Bridge to Life

DURAENT LIFESCIENCES LLP

Perfusion Made Simple.

VitaSmart

Hypothermic Oxygenated Machine Perfusion

The VitaSmart brings simplicity and value to organ perfusion so that hospitals find it easy to pump kidneys and livers as the everyday standard of care.

With Hypothermic Oxygenated Perfusion (HOPE) protocol, the increased cellular energy within the organ and its improved graft function may help increase the use of DCD or extended criteria organs.

- **Why HOPE?**
- **Do you need Oxygen - or is HMP enough?**
- **Evidence of the benefits of simple end-ischemic HOPE perfusion**

Why HOPE?

The role of oxygen in hypothermic machine perfusion

Philipp Dutkowski

Mitochondrial derived Reactive Oxygen Species (ROS) are released during the first minutes of normothermic reperfusion. In contrast, oxygenation of the mitochondrial electron chain of ischemic cells under hypothermic conditions, does not provoke damaging ROS release.

In addition, mitochondrial respiration switches from anaerobic to aerobic metabolism during HOPE, providing significant upload of cellular adenine nucleotides.

Treatment by HOPE results therefore in an elimination of pro-ROS conditions and protects consecutively cells from further reperfusion injury upon implantation. This effect is similar for DCD and steatotic livers, and also for DCD kidneys.

Due to less down-stream signalling, HOPE is also effective against activation of immune response pathways. These results strongly depend on the presence of oxygen and mitochondrial activity. (continued)

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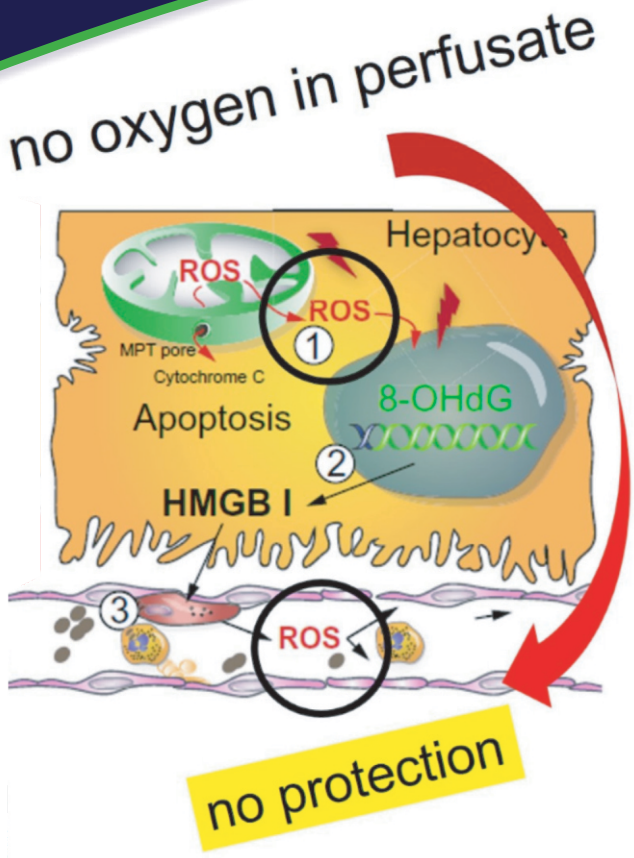


