World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2025 June 9; 14(2): 101777

DOI: 10.5492/wjccm.v14.i2.101777

ISSN 2220-3141 (online)

MINIREVIEWS

Post-reperfusion syndrome in liver transplant recipients: What is new in prevention and management?

Austin James Puchany, Ibtesam Hilmi

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A, Grade B, Grade B, Grade B

Novelty: Grade A, Grade B, Grade B, Grade B

Creativity or Innovation: Grade A, Grade B, Grade C, Grade C

Scientific Significance: Grade A, Grade B, Grade B, Grade B

P-Reviewer: Semash K; Wang L; Wang Y

Received: September 26, 2024

Revised: November 22, 2024

Accepted: December 19, 2024

Published online: June 9, 2025

Processing time: 85 Days and 6.7 Hours

Austin James Puchany, Department of Anesthesiology & Perioperative Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, United States

Ibtesam Hilmi, School of Medicine, University of Pittsburgh, Pittsburgh, PA 15213, United States

Ibtesam Hilmi, Department of Anesthesiology and Perioperative Medicine, Clinical and Translational Science Institute, University of Pittsburgh, School of Medicine, Pittsburgh, PA 15213, United States

Corresponding author: Ibtesam Hilmi, FRCA, MBChB, Doctor, Professor, School of Medicine, University of Pittsburgh, 200 Lothrop St, Pittsburgh, PA 15213, United States.
hilmiia@upmc.edu

Abstract

Post-reperfusion syndrome (PRS) in liver transplant recipients remains one of the most dreaded complications in liver transplant surgery. PRS can impact the short-term and long-term patient and graft outcomes. The definition of PRS has evolved over the years, from changes in arterial blood pressures and heart and/or decreases in the systemic vascular resistance and cardiac output to including the fibrinolysis and grading the severity of PRS. However, all that did not reflect on the management of PRS or its impact on the outcomes. In recent years, new scientific techniques and new technology have been in the pipeline to better understand, manage and maybe prevent PRS. These new methods and techniques are still in the infancy, and they have to be proven not in prevention and management of PRS but their effects in the patient and graft outcomes. In this article, we will review the long history of PRS, its definition, etiology, management and most importantly the new advances in science and technology to prevent and properly manage PRS.

Key Words: Liver transplant; Post-reperfusion syndrome; Machine perfusion; Hypothermic machine perfusion; Normothermic machine perfusion; Caval blood flush vent; Ischemic pre-conditioning

Core Tip: In this article, we review the newest updates in the definition, pathophysiology and risk factors for post-reperfusion syndrome (PRS). We discuss the latest recommendations for management of PRS. We analyze and the novel advances in liver donor preservation and their potential impact on prevention of PRS.

Citation: Puchany AJ, Hilmi I. Post-reperfusion syndrome in liver transplant recipients: What is new in prevention and management? *World J Crit Care Med* 2025; 14(2): 101777
URL: https://www.wjgnet.com/2220-3141/full/v14/i2/101777.htm
DOI: https://dx.doi.org/10.5492/wjccm.v14.i2.101777

INTRODUCTION

Liver transplantation represents a life-saving intervention for patients with end-stage liver disease. The surgical process involves complex steps, including the critical moment of reperfusion, where blood flow is restored to the graft liver. One of which is unclamping of the portal vein which can lead to hemodynamic instability. This spectrum of hemodynamic changes and its complications can lead to post-reperfusion syndrome (PRS). PRS is a well-recognized complication that can significantly impact the immediate and long-term outcomes of liver transplant recipients. PRS can promote more intraoperative transfusion as well as prolong intensive care unit (ICU) and overall hospital length of stay, therefore it has impact on morbidity and mortality for the recipient[1,2]. This syndrome is characterized by a spectrum of physiological disturbances and clinical symptoms that can jeopardize graft function and patient recovery.

PRS in liver transplantation is classically defined as a decrease in mean arterial pressure (MAP) by 30% from baseline for 1 minute and occurring withing 5 minutes of graft reperfusion. Other associated hemodynamic factors include decreased systemic vascular resistance (SVR) and heart rate (HR) as well as increased central venous pressure (CVP) and pulmonary capillary wedge pressure[3]. PRS can further be classified on degree of severity based on magnitude and length of hemodynamic changes[4]. For example, mild PRS is when there is < 30% decrease in MAP or HR < 5 minutes that is responsive to a fluid bolus, 1 g of IV calcium or epinephrine less than 100 ug without the need for continuous vasopressors intraoperatively. Significant PRS occurs with > 30% decline in MAP or HR, arrythmias promoting hemodynamic instability or asystole and the need for a continuous infusion of vasopressors intraoperatively. Additionally significant PRS includes prolonged (> 30 minutes) or recurrent (reappearing within 30 minutes after resolution) fibrinolysis requiring treatment with antifibrinolytics[5]. One study tested both definitions (Aggarwal *et al*[3] and Hilmi *et al*[5]) and found that both were able to reasonably predict 3-month mortality following orthotopic liver transplant (OLT)[6].

ETIOLOGY AND PATHOPHYSIOLOGY

PRS is believed to result from a cascade of physiological events triggered by the restoration of blood flow to the ischemic liver graft. Following release of the portal vein clamp the right heart is exposed to, cold, acidic blood with vasoactive inflammatory reactants that results in increases in CVP, pulmonary vascular resistance, and pulmonary artery pressures with decreased systemic pressure. The elevated pulmonary pressures can cause right ventricular failure which can lead to decreased left ventricular filling pressures precipitating the hemodynamic changes associated with PRS[7-9].

The release of ischemic byproducts following unclamping of the portal vein and inferior vena cava (IVC) clamps can precipitate the metabolic derangements associated with PRS, these include lactic acidosis, hyperkalemia, and hypocalcemia. These electrolyte derangements can evoke arrythmias and ST and T-wave changes. Additionally, there is often an increase in partial pressure of carbon dioxide, a metabolic byproduct of cellular respiration and metabolism in the new organ which can affect blood flow and ventilation dynamics[10]. Other byproducts of ischemia such as heparinoids, cytokines and chemokines can evoke a systemic inflammatory response (SIRS) and lead to coagulopathy. As well as the endogenous heparin release from the donor liver can contribute to coagulopathy. Fibrinolysis can occur *via* decreased activity of plasminogen activator inhibitor and from tissue-plasminogen activator released from the donor liver and ischemic tissues below the clamp[11].

Ischemia during the preservation stage of the transplantation process can also result in ischemic reperfusion injury of the new liver graft which is thought to contribute to PRS. During storage, Ischemia produces lytic enzymes like xanthine oxidase and NADPH oxidase that can produce reactive oxygen species (ROS) that can damage the new liver and surrounding tissues. These ROS are sensed by Kupffer cells in the liver which release cytokines like tumor necrosis factor alpha (TNF-α) and other inflammatory substances that can produce a SIRS response[12,13]. One study found that the levels of TNF-α secreted from the liver correlated to vasopressor requirements following reperfusion.

Microcirculatory changes occur due to an imbalance of endothelin-1 and nitric oxide (NO) in the sinusoids which lead to accumulation of neutrophils and platelets in blood vessels leading to ischemia. This promotes hepatocellular necrosis and activation of local inflammatory reactants (Kupffer cells) leading to further oxidative injury[14]. Intestinal bacteria can play a role in PRS through bacterial translocation from disruption of the intestinal barrier from surgical manipulation and portal venous congestion. Endotoxemia can occur within 30 minutes of liver ischemia due to lack of protection from removed Kupffer cells in anhepatic phase. Also, gut translocation can activate the complement cascade with formation of

the membrane attack complex potentially leading to post-reperfusion hypotension, but this exact mechanism remains unclear[15].

