

# Renal Preservation

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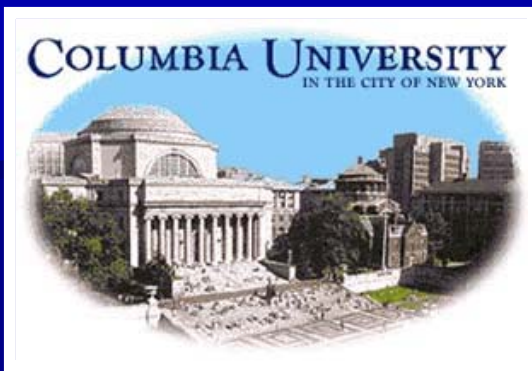
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# Metabolic Inhibition by Hypothermia

- Hypothermia decreases rate of enzymatic degradation of cellular components
- By slowing the reaction and cell death, hypothermia greatly extends preservation time
- Protective effect is incomplete
  - Hypothermia does not entirely stop metabolism
  - Ultimately organs cease to function

# Effects of Cold Ischemia

- Intracellular acidosis
- Stimulation of intracellular lysosomal enzymes
- Mitochondrial damage
- Free radical accumulation

# Clinical Hypothermia/ Cold Storage

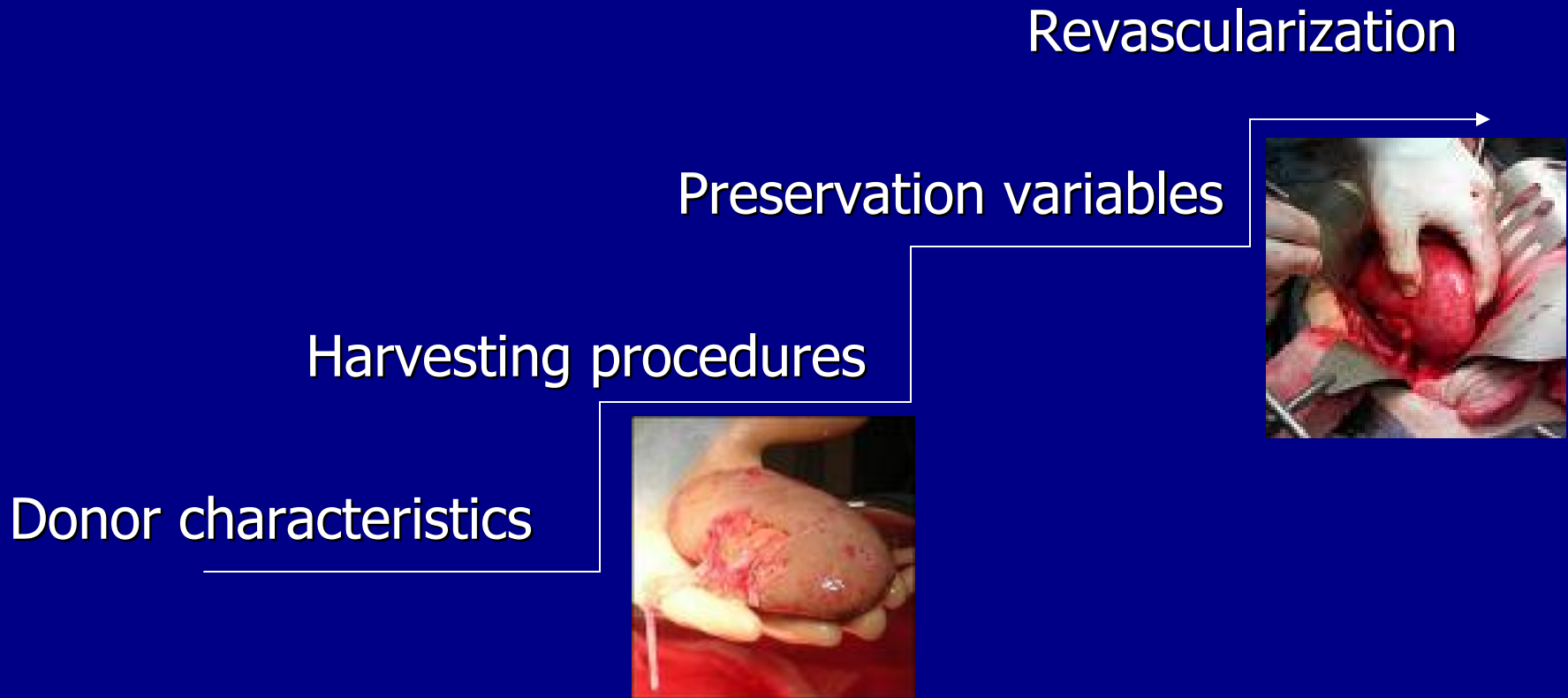
- Cheap, easy, reproducible
- Maintained between 4-7°C
- Ideal temp?
- Cold ischemia is good, but not perfect
- Significantly reduces tissue metabolic rate to 10% of normal
- Decrease in enzymatic activity
  - 1.5-2.0 fold for every 10°C
  - Membrane-bound enzymes usually more affected than soluble enzyme systems

