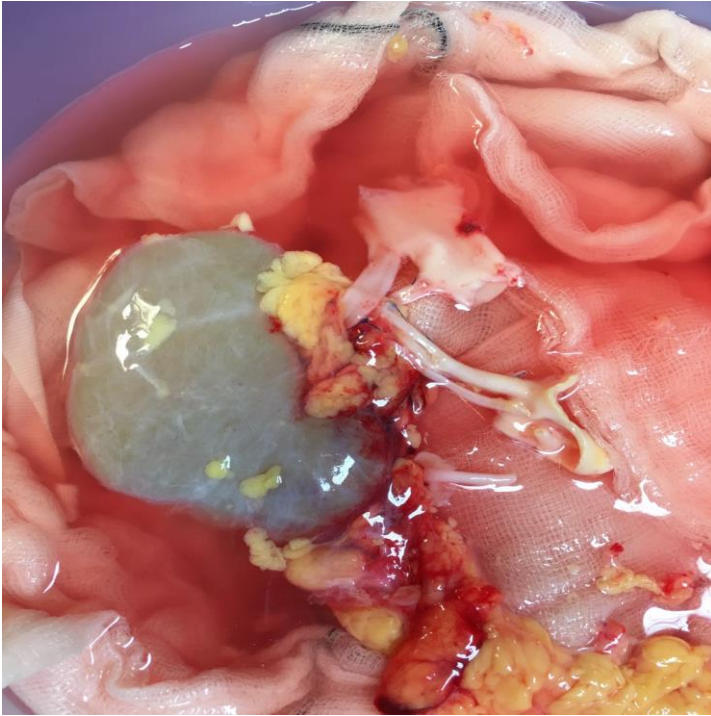
KRUK-funded studies (2)

- Quality Assessment Study (QAS)
 - Open label, non-randomised
 - 3 sites (Cambridge, Newcastle, Guy's)
 - Aim: to increase the number of kidneys for transplantation by using EVNP to assess quality of organs declined by other centres that would otherwise have been discarded
 - Outcome measures: PNF, DGF, DGF duration, fDGF, LOS, BPAR, 12m eGFR, PS, DCGS, quality of life, pump parameters
 - Duration of follow-up: one year

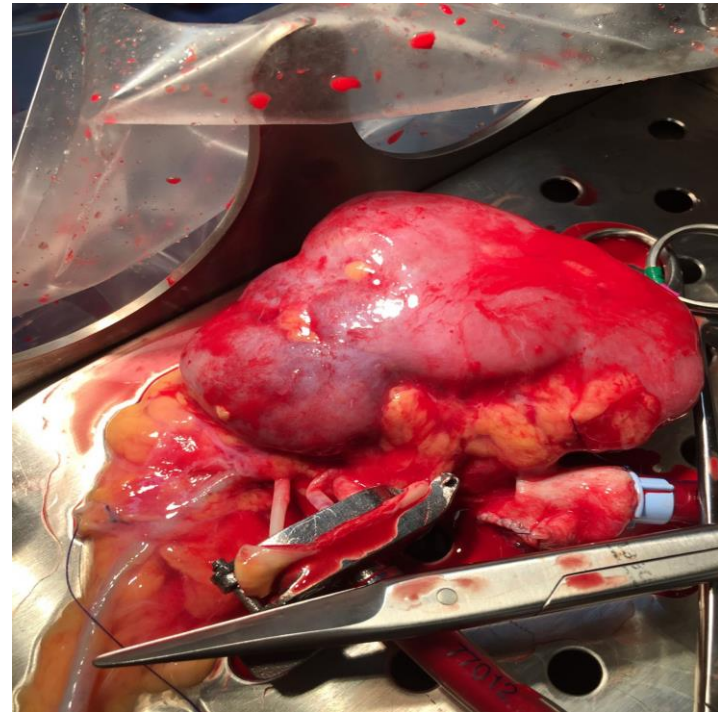
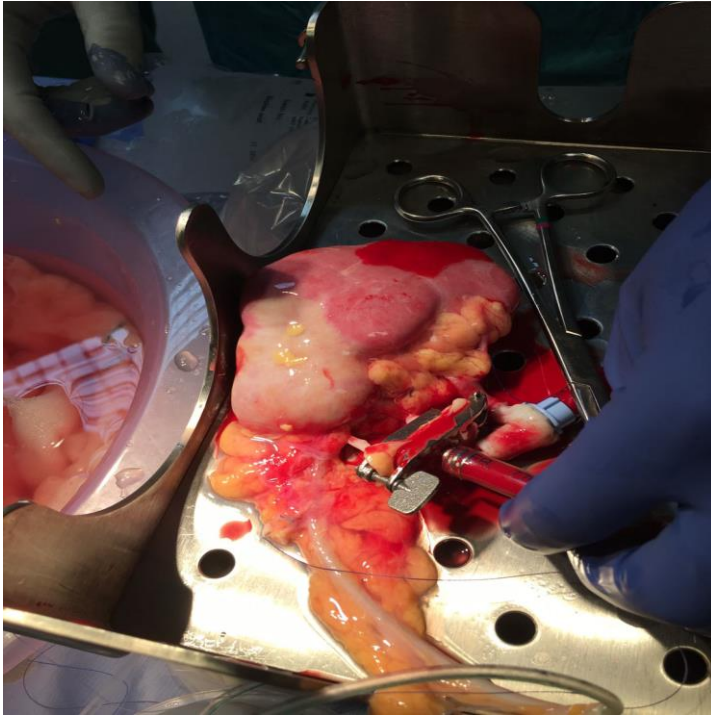
KRUK-funded studies (2)

