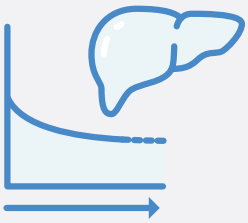
HOPE IN LIVER TRANSPLANTATION

COCHRANE REVIEW 2023[1]

Superior clinical outcomes compared to cold storage with HOPE[1]

HOPE was associated with **improvement in clinically relevant outcomes** in a **meta-analysis of 4 RCTs** evaluating the efficacy and safety of this machine perfusion technique compared with SCS.

HOPE vs. SCS[1]



DBD & DCD:
IMPROVED graft survival

HR 0.45; 95 % CI 0.23–0.87
P = 0.02

ECD-DBD: **LOWER** number of serious adverse events

OR 0.45; 95 % CI 0.22–0.91
P = 0.03

DCD: **REDUCED** damage to the bile ducts

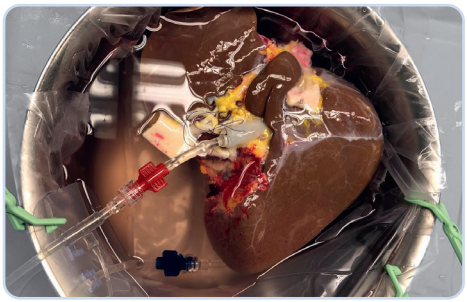
OR 0.31; 95 % CI 0.11–0.92
P = 0.03

HOPE Key Facts

Simple and effective hypothermic liver perfusion

Timepoint: end-ischemic in recipient center

Perfusate	Belzer MPS® (actively oxygenated)
Timing & Duration	End-ischemic after standard procurement and transport. Duration min. 2 h, **clinical data support safe perfusion up to 20 h.**[2]
Temperature	4–12 °C
Perfusate oxygenation	> 60 kPa > 450 mmHg
Technique	♦ Single portal perfusion ♦ Allows for various HOPE protocols



Liver perfusion with the VitaSmart™ System

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HOPE CLINICAL RESULTS

Evidence from RCTs in liver transplantation

	N	EAD	Graft Survival	Patient Survival	Complications/ SAEs	Biliary complications	NAS
DBD							
Czigany – ECD-DBD (2021): improved 1-year graft survival + less 90-day major complications[3,4]							
		n.s.	**1-year P = 0.029**	1 year n.s.	**90d CD ≥ 3a P = 0.036**	All n.s.	
HOPE	23	17%	**91%**	91%	**44%**	17%	X
SCS	23	35%	**78%**	83%	**74%**	26%	X
Ravaioli – ECD-DBD (2022): lower rate of EAD + improved 1-year graft survival[5]							
		P = 0.007	**1-year P = 0.03**		90d CD ≥ 3b n.s.	All n.s.	
HOPE	55	**13%**	**98%**	X	22%	16%	X
SCS	55	**35%**	**87%**	X	33%	13%	X
Schlegel (2023): decrease in liver-related graft loss[6]							
			Liver-rel GL P = 0.004	Patient-rel GL n.s.	90d CD ≥ 3a n.s.	AS	
HOPE	85	17%	**0%**	5%	52%	17%	1%
SCS	85	46%	**7%**	1%	54%	21%	4%
DCD							
Van Rijn (2021): less non-anastomotic biliary strictures[7]							
					90d CD ≥ 3a	AS	**P = 0.03**
HOPE	78	26%	X	X	N = 101	X	**6%**
SCS	78	40%	X	X	N = 132	X	**18%**
DBD & DCD							
Panayotova (2023): non-inferiority for EAD established[8]							
			1-year liver-rel GL n.s.	1-year mortality n.s.	SAE	All	
HOPE	90	**11%**	2%	6%	13%; N = 15	13%	0
SCS	89	**16%**	6%	3%	27%; N = 37	26%	6%
Reich – interim analysis* (2023): lower rate of EAD[9]							
		P = 0.003			Liver/TPL-rel SAE		Awaited
HOPE	46/15	**20%**	100%	100%	26%	X	X
SCS	40/14	**44%**	98%	100%	39%	X	X

* At mean follow up of 141 ± 80 days (HOPE) and 139 ± 75 days (SCS).[9]

Additional relevant clinical outcomes

Reduction in acute cellular rejection with HOPE compared to SCS[10]

All grafts (N = 211)	DCD grafts (N = 153)
OR **0.54**	OR **0.37**
95% CI 0.29–1	95% CI 0.14–1
P = 0.05	P = 0.05

Maspero – meta-analysis: 6 studies (2023)[10]