Following reperfusion, exposure of the recipient's blood to basement membrane of the damaged transplanted sinusoidal cell endothelium can evoke activation of the kallikrein-kinin system leads to breakdown of kininogen increases bradykinin levels, a vasoactive substance that can contribute to PRS[16].

Patients with advanced cirrhosis have higher levels of NO due to endotoxin-induced stimulation of the inducible NO synthase, NO produces cyclic guanosine monophosphate (cGMP) which decreases SVR and causes hypotension as well as ROS that cause further oxidative injury. Studies have shown that higher baseline levels of cGMP have been associated with higher catecholamine vasopressor requirement and longer ICU stay[17].

Some risk factors for developing PRS include donor age, recipient age, Model for End-Stage Liver Disease Score, organ size difference, degree of microvascular steatosis, patient specific factors such as elevated creatinine, low calcium and hemoglobin levels, left ventricular diastolic dysfunction and prolonged cold ischemic time[18] (Table 1).

PREVENTION

PRS can have a significant impact on patient morbidity, mortality and outcomes. As previously stated, it can prolong hospital and ICU stay as well as increase the likelihood of graft failure, therefore its prevention is essential. A number of approaches have been reported to prevent PRS attempting to reduce its hemodynamic and other systemic effects as well as decrease the incidence and severity. Prior to reperfusion, metabolic and electrolyte abnormalities should be corrected, and volume status should be assessed and optimized, as the cardiac and hemodynamic effects of PRS can occur abruptly.

Metabolic and electrolyte correction

Reperfusion can induce a large potassium release leading to hyperkalemia. Hyperkalemia has been associated with higher post-op mortality following OLT[19]. Higher baseline potassium, plus intraoperative red blood cell (RBC) transfusions are independent risk factors for developing post reperfusion hyperkalemia[20]. Administration of insulin doses (1-2 units) with each unit of RBCs as opposed to one large bolus immediately prior to reperfusion have been shown to lower pre-reperfusion serum potassium levels. Additionally, a bolus of calcium (chloride or gluconate) directly before graft reperfusion can treat the hypocalcemia generally associated with transfusion and reperfusion, as well as stabilize the myocardium from an abrupt increase in serum potassium following reperfusion. The use of sodium bicarbonate surrounding reperfusion is controversial. Some propose that it can counter hyperkalemia and attempt to optimize serum pH to increase the effectiveness of vasopressors if need following reperfusion[21]. However, there is emerging evidence that a moderate to severe acidotic state may have protective effects on the brain, myocardium, liver and kidneys, therefore aggressive correction of acidosis with sodium bicarbonate has been shown to worsen the ischemic reperfusion induced oxidative stress injured cells[22-26].

Agents for hemodynamic augmentation

Reperfusion can release vasoactive substances from the transplanted liver that can evoke bradycardia, decrease cardiac contractility and decrease SVR. Vasopressor Pretreatment has been implemented to combat hypotension following reperfusion, given that hypotension has been associated with greater incidence of graft malfunction, post-operative renal failure and mortality. Atropine can be given to prevent bradycardia but does not help raise MAP. A 10-20 microgram bolus of epinephrine is more effective at attenuating PRS given the ability to increase both HR and MAP[4,27]. Preemptive phenylephrine and epinephrine administration have been shown to reduce the incidence of PRS but did not have an effect on hospital length or stay or mortality. Other vasopressors like norepinephrine, ephedrine, dopamine and vasopressin have been used. Norepinephrine may be favorable over phenylephrine given it can increase cardiac contractility in addition to SVR *vs* just SVR alone with phenylephrine. Ephedrine started 5 minutes prior to reperfusion at a rate of 2.5-5 mg/minute (with targeted MAP goal of 85-100 mmHg), was shown to reduce the incidence of PRS and need for rescue vasopressors following reperfusion[28]. Patients with severe liver disease tend to be catecholamine and vasopressin depleted therefore exogenous vasopressin administration has been effective for treatment of PRS refractory to other catecholamine inducing vasopressors[29]. It can be effective in patients with severe acidosis to which epinephrine and norepinephrine are less effective[30].

Methylene blue and hydroxocobalamin

Methylene blue (MB) is an inhibitor of NO synthase which decreases production of NO a potent vasodilator released in following ischemic reperfusion. MB inhibits NO and the production of cGMP as well as increases vascular smooth muscle and myocardium sensitivity to catecholamines thus increasing SVR, MAP and cardiac contractility. Prophylactic administration of MB prior to reperfusion allowed for significant increases in MAP and cardiac index without significant changes in SVR following reperfusion, when compared with placebo. Additionally, patients given MB had lower lactate levels following reperfusion suggesting a benefit to graft function[31]. MB can also be used to treat hypotension refractory catecholamines and vasopressin at a dose of 100 mg or 2 mg/kg[32].

Hydroxocobalamin is a strong NO scavenger and can be used for refractory vasoplegia in OTL. Additionally, it takes up hydrogen sulfide, a substance released in patients with liver failure that causes vasodilation. Hydroxocobalamin can be effective when MB is contraindicated (such as in G6DP deficiency due to risk of hemolysis or in patients taking MAO-Is due to risk of serotonin syndrome)[33].

Table 1 Potential cellular and physiologic causes of post-reperfusion syndrome

Category	Physiologic change	Hemodynamic change
Release of vasoactive substances	Inflammatory cytokines (nitrous oxide, endothelin-1, bradykinin, reactive oxygen species)	Increased CVP; increased PVR; increased PAP; decreased SVR; decreased ABP; decreased CI; decreased HR; ST changes; T-wave changes
Electrolyte disturbances	Hypothermia; acidosis; hyperkalemia; hypocalcemia; hyperphosphatemia	
Embolic phenomena	Thromboembolic; air emboli	

ABP: Arterial blood pressure; CI: Cardiac index; CVP: Central venous pressure; HR: Heart rate; PAP: Pulmonary artery pressure; PVR: Pulmonary vascular resistance; SVR: Systemic vascular resistance.

MANAGEMENT

Protease inhibitors

Protease Inhibitors like aprotinin were designed for inhibition of fibrinolysis and were studied in OLT to assess the need for blood transfusion perioperatively but were shown to decrease the hemodynamic effects associated with PRS. Aprotinin works by inhibiting plasmin generation and thus fibrinolysis, but at higher doses it can inhibit serine proteases like those necessary for the kallikrein-kinin system thus blunting the production of bradykinin a strong vasodilator released during ischemic-reperfusion. The improved vascular tone and not necessarily reduced bleeding is thought to be the main benefit from protease inhibitor use in PRS[34,35]. These results were seen with a bolus of aprotinin following induction of anesthesia, followed by a continuous infusion. Aprotinin has been shown to combat the SIRS associated with reperfusion and PRS. Of note there is an increased risk for intracardiac thrombus formation with use of antifibrinolytics in OLT[36]. Numerous studies have been done with aprotinin in numerous settings and the drug is no longer used due to safety concerns. Other antifibrinolytic agents such as epsilon-aminocaproic acid (EACA) and Tranexamic Acid (TXA) have been studied for use in OLT and have shown lower incidence of PRS and reduced blood product requirements with TXA proving superior to EACA[37].

