Ex situ machine perfusion strategies in liver transplantation

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Published in:
Journal of Hepatology

DOI:
10.1016/j.jhep.2018.09.019

Publication date:
2019

Hepatology Snapshot:

Ex situ machine perfusion strategies in liver transplantation

JOURNAL OF HEPATOLOGY

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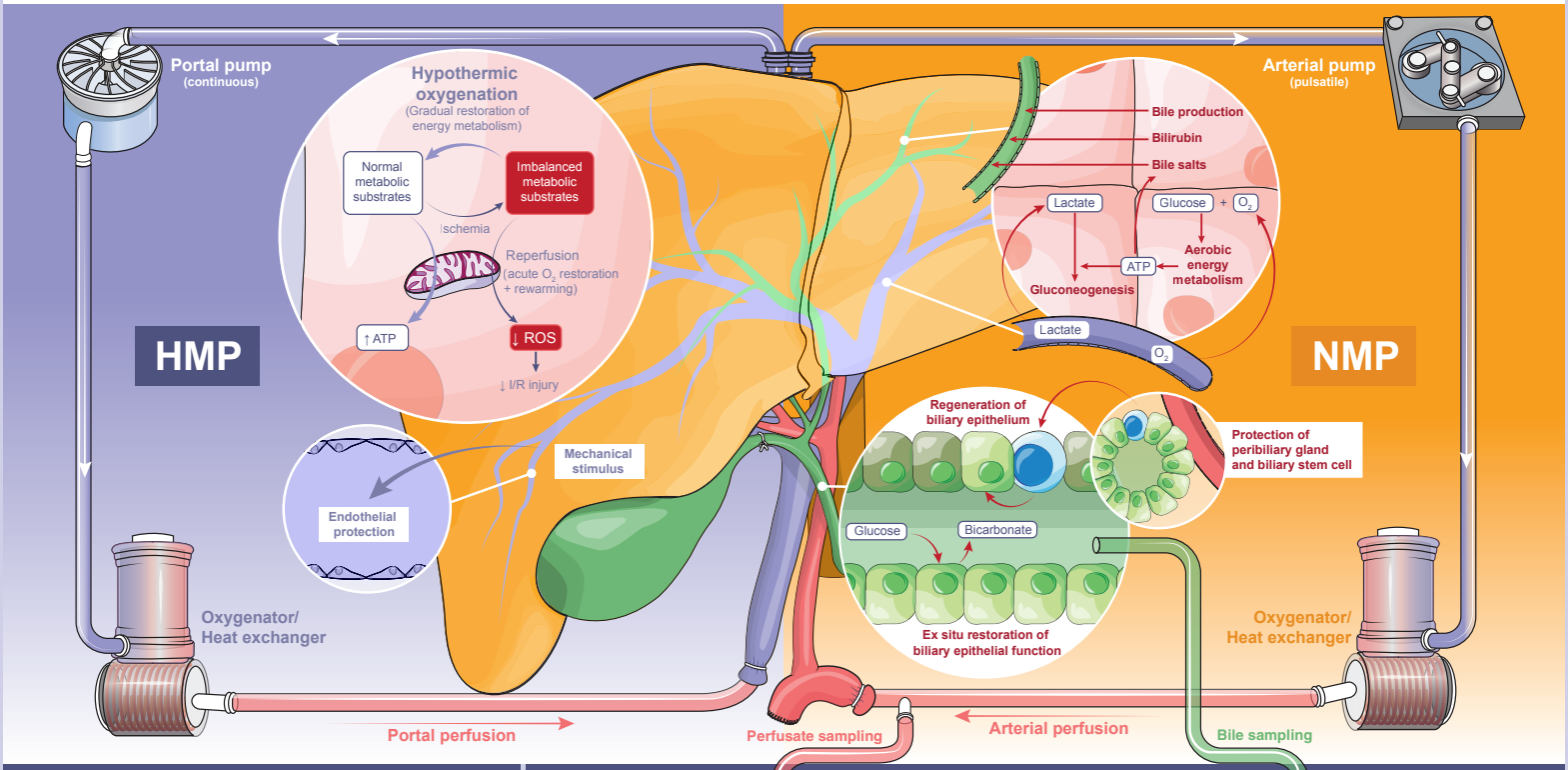
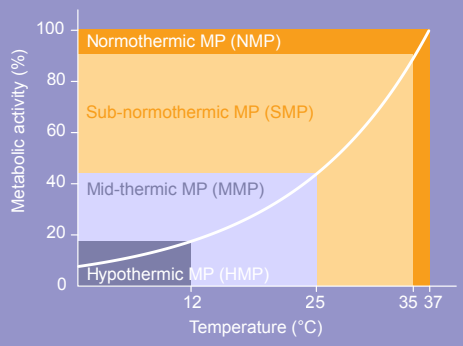
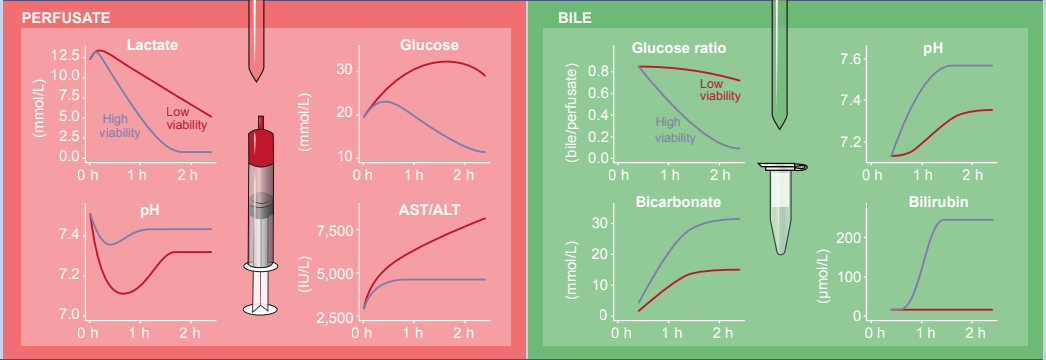
PROTECTIVE MECHANISMS OF *EX SITU* MACHINE PERFUSION



