Machine organ perfusion: a toy or the future?

David Talbot
Newcastle NHBD programme from 1988

OMG!!

I thought u were dead!

Percent graft survival

NHBD Program - Newcastle upon Tyne

90.5%  45.5%  91.7%
A New Machine?
Schlok and Gok

Dialysis Machine
Kidney in bowl
Bubble Trap
Arterial Line
Venous Return
Cooling
STERILE
NON STERILE

FOR KIDNEY DIALYSIS ONLY
NOT FOR PATIENT USE
Phase I (1988-93) 90.5%  
n = 19  

Phase II (1994-98) 45.5%  
n = 10  

Phase III (1998-99) 91.7%  
n = 14  

NHBD Program - Newcastle upon Tyne
Impact of warm ischaemia on machine perfusion parameters

Organ donation and Transplantation after cardiac death
Graft survival according to Maastricht category-
Sanni et al AJT 2007; 7:400
Newcastle developments aimed at MII donor kidneys:

- Machine perfusion (Transplantation 2000; 69: 842)
- Thrombolysis (Transplantation 2003; 76: 1714)
- HTK flush KPS machine perfusion versus Marshalls flush machine perfusion with Newcastle solution (Transplantation 2004; 78:1008)
- Delay use of CNI (BJS 2005; 92:681)
- Dual Transplantation (J Urol 2008; 79:2305)
- Peritoneal cooling (AJT 2009; 9:1317)
GFR Maastricht II versus III post 2004: Aditya Kanwar, Muhammed Khurram
DCD kidney outcome reflects the donor source: standard versus expanded.

Figure 3. Kaplan-Meier (KM) death-censored graft survival (DCGS) curves for recipients of standard criteria donor (SCD) kidneys, donation after cardiac death (DCD) kidneys from donors younger than 50 years, DCD kidneys from donors older than 50 years and expanded criteria donor kidneys (ECD). With regard to 5-year DCGS, SCD kidneys and DCD kidneys from donors younger than 50 years have equivalent outcomes, and ECD kidneys and DCD kidneys from donors older than 50 years have equivalent outcomes.
Kidney transplant outcomes for DBD/DCD donors (NHS BT)

Graft survival

Patient survival

% patient survival

% graft survival

years post-transplant

years post-transplant

DBD

DCD

0 1 2 3 4 5

0 1 2 3 4 5

40 50 60 70 80 90 100

40 50 60 70 80 90 100
Bristol versus Newcastle

Cold Ischaemic Time

- Mean ± SD
- HMP
- SCS
- * p<0.0001

Percentage

- PNF
- DGF
- HMP
- SCS
- 3.3
- 4
- 36.2
- 38.4

eGFR

- eGFR mL/min/1.73m² (Mean ± SD)
- 3 mon HMP
- 3 mon SCS
- 1 Yr HMP
- 1 Yr SCS
- 60
- 50
- 40
- 30
- 20
- 10
- 0
Cox Proportional Hazards Model - Tx Survival

Method of storage: static/machine
Dominic Summers 2010

Machine perfusion group: 94%
Static cold storage group: 90%
p = 0.04
MACHINE PERFUSION VERSUS COLD STORAGE PRESERVATION IN NON-HEART-BEATING KIDNEY DONATION AND TRANSPLANTATION: FIRST RESULTS OF A MULTICENTRE TRIAL IN EUROTRANSPLANT


• 82 consecutive NHBD pairs - 82 machine perfused + 82 static stored

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Static</th>
<th>MP</th>
<th>P</th>
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<tbody>
<tr>
<td>Recipient age/yrs</td>
<td>52</td>
<td>49</td>
<td>0.81</td>
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<tr>
<td>Dialysis duration/d</td>
<td>1448</td>
<td>1542</td>
<td>0.48</td>
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<tr>
<td>1st transplant</td>
<td>41%</td>
<td>41%</td>
<td>NS</td>
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<tr>
<td>Mismatch</td>
<td>3.7</td>
<td>2.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Cold Ischaemic time/hrs</td>
<td>15.9</td>
<td>15.0</td>
<td>0.7</td>
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82 static versus 82 MP NHBD kids

