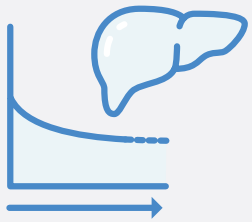
HOPE IN LIVER TRANSPLANTATION

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

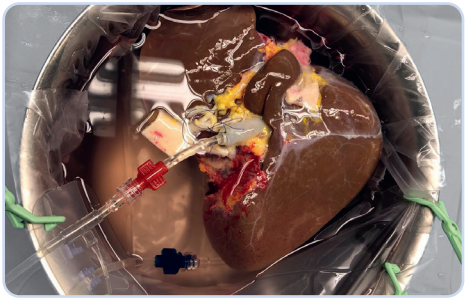
OR 0.31; 95% CI 0.11–0.92
P = 0.03

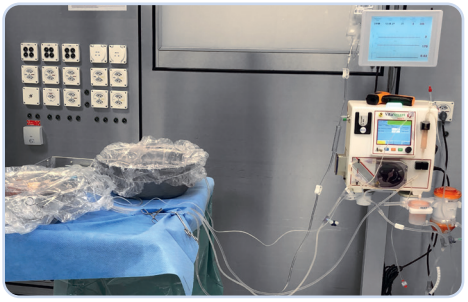
HOPE Key Facts

Simple and effective hypothermic liver perfusion

Timepoint: end-ischemic in recipient center

Perfusate	Belzer MPS® (actively oxygenated)
Timing & Duration	**Safe perfusion up to 11.5 hours[2]** and a **total preservation window up to 20 hours[3]**
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 for HOPE in liver transplantation

	N	EAD	Graft Survival	Patient Survival	Complications/ SAEs	Biliary complications	NAS
DBD							
Czigany – ECD-DBD (2021): improved 1-year graft survival + fewer 90-day major complications[5]							
		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[6]							
		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): less liver-related graft loss[7]							
			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): fewer non-anastomotic biliary strictures[8]							
					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							
Eden (2024): excellent 5-year patient survival and death-censored graft survival in higher risk donors (ECD-DBD, DCD) following HOPE, similar to benchmark results for unperfused, standard criteria DBDs[9]							
			5 year Death Censored	5 year			24 months
DBD	768	X	90%	85%	X	X	2.50%
DCD	434	X	81%	78%	X	X	11.50%
Reich – (under review): lower rate of EAD + fewer complications[10]							
		P<0.001	n.s.	n.s.	1-year CD ≥3a per pt P = 0.048	n.s.	Clinically Relevant (DCD)
HOPE	109	**20%**	95%	97%	2.2	21%	11%
SCS	110	**37%**	93%	96%	1.9	28%	19%

Additional relevant clinical outcomes

Reduction in acute cellular rejection with HOPE compared to SCS[11]

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)[11]

Less HCC recurrence with HOPE in DCD grafts, compared to unperfused DBD grafts[12]

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)[12]

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PROTECTIVE MECHANISMS OF HOPE

Ischemia: mitochondrial injury in liver cells[13,14]

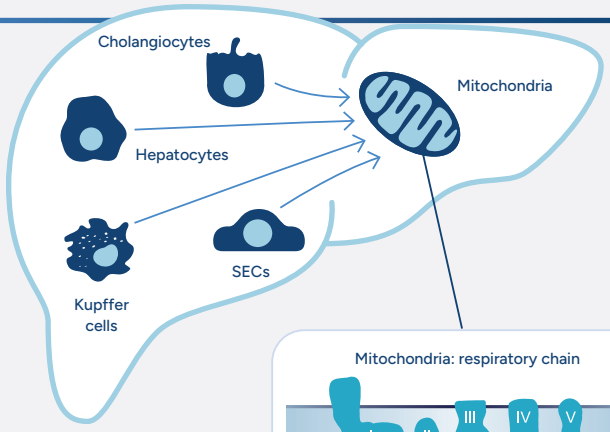
Mitochondria suffer **severe metabolic changes during ischemia,** which become evident and aggravated after reperfusion (reoxygenation). As a consequence of normothermic reperfusion (on a device or at implantation), the full picture of the **inflammatory ischemia reperfusion injury (IRI)** cascade develops, including release of **reactive oxygen species (ROS)** from mitochondria.[13]

Ischemia (hypoxia)

– O_2

Anaerobic metabolism

- Rapid ATP loss
- Accumulation of succinate + NADH



Reperfusion (reintroduction of O_2)

+ O_2

Re-establishing aerobic metabolism[15]

- 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.[16]

Graphic modified from Schlegel A, et al. *J Hepatol.* 2022.[14]

HOPE acts before the injury occurs[14,15,17]

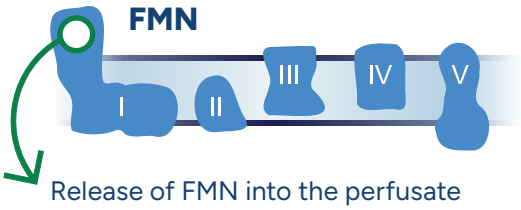
SUPPORTS
NADH + ATP reloading

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.[15,18]**



Release of FMN into the perfusate

- FMN from complex-I can be **quantified** during HOPE[15,19]
- Perfusate levels of FMN correspond with clinical outcomes[19]
- First assessment after **30 min** of perfusion[15,19]
- Internationally validated approach published[20]
- FMN validated as a predictor of EAD and patient survival[21]

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BRIDGE TO HOPE US TRIAL RESULTS

Bridge to HOPE randomized trial demonstrates promising benefits for HOPE over SCS alone[10]

EAD
HOPE = 20%, vs.
SCS = 37%, p<0.001

Steroid resistant rejection
HOPE = 1%,
SCS = 8%, p=0.03

Overall CD ≥3a complications/ patient
HOPE = 138 complications in 73 patients,
SCS = 170 complications in 78 patients, p=0.048

Liver-related CD ≥3a complications/ patient
HOPE = 51 complications in 36 patients,
SCS = 78 complications in 54 patients , p=0.014

Median hospital length of stay
HOPE = 8 days,
SCS = 11 days, p=0.04

For more information about HOPE and other innovative products, visit www.bridgetolife.com

Download a digital copy of this and other HOPE and product documents.

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; **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; **SCS:** static cold storage

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VitaSmart™ is CE Marked and available for sale in several markets outside of the United States.
VitaSmart™ has not been cleared by the FDA, and the safety and effectiveness of VitaSmart™ has not been established in the US.

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