- Quality Assessment Study (QAS)
 - Pathway
 - >100 kidneys offered
 - 14 kidneys perfused with EVNP

Quality assessment



Lower pole artery injury



NIHR

Blood and Transplant Research Unit
in Organ Donation and Transplantation
at Cambridge and Newcastle Universities

Quality Assessment Study

10 DCD kidneys Declined for Transplantation

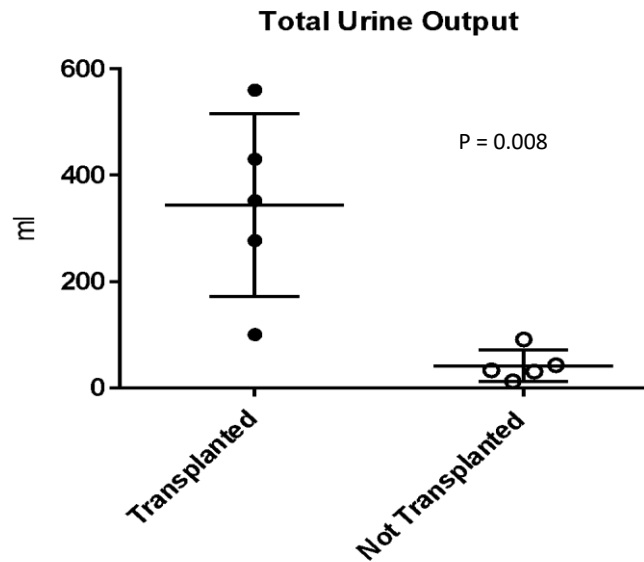
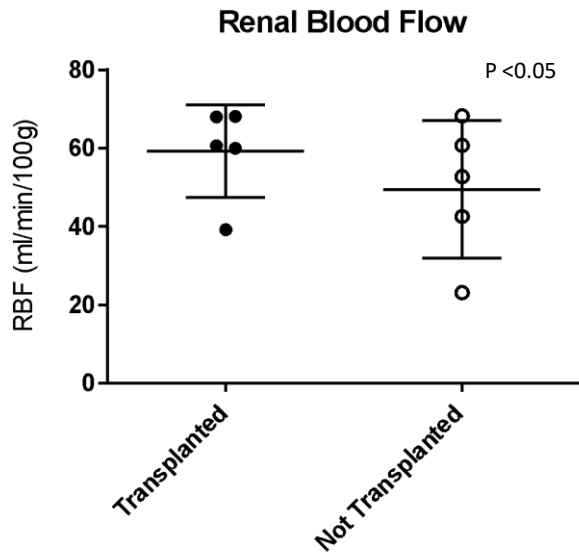
Recruited Kidneys

	Donor Age (y)	Reason for Decline	Cold Ischaemia (h. min)
QAS 01	35	Poor in-situ flush	17.24
QAS 02	35	Poor in-situ flush	19.44
QAS 05	53	Poor in-situ flush + stripped ureter	18.55
QAS 08	51	Poor in-situ flush	7.49
QAS 09	51	Poor in-situ flush	9.27
QAS 03	75	Poor in-situ flush	14.04
QAS 04	36	Poor in-situ flush	15.27
QAS 06	78	Older donor	12.30
QAS 07	78	Older donor	14.27
QAS 10	60	Poor in-situ flush	17.14

Non Transplanted Kidneys

Unused kidneys	QAS Score	Declined
QAS 03	3	Logistics – prolonged CI after NP
QAS 04	3	Poor function/integrity of microcirculation
QAS 06	1	High Remuzzi score (chronic injury)
QAS 07	4	QAS score and high Remuzzi score
QAS 10	4	QAS score

Perfusion Parameters



Organ Quality Assessment (OrQA)

1. Capture images of donor organ, combine with clinical data and store the information in a secure database that can be accessed via the internet

2. Provide rapid, point-of-use assessment of donor organ quality based upon image analysis of the organ's macroscopic appearance. Simple and intuitive stand-alone system that can be used by SNOD without the need for any other equipment. Aims to provide a numerical score that mimics expert clinical judgement and which can be rapidly communicated within NHS-BT. Information synced to database when convenient

3. AI/ machine learning. Longer term (but potentially more powerful) system for predicting transplant outcomes based upon analysis of the database

Capture & sync
Images

Calibrate Images

Analyse Image &
colour space

Provide quantitative
score

1

UNIVERSITY of BRADFORD
Blood and Transplant NHS

Donor organ quality assay

Create New Assay

View Unsent Assays

Log Out

Version: 1.0.6

2

Log in and record
image assay data
using iPad App

Exit Help

ODT donor number * Organ type *

Year of birth * Gender *

Hospital *

Transplantable * Donor * Texture

Perfusion Quality Arterial O2 on inhaled FIO2

Next

- The app is fully secure, only registered users can log in and access. After log-in the user can start a new image assay or manage previous ones, allowing you to work wholly offline and then sync with the central server later.