MP VARIATIONS IN TEMPERATURE



POTENTIAL VIABILITY TESTS



CLINICAL STRATEGIES OF *EX SITU* MACHINE PERFUSION

	DONOR HOSPITAL	TRANSPORTATION	TRANSPLANT HOSPITAL			
Current standard	Procurement	SCS	SCS	Back table	Warm ischemia (implantation)	Reperfusion
Post-SCS MP	Procurement	SCS	Back table: HMP (HOPE, DHOPE) + Resuscitation (0 h 1 h 2 h 3 h 4 h); NMP + Viability tests (0 h 1 h 2 h 3 h 4 h); HMP + COR + NMP + Resuscitation + Viability tests (0 h 1 h 2 h 3 h 4 h)	Back table	Warm ischemia (implantation)	Reperfusion
Preservation MP	Procurement / Back table	NMP	NMP		Warm ischemia (implantation)	Reperfusion
Ischemia free liver transplantation	Procurement under NMP	NMP	NMP		Implantation under NMP	Reperfusion

Keywords: Liver transplantation; Machine perfusion; Dynamic preservation; Organ preservation; Organ resuscitation, Graft viability tests.

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COR, controlled oxygenated rewarming; DHOPE, dual HOPE; HOPE, hypothermic oxygenated machine perfusion; MP, machine perfusion; ROS, reactive oxygen species; SCS, static cold storage.

Received 11 June 2018; received in revised form 25 August 2018; accepted 18 September 2018.

Introduction

A continuing discrepancy between organ availability and demand has forced utilization of extended criteria donor (ECD) livers, including donation after circulatory death, elderly or steatotic grafts, which are at increased risk of failure after transplantation. Especially for ECD grafts, dynamic preservation using *ex situ* machine perfusion (MP) allows reconditioning and viability assessment of livers prior to transplantation, rather than standard static cold storage (SCS) alone. MP is revolutionizing the field of liver transplantation and is undergoing rapid clinical implementation, albeit with several technical variations.[1] This snapshot summarizes the different clinical strategies.