Magnesium sulfate

Supplementation with magnesium sulfate has shown to be protective in PRS for various reasons. It provides cellular protection during ischemia by blocking excess calcium influx thus stabilizing the electrical transmembrane potential. Magnesium administration prior to reperfusion has been shown to reduce serum lactate levels suggesting possible protection against ischemic reperfusion-injury[38]. Magnesium blocks immunologic response reducing production of interferon-y and increasing production of interlukin-4 and interlukin-10 creating a better balance of cytokines and improved hemodynamics after reperfusion[39]. Overcorrection of magnesium should be avoided because hypermagnesemia can cause hypotension.

Ischemic preconditioning

Ischemic preconditioning (IPC) is a method of applying brief periods of ischemia and reperfusion to tissue prior to a longer ischemic event. It was first used on heart muscles but has been trialed on other tissues including liver[40]. It was thought that this strategy can decrease ischemic reperfusion injury and thus decrease incidence and severity of PRS. Multiple studies including a Cochrane review have tested IPC in OLT, but these have only demonstrated a reduction in ischemic reperfusion injury but not improvements in long term outcomes. There was no statistically significant difference in ICU stay, hospital length of stay, primary graft function, need for transplantation or mortality between the two groups [41].

NEW ADVANCES

Machine perfusion

The type of liver graft (*i.e.,* those taken after cardiac death) can play a role in graft success. Those taken after cardiac death are underutilized because they are associated with increased risk of primary graft failure. They are more susceptible to ischemia reperfusion injuries and biliary system complications[42,43]. Static cold storage (SCS) has been the gold standard for graft preservation but allows for anerobic metabolism to persist leading to depletion of ADP and accumulation of ROS. SCS has four primary limitations: The storage duration is restricted, it may cause additional harm during organ storage, it does not reverse ongoing organ damage and organ viability cannot be assessed during storage. This can be critical in "high risk" donors[44].

Machine perfusion (MP) is a new method of preservation being implemented and studied to help ameliorate the downfalls of SCS. It allows for more useable organs especially from "high risk" donors. It can decrease cold ischemic time and thus reduce potential damage in organs more susceptible to ischemia[45]. There are two primary forms of MP, normothermic MP (NMP) and hypothermic MP (HMP).

NMP

NMP maintains graft normothermia while delivering ample oxygen and nutrients during graft harvesting, preservation and implementation. NMP allows for assessment of objective graft parameters and the ability to detect and remove organs that are not transplantable. NMP can be used to estimate graft survival by analyzing hemodynamic parameters, liver and bile duct function and liver injury indices[46,47]. A phase III multicenter randomised controlled trial (RCT) found that NMP subjects had lower incidence of graft injury, organ loss and longer mean preservation time[48]. Mergental *et al*[49] found that high risk donor livers that under went SCS then NMP had good immediate post-operative function after 7 months follow-up. This showed that a viability assessment with NMP allows for livers previously deemed unusable to be successfully transplanted in lower risk patients[49]. No studies have been conducted that measured the effects of NMP with direct reduction in PRS and but there is thought that a more adequately preserved graft could reduce the incidence of PRS and thus these studies should be pursued.

Normothermic regional perfusion

Normothermic regional perfusion (NRP) is a method of providing in situ perfusion to a portion of the donor's body following circulatory arrest[50,51]. It can only be used in donation after cardiac death (DCD) liver allografts compared with hypothermic oxygenated perfusion (HOPE) and NMP which can be used in both donation after brain death (DBD) and DCD donors. Five to twenty minutes following circulatory arrest, extracorporeal membrane oxygenation (ECMO) is initiated *via* cannulation of the aorta or femoral artery and venous return from the IVC or femoral vein[52]. There are two types of NRP, abdominal-NRP (A-NRP) and thoracoabdominal-NRP (TA-NRP). A-NRP provides *in situ* perfusion to abdominal organs through the IVC and intrarenal aorta. TA-NRP provides *in situ* perfusion of abdominal and thoracic organs *via* cannulation of the aortic arch and right atrium. Through TA-NRMP there is restoration of cardiac function with aortic clamping to prevent brain perfusion[53]. There are ethical concerns with restarting cardiac function, so this method has been controversial in is being reviewed in some institutions[54]. There has not been a RCT on NRP documented in the literature however there is retrospective studies showing better results than SCS. Results show that NRP can improve outcomes in DCD organ transplant through prevention of early allograft dysfunction (EAD), decreasing biliary complications, improving graft survival and decreasing retransplantation risk[52,55].

When assessing long term outcomes of NMP and NRP, more data is needed however some early studies some promise. Gaurav *et al*[56] performed a single center retrospective analysis looking at donors preserved with NRP, NMP and SCS. They found that the NRP group had higher 6-month survival (NRP: 94%, NMP: 90%, and SCS: 87%) and 3 year survival (NRP: 90%, NMP & SCS: 76%). Additionally, two observational cohort studies by Hessheimer *et al*[50,57] compared NRP and SCS preserved livers and found that the NRP group had lower incidence of overall biliary complications, ischemic-type biliary lesions, and graft loss and patient death. Finally, a retrospective analysis by Watson *et al*[58] comparing NRP *vs* standard DCD prepared donors, the NRP group had less incidence of Ischemic cholangiopathy which can lead to improved long-term outcomes.

HMP

HMP uses cold temperature to slow cellular metabolism while flushing out metabolites. One form HOPE delivers the perfusate through the portal vein. Dual HOPE involves delivering perfusate through the portal vein and hepatic artery [59]. Multiple studies have shown that liver grafts obtained from DCD have comparable postoperative outcomes to those from DBD. Additionally, HOPE has been compared to SCS in DCD allografts with the HOPE treated grafts showing lower incidence of PRS, early allograft injury, and graft failure as well as improved long term graft survival and decreased late onset morbidity[60,61].

HOPE was shown to have less complications and enhanced graft survival. Because of these positive effects it may allow for increased use of less optimal organs which will help with the increased demand for organs. A study by Horné *et al*[62] compared 100 liver transplants with 50 preconditioned with HOPE and 50 treated with SCS and found that 12% of HOPE treated organs experienced PRS compared to 42% that underwent SCS. HOPE treated livers also had lower vasopressor requirements and potassium levels and the overall incidence of EAD decreased by 44%. This suggests that HOPE offers greater hemodynamic stability and less EAD and PRS compared to the traditional SCS method[62].

There remains limited data on the long term outcomes of HOPE, however there are a few studies that show improvements in long term out comes. A RCT by Czigany *et al*[61] found that HOPE reduced late onset morbidity and enhanced log-term graft survival. Another RCT by Ravaioli *et al*[63] found that HOPE treated grafts had lower graft dysfunction rates and longer graft survival compared to SCS. Additionally, van Rijn *et al*[64] found that HOPE was associated with fewer non-anastomotic biliary strictures compared to SCS treated donors.