ORQA – Current functionality

iPad

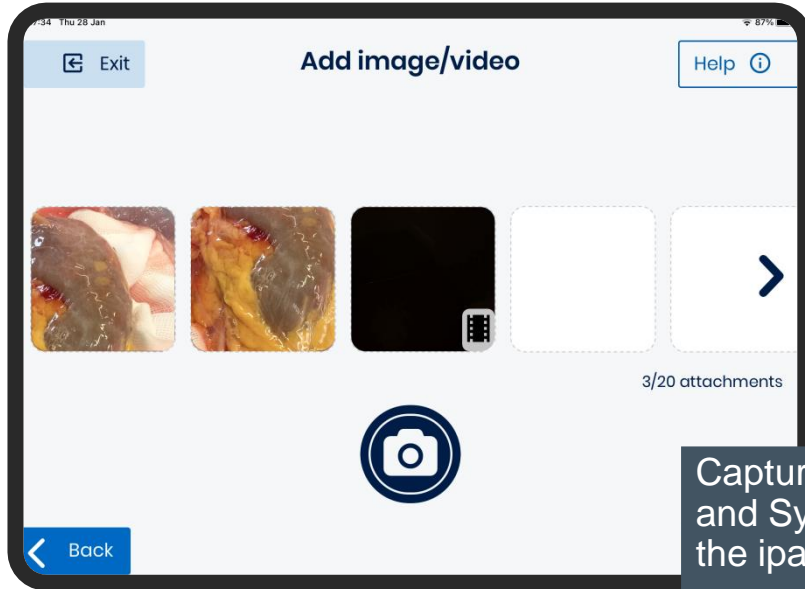
Capture & sync
Images

▶ Calibrate Images

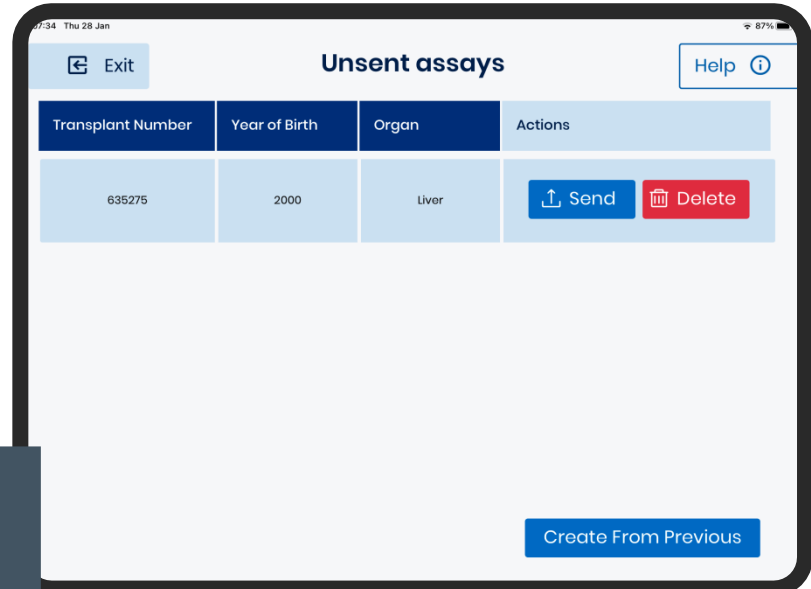
Analyse Image &
colour space

▶ Provide qualitative
score

3



4



Capture images
and Sync using
the iPad APP

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Blood and Transplant Research Unit
in Organ Donation and Transplantation
at Cambridge and Newcastle Universities

ORQA – Current functionality

Capture & Sync
Images

▶ Calibrate Images

▶ Analyse Image &
colour space

▶ Provide qualitative
score

5

6

Central
management
of assay via
Web browser

ORQA Hello, Nigel

List of assays

Filter Results:

Hospital: Please select Organ type: Please select Filter assays Clear Filter

User	Hospital	Organ type	Date	Actions
Bradford Admin User	Test hospital 1	Liver	12/18/2020	View
Bradford Admin User	Test hospital 1	Liver	12/14/2020	View
Bradford Admin User	Test hospital 1	Kidney	12/18/2020	View
Bradford Admin User	Test hospital 1	Liver	12/18/2020	View
Bradford Admin User	Test hospital 1	Liver	12/14/2020	View

Showing 1 - 5 of 27 results

Previous 1 2 3 4 5 6 Next

ORQA Hello, Nigel

Assay detail screen

Date of assay: 28/2021 Donor year of birth: 2000

Donor gender: male SNOD name: Nigel Green

Hospital: Test hospital 1 Organ type: Liver

ODT Number: 635275 Transplantable: Yes

Donor: DBD Texture: good

Perfusion Quality: fair Arterial O2 on inhaled FIO2:

Images:

Comments

Add Comment

On 29/1/2021 at 13:32:31 Nigel Green commented

All comments are timestamped and show the user who posted it.

On 29/1/2021 at 13:28:5 Nigel Green commented

These are free text so can contain any data - maybe commenting on the photos of the organ.

On 29/1/2021 at 13:27:35 Nigel Green commented

Users can add comments here to add additional data to the assay.