<table>
<thead>
<tr>
<th>Factor</th>
<th>Static</th>
<th>MP</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Incidence DGF/%</td>
<td>69.5</td>
<td>53.7</td>
<td>0.027</td>
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<tr>
<td>DGF duration/days</td>
<td>13</td>
<td>9</td>
<td>0.04</td>
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<tr>
<td>GFR day 7</td>
<td>9</td>
<td>13</td>
<td>0.009</td>
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<td>GFR day 14</td>
<td>13</td>
<td>23</td>
<td>0.001</td>
</tr>
<tr>
<td>GFR month 1</td>
<td>38</td>
<td>46</td>
<td>0.078</td>
</tr>
<tr>
<td>GFR month 3</td>
<td>49</td>
<td>57</td>
<td>0.19</td>
</tr>
<tr>
<td>PNF</td>
<td>2.4%</td>
<td>2.4%</td>
<td>NS</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>12.2%</td>
<td>7.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Patient survival</td>
<td>100%</td>
<td>98.7%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Evaluation of the impact of preservation by machine perfusion and perfusion parameters on outcome of kidneys from donors after cardiac death


Nuffield Department of Surgery, University of Oxford and Oxford Transplant Centre, Oxford, United Kingdom

- DGF for static: 83% (25/30)
- DGF for machine: 30% (15/50) (p<0.0001)
• Cold Machine Perfusion Versus Static Cold Storage of Kidneys Donated After Cardiac Death: A UK Multicenter Randomized Controlled Trial.

  - Watson CJ; Wells AC; Roberts RJ; Akoh JA; Friend PJ; Akyol M; Calder FR; Allen JE; Jones MN; Collett D; Bradley JA


• No difference in outcome
Question 1

• If you were to be a patient and receiving a kidney from a MIII non heart beating donor. Would you rather have machine perfusion or static storage for your kidney, assuming best available solution?
Machine Perfusion or Cold Storage in Deceased-Donor Kidney Transplantation

To the Editor: Moers et al. (Jan. 1 issue)² report on their trial of machine perfusion versus static storage of kidneys from deceased donors. The benefit of machine perfusion² is probably that it ensures a uniform distribution of preservation fluid throughout the organ, which is better than a single flush.

Perhaps this benefit can be illustrated best by our experience with a series of 38 poorly preserved kidneys obtained at our center from 19 donors after cardiac death, all of whom had undergone femoral cannulation and were Maastricht category II or III donors.³ (Patients in Maastricht category III generally had a misplaced cannula.) In these donors, the kidneys were blue and poorly perfused at laparotomy, and these indicators did not improve with a single flush after recovery. On the basis of standard criteria, these organs were not suitable for transplantation; however, after machine perfusion, only four kidneys were not transplanted. The appearance and flow were improved by means of machine perfusion, and this method of preservation resulted in 10 dual and 14 single kidney transplantations.

Machine perfusion may improve the appearance and usability of kidneys that otherwise would not be transplanted.⁴

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To the Editor: In their editorial, Tullius and García-Cardeña¹ describe solid-organ transplantation as beginning with renal isografts in the 1950s. However, corneal transplantation has a much longer history. Eduard Zirm successfully transplanted a full-thickness corneal allograft in...
<table>
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<tr>
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<th>Total</th>
<th>%</th>
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<tr>
<td>Donors</td>
<td>173</td>
<td></td>
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<tr>
<td>Kidneys retrieved</td>
<td>340</td>
<td></td>
</tr>
<tr>
<td>Kidneys used</td>
<td>289</td>
<td>85.%</td>
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</table>

Units not using machine perfusion (April 2008-2009)-South Thames/Leeds censored
Use rate between machine perfusion sites (April 2008-9)

<table>
<thead>
<tr>
<th></th>
<th>Ncl</th>
<th>Oxford</th>
<th>Plym</th>
<th>Sheff</th>
<th>Total</th>
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<tr>
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<td>11</td>
<td>14</td>
<td>31</td>
<td>4</td>
<td>60</td>
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<tr>
<td>Kids</td>
<td>22</td>
<td>28</td>
<td>62</td>
<td>8</td>
<td>120</td>
</tr>
<tr>
<td>Kids used</td>
<td>21</td>
<td>27</td>
<td>57</td>
<td>7</td>
<td>112</td>
</tr>
<tr>
<td>% used</td>
<td>95</td>
<td>96</td>
<td>92</td>
<td>87.5</td>
<td>93.3</td>
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*: 0.0099 Chi square versus other centres
GFR Criteria