Caval blood flush vent

Many studies have assessed flushing and venting grafts with different types of fluid (LR, albumin, blood) and *via* different routes (arterial, portal and caval) but most of these studies found inconsistent results on metabolic changes (potassium) and on outcomes[65-70]. It was thought that adding caval venting following a LR/albumin portal vein flush could prevent metabolic changes (acidic, hypothermic, hyperkalemic blood) from the initial reperfusion bolus from entering the systemic circulation allowing for better hemodynamic stability and thus decreasing the incidence of PRS. Stoll *et al*[71] performed a prospective observational study that analyzed 20 Liver transplants, with 16 receiving a caval blood flush vent (along with a standard chilled LR/albumin portal vein flush) and 4 who did not receive the caval flush. They found that those who underwent caval flush had better preservation of MAP and HR but CVP and lab values (blood gas, electrolytes and hemoglobin) were similar between the two groups. They concluded that caval venting (along with traditional portal vein chilled LR/albumin flush) could have favorable hemodynamic protection but the literature is

Table 2 Comparison of Techniques for preventing post-reperfusion syndrome including advantages and limitations

Technique	Advantages	Limitations
Static cold storage	Cheaper, current gold standard, many studies showing efficacy	Storage duration is restricted, potential for harm during storage, does not reverse ongoing damage, organ viability can't be assessed during storage
Hypothermic machine perfusion	Can use on high risk donors, can use in DBD and dcd allografts, lower incidence of graft injury, organ loss, allows for longer mean preservation time, enhance organ availability reduce waitlist mortality	Limited data on long term benefits, need to cool to sub-physiologic temperature
Normothermic machine perfusion	Can use at physiologic temperatures, can use on high-risk donors, can use in DBD and DCD allografts, lower incidence of graft injury, organ loss, allows for longer mean preservation time, enhance organ availability reduce waitlist mortality	Limited data on long term benefits
Normothermic regional perfusion	Very affective for DCD donors	Only used in DCD liver allograft management, ethical considerations with TA-NRP
Caval blood flush vent	Hemodynamic protection cheapest, decreased requirement for vasopressors and inotropes	Limited studies on short and long term benefits
ECMO	Eliminate the need for extensive immunosuppressive treatments, expand the donor organ pool, cheaper than MP	Patients usually very ill with multi-organ failure and systemic infections, bilirubin levels hard to measure in short term, limited data on long term benefits, ethical concerns

DBD: Donation after brain death; DCD: Donation after circulatory death; ECMO: Extracorporeal membrane oxygenation; MP: Machine perfusion; TA-NRP thoracoabdominal normothermic regional perfusion.

sparse, and more studies are needed[71]. Further research is needed to evaluate the effects of caval venting on graft function, morbidity, and mortality, and we encourage including real-time transesophageal echocardiography to better explain the proposed mechanism of hemodynamic changes.

Application of extracorporeal therapies

The demand for organ donation is continuously outgrowing the supply of viable organs. This is true in liver transplantation. Numerous strategies have been developed to help address this issue. One strategy is using ECMO at the time of death to increase organ viability, however there is limited studies and guidelines on the use of this strategy. One study by Rajsic *et al*[72] analyzed the existing evidence and found 20 publications that reported on 147 patients (who were diagnosed of death by standard neurological criteria) whose organs were procured while on ECMO support. The organs of these donors were used in 359 recipients with 85/359 being liver transplantations, with an 89% graft survival rate. Overall, the organs treated with ECMO support had 92% graft survival rate and 98% recipient survival rate. A retrospective trail by Hsieh *et al*[73] reviewed ECMO with DBD and ECMO with DCD *vs* just a DBD group alone. They found that the DCD with ECMO group had longer cold ischemic time, warm ischemic time, and split liver transplantation than the DBD group alone, with statistical significance. The DBD with EMCO and DCD with ECMO groups had less vasopressor requirements than the DBD group and the DBD with ECMO had a higher survival rate than DBD alone, however these results were statistically insignificant. This highlights a potential strategy for improved graft procurement and graft survival. Further studies are needed to investigate the role of ECMO in graft preservation and viability and the role of ECMO treated grafts in reducing PRS.

In patients with acute liver failure where organ recovery might occur, extracorporeal liver perfusion (ECLP) *via* a genetically modified pig donor may offer an approach to preserve organ viability. It may decrease the need for immunosuppressive therapies and liver transplant at all. Some preclinical studies showed that ECLP with pig livers can possibly preserve injured human livers for approximately 1 week. Although the numbers were small, they showed a survival benefit and may highlight safe technique for bridging patients to liver transplantation[74-78] (Table 2).

CONCLUSION

PRS remains a significant challenge in liver transplantation, with complex underlying mechanisms and substantial clinical implications. The underlying direct mechanisms of PRS remain unknown, however the metabolic and hemodynamic changes associated with it are largely apparent and should be optimized throughout surgery to help lessen the effects and prevent PRS. A comprehensive understanding of PRS, coupled with vigilant monitoring and targeted management strategies, is essential for optimizing outcomes in liver transplant recipients. Most of the studies regarding PRS are performed on recipient from deceased donors however, in our clinical experience PRS has been shown to be milder in recipients from live-liver donors, which is believed to be due to short ischemia time and improved graft quality. There is limited data comparing graft and patient outcomes between these two donor groups and future studies are necessary. Additionally, Further studies into the efficacy of MP, IPC, caval venting and ECMO and their effects on PRS, graft function and morbidity/mortality are essential to implementation of this technology and ultimately improving

patient outcomes.

FOOTNOTES

Author contributions: Puchany AJ performed literature review, writing – original draft; Hilmi I performed conceptualization, review, and editing.

Conflict-of-interest statement: Both authors have nothing to disclose.

Country of origin: United States

ORCID number: Austin James Puchany 0009-0002-1436-3454; Ibtesam Hilmi 0000-0002-3843-4598.