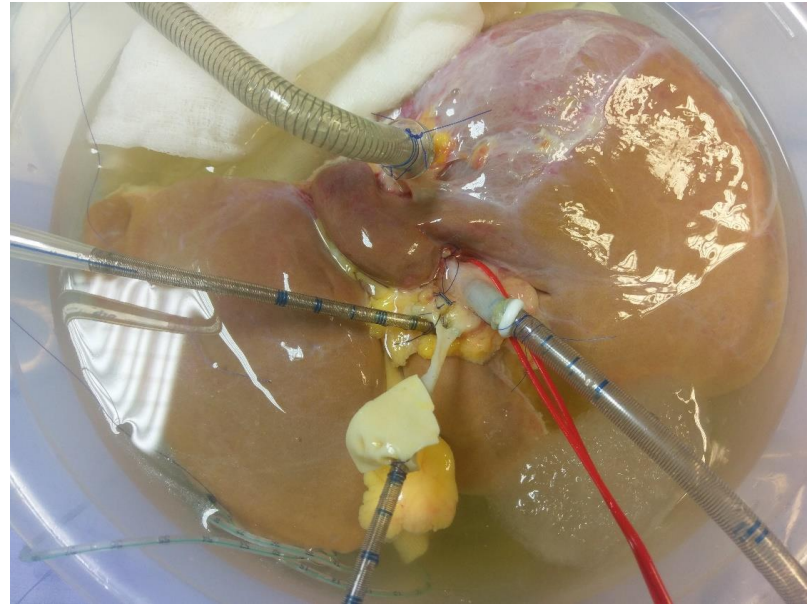
VIABILITY ASSESSMENT DURING D-HOPE

LIVER PERFUSION



Royal College
of Surgeons

ADVANCING SURGICAL CARE

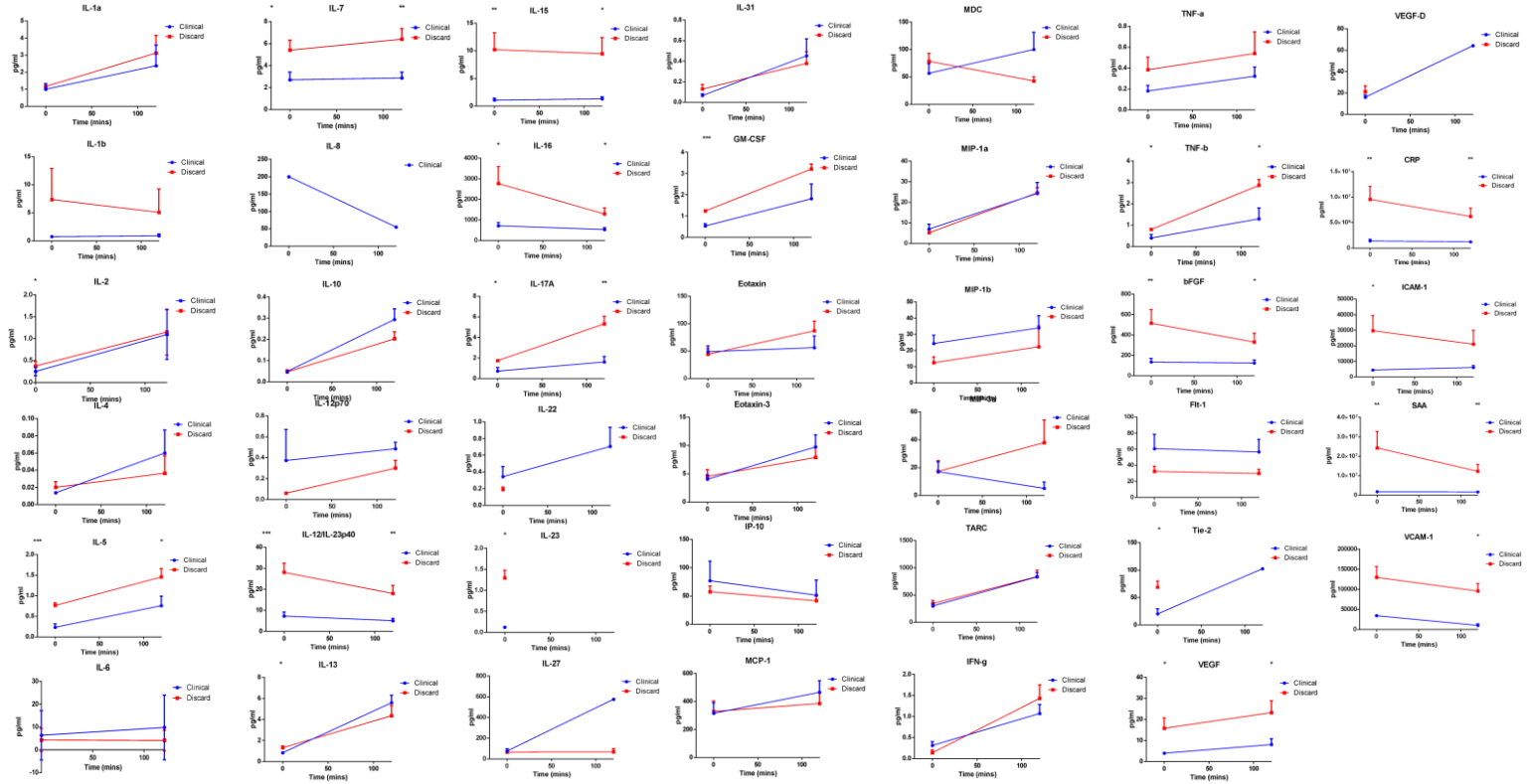


NIHR

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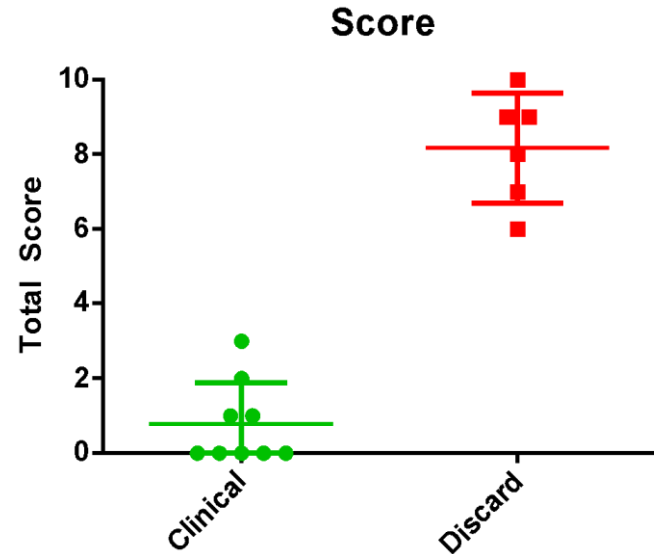
How to discriminate ?

- Took samples from 9 excellent livers and 9 very bad livers
- Microarray to separate out all the proteins at different time points



Combined Scoring System

- All discard livers ≥ 6
- All clinical livers ≤ 3
 - 6 proteins at 20 minutes perfusion
- $p < 0.0001$



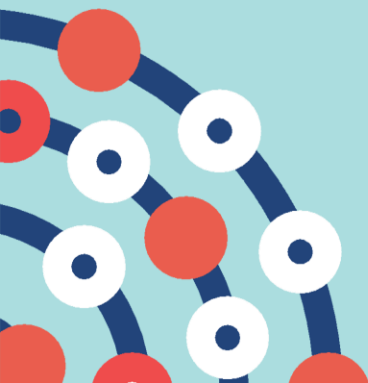
Possibilities

- Now patented
 - Psyros/ Bridge to Life collaboration