Less HCC recurrence with HOPE in DCD grafts, compared to unperfused DBD grafts[11]

HCC recurrence HOPE DCD	5Y tumor-free survival HOPE DCD
6 %	**92 %**
VS. SCS DBD 26%; P = 0.002	VS. SCS DBD 73%; P = 0.027

Mueller – matched cohort study: N = 70 per group (2020)[11]

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PROTECTIVE MECHANISMS OF HOPE

Ischemia: mitochondrial injury in liver cells[12,13]

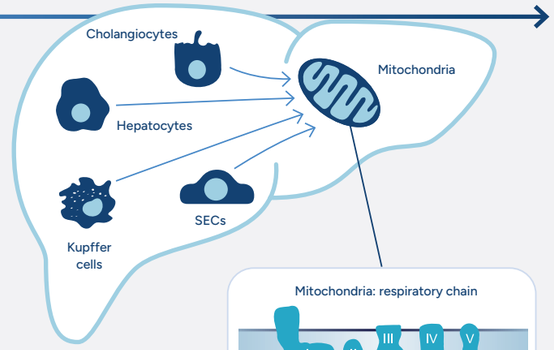
Mitochondria suffer **severe metabolic changes during ischemia,** which become evident and aggravated after reperfusion (reoxygenation). As a consequence of normothermic reperfusion (on a device or at implantation), the full picture of the **inflammatory ischemia reperfusion injury (IRI)** cascade develops, including release of **reactive oxygen species (ROS)** from mitochondria.[12]

Ischemia (hypoxia)

– O_2

Anaerobic metabolism

- Rapid ATP loss
- Accumulation of succinate + NADH



Reperfusion (reintroduction of O_2)

+ O_2

Re-establishing aerobic metabolism[14]

- Slow ATP recovery
- ROS and cytokine release
- Ubiquitous inflammation of the entire organ

The key instigator is **mitochondrial complex-I,** where most ROS are released immediately.[15]

Graphic modified from Schlegel A, et al. *J Hepatol.* 2022.13

HOPE acts before the injury occurs[13,14,16]

SUPPORTS NADH + ATP RELOADING » **DECREASES** ROS release & IRI-related inflammation » **REDUCES** downstream complications after LT

Viability testing during HOPE with FMN

In addition to ROS, **flavinmononucleotide (FMN)** is a complex-I molecule that is released into the perfusate upon reintroduction of oxygen. The amount of FMN released **increases with the degree of mitochondrial injury** and can be easily measured by spectroscopy, making it a **useful target for viability testing.**[14,17]

- FMN from complex-I can be **quantified** during HOPE[14,18]
- Perfusate levels of FMN correspond with clinical outcomes[18]
- First assessment after **30 min** of perfusion[14,18]

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HOPE WITH THE VITASMART™ HYPOTHERMIC OXYGENATED PERFUSION SYSTEM

Designed to Protect the Organ

- Pressure-controlled
- Automated flow
- Integrated air detector
- Protective hypothermic environment

Easy to Operate

- Simple set up and fast learning curve
- Compact size, easy to move within the hospital
- Allows for various HOPE protocols
- Registered for use in Liver and Kidney perfusion in all countries where the CE mark is accepted

Bridge to HOPE US randomized trial demonstrates promising interim results (N = 115) at ATC 2023[9]

EAD
HOPE 20 %
vs. 44 % SCS
P = 0.004

TPL-related SAEs
HOPE 26 %
vs. 39 % SCS

GS
HOPE 100 %
vs. 98 % SCS*

Find out more about HOPE and other solutions from Bridge to Life at www.bridgetolife.com.

* At mean follow up of 141 ± 80 days (HOPE) and 139 ± 75 days (SCS).9

Abbreviations
AS: anastomotic strictures; **ATP:** adenosine triphosphate; **CD:** Clavien-Dindo classification; **CI:** confidence interval; **DBD:** donation after brain death; **DCD:** donation after circulatory death; **EAD:** early allograft dysfunction; **ECD:** extended-criteria donor; **FMN:** flavinmononucleotide; **GL:** graft loss; **GS:** graft survival; **HCC:** hepatocellular carcinoma; **HOPE:** hypothermic oxygenated machine perfusion; **HR:** Hazard Ratio; **IRI:** ischemia/reperfusion injury; **LT:** liver transplantation; **MPS:** machine perfusion solution; **NADH:** nicotinamide adenine dinucleotide; **NAS:** non-anastomotic strictures; **OR:** odds ratio; **RCT:** randomized controlled trial; **ROS:** reactive oxygen species; **SAE:** severe adverse event; **SCS:** static cold storage; **TPL:** transplantation.

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