# New Clinical Challenges

- What should be done when conditions are not “perfect”
  - Marginal donors
  - Non-heartbeating donors
  - Donors with decreased or fluctuating blood pressure
  - Donors with increased creatinine
  - Warm ischemic injury
- Clinical preservation times
  - Kidney 24-36 hours- 20-30% ATN
  - Liver 8-10 hours
  - Heart 4-6 hours

# Clinical Scenario

## Donor-Recipient Path Many Steps to Good Organ Function



**So, Cold Ischemia is  
good for organ storage  
up to a point.**

# Why is Cold Ischemia Damaging?

- Metabolic disruption at low temperatures
- Interruption of oxygen
- Reperfusion injury
- Edema dysfunction ( $\text{Na}^+/\text{K}^+$  pumps)
- Failure of ATP supply

# Limits to Clinical Cold Ischemia Preservation

- Events surrounding harvesting
- Length of storage
- Events surrounding transplantation

# Ability of Cold Ischemia to Protect Organs Based on:

- Appropriate ideal temperature
- Lowering metabolic demands
- Lowering metabolic function pathways

**Table 2. Components of UW, HTK and Celsior solutions**

	<b>UW</b>	<b>HTK</b>	<b>Celsior</b>
Year of Introduction	1987	1975	1994
Source	Belzer (USA)	Bretschneider (Germany)	Pasteur-Merieux (France)
<b>Components</b>			
Na <sup>+</sup> (mmol/L)	25-30	15	100
K <sup>+</sup> (mmol/L)	125-130	10	15
Mg <sup>2+</sup> (mmol/L)	5	13	4
Ca <sup>2+</sup> (mmol/L)	–	0.25	0.015
Mannitol (g/L)	–	30	60
Lactobionic acid (mmol/L)	100	–	80
HES (g/L)	50	–	–
Raffinose (mmol/L)	30	–	–
Histidine (mmol/L)	–	180	30
H <sub>2</sub> PO <sub>4</sub> /HPO <sub>4</sub> (mmol/L)	25	–	–
OH (mmol/L)	–	–	100
Glutathione (mmol/L)	3	–	3
Allopurinol (mmol/L)	–	1	–
Adenosine (mmol/L)	5	–	–
Acetone dicarboxylic acid (mmol/L)	–	1	–
Tryptophan (mmol/L)	–	2	–
Aminoglutaminic acid (mmol/L)	–	–	20
mOsm/L	320	310	320
pH	7.4	7.2	7.3

# Improvements of Static Cold Storage

- Minimal, except:
  - Advent of new solutions
- Other improvements at best are moderate

It appears then,  
Cold Ischemia by itself cannot  
consistently  
protect all organs.

