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# Hypo- and normothermic perfusion of the liver: Which way to go?

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A B S T R A C T

The demand of donor livers for transplantation exceeds the supply. In an attempt to maximize the number of potentially usable donor livers, several centers are exploring the role of machine perfusion. This review provides an update on machine perfusion strategies and basic concepts, based on current clinical issues, and discuss challenges, including currently used biomarkers for assessing the quality and viability of perfused organs. The potential benefits of machine perfusion on immunogenicity and the consequences on post-operative immunosuppression management are discussed.



## Introduction

The success of liver transplantation has driven increased indication, resulting in far more candidates on waiting lists, than donor organs available [1–3]. This still growing gap between liver supply and demand has forced professionals to utilize livers from older, fattier, ischemically damaged or otherwise extended criteria donors (ECD) [4]. Such livers carry high risk of post-transplant complications, including primary-non-function (PNF), early allograft dysfunction (EAD), biliary complications and graft loss [5–7]. Key factors for liver graft dysfunction include donor warm ischemia (donation after circulatory arrest (DCD) donation), graft steatosis and prolonged cold storage of more than 10 h [2,3,8]. Graft optimization or repair strategies are therefore currently emerging to improve clinical outcomes. This review will focus first on underlying mechanisms of injury throughout the process of organ donation, preservation and implantation. Furthermore, we will report on perfusion strategies and discuss the clinical implementations and potential future developments.

## Accumulation of injury from the donor to the recipient

Organ injury already starts before organ procurement, due to donor warm ischemia in donation after cardiac death (DCD) or during brain death (DBD) [8]. Following this initial hit, donor livers undergo the process of retrieval surgery, including cold flush and static cold storage (SCS). Cooling slows down metabolism and prolongs the time of oxygen deprivation with minimal loss of viability [9]. However, energy consumption is not completely stopped, but reduced (approximately 12-fold, Fig. 1) and a number of negative effects have been reported, e.g. depletion of the adenine nucleotide pool [10], lactate acidosis [11], intracellular calcium accumulation [12], and sinusoidal endothelial damage [13]. All these effects are initiated by anaerobic metabolism and limit the maximum time period for SCS. Cells swell and lyse due to deleterious effects on plasma membrane lipids, cytoskeleton, microtubules, and mitochondria (disabling the ion-exchange pumps) [14].

During implantation, liver grafts are exposed to ischemia rewarming, further aggravating anaerobic metabolism. Subsequently, the sudden exposure to normothermic blood and oxygen during reperfusion triggers an immediate release of reactive

*Abbreviations:* MELD, Model of end stage liver disease; ROS, Oxygen free radicals; MPT, Mitochondrial pore transition; ER, Endoplasmic reticulum; DAMP's, Danger associated molecular pattern's; KC's, Kupffer cells; TLR-4, Roll-like-receptor-4; SEC, Sinusoidal endothelial cells; HO, Heme oxygenase; NO, Nitric oxide; IP, Ischemic preconditioning; RIPC, Remote ischemic preconditioning; VEGF, Vascular endothelial growth factor; AKT, Aldo ketoreductase; HIF, Hypoxia-inducible factor; DCD, Donation after circulatory death; NAC, N-acetylcysteine; IPC, Ischemic post conditioning; DBD, Donation after brain death; NRP, Normothermic regional perfusion; HMP, Hypothermic machine perfusion; HOPE, Hypothermic oxygenated perfusion; HCC, Hepatocellular carcinoma; NASH, Nonalcoholic steatohepatitis; NMP, normothermic machine perfusion; PSC, Primary sclerosing cholangitis; PBC, Primary biliary cholangitis; NK, Natural killer cells; APC, antigen presenting cells; ICAM, Intercellular adhesion molecule; ATP, Adenosine triphosphate; IL, Interleukin; TLR, Toll-like-receptor; SCS, Static cold storage.

