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WORD COUNT	1890	TIME SUBMITTED	23-FEB-2024 02:38PM
		PAPER ID	107092021

Name of Journal: *World Journal of Gastroenterology*
Manuscript NO: 91704
Manuscript Type: EDITORIAL

Routine utilization of machine perfusion in liver transplantation: ready for prime time?

Machine perfusion in liver transplantation

Alessandro Parente, Keyue Sun, Philipp Dutkowski, A.M. James Shapiro, Andrea Schlegel

Abstract

The last decade has been notable for increasing high-quality research and dramatic improvement in outcomes with dynamic liver preservation. Robust evidence from numerous randomized controlled trials has been pooled by meta-analyses, providing the highest available evidence on the protective effect of machine perfusion over static cold storage in liver transplantation. Based on a protective effect with less complications and improved graft survival, the field has seen a paradigm shift in organ preservation. This editorial focuses on the role of machine perfusion in liver transplantation and how it could become the new "gold standard". Strong collaborative efforts are needed to explore its effects on long-term outcomes.

Key Words: liver transplantation; machine perfusion; viability assessment; hypothermic oxygenated perfusion; normothermic machine perfusion

Parente A, Sun K, Dutkowski P, Shapiro AJ, Schlegel A. Routine utilization of machine perfusion in liver transplantation: ready for prime time? *World J Gastroenterol* 2024; In press

Core Tip: Machine perfusion has garnered the interest of the transplant community given its proven beneficial effects on the clinical outcomes after liver transplantation. Herein, we discuss the historical background of machine perfusion in liver transplantation and the available clinical evidence. Furthermore, we highlighted the obstacles and the need for future research, in particular with respect to viability assessment and prolonged preservation times.

INTRODUCTION

Machine perfusion (MP) technology is an ~~rather~~ old concept first introduced by Alexis Carrell and Charles Lindberg in the 1920's, then utilized first in clinical kidney transplantation in 1968 [1], however static cold storage (SCS) appeared simpler and more

practical, effectively ~~effective~~ hindering ~~the~~ progress in MP technology development for more than 3 decades. Recently, MP has emerged as one of the most promising approaches to improve post-transplant outcomes after liver transplantation (LT).

Two main ex-situ liver perfusion and one in-situ donor approach are increasingly used in clinical practice today [2]. The first ex-situ technique is known as hypothermic oxygenated perfusion (HOPE) using a highly oxygenated (pO_2: >60 kPa) artificial solution at hypothermic temperatures (8-12 °C) [2]. The second perfusion technique, normothermic machine perfusion (NMP), uses a blood-based perfusates at 37 °C, thus recreating a near-physiologic environment. Both HOPE and NMP are mainly applied after SCS, however NMP-preservation is also started upfront after minimal SCS of 2-3hrs or as described with "ischemia-free organ transplantation (IFOT)", as a technique avoiding all SCS[2]. In contrast, during in-situ normothermic regional perfusion (NRP) a veno-arterial extracorporeal membrane oxygenation technique is used to recirculate and oxygenate donor blood immediately after circulatory arrest in donation after circulatory death (DCD) donors [2].

The importance of oxygen was understood early with the use of HOPE in kidney transplants in 1968, however the earlier perfusion concepts in LT were simply hypothermic (HMP). Guarrera *et al* presented the first clinical study in LT in 2010 with HMP using a homegrown device (**Figure 1**) [3].

NRP was used first in uncontrolled DCD in 2007 [4] and NMP started later off in clinics in 2016 [5].

The very first randomized controlled trial (RCT) with NMP and the Organox-Metra® device was published in 2018 by Nasralla *et al* [6]. The authors demonstrated less early allograft dysfunction (EAD) and lower peak AST levels during the first week after transplant in the recipient of NMP-treated grafts compared to SCS [6]. Only one year later, similar results in terms of EAD were illustrated by another single center RCT, however with much smaller number of patients [7].

Next, in 2021, another two important RCTs were published. The first was focused on HOPE in DCD livers and demonstrated a four times lower risk of non-anastomotic biliary

strictures compared to SCS, together with lower EAD-rates, postreperfusion syndrome and retransplantation [8]. And the second RCT paralleled such results with HOPE and showed less 90-days post-operative complications, shorter intensive care and hospital stay compared to SCS in extended criteria donor livers after brain death DBD) [9]. The following 2 years, the findings of these studies with HOPE were supported by further RCTs. The Bologna team showed that patients receiving HOPE-treated extended criteria DBD livers had significantly lower EAD-rates, better 1-year graft survival, less post-LT complications and lower hospital re-admission rates compared to SCS[10]. Authors from the US published the results of another multicenter RCT using the portable OCS™ device provided by Transmedics for upfront NMP[11]. The NMP group in this study had significantly lower EAD-rates and less signs of ischemia-reperfusion injury on histopathology[11].

In the first half of 2023, two RCTs were published: the largest RCT ever conducted with HOPE and the first one with ischemia-free organ transplantation (IFOT). In the former, the authors illustrated that, although the number of serious complications between HOPE and SCS was similar, a post hoc analysis revealed that liver-related serious complications occurred less frequently in the HOPE group compared to SCS. Notably, graft failure due to liver-related complications did not occur with HOPE but in 7% of SCS grafts (6 of 85) [12]. Subsequently, a Chinese group reported the results of the first RCT of DBD livers randomly assigned to SCS or IFOT, demonstrating significantly reduced EAD-rates, post-reperfusion syndrome, less non-anastomotic biliary stricture, and less cumulative post-operative complications at 12 months [13]. A group from Poland assessed the role of HOPE in their country. In low-risk DBD donors HOPE had no impact on outcomes, however authors demonstrated significantly lower EAD-rates and post-operative complications in donor livers with higher risk, i.e., with a donor risk index of > 1.7)[14]. Two additional RCTs were recently presented with NMP and HOPE in the US. NMP with the Organox-Metra® device had a positive effect on the post-reperfusion syndrome [15]. And HOPE showed lower PBF, less EAD rates and reduced biliary strictures [16].