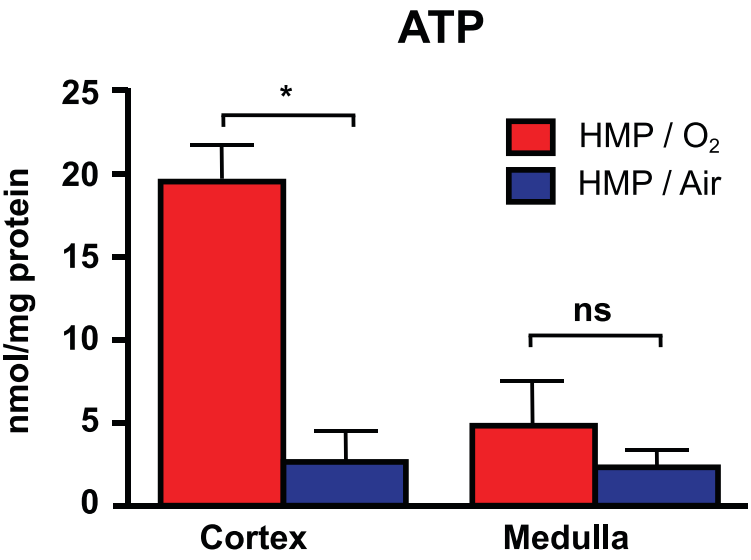
IMPORTANT CONCLUSIONS

- Oxygen is needed during cold perfusion for mitochondrial switch
- 1-2 hours of cold oxygenated perfusion sufficient to convert metabolism from pro-ROS to low-ROS
- Significant upload of cellular energy charge
- Numerous implications on down-stream signalling expected, e.g. immune response & anticancer effects & ageing
- Prediction of graft function possible by analyzing mitochondrial damage during perfusion

Do you need oxygen - or is HMP enough?

'The supplementation of perfusion fluid with high-concentration oxygen (95%) results in a greater degree of aerobic metabolism versus aeration (21%) in the nonphysiological environment of HMP, with reciprocal changes in adenoside triphosphate levels'

ref. Patel et al. Transplantation 2019; 103: 314-322



ATP levels in the cortex and medulla of HMP/O2 HMP/Air kidneys.

** 0.01 < P < 0.05.*

COPE Compare

83 DCD KIDNEY PAIRS
included in Primary analysis
ALL MACHINE PERFUSED

50% WITH OXYGEN	50% WITHOUT OXYGEN
Acute rejection: 15	Acute rejection: 30
Graft loss (at 12 months): 3	Graft loss (at 12 months): 11
n=106	n=106

The 'WITH OXYGEN' kidneys had a clinically significant 5ml/min/1.73m2 higher eGFR at 12 months, than 'WITHOUT OXYGEN' (47.6ml/min/1.73m2 vs. 42.6ml/min/1.73m2 (p=0.035)) following sensitivity analysis.

Graft loss and acute rejection also significantly lower in the 'WITH OXYGEN' group.

UK NICE Guidance on Perfusion of Livers - Issued 16th January 2019

- **No major safety concerns**
- **Efficacy not yet proven**
- **Hypothermic or Normothermic**
- **Oxygenated perfusate**

Clinical experience with hypothermic oxygenated perfusion of livers and kidneys

Matteo Ravaioli

The Sant'Orsola-Malpighi University Hospital of Bologna performed the first Italian interventional clinical trial on hypothermic oxygenated machine perfusion (HOPE) in liver and kidney transplantation of extended-criteria braindead donors (ECD-DBD).

The results of the study suggest that the newly developed hypothermic oxygenated pump used in this clinical trial is effective and safe in both liver and kidney perfusion. (continued)

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Liver Results:

Livers	HOPE (N = 10)	Control (N = 30)	p value
PNF, n (%)	0 (0%)	2 (6.6%)	0.8942
EAD, n (%)	0 (0%)	7 (23.3%)	0.6135
Peak AST within 7 days (U/L), median (range)	344.5 (166-1132)	637 (124-2001)	0.0060*
Peak ALT within 7 days (U/L), median (range)	330 (122-1350)	601 (114-1837)	0.1438
Bilirubin at day 7 (mg/dL), median (SD)	3.14 ± 1.54	3.62 ± 3.22	0.5386
INR at day 7, median (range)	1.17 (1.08-1.46)	1.24 (1.02-1.64)	0.0434*
Hospital stay (days), median (range)	11.5 (7-29)	12.5 (7-109)	0.2350
30-day graft survival, n (%)	10 (100%)	27 (90%)	0.8394

Control: *Static Cold Storage*

In a study of 50 DCD hypothermic oxygenated perfused livers (2 hours end-ischemic) compared with 50 DCD non-machine perfused livers:

	DCD (HOPE)	DCD (SCS)	
Graft loss (non tumour-related)	4/50	16/50	P=0.09
5 year graft survival	94%	78%	P=0.024
Non-anastomotic strictures	4/50	11/50	P=0.362

'We would like to emphasize that we found a clear improvement in most endpoints in HOPE-perfused livers, despite longer donor warm ischemia times, compared to untreated livers.'

'These results suggest that a simple end-ischemic perfusion approach is very effective and may open the field for safe utillisation of extended DCD liver grafts.'

ref. Schlegel et al. HOPE paper J.Hep 2018

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