R Risk
- \( S_{Cr} \) increased 1.5x or GFR decreased by > 25%

I Injury
- \( S_{Cr} \) increased 2x or GFR decreased by > 50%

F Failure
- \( S_{Cr} \) increased 3x or GFR decreased by 75%
  - \( S_{Cr} \geq 4 \text{ mg/dl} \) in setting of acute rise of \( \geq 0.5 \text{ mg/dl} \)

UO Criteria

- UO < 0.5 ml/kg/hr for 6 hr
- UO < 0.5 ml/kg/hr for 12 hr
- UO < 0.3 ml/kg/hr for 24 hr
  - or
  - Anuria for 12 hr

L Loss
- Persistent ARF = complete loss of kidney function for > 4 wk

E End Stage
- End-stage kidney disease (> 3 mo)

High Sensitivity

High Specificity
<table>
<thead>
<tr>
<th>Recipient</th>
<th>Donor</th>
<th>Scr 24h pre-arrest</th>
<th>Retrieval Scr</th>
<th>RIFLE Category</th>
<th>3/12 GFR</th>
<th>12/12 GFR</th>
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<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>89</td>
<td>247</td>
<td>Injury</td>
<td>52.8</td>
<td>59.7</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>89</td>
<td>247</td>
<td>Injury</td>
<td>47.1</td>
<td>59.7</td>
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<tr>
<td>C</td>
<td>2</td>
<td>107</td>
<td>154</td>
<td>Risk</td>
<td>41.0</td>
<td>46.0</td>
</tr>
<tr>
<td>D</td>
<td>2</td>
<td>107</td>
<td>154</td>
<td>Risk</td>
<td>19.9</td>
<td>18.9</td>
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<tr>
<td>E</td>
<td>3</td>
<td>134</td>
<td>260</td>
<td>Risk</td>
<td>79.0</td>
<td>44</td>
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<tr>
<td>F</td>
<td>4</td>
<td>58</td>
<td>102</td>
<td>Risk</td>
<td>PNF</td>
<td>PNF</td>
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<tr>
<td>G</td>
<td>4</td>
<td>58</td>
<td>102</td>
<td>Risk</td>
<td>33.9</td>
<td>29.7</td>
</tr>
<tr>
<td>H</td>
<td>5</td>
<td>64</td>
<td>118</td>
<td>Risk</td>
<td>50.6</td>
<td>NA</td>
</tr>
<tr>
<td>I</td>
<td>5</td>
<td>64</td>
<td>118</td>
<td>Risk</td>
<td>38.6</td>
<td>NA</td>
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</tbody>
</table>
Sharing NHBD kidneys

• Because the proportion of NHBD kidneys is increasing, kidneys need to go with pancreases, cold ischaemic time could be shorter with sharing

• The relevance of machine perfusion to outcome appears to be similar to static storage. Therefore kidneys will be shipped static
Recent example 1

- 18.8.10, 0000hrs: 47 male cardiac arrest at home, wife started CPR, paramedics attended and brought to Western General hospital. ‘Down time’ 1 hour.
- ‘You don’t want these kidneys do you?’
- ‘Yes they got him back but he is on a shed load of inotropes’
- Doesn’t Glasgow want them?’ ‘no’
Recent example 1

- ‘Doesn’t sound great but I suppose if they were on a machine perfusion system and they looked good well maybe yes’
- 2\textsuperscript{nd} phone call: ‘shouldn’t have been offered to you, should have been Edinburgh’
- 3\textsuperscript{rd} phone call: ‘Edinburgh doesn’t want them, if you want them machine perfused you have to come and get them yourselves’
Recent example 1

- 4th phone call: ‘OK Edinburgh will retrieve and they will loan their pods on pain of death that they are returned’
- 5th phone call: ‘withdrawing at 8am liver placed with Kings!’
- Actually withdrew 1003, 1018 dead
- 10.35 perfusion started
- Kidneys arrived flows through kidneys good and looked good.
Recent example 1

• GS last haemodialysis day 1. Creat 202µmol/l at 12 days on discharge to referring hospital.
• SC No dialysis postop. Creat 91µmol/l (2/12)
Recent example 2

- 21.8.2010 40 yr old female admitted Sheffield Northern General Hospital, 5/7 before offer.
- Since then acute renal failure, patient on CVVHD, do we want kidneys as about to withdraw support? Leeds would be retrieve.
- Cant machine perfuse, Flush with UW please, static storage on ice.
Recent example 2