S-Editor: Lin C
L-Editor: A
P-Editor: Guo X

REFERENCES

1 **Chung IS**, Kim HY, Shin YH, Ko JS, Gwak MS, Sim WS, Kim GS, Lee SK. Incidence and predictors of post-reperfusion syndrome in living donor liver transplantation. *Clin Transplant* 2012; **26**: 539-543 [PMID: 22168355 DOI: 10.1111/j.1399-0012.2011.01568.x]
2 **Paugam-Burtz C**, Kavafyan J, Merckx P, Dahmani S, Sommacale D, Ramsay M, Belghiti J, Mantz J. Postreperfusion syndrome during liver transplantation for cirrhosis: outcome and predictors. *Liver Transpl* 2009; **15**: 522-529 [PMID: 19399736 DOI: 10.1002/lt.21730]
3 **Aggarwal S**, Kang Y, Freeman JA, Fortunato FL, Pinsky MR. Postreperfusion syndrome: cardiovascular collapse following hepatic reperfusion during liver transplantation. *Transplant Proc* 1987; **19**: 54-55 [PMID: 3303534]
4 **Fukazawa K**, Yamada Y, Gologorsky E, Arheart KL, Pretto EA Jr. Hemodynamic recovery following postreperfusion syndrome in liver transplantation. *J Cardiothorac Vasc Anesth* 2014; **28**: 994-1002 [PMID: 25107717 DOI: 10.1053/j.jvca.2014.02.017]
5 **Hilmi I**, Horton CN, Planinsic RM, Sakai T, Nicolau-Raducu R, Damian D, Gligor S, Marcos A. The impact of postreperfusion syndrome on short-term patient and liver allograft outcome in patients undergoing orthotopic liver transplantation. *Liver Transpl* 2008; **14**: 504-508 [PMID: 18383079 DOI: 10.1002/lt.21381]
6 **Siniscalchi A**, Gamberini L, Bardi T, Laici C, Ravaioli M, Bacchi Reggiani ML, Faenza S. Post-reperfusion syndrome during orthotopic liver transplantation, which definition best predicts postoperative graft failure and recipient mortality? *J Crit Care* 2017; **41**: 156-160 [PMID: 28551489 DOI: 10.1016/j.jcrc.2017.05.020]
7 **Siniscalchi A**, Aurini L, Spedicato S, Bernardi E, Zanoni A, Dante A, Cimatti M, Gamberini L, Faenza S. Hyperdynamic circulation in cirrhosis: predictive factors and outcome following liver transplantation. *Minerva Anestesiol* 2013; **79**: 15-23 [PMID: 23090103]
8 **Jeong SM**. Postreperfusion syndrome during liver transplantation. *Korean J Anesthesiol* 2015; **68**: 527-539 [PMID: 26634075 DOI: 10.4097/kjae.2015.68.6.527]
9 **Siniscalchi A**, Gamberini L, Laici C, Bardi T, Ercolani G, Lorenzini L, Faenza S. Post reperfusion syndrome during liver transplantation: From pathophysiology to therapy and preventive strategies. *World J Gastroenterol* 2016; **22**: 1551-1569 [PMID: 26819522 DOI: 10.3748/wjg.v22.i4.1551]
10 **Tsinari KK**, Misiakos EP, Lawand CT, Chatzipetrou MA, Lampadariou KV, Bakonyi Neto A, Llanos JC, Tamura S, Gyamfi AR, Tzakis AG. Factors affecting metabolic and electrolyte changes after reperfusion in liver transplantation. *Transplant Proc* 2004; **36**: 3051-3056 [PMID: 15686692 DOI: 10.1016/j.transproceed.2004.11.098]
11 **Kang Y**. Coagulation and liver transplantation: current concepts. *Liver Transpl Surg* 1997; **3**: 465-467 [PMID: 9346786 DOI: 10.1002/lt.500030426]
12 **Nastos C**, Kalimeris K, Papoutsidakis N, Tasoulis MK, Lykoudis PM, Theodoraki K, Nastou D, Smyrniotis V, Arkadopoulos N. Global consequences of liver ischemia/reperfusion injury. *Oxid Med Cell Longev* 2014; **2014**: 906965 [PMID: 24799983 DOI: 10.1155/2014/906965]
13 **Garcea G**, Gescher A, Steward W, Dennison A, Berry D. Oxidative stress in humans following the Pringle manoeuvre. *Hepatobiliary Pancreat Dis Int* 2006; **5**: 210-214 [PMID: 16698577]
14 **Mendes-Braz M**, Elias-Miró M, Jiménez-Castro MB, Casillas-Ramírez A, Ramalho FS, Peralta C. The current state of knowledge of hepatic ischemia-reperfusion injury based on its study in experimental models. *J Biomed Biotechnol* 2012; **2012**: 298657 [PMID: 22649277 DOI: 10.1155/2012/298657]
15 **Filos KS**, Kirkilesis I, Spiliopoulou I, Scopa CD, Nikolopoulou V, Kouraklis G, Vagianos CE. Bacterial translocation, endotoxaemia and apoptosis following Pringle manoeuvre in rats. *Injury* 2004; **35**: 35-43 [PMID: 14728953 DOI: 10.1016/s0020-1383(03)00288-2]
16 **Scholz T**, Backman L, Mathisen O, Buø L, Karlsrud T, Johansen HT, Bergan A, Klintmalm GB, Aasen AO. Activation of the plasma contact system and hemodynamic changes after graft revascularization in liver transplantation. *Transplantation* 1995; **60**: 36-40 [PMID: 7542812 DOI: 10.1097/00007890-199507150-00007]
17 **Bezinover D**, Kadry Z, Uemura T, Sharghi M, Mastro AM, Sosnoski DM, Dalal P, Janicki PK. Association between plasma cyclic guanosine monophosphate levels and hemodynamic instability during liver transplantation. *Liver Transpl* 2013; **19**: 191-198 [PMID: 23161851 DOI: 10.1002/lt.23570]

18 **Manning MW**, Kumar PA, Maheshwari K, Arora H. Post-Reperfusion Syndrome in Liver Transplantation-An Overview. *J Cardiothorac Vasc Anesth* 2020; **34**: 501-511 [PMID: 31084991 DOI: 10.1053/j.jvca.2019.02.050]

19 **Dawwas MF**, Lewsey JD, Watson CJ, Gimson AE; UK, Ireland Liver Transplant Audit. The impact of serum potassium concentration on mortality after liver transplantation: a cohort multicenter study. *Transplantation* 2009; **88**: 402-410 [PMID: 19667945 DOI: 10.1097/TP.0b013e3181aed8e4]

20 **Xia VW**, Ghobrial RM, Du B, Chen T, Hu KQ, Hiatt JR, Busuttil RW, Steadman RH. Predictors of hyperkalemia in the prereperfusion, early postreperfusion, and late postreperfusion periods during adult liver transplantation. *Anesth Analg* 2007; **105**: 780-785 [PMID: 17717240 DOI: 10.1213/01.ane.0000271914.54261.17]

21 **Merritt WT**. Metabolism and liver transplantation: review of perioperative issues. *Liver Transpl* 2000; **6**: S76-S84 [PMID: 10915196 DOI: 10.1002/lt.500060515]

22 **Weinberg L**, Broad J, Pillai P, Chen G, Nguyen M, Eastwood GM, Scurrah N, Nikfarjam M, Story D, McNicol L, Bellomo R. Sodium bicarbonate infusion in patients undergoing orthotopic liver transplantation: a single center randomized controlled pilot trial. *Clin Transplant* 2016; **30**: 556-565 [PMID: 26915026 DOI: 10.1111/ctr.12721]

23 **Preckel B**, Schlack W, Obal D, Barthel H, Ebel D, Grunert S, Thämer V. Effect of acidotic blood reperfusion on reperfusion injury after coronary artery occlusion in the dog heart. *J Cardiovasc Pharmacol* 1998; **31**: 179-186 [PMID: 9475258 DOI: 10.1097/00005344-199802000-00002]

24 **Rehncrona S**, Hauge HN, Siesjö BK. Enhancement of iron-catalyzed free radical formation by acidosis in brain homogenates: differences in effect by lactic acid and CO2. *J Cereb Blood Flow Metab* 1989; **9**: 65-70 [PMID: 2492027 DOI: 10.1038/jcbfm.1989.9]

25 **Bonventre JV**, Cheung JY. Effects of metabolic acidosis on viability of cells exposed to anoxia. *Am J Physiol* 1985; **249**: C149-C159 [PMID: 4014448 DOI: 10.1152/ajpcell.1985.249.1.C149]

26 **Bond JM**, Chacon E, Herman B, Lemasters JJ. Intracellular pH and Ca2+ homeostasis in the pH paradox of reperfusion injury to neonatal rat cardiac myocytes. *Am J Physiol* 1993; **265**: C129-C137 [PMID: 8338121 DOI: 10.1152/ajpcell.1993.265.1.C129]

27 **Acosta F**, Sansano T, Contreras RF, Reche M, Roques V, Beltran R, Rodriguez MA, Robles R, Bueno FS, Ramirez P, Parrilla P. Phenylephrine treatment of the postreperfusion syndrome in liver transplantation. *Transplant Proc* 1999; **31**: 2373-2374 [PMID: 10500625 DOI: 10.1016/s0041-1345(99)00386-3]

28 **Fayed NA**, Murad WS. Goal directed preemptive ephedrine attenuates the reperfusion syndrome during adult living donor liver transplantation. *Egypt J Anaesth* 2014; **30**: 187-195 [DOI: 10.1016/j.egja.2013.10.002]

29 **Wagener G**, Kovalevskaya G, Minhaz M, Mattis F, Emond JC, Landry DW. Vasopressin deficiency and vasodilatory state in end-stage liver disease. *J Cardiothorac Vasc Anesth* 2011; **25**: 665-670 [PMID: 21126886 DOI: 10.1053/j.jvca.2010.09.018]