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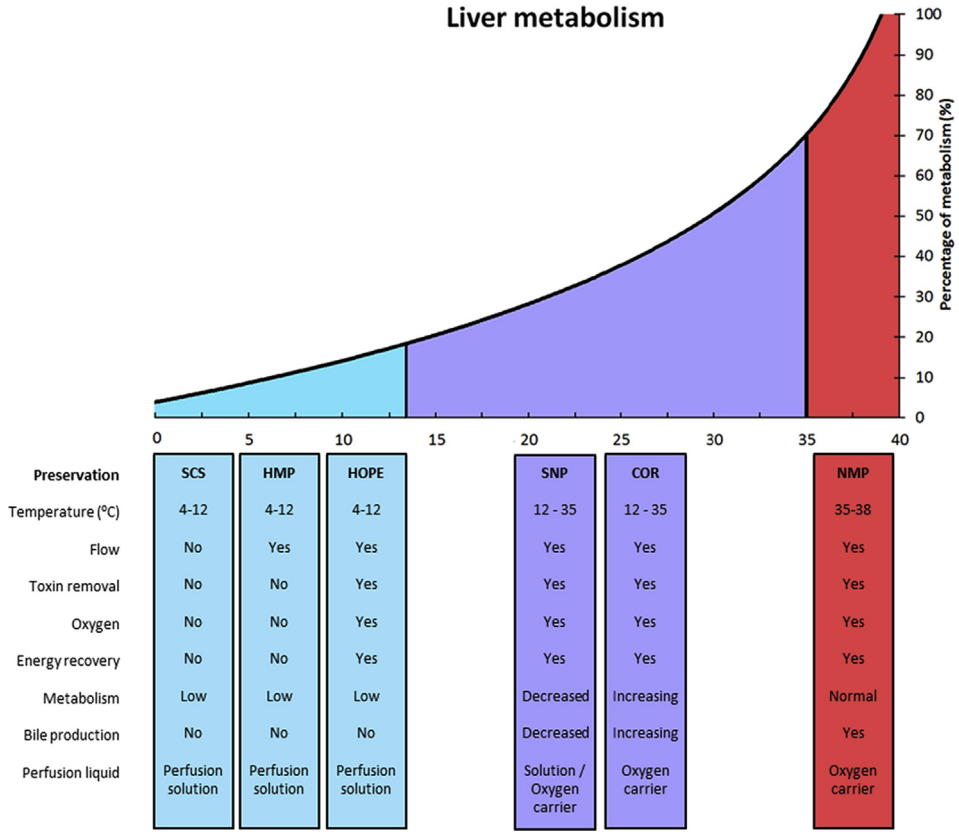


**Fig. 1.** Schematic representation of perfusion strategies and their characteristics. (SCS = static cold storage, HMP = hypothermic machine perfusion, HOPE = hypothermic oxygenated perfusion, SNP = subnormothermic machine perfusion, COR = controlled oxygenated rewarming, NMP = normothermic machine perfusion).

oxygen species (ROS) within the first minutes of reperfusion (Fig. 2A) [15]. The main mechanism behind is mitochondrial damage [16,17], caused by electron leaks [11,17–19], with subsequent oxidative injury of mitochondrial and nuclear DNA. This results in downstream activation of danger associated molecular patterns (DAMPs, Fig. 1A) [20], activation of toll-like-receptors (TLR) on non-parenchymal liver cells, and release of numerous inflammatory mediators (Fig. 2B) [15,21]. These compounds start an

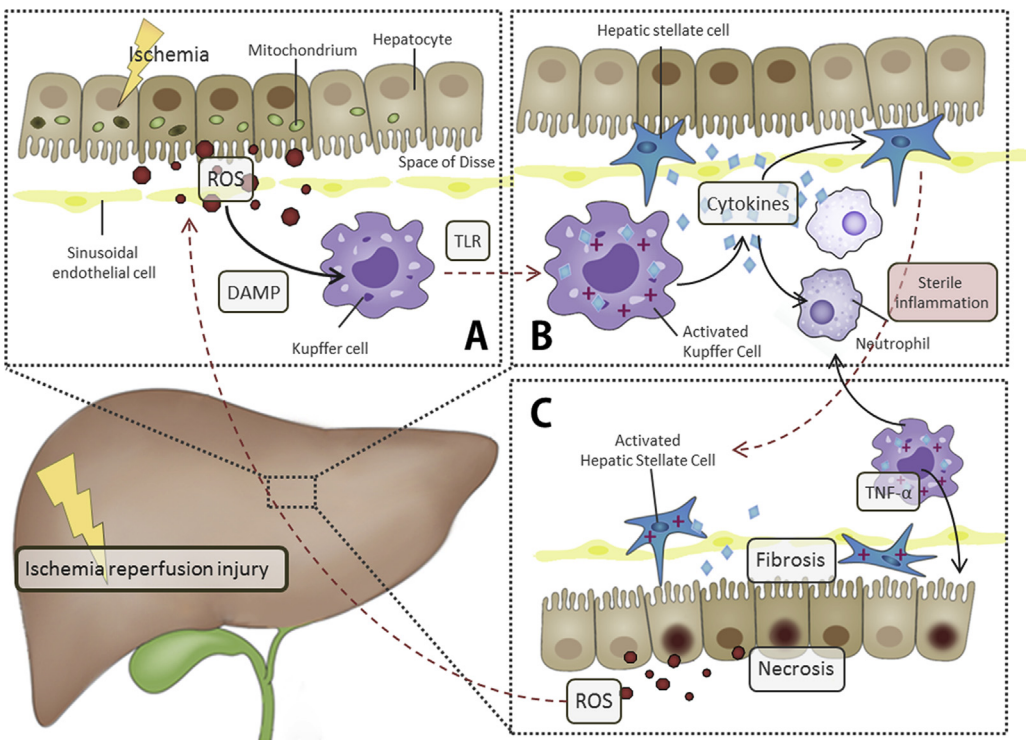


**Fig. 2.** Mechanism of injury following ischemia/reperfusion and potential targets of protection through machine perfusion approaches.

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