- Move into other organs/ warm temperatures
 - Thanks to Chris Watson, Philip Dutkowski
- Personalised transplantation
 - Target certain organs for certain recipients
 - HCC



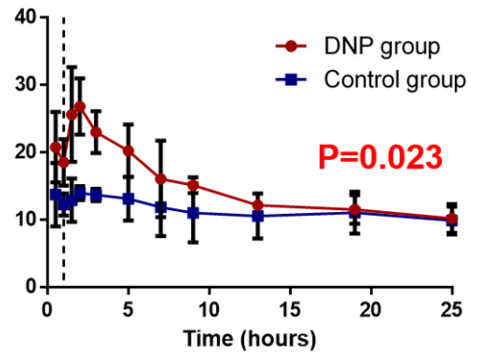
Sam Tingle

Academic Clinical Fellow in Transplantation
Newcastle upon Tyne

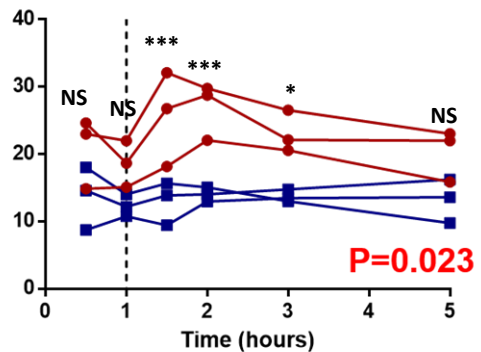


2,4-Dinitrophenol for steatotic human livers; pharmacological considerations for NMP therapeutics

Oxygen consumption per kg (ml/min/kg)



Oxygen consumption per kg (ml/min/kg)

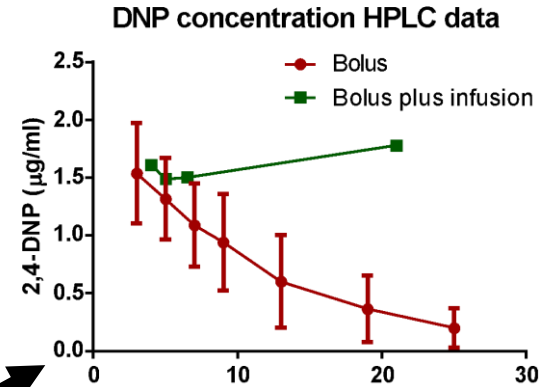


2,4-Dinitrophenol for steatotic human livers



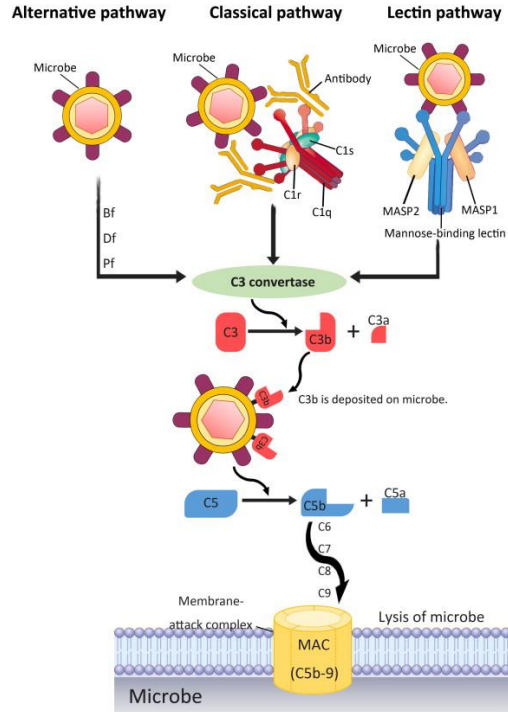
DNP displays one-phase decay when delivered during NMP:

- **Half Life = 7.703 hours** (95% CI = 5.076-15.97)
- **Exponential Decay Constant = 0.08999/hr** (0.0434 - 0.1366)
- 15mg/kg bolus, an infusion at 1.35 mg/kg/hour should maintain steady perfusate DNP concentration



- Experiments on discard livers
- Levels of complement component in machine perfused livers - comparing DCD with DBD livers
- Deposition of complement within the tissue architecture

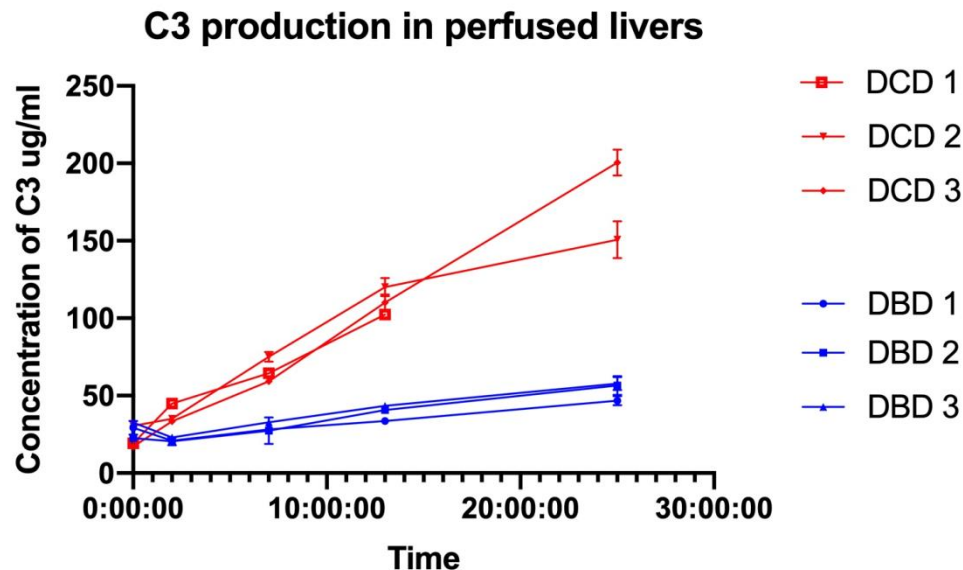
Complement system



- Proteins made in the liver
- Important for defence
- Can attack own cells

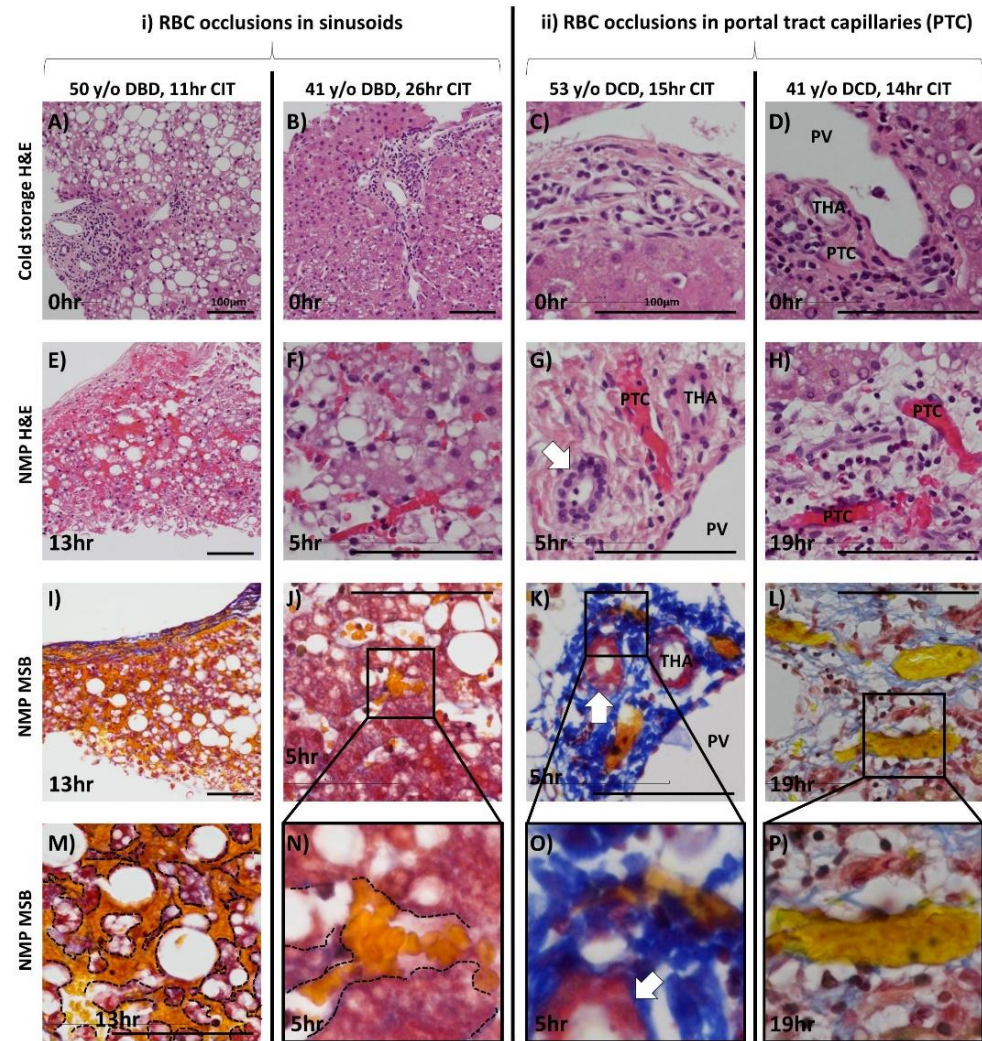
C3 production over time

- DCD vs DBD
- Normal range 80-160mg/ml



Red cell aggregates during normothermic machine perfusion of human livers

- Series of research livers undergoing normothermic machine perfusion: 2 DCD, 5 DBD; mean age 48yrs; mean CIT 15hrs 27mins
- No RBC aggregates following cold storage, but every liver accumulated aggregates during NMP
- RBC aggregates form in sinusoids and in the **portal tract capillaries** which supply ischaemia-sensitive bile ducts.