30 **Lavigne D**. Vasopressin and methylene blue: alternate therapies in vasodilatory shock. *Semin Cardiothorac Vasc Anesth* 2010; **14**: 186-189 [PMID: 20705641 DOI: 10.1177/1089253210379271]

31 **Koelzow H**, Gedney JA, Baumann J, Snook NJ, Bellamy MC. The effect of methylene blue on the hemodynamic changes during ischemia reperfusion injury in orthotopic liver transplantation. *Anesth Analg* 2002; **94**: 824-829, table of contents [PMID: 11916779 DOI: 10.1097/00000539-200204000-00009]

32 **Cheng SS**, Berman GW, Merritt GR, Hendrickse A, Fiegel MJ, Teitelbaum I, Campsen J, Wachs M, Zimmerman M, Mandell MS. The response to methylene blue in patients with severe hypotension during liver transplantation. *J Clin Anesth* 2012; **24**: 324-328 [PMID: 22608589 DOI: 10.1016/j.jclinane.2011.10.010]

33 **Boettcher BT**, Woehlck HJ, Reck SE, Hong JC, Zimmerman MA, Kim J, Zundel MT, Freed JK, Pagel PS. Treatment of Vasoplegic Syndrome With Intravenous Hydroxocobalamin During Liver Transplantation. *J Cardiothorac Vasc Anesth* 2017; **31**: 1381-1384 [PMID: 28012726 DOI: 10.1053/j.jvca.2016.10.011]

34 **Molenaar IQ**, Begliomini B, Martinelli G, Putter H, Terpstra OT, Porte RJ. Reduced need for vasopressors in patients receiving aprotinin during orthotopic liver transplantation. *Anesthesiology* 2001; **94**: 433-438 [PMID: 11374602 DOI: 10.1097/00000542-200103000-00012]

35 **Porte RJ**, Molenaar IQ, Begliomini B, Groenland TH, Januszkiewicz A, Lindgren L, Palareti G, Hermans J, Terpstra OT. Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomised double-blind study. EMSALT Study Group. *Lancet* 2000; **355**: 1303-1309 [PMID: 10776742 DOI: 10.1016/s0140-6736(00)02111-5]

36 **Sanchez RA**, Kim B, Berumen J, Schmidt U. Transesophageal Echocardiography-Guided Thrombus Extraction and Catheter-Directed Thrombolytic Therapy During Orthotropic Liver Transplantation. *J Cardiothorac Vasc Anesth* 2017; **31**: 2127-2130 [PMID: 28939324 DOI: 10.1053/j.jvca.2017.04.042]

37 **Dalmau A**, Sabaté A, Acosta F, Garcia-Huete L, Koo M, Sansano T, Rafecas A, Figueras J, Jaurrieta E, Parrilla P. Tranexamic acid reduces red cell transfusion better than epsilon-aminocaproic acid or placebo in liver transplantation. *Anesth Analg* 2000; **91**: 29-34 [PMID: 10866882 DOI: 10.1097/00000539-200007000-00006]

38 **Kim JE**, Jeon JP, No HC, Choi JH, Lee SH, Ryu KH, Kim ES. The effects of magnesium pretreatment on reperfusion injury during living donor liver transplantation. *Korean J Anesthesiol* 2011; **60**: 408-415 [PMID: 21738843 DOI: 10.4097/kjae.2011.60.6.408]

39 **Chung HS**, Park CS, Hong SH, Lee S, Cho ML, Her YM, Sa GJ, Lee J, Choi JH. Effects of magnesium pretreatment on the levels of T helper cytokines and on the severity of reperfusion syndrome in patients undergoing living donor liver transplantation. *Magnes Res* 2013; **26**: 46-55 [PMID: 23816766 DOI: 10.1684/mrh.2013.0338]

40 **Murry CE**, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; **74**: 1124-1136 [PMID: 3769170 DOI: 10.1161/01.cir.74.5.1124]

41 **Gurusamy KS**, Kumar Y, Sharma D, Davidson BR. Ischaemic preconditioning for liver transplantation. *Cochrane Database Syst Rev* 2008; **2008**: CD006315 [PMID: 18254099 DOI: 10.1002/14651858.CD006315.pub2]

42 **Malkawi D**, Savsani K, Alfonso A, Lee SD, James N, Sarkar D, Imai D, Khan A, Sharma A, Kumaran V, Bruno D, Cotterell A, Levy MF. The Role of Normothermic Machine Perfusion in Extended Criteria Donor Grafts: A New Direction in Liver Graft Assessment and Preservation. *Livers* 2023; **3**: 709-726 [DOI: 10.3390/livers3040046]

43 **Czigany Z**, Lurje I, Schmelzle M, Schöning W, Öllinger R, Raschzok N, Sauer IM, Tacke F, Strnad P, Trautwein C, Neumann UP, Fronek J, Mehrabi A, Pratschke J, Schlegel A, Lurje G. Ischemia-Reperfusion Injury in Marginal Liver Grafts and the Role of Hypothermic Machine Perfusion: Molecular Mechanisms and Clinical Implications. *J Clin Med* 2020; **9** [PMID: 32244972 DOI: 10.3390/jcm9030846]

44 **Jing L**, Yao L, Zhao M, Peng LP, Liu M. Organ preservation: from the past to the future. *Acta Pharmacol Sin* 2018; **39**: 845-857 [PMID: 29565040 DOI: 10.1038/aps.2017.182]

45 **Ozgur OS**, Namsrai BE, Pruett TL, Bischof JC, Toner M, Finger EB, Uygun K. Current practice and novel approaches in organ preservation.

Front Transplant 2023; **2**: 1156845 [PMID: 38993842 DOI: 10.3389/frtra.2023.1156845]

46 **Li J**, Lu H, Zhang J, Li Y, Zhao Q. Comprehensive Approach to Assessment of Liver Viability During Normothermic Machine Perfusion. *J Clin Transl Hepatol* 2023; **11**: 466-479 [PMID: 36643041 DOI: 10.14218/JCTH.2022.00130]

47 **Mergental H**, Laing RW, Kirkham AJ, Perera MTPR, Boteon YL, Attard J, Barton D, Curbishley S, Wilkhu M, Neil DAH, Hübscher SG, Muiesan P, Isaac JR, Roberts KJ, Abradelo M, Schlegel A, Ferguson J, Cilliers H, Bion J, Adams DH, Morris C, Friend PJ, Yap C, Afford SC, Mirza DF. Transplantation of discarded livers following viability testing with normothermic machine perfusion. *Nat Commun* 2020; **11**: 2939 [PMID: 32546694 DOI: 10.1038/s41467-020-16251-3]

48 **Nasralla D**, Coussios CC, Mergental H, Akhtar MZ, Butler AJ, Ceresa CDL, Chiocchia V, Dutton SJ, García-Valdecasas JC, Heaton N, Imber C, Jassem W, Jochmans I, Karani J, Knight SR, Kocabayoglu P, Malagò M, Mirza D, Morris PJ, Pallan A, Paul A, Pavel M, Perera MTPR, Pirenne J, Ravikumar R, Russell L, Upponi S, Watson CJE, Weissenbacher A, Ploeg RJ, Friend PJ; Consortium for Organ Preservation in Europe. A randomized trial of normothermic preservation in liver transplantation. *Nature* 2018; **557**: 50-56 [PMID: 29670285 DOI: 10.1038/s41586-018-0047-9]