Such RCTs were recently combined with other retrospective studies in several meta-analyses [17], summarizing the beneficial effects of MP over SCS [18, 19]. Currently, there are no available RCTs comparing HOPE and NMP, however results of ongoing RCT are awaited (Clinicaltrials.gov: NCT04644744)

While there are no RCT with NRP available yet, this technology appears to be beneficial to reduce biliary complications, improve graft survival and increase organ utilization if combined with limited SCS up to 6-7hrs [20, 21, 22]. It seems unlikely that a RCT would proceed as the clinical outcomes have been so positive to date – in fact it is currently mandated in France and other European countries that DCD donation should not proceed unless NRP is applied. Clinical studies demonstrated however several limitations, especially when donor warm ischemia time before or SCS after NRP are prolonged or when these grafts were used for retransplant candidates [25, 26]. Perfusion technologies are not mutually exclusive, and indeed when looking at real-world data have been combined with satisfactory outcomes [27]. In particular, in Italy where the no-touch period following DCD donation is 20 minutes, combining NRP and HOPE has yielded good outcomes [28].

Despite its clinical benefits, MP is still not routinely used worldwide. There are several reasons behind this which have been identified as lack of funding, clarity as to what is research and what is accepted clinical care delivery, knowledge and availability of healthcare staff trained in the operation of this equipment [29, 30]. In addition, it must be noted that the current available evidence is limited at one year follow-up. In fact, all RCTs and meta-analyses that have been published have reported their outcomes at one year. This appears to be one of the main limitations of the current available literature. As life expectancy of LT recipients continues to increase, exceeding 70% at 5 years [31], more evidence is needed to better understand the impact of MP on long-term outcomes after LT. Additionally, many RCTs have reported similar study endpoint outcome measures with however heterogenous definitions often lacking certain endpoints [18]. Future

research will need to endeavor in more homogeneous outcome reporting to provide replicable data worldwide.

Perfusing marginal organ with the aim to increase liver utilization rates necessitate reliable viability tests. Although there are several biochemical factors that have been explored both for HOPE and NMP [32, 33], there are no clear guidelines regarding a systematic viability assessment during liver perfusion and available parameters often lack sensitivity and acceptable positive predictive value to discriminate between livers of metabolically good quality and others with too high risk for failure in the recipient. Most viability parameters are usually measured in the perfusate, with arbitrary timepoints and cutoffs, reflecting a post ischemia-reperfusion injury downstream of instigating mitochondria in hepatocytes, including perfusate lactate, transaminases, cytokine, and LDH. Bile chemistry is also applied to assist identification of livers at risk of ischemic cholangiopathy ~~to develop non anastomotic strictures~~. The early occurring cellular damage during MP was recently assessed with proteomics analysis of bile collected during sequential HOPE, rewarming and subsequent NMP [34]. On the other hand, mitochondrial transition pore opening with danger signal release appears to be a more upfront parameter of liver injury [33, 35]. There is evidence that MP could be utilized to reprogram mitochondrial metabolism during HOPE before normothermic reperfusion. The slow metabolism of succinate and concomitant ATP reloading are two protective mechanisms described with HOPE. A recent study has demonstrated that the analysis of flavin mononucleotide from complex I, perfusate NADH, and mitochondrial CO2 production during HOPE allows a more objective viability assessment of liver quality on a subcellular level which seems to be more reliable when compared to donor derived data, in particular for high-risk organs such as DCD [33].

In the real world, MP is used also for logistic reasons and prolonged liver preservation is increasingly used to enable timely LT with both NMP and HOPE [6, 11, 15, 37]. A human liver graft was preserved for 3 days and successfully transplanted [38] and some discarded

livers were preserved with MP up to 7 days with satisfactory viability parameters [39]. Although this approach might be of interest in the future to enable the modification of cellular metabolisms during ex-situ MP, its daily applicability is still limited to small number of cases and challenges with difficult devices required particularly for prolonged NMP [40].

Next to a prolonged *ex-situ* perfusion, super cooling and cryopreservation are potential but as yet untested clinically as ~~appears as~~ additional technique to prolong organ preservation. A recent study has explored the concept of cryopreservation which enabled to preserve experimental kidney grafts for 100 days through vitrification and nanowarming[41]. Despite being compelling novel strategies, such techniques are currently limited to animal models or small studies and their potential future applications remains unclear.

CONCLUSION

In summary, within the past 5 years, increasing evidence has demonstrated the clinical benefits of MP in the setting of LT (Figure 1). We believe that this progress with MP technology and the clear beneficial effects will soon outpace and replace the standard SCS preservation for the human liver grafts, and now necessitates both a paradigm shift and rapid change in clinical practice to capitalize on these advances. This will pave the way for a new era in organ transplantation, leading to the application of MP routinely in clinical practice, in particular for marginal organs. However, several challenges remain and will need to be addressed in future research.

ACKNOWLEDGEMENTS

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