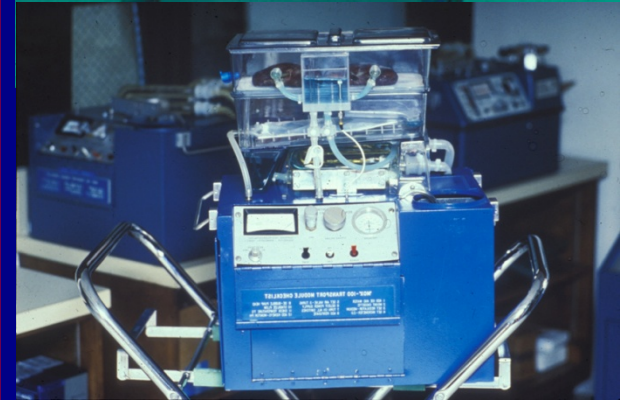
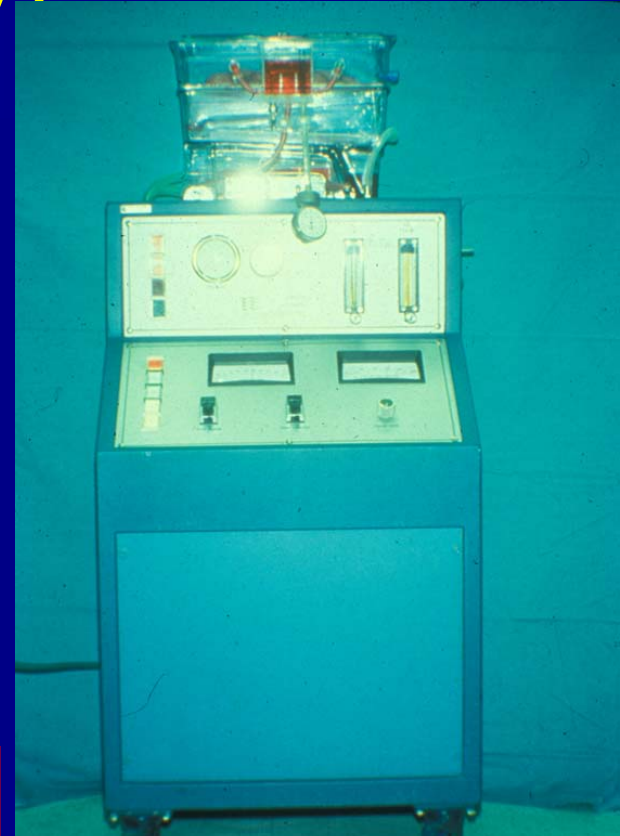
# New Developments

- Studying mammalian hibernators as natural models
- Hibernation induced gene expression
- Protein upregulation during hibernation: serpins, heat shock proteins, antioxidants, membrane transporters
- Molecular/Gene Therapy- Knockdown of genes that are implicated in the reperfusion injury cascade
  - Cytokines
  - Apoptotic triggers

# Renal Preservation: Hypothermic Pulsatile Perfusion

- First described by Belzer in 1967 (allowed 17 hour CIT)
- Used widely until 80s→Eurocollins/UW cold storage safe effective and logistically easier
- Recent resurgence in perfusion in 1990s
- Today about 20% of cadaver renal grafts are pumped
- Varies widely from region to region

# Progress in perfusion technology (and portability)



# Machine Perfusion: Beneficial mechanisms

- Continuous circulation of preservation solution and metabolic substrates for ATP generation
- Removes waste products from direct endothelial/parenchymal contact → “washout effect”
- Stabilizes the microcirculation
- Allows pharmacologic manipulation
- Pretransplant assessment of graft