- Kidneys retrieved and transported back to Newcastle, put on machine perfusion straight away. Good flows.
- Transplanted KS PD continued for 2/7, discharged back to referring hospital at day 15 creat 267μmol/l
- Transplanted JH (WIT 56mins!) last haemodialysis at 9 days post op (some rejection on biopsy). Creat 362 at discharge to referring hosp- day 22.
Question 2

• If you were a surgeon/physician importing a kidney from another centre from a Non heart beating donor with acute renal failure and a surgeon you didn’t know, would machine perfusion be mandatory? ie revealing good flow
USING PRESSURE FLOW CHARACTERISTICS OF THE MACHINE PERFUSED KIDNEYS IN ASSESSMENT OF KIDNEYS RETRIEVED FROM HYPERTENSIVE NON-HEART BEATING DONORS

E-mail: soroush01@gmail.com Liver and Renal Transplant Unit, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne, NE7 7DN, UK

Pressure-Flow Characteristics of the perfused NHB kidneys using hypothermic machine perfusion. HT-D Hypertensive donor group, Control-D Control Donor group, PFI Perfusion Flow Index, GST Glutathione-S-Transferase, Resistance is after 4 hours of machine perfusion Bars and error bars represent Mean and 95% Confidence Interval

a $p = <0.001$, b $p = <0.001$, c $p = 0.040$, d $p = 0.705$
Cold Machine perfusion of non renal grafts

Liver-20 cases AJT
Feb 2010

James Guarrera
Pancreas: Mettu Reddy
Weight gain after 6 hrs of perfusion

- Time 1: 17.60%
- Time 2: 44%
- Time 3: 10%
- Time 4: 18%
- Time 5: 13.60%
Pancreas- cold perfusion

Static

Machine perfusion
Hypothermic machine perfusion circuit

- Perfusion pump
- Perfusion tubing
- Pressure tracing
- Pressure transducer
- Filter
- Pancreas in UW solution
- Ice bath
Hypothermic machine perfusion
Venous oxygen persufflation circuit

Oxygen

Pancreas in UW solution

Ice bath

Pressure tracing

Pressure transducer

Oxygen flow-meter

Filter
Portal venous oxygen persufflation
Comparison of purified islet count and equivalents among control (minimal ischaemia) and various NHBD preservation groups.
Figure 36 Morphology of islets retrieved from positive control and non-heart-beating donor pancreases

The islets were double stained with dithizone and trypan blue. Islets isolated from positive control pancreas (A) are globular with smooth margins and minimal staining with trypan blue. Islets from static cold storage pancreas (B) are small, irregular and frequently fragmented. They also have increased staining with trypan blue suggestive of poor viability. Islets isolated from hypothermic machine perfusion (C) and portal venous oxygen persufflation (D) are less fragmented as compared to static cold storage group. The margins are not smooth and there is evidence of trypan blue staining of the larger islets. This is more prominent in the islets from pancreases preserved by hypothermic machine perfusion (C).
Assessment of vital organs: machine perfusion warm-lung
Lung warm perfusion example:

Initially experimental, with improvement in appearance and gas exchange, now used routinely for transplant (Danai/Dark)
Machine perfusion warm liver

- Liver retrieval after warm ischaemia
- Warm perfusion with oxygenated blood
- Transplant
- Success in an animal model - Oxford
Machine perfusion warm-heart
Summary

• Cold machine perfusion ensures uniform distribution of perfusate
• In randomised trials it either produces a reduction of delayed graft function with improvement of graft survival at 1 year—or it doesn’t
• If there is a problem with cannulation or the agonal phase is protracted then the kidneys are blue at retrieval. This does not necessarily improve with a back table flush
• However in virtually all cases the kidneys are improved by machine perfusion
Summary 2

• This improvement is likely to mean use rate is better

• Cold machine perfusion of pancreases is not likely to confer benefit to either pancreas transplant or islet retrieval but $O_2$ persufflation will
Summary 3

• Isolated warm perfusion necessary for vital organs where they are considered too high risk to determine function:
  • Successful in humans for: lung
  • Successful in animals for: liver
  • ?heart in future
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Aqix Technology Strategy Board
after exposure to e.g. 60 min WI (non-functioning grafts)

medio- to macrovesicular vacuolisation, sinusoidal congestion and focal cell drop out
Porcine livers on the LTR (liver transporter)