49 **Mergental H**, Perera MT, Laing RW, Muiesan P, Isaac JR, Smith A, Stephenson BT, Cilliers H, Neil DA, Hübscher SG, Afford SC, Mirza DF. Transplantation of Declined Liver Allografts Following Normothermic Ex-Situ Evaluation. *Am J Transplant* 2016; **16**: 3235-3245 [PMID: 27192971 DOI: 10.1111/ajt.13875]

50 **Hessheimer AJ**, de la Rosa G, Gastaca M, Ruíz P, Otero A, Gómez M, Alconchel F, Ramírez P, Bosca A, López-Andújar R, Atutxa L, Royo-Villanova M, Sánchez B, Santoyo J, Marín LM, Gómez-Bravo MÁ, Mosteiro F, Villegas Herrera MT, Villar Del Moral J, González-Abos C, Vidal B, López-Domínguez J, Lladó L, Roldán J, Justo I, Jiménez C, López-Monclús J, Sánchez-Turrión V, Rodríguez-Laíz G, Velasco Sánchez E, López-Baena JÁ, Caralt M, Charco R, Tomé S, Varo E, Martí-Cruchaga P, Rotellar F, Varona MA, Barrera M, Rodríguez-Sanjuan JC, Briceño J, López D, Blanco G, Nuño J, Pacheco D, Coll E, Domínguez-Gil B, Fondevila C. Abdominal normothermic regional perfusion in controlled donation after circulatory determination of death liver transplantation: Outcomes and risk factors for graft loss. *Am J Transplant* 2022; **22**: 1169-1181 [PMID: 34856070 DOI: 10.1111/ajt.16899]

51 **Brubaker AL**, Sellers MT, Abt PL, Croome KP, Merani S, Wall A, Abreu P, Alebrahim M, Baskin R, Bohorquez H, Cannon RM, Cederquist K, Edwards J, Huerter BG, Hobeika MJ, Kautzman L, Langnas AN, Lee DD, Manzi J, Nassar A, Neidlinger N, Nydam TL, Schnickel GT, Siddiqui F, Suah A, Taj R, Taner CB, Testa G, Vianna R, Vyas F, Montenovo MI. US Liver Transplant Outcomes After Normothermic Regional Perfusion vs Standard Super Rapid Recovery. *JAMA Surg* 2024; **159**: 677-685 [PMID: 38568597 DOI: 10.1001/jamasurg.2024.0520]

52 **Eden J**, Sousa Da Silva R, Cortes-Cerisuelo M, Croome K, De Carlis R, Hessheimer AJ, Muller X, de Goeij F, Banz V, Magini G, Compagnon P, Elmer A, Lauterio A, Panconesi R, Widmer J, Dondossola D, Muiesan P, Monbaliu D, de Rosner van Rosmalen M, Detry O, Fondevila C, Jochmans I, Pirenne J, Immer F, Oniscu GC, de Jonge J, Lesurtel M, De Carlis LG, Taner CB, Heaton N, Schlegel A, Dutkowski P. Utilization of livers donated after circulatory death for transplantation - An international comparison. *J Hepatol* 2023; **78**: 1007-1016 [PMID: 36740047 DOI: 10.1016/j.jhep.2023.01.025]

53 **Croome KP**, Brown TE, Mabrey RL, Sonnenwald SL, Burns JM, Mao SA, Clendenon JN, Nguyen JH, Perry DK, Maddox RG, Taner CB. Development of a portable abdominal normothermic regional perfusion (A-NRP) program in the United States. *Liver Transpl* 2023; **29**: 1282-1291 [PMID: 37040930 DOI: 10.1097/LVT.0000000000000156]

54 **Entwistle JW**, Drake DH, Fenton KN, Smith MA, Sade RM; Cardiothoracic Ethics Forum. Normothermic regional perfusion: Ethical issues in thoracic organ donation. *J Thorac Cardiovasc Surg* 2022; **164**: 147-154 [PMID: 35369998 DOI: 10.1016/j.jtcvs.2022.01.018]

55 **Antoine C**, Jasseron C, Dondero F, Savier E; French National Steering Committee of Donors After Circulatory Death. Liver Transplantation From Controlled Donors After Circulatory Death Using Normothermic Regional Perfusion: An Initial French Experience. *Liver Transpl* 2020; **26**: 1516-1521 [PMID: 32531132 DOI: 10.1002/lt.25818]

56 **Gaurav R**, Butler AJ, Kosmoliaptsis V, Mumford L, Fear C, Swift L, Fedotovs A, Upponi S, Khwaja S, Richards J, Allison M, Watson CJE. Liver Transplantation Outcomes From Controlled Circulatory Death Donors: SCS vs in situ NRP vs ex situ NMP. *Ann Surg* 2022; **275**: 1156-1164 [PMID: 35258511 DOI: 10.1097/SLA.0000000000005428]

57 **Hessheimer AJ**, Coll E, Torres F, Ruíz P, Gastaca M, Rivas JI, Gómez M, Sánchez B, Santoyo J, Ramírez P, Parrilla P, Marín LM, Gómez-Bravo MÁ, García-Valdecasas JC, López-Monclús J, Boscá A, López-Andújar R, Fundora-Suárez J, Villar J, García-Sesma Á, Jiménez C, Rodríguez-Laíz G, Lladó L, Rodríguez JC, Barrera M, Charco R, López-Baena JÁ, Briceño J, Pardo F, Blanco G, Pacheco D, Domínguez-Gil B, Sánchez Turrión V, Fondevila C. Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *J Hepatol* 2019; **70**: 658-665 [PMID: 30582980 DOI: 10.1016/j.jhep.2018.12.013]

58 **Watson CJE**, Hunt F, Messer S, Currie I, Large S, Sutherland A, Crick K, Wigmore SJ, Fear C, Cornateanu S, Randle LV, Terrace JD, Upponi S, Taylor R, Allen E, Butler AJ, Oniscu GC. In situ normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival. *Am J Transplant* 2019; **19**: 1745-1758 [PMID: 30589499 DOI: 10.1111/ajt.15241]

59 **Monbaliu D**, Brassil J. Machine perfusion of the liver: past, present and future. *Curr Opin Organ Transplant* 2010; **15**: 160-166 [PMID: 20125022 DOI: 10.1097/MOT.0b013e328337342b]

60 **Czigany Z**, Pratschke J, Froněk J, Guba M, Schöning W, Raptis DA, Andrassy J, Kramer M, Strnad P, Tolba RH, Liu W, Keller T, Miller H, Pavicevic S, Uluk D, Kocik M, Lurje I, Trautwein C, Mehrabi A, Popescu I, Vondran FWR, Ju C, Tacke F, Neumann UP, Lurje G. Hypothermic Oxygenated Machine Perfusion Reduces Early Allograft Injury and Improves Post-transplant Outcomes in Extended Criteria Donation Liver Transplantation From Donation After Brain Death: Results From a Multicenter Randomized Controlled Trial (HOPE ECD-DBD). *Ann Surg* 2021; **274**: 705-712 [PMID: 34334635 DOI: 10.1097/SLA.0000000000005110]

61 **Czigany Z**, Uluk D, Pavicevic S, Lurje I, Froněk J, Keller T, Strnad P, Jiang D, Gevers T, Koliogiannis D, Guba M, Tolba RH, Meister FA, Neumann UP, Kocik M, Kysela M, Sauer IM, Raschzok N, Schöning W, Popescu I, Tacke F, Pratschke J, Lurje G. Improved outcomes after hypothermic oxygenated machine perfusion in liver transplantation-Long-term follow-up of a multicenter randomized controlled trial. *Hepatol Commun* 2024; **8** [PMID: 38315126 DOI: 10.1097/HC9.0000000000000376]