- Future research should investigate the use of agents which could prevent this '**aggregative microangiopathy**' and clear the microcirculation

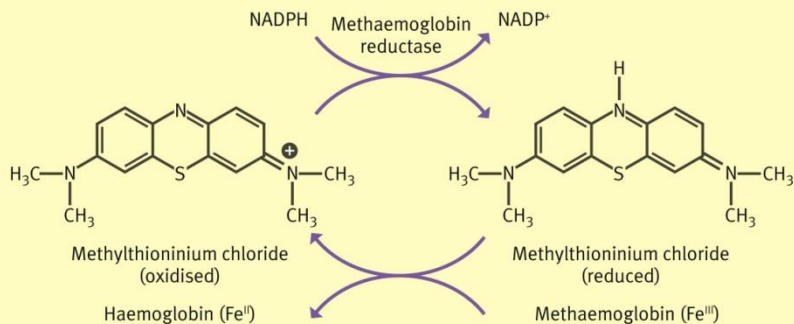


Haemopure

- Hemopure is a hemoglobin-based oxygen carrier (HBOC) ready for immediate infusion, that transports and delivers oxygen from the plasma and expands the circulating volume. The product is supplied in sterile, flexible infusion bags with a fill volume of 250mL. Consisting of 32.5 g purified, glutaraldehyde-polymerized, bovine hemoglobin (Hb) in an iso-oncotic balanced modified Ringer's lactate, it can be stored at room temperature for at least three years.

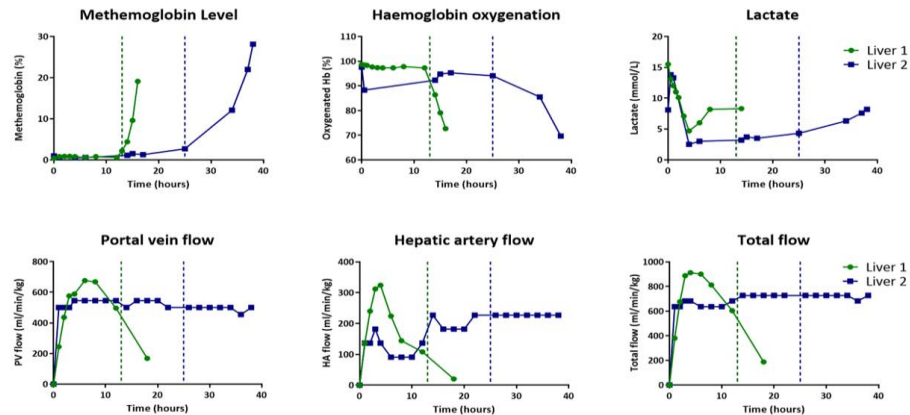
Too much Oxygen...

The reduction of methaemoglobin by methylthionium chloride

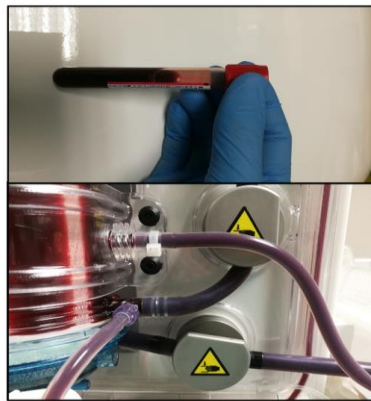


NADP⁺, oxidized form of nicotinamide-adenine dinucleotide phosphate;
 NADPH, reduced form of nicotinamide-adenine dinucleotide phosphate.