Ex situ MP strategies may differ in timing (*i.e.* at procurement, during transport, and/or pre-implantation), duration, as well as temperature of perfusion. Additional technical differences are type of perfusion fluid, single (portal vein only) *vs.* dual (portal vein and hepatic artery) perfusion, active *vs.* no active oxygenation, and variations in perfusion pressures.[2] Clinically, the most applied strategies are hypothermic (0–12 °C) MP (HMP) and/or normothermic (35–38 °C) MP (NMP) as an adjunct to SCS preservation, or preservation NMP as an alternative for SCS preservation.

MP technology may optimize donor liver utilization and reduce post-transplant complications by i) graft reconditioning, ii) viability assessment, iii) improved preservation, and iv) potential therapeutic intervention.

Reconditioning

Although cellular metabolism during SCS preservation is significantly reduced, residual oxygen and nutrient consumption result in intracellular depletion of adenosine triphosphate. During reperfusion and re-oxygenation, radical oxygen species (ROS) and damage-associated molecular patterns are generated, leading to cellular injury and a disproportionate (and sometimes detrimental) immune response, collectively known as ischemia-reperfusion injury.[3] Especially for ECD grafts which sustain greater injury during SCS, reconditioning using HMP is promising. Oxygenated HMP restores mitochondrial function and increases endothelial function and integrity, thereby alleviating ROS production and the inflammatory response upon reperfusion.[4] First clinical experiences suggest that post-SCS oxygenated HMP results in superior outcome, compared to transplantation of SCS-only preserved human livers.[5,6]

Viability assessment

While in hypothermic conditions liver metabolism is minimal, normal metabolic function during NMP enables assessment of hepatocyte and cholangiocyte viability. Especially for ECD grafts with increased risk of primary non-function or biliary complications, viability assessment is currently explored prior to transplantation. Proposed markers of hepatocellular function include bile production, and perfusate glucose and lactate levels. Hepatocyte injury markers include perfusate aminotransferase levels. Important markers of cholangiocellular function include bile pH, bicarbonate, and glucose levels.[7] NMP can be preceded by HMP followed by controlled oxygenated rewarming (*i.e.*, a gradual increase of perfusion temperature) to allow sequential graft reconditioning and viability assessment.

Improved preservation

Preservation MP can be applied from graft retrieval until transplantation, although during organ procurement and machine (dis)connection there are short periods of graft ischemia. Preservation NMP has been shown to be safe, reduce cold storage length and may provide logistical advances, compared to SCS.[8] Interestingly, the first successful human ischemia-free liver transplantation was performed using continuous NMP during procurement, preservation and graft implantation.[9]

Therapeutic potential

An additional advantage of NMP is the opportunity to prolong the preservation period and to potentially apply repair strategies to improve graft quality. As proof-of-concept, a human discarded liver was preserved for 86 h using *ex situ* NMP,[10] and an initially declined human liver was successfully transplanted after preservation for 26 h, of which 8.5 h were with NMP.[11] Other potential therapeutic interventions include pharmacological defatting strategies, gene and (stem)cell therapy during NMP. These applications, however, require further confirmation in pre-clinical transplant experiments.

Conclusion

In conclusion, dynamic preservation using *ex situ* MP facilitates enhanced utilization of (ECD) liver grafts for transplantation. The first clinical experiences with HMP and NMP are promising. Aforementioned MP strategies are not mutually exclusive, and complementary techniques may be combined. The optimal and most cost-effective strategy as well as thresholds regarding which (ECD) graft requires which dynamic preservation method remain to be defined. Future studies are needed to examine the impact of MP on long-term graft function, survival and biliary complications.

Financial support

Masato Fujiyoshi was supported by grants from the International Hepato-Pancreato-Biliary Association (Kenneth Warren Fellowship) and the International Liver Transplantation Society (International Scholar Award).

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Vincent E. de Meijer, MD, PhD: conceptualizing the figure and manuscript preparation. Masato Fujiyoshi, MD, PhD:

Please cite this article in press as: de Meijer VE, Fujiyoshi M. . J Hepatol (2018), https://doi.org/10.1016/j.jhep.2018.09.019

conceptualizing the figure and critical input in manuscript preparation. Robert J. Porte, MD, PhD: critical input in conceptualizing the figure and manuscript preparation.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.09.019.

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Author names in bold designate shared co-first authorship

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