# Disadvantages of Machine Perfusion

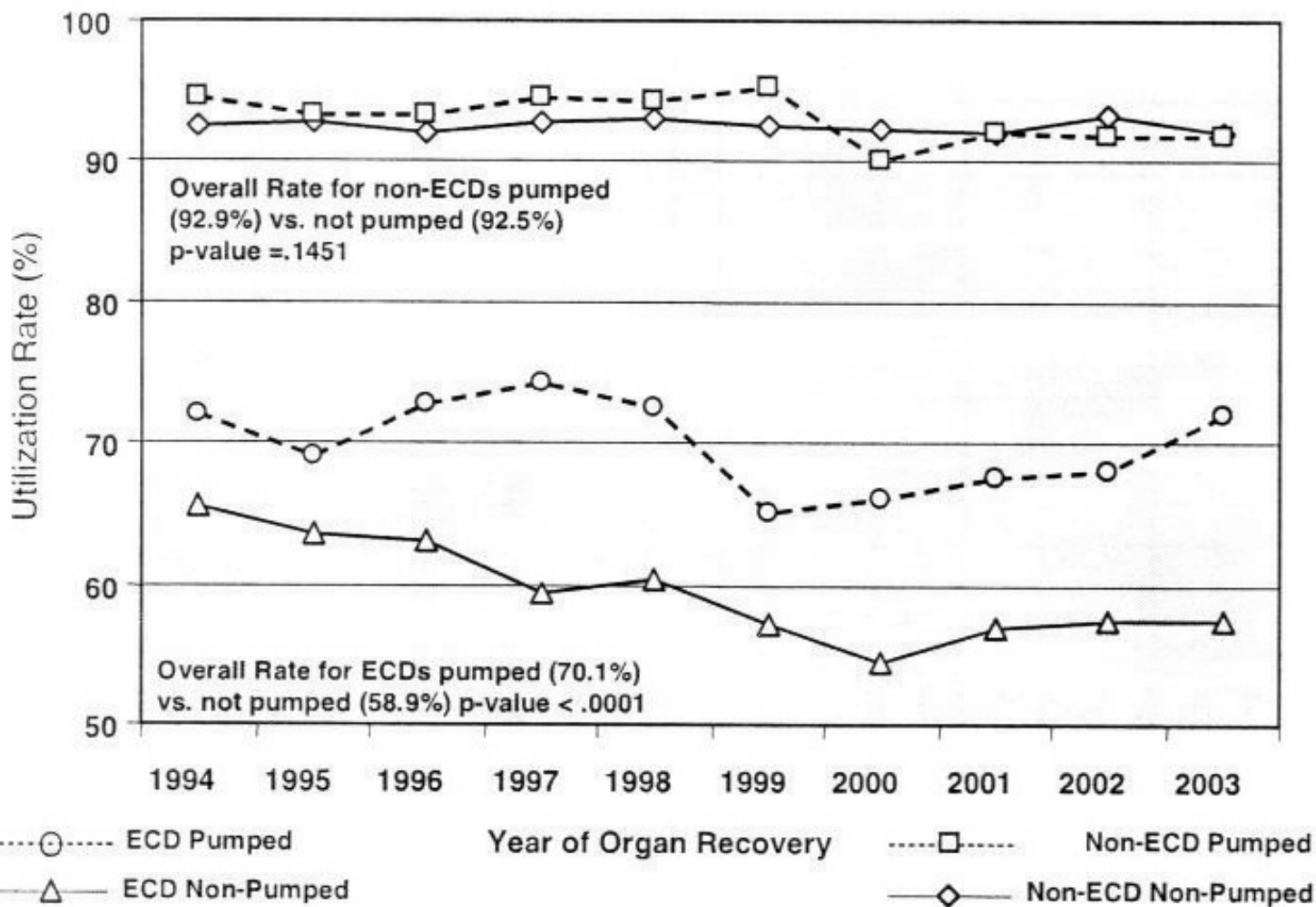
- Requires specialized equipment/facilities
- Pump
  - Disposables: lines/drapes/cassette
  - Solution (in addition to flush/storage solution)
  - Sterile room
  - Technical staff requires special training
- Potential for technical/equipment failure
- More expensive per case
  - Costs may be recovered ultimately

# PERFUSION BENEFITS

- Stimulates ATP synthesis
- Removes waste products
- Allows dynamic evaluation of viability prior to transplant
- Allows pharmacologic manipulation of kidneys
- Allows longer preservation period
- Kidneys pumped 30 plus hrs equal to kidneys cold stored less than 12 hours
- Expands donor pool
- Less DGF/ Shorter LOS

# Schold et al. AJT 2005

## Increased utilization of ECD kidneys with MP



# Schold et al. AJT 2005 (cont)

- Strong association of decreased DGF with pulsatile perfusion
  - Effect greatest in high risk (ECD) donors
- Mild improvement in long term graft survival: more pronounced in recent years
- Results verified in a paired kidney analysis
- Most important finding:
- **HIGHER UTILIZATION RATE OF ECD KIDNEYS WITH PULSATILE PERFUSION**