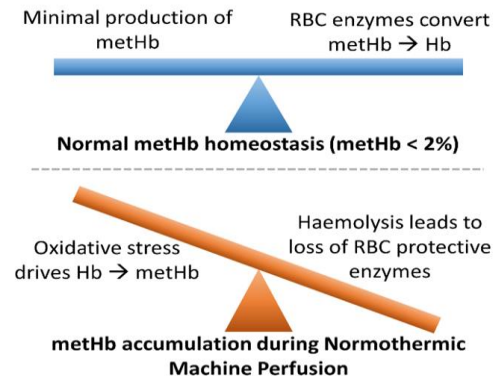
A)



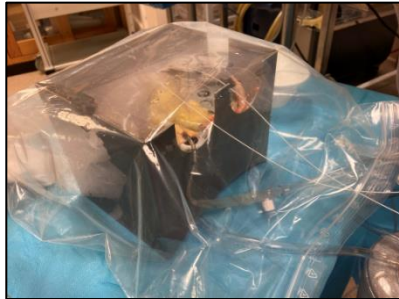
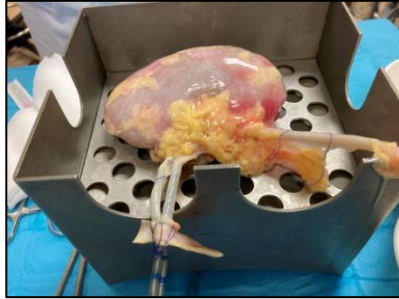
B)



C)



Prolonged perfusion



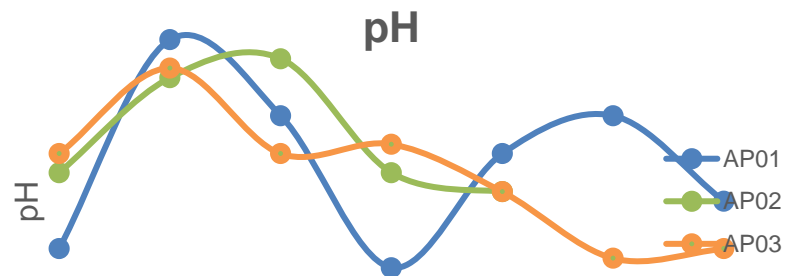
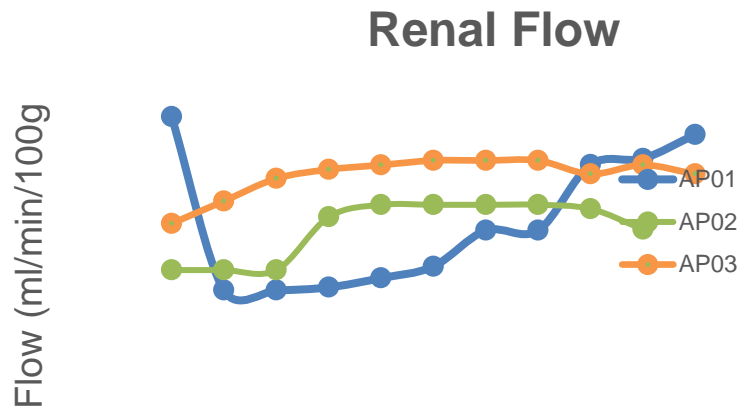
Perfusate (32°C) MAP 65mmHg

- Ringer's solution
- Human serum albumin 20%
- Dexamethasone
- Sodium bicarbonate 8.4%
- Mannitol 10%
- 10ml Calcium gluconate 10%
- 95% oxygen/5% carbon dioxide 0.1L/min
- Prostacyclin, GTN, verapamil
- Nutrients, glucose

Oxygen 95%
60-70kPA



Perfusion parameters



	AP01 (24h)	AP02 (18h)	AP03 (24h)
Mean flow (ml/min/100g)	121	104	148
Temperature (°C)	31.8	31.8	31.9
Arterial Pressure (mmHg)	64	59	62.2
Total urine output (ml)	360	414	163

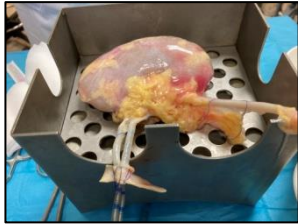
Reperfusion

AP03

67y DCD kidney (WIT 16min)

Rejected for transplant

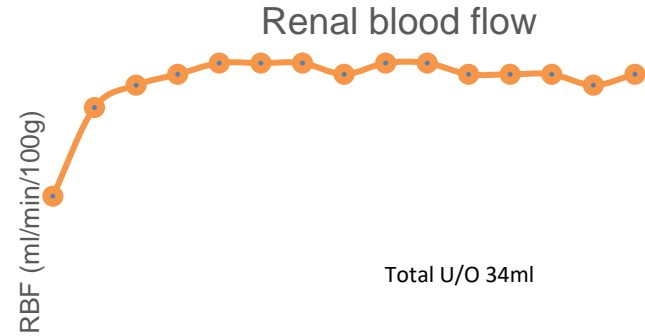
CIT 20h



24h perfusion 32°C



2h reperfusion RBC 36°C





The Newcastle upon Tyne Hospitals



NHS Foundation Trust

- IoT Transplant Team
- NHSBT and NIHR BTRU support
- All the staff



Thank you to the Donors
and their families