62 **Horné F**, Drefs M, Schirren MJ, Koch DT, Cepele G, Jacobi SJ, Payani E, Börner N, Werner J, Guba MO, Koliogiannis D. Hypothermic Oxygenated Machine Perfusion (HOPE) Prior to Liver Transplantation Mitigates Post-Reperfusion Syndrome and Perioperative Electrolyte Shifts. *J Clin Med* 2022; **11** [PMID: 36555997 DOI: 10.3390/jcm11247381]

63 **Ravaioli M**, Germinario G, Dajti G, Sessa M, Vasuri F, Siniscalchi A, Morelli MC, Serenari M, Del Gaudio M, Zanfi C, Odaldi F, Bertuzzo VR, Maroni L, Laurenzi A, Cescon M. Hypothermic oxygenated perfusion in extended criteria donor liver transplantation-A randomized clinical trial. *Am J Transplant* 2022; **22**: 2401-2408 [PMID: 35671067 DOI: 10.1111/ajt.17115]

64 **van Rijn R**, Schurink IJ, de Vries Y, van den Berg AP, Cortes Cerisuelo M, Darwish Murad S, Erdmann JI, Gilbo N, de Haas RJ, Heaton N, van Hoek B, Huurman VAL, Jochmans I, van Leeuwen OB, de Meijer VE, Monbaliu D, Polak WG, Slangen JJG, Troisi RI, Vanlander A, de

Jonge J, Porte RJ; DHOPE-DCD Trial Investigators. Hypothermic Machine Perfusion in Liver Transplantation - A Randomized Trial. *N Engl J Med* 2021; **384**: 1391-1401 [PMID: 33626248 DOI: 10.1056/NEJMoa2031532]

65 **Fukuzawa K**, Schwartz ME, Acarli K, Katz E, Gabrielson G, Gettes M, Jacobs E, Miller CM. Flushing with autologous blood improves intraoperative hemodynamic stability and early graft function in clinical hepatic transplantation. *J Am Coll Surg* 1994; **178**: 541-547 [PMID: 8193745]

66 **Emre S**, Schwartz ME, Mor E, Kishikawa K, Yagmur O, Thiese N, Sheiner P, Jindal RM, Chiodini S, Miller CM. Obviation of prereperfusion rinsing and decrease in preservation/reperfusion injury in liver transplantation by portal blood flushing. *Transplantation* 1994; **57**: 799-803 [PMID: 8154023 DOI: 10.1097/00007890-199403270-00004]

67 **Millis JM**, Melinek J, Csete M, Imagawa DK, Olthoff KM, Neelankanta G, Braunfeld MY, Sopher MJ, Chan SM, Pregler JL, Yersiz H, Busuttil AA, Shackleton CR, Shaked A, Busuttil RW. Randomized controlled trial to evaluate flush and reperfusion techniques in liver transplantation. *Transplantation* 1997; **63**: 397-403 [PMID: 9039930 DOI: 10.1097/00007890-199702150-00012]

68 **Mirza DF**, Gunson BK, Khalaf H, Freeman JW, Buckels JA, McMaster P, Mayer AD. Effect of pre-reperfusion portal venous blood flush on early liver transplant function. *Transpl Int* 1996; **9** Suppl 1: S188-S190 [PMID: 8959823 DOI: 10.1007/978-3-662-00818-8_47]

69 **Brems JJ**, Takiff H, McHutchison J, Collins D, Biermann LA, Pockros P. Systemic versus nonsystemic reperfusion of the transplanted liver. *Transplantation* 1993; **55**: 527-529 [PMID: 8456472 DOI: 10.1097/00007890-199303000-00013]

70 **Gurusamy KS**, Naik P, Abu-Amara M, Fuller B, Davidson BR. Techniques of flushing and reperfusion for liver transplantation. *Cochrane Database Syst Rev* 2012; CD007512 [PMID: 22419324 DOI: 10.1002/14651858.CD007512.pub2]

71 **Stoll WD**, Hand WR, Chavin KD, Felton DH, Wolf BO, Davis GP, Harvey NR, Whiteley JR, Mester RA, Bolin ED. Post-Reperfusion Syndrome in Liver Transplantation: Does a Caval Blood Flush Vent Help? *Ann Transplant* 2019; **24**: 631-638 [PMID: 31831725 DOI: 10.12659/AOT.920193]

72 **Rajsic S**, Treml B, Innerhofer N, Eckhardt C, Radovanovic Spurnic A, Breitkopf R. Organ Donation from Patients Receiving Extracorporeal Membrane Oxygenation: A Systematic Review. *J Cardiothorac Vasc Anesth* 2024; **38**: 1531-1538 [PMID: 38643059 DOI: 10.1053/j.jvca.2024.03.020]

73 **Hsieh CE**, Hsu YL, Chen YL, Liang HR, Lin KH, Chen WY, Wu HM, Hunang SB, Hung YJ. Using extracorporeal membrane oxygenation in donations after cardiac death or brain death: A single-center experience and long-term outcome. *Ann Gastroenterol Surg* 2024; **8**: 312-320 [PMID: 38455485 DOI: 10.1002/ags3.12749]

74 **Eshmuminov D**, Becker D, Bautista Borrego L, Hefti M, Schuler MJ, Hagedorn C, Muller X, Mueller M, Onder C, Graf R, Weber A, Dutkowski P, Rudolf von Rohr P, Clavien PA. An integrated perfusion machine preserves injured human livers for 1 week. *Nat Biotechnol* 2020; **38**: 189-198 [PMID: 31932726 DOI: 10.1038/s41587-019-0374-x]

75 **Horslen SP**, Hammel JM, Fristoe LW, Kangas JA, Collier DS, Sudan DL, Langnas AN, Dixon RS, Prentice ED, Shaw BW Jr, Fox IJ. Extracorporeal liver perfusion using human and pig livers for acute liver failure. *Transplantation* 2000; **70**: 1472-1478 [PMID: 11118093 DOI: 10.1097/00007890-200011270-00014]

76 **Chari RS**, Collins BH, Magee JC, DiMaio JM, Kirk AD, Harland RC, McCann RL, Platt JL, Meyers WC. Brief report: treatment of hepatic failure with ex vivo pig-liver perfusion followed by liver transplantation. *N Engl J Med* 1994; **331**: 234-237 [PMID: 8015570 DOI: 10.1056/NEJM199407283310404]

77 **Cooper DKC**, Wijkstrom M, Hariharan S, Chan JL, Singh A, Horvath K, Mohiuddin M, Cimeno A, Barth RN, LaMattina JC, Pierson RN 3rd. Selection of Patients for Initial Clinical Trials of Solid Organ Xenotransplantation. *Transplantation* 2017; **101**: 1551-1558 [PMID: 27906824 DOI: 10.1097/TP.0000000000001582]

78 **Levy MF**, Crippin J, Sutton S, Netto G, McCormack J, Curiel T, Goldstein RM, Newman JT, Gonwa TA, Banchereau J, Diamond LE, Byrne G, Logan J, Klintmalm GB. Liver allotransplantation after extracorporeal hepatic support with transgenic (hCD55/hCD59) porcine livers: clinical results and lack of pig-to-human transmission of the porcine endogenous retrovirus. *Transplantation* 2000; **69**: 272-280 [PMID: 10670638 DOI: 10.1097/00007890-200001270-00013]