# MP reduces incidence of DGF

	Cold storage	Pulsatile perfusion	p-Value
Delayed graft function (%)	37.1	25.8	<0.001
Primary nonfunction (%)	3.2	2.6	0.37
Rejection (%)			
Initial hospital stay	7.5	6.8	0.46
At 6 months	16.4	16.0	0.80
At 1 year	18.9	19.0	0.96

# WHEN GOOD KIDNEYS PUMP BADLY: OUTCOMES OF RENAL TRANSPLANTS WITH POOR PERFUSION CHARACTERISTICS

**Flow <80cc/min and Resistance >0.4**

Patients (N)	No Hemodialysis	>3 Hemodialysis	LOS (days)
<b>11</b>	<b>7 (63.6%)</b>	<b>2 (18.2%)</b>	<b>4.9±1.1</b>
3-month SCr	1-year SCr	Functioning Graft	Survival
<b>0.6 (mg/dL)</b>	<b>0.5 (mg/dL)</b>	<b>100%</b>	<b>100%</b>

Median CIT: 22 hours (r, 14-48 hours)

Median MP time: 13 hours (r, 6-30 hours)

# ONE-YEAR OUTCOMES - RENAL TRANSPLANT WITH COLD ISCHEMIA TIME $\geq 30$ Hrs

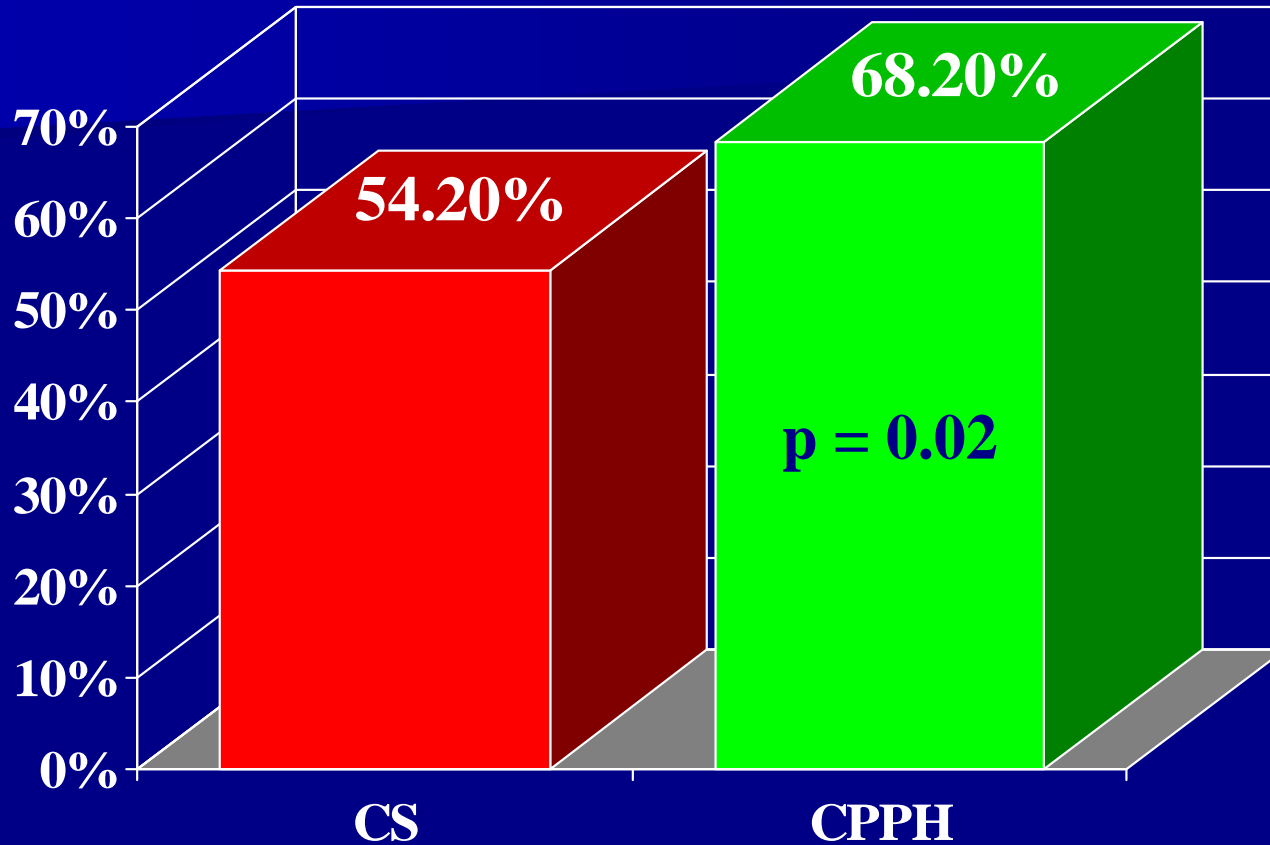
- Twenty-three patients with CIT  $\geq 30$  hours were identified.
- Donor age was  $45 \pm 20.7$  years –
- Terminal SCr was  $1.6 \pm 0.95$ .
- 9 grafts (39%) met UNOS ECD criteria.
- Cold Ischemia Time was  $36.7 \pm 5.7$  hours (range, 30-49 hours)
- 14 patients (61%) had  $\geq 6$  hours of machine perfusion as part of CIT.



# Prolonged CIT- Columbia Experience

- DGF occurred in 65.2% of patients (15/23).
- Actual patient survival was 91.3%.
- All remaining patients are alive with a functioning graft
- Mean follow-up of  $19.9 \pm 2.4$  months (r, 16-24 months)
- 6-month and 1-year SCr were  $1.5 \pm 0.4$  and  $1.5 \pm 0.6$  mg/dl respectively.

# Death-uncensored kidney graft survival



Living with functional graft:

MP: 155/227 patients,

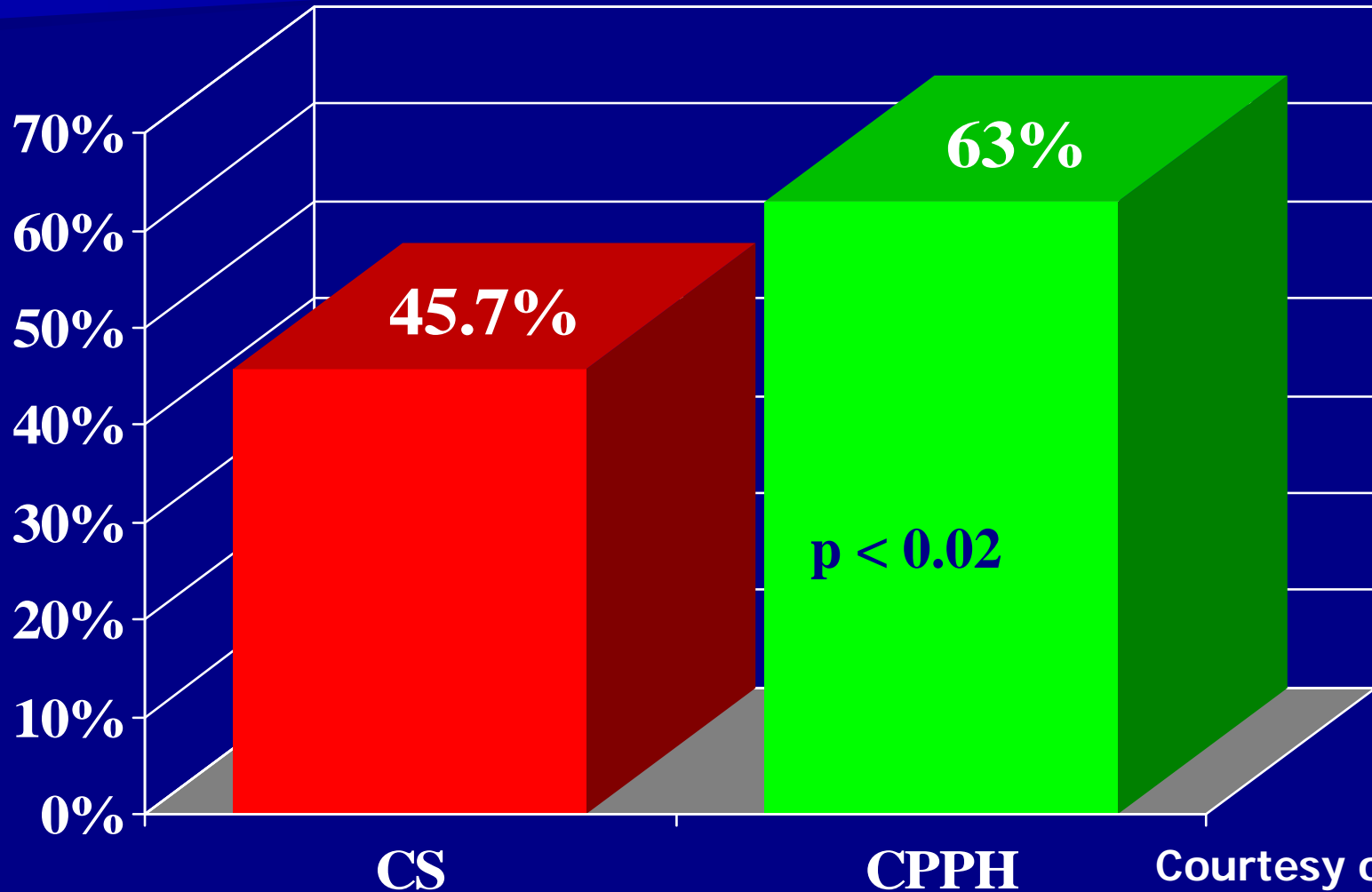
CS: 102/188 pts;

Courtesy of  
Prof. W. Rowinski

mean follow-up: 7.23 yrs

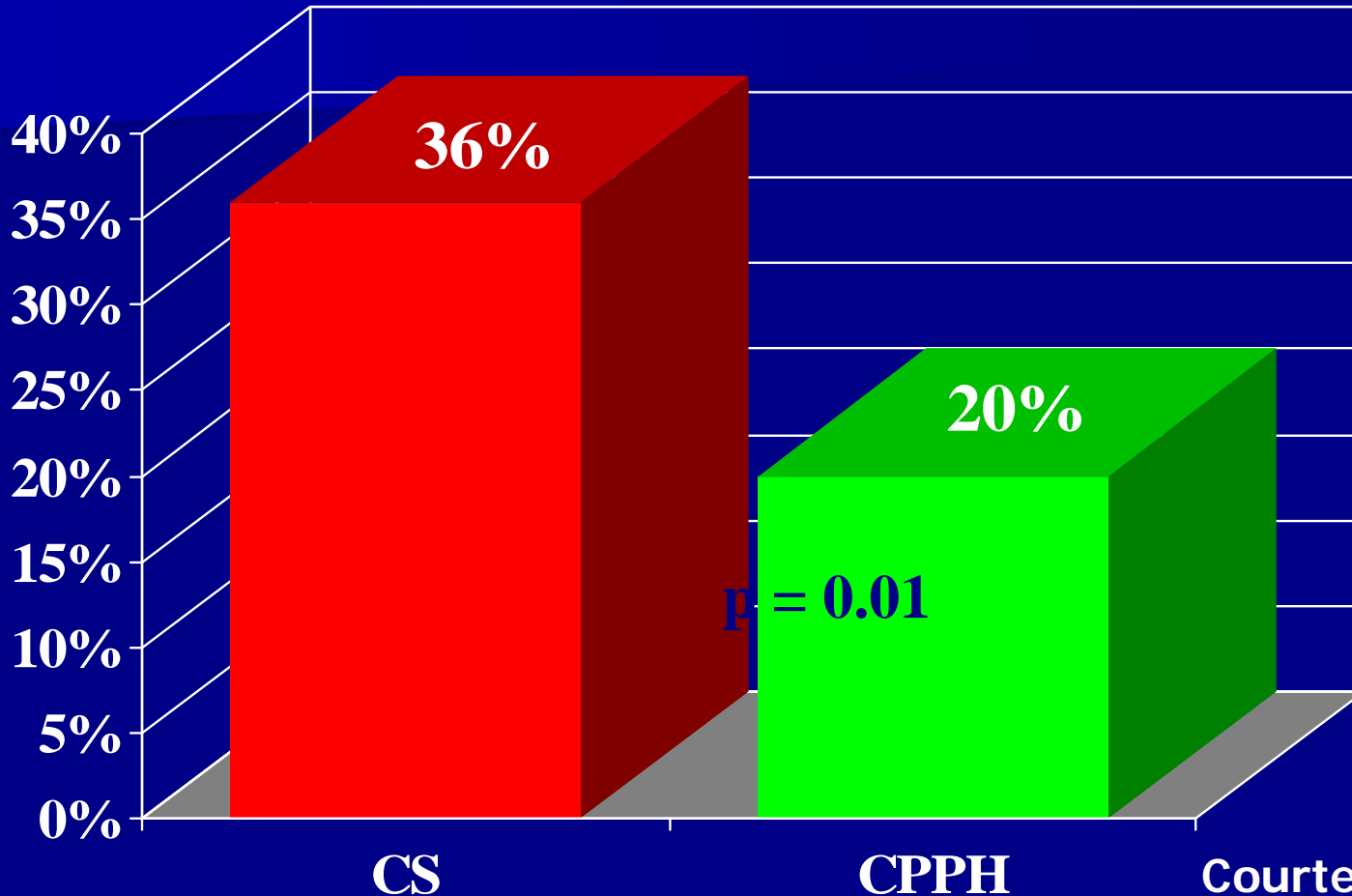
5 years after Tx:

patients with serum creatinine <2mg/dl



Courtesy of  
Prof. W. Rowinski

# Return to dialysis



Courtesy of  
Prof. W. Rowinski

Back on dialysis: CPPH 44 patients, CS 66 pts

# Kidney biopsy changes – MP vs CS 5 – 10 years after Tx

	<b>MP</b> <b>n=(22)</b>	<b>CS</b> <b>(n=24)</b>	<b>P Value</b>
<b>Chronic rejection</b>	0%	37%	< 0.0017
<b>Chronic allograft nephropathy</b>	54%	75%	<0.023
<b>Vascular changes</b>	45%	79%	< 0.04

Courtesy of  
Prof. W. Rowinski

Banff classification 2005

## Machine Perfusion or Cold Storage in Deceased-Donor Kidney Transplantation

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### ABSTRACT

#### BACKGROUND

Static cold storage is generally used to preserve kidney allografts from deceased donors. Hypothermic machine perfusion may improve outcomes after transplantation, but few sufficiently powered prospective studies have addressed this possibility.

#### METHODS

In this international randomized, controlled trial, we randomly assigned one kidney from 336 consecutive deceased donors to machine perfusion and the other to cold storage. All 672 recipients were followed for 1 year. The primary end point was delayed graft function (requiring dialysis in the first week after transplantation). Secondary end points were the duration of delayed graft function, delayed graft function defined by the rate of the decrease in the serum creatinine level, primary nonfunction, the serum creatinine level and clearance, acute rejection, toxicity of the calcineurin inhibitor, the length of hospital stay, and allograft and patient survival.

#### RESULTS

Machine perfusion significantly reduced the risk of delayed graft function. Delayed graft function developed in 70 patients in the machine-perfusion group versus 89 in the cold-storage group (adjusted odds ratio, 0.57;  $P=0.01$ ). Machine perfusion also significantly improved the rate of the decrease in the serum creatinine level and reduced the duration of delayed graft function. Machine perfusion was associated with lower serum creatinine levels during the first 2 weeks after transplantation and a reduced risk of graft failure (hazard ratio, 0.52;  $P=0.03$ ). One-year allograft survival was superior in the machine-perfusion group (94% vs. 90%,  $P=0.04$ ). No significant differences were observed for the other secondary end points. No serious adverse events were directly attributable to machine perfusion.

#### CONCLUSIONS

Hypothermic machine perfusion was associated with a reduced risk of delayed graft function and improved graft survival in the first year after transplantation. (Current Controlled Trials number, ISRCTN83876362.)

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\*Trial investigators are listed in the Appendix.

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# Conclusions

- Cold storage is standard and ok for many cases
- Machine Preservation has significant advantages over cold storage and is especially useful in ECD organs
- DGF reduction is durable and reproducible in multiple studies. Recent evidence shows that **MP INCREASES UTILIZATION OF KIDNEYS.**
- There is RCT evidence that there may be long term benefits of MP on graft survival