Addressing the Donor Liver Shortage with *EX VIVO* Machine Perfusion

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ABSTRACT

Despite a critical shortage of viable donor livers for transplantation, only a fraction of the available organs are used. Donor organ defects, which in the majority of cases are caused by extensive exposure to ischemia, cannot be reversed by static cold storage, the current gold standard of organ preservation. In this review, the role of machine perfusion (MP) in the recovery of non-transplantable ischemic donor organs is discussed. Though still in the experimental phase, various models of MP have consistently demonstrated that ischemic donor organs can be recovered to a transplantable state through continuous perfusion. MP can also provide dynamic quantitative assessments of the extent of ischemia, in addition to predicting the likelihood of organ recovery. Continued endeavors to translate MP into clinical use and eventually incorporate it into routine donor organ care will have a significant impact on the quality and availability of transplantable donor organs.

Keywords: machine perfusion, normothermic, hypothermic, subnormothermic, transplantation

1. INTRODUCTION

Liver transplantation is severely limited by the scarcity of healthy donor organs. In the U.S., 6,291 transplants were performed in 2010, treating only 28% of the waitlisted patients [1]. It is estimated that the actual need for donor livers is much higher, with approximately 76,000 deaths occurring every year from end-stage liver disease [2] and acute liver failure [3]. Organ donation rates are poor globally and only a fraction of donors meet the eligibility criteria, leaving much room for organ procurement optimization [4, 5]. Specifically, techniques to recover a presently untapped resource of

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reversibly damaged ischemic, steatotic and infected donor organs need to be developed. It is estimated that the recovery of ischemic livers alone would increase the donor pool by 300% [6]. This paper reviews the progress of machine perfusion (MP) in maximizing the use of available donor organs. A general overview is first provided on the rationale behind MP designs, followed by a comparison with the gold standard of static organ preservation, and an exploration of treatment of organs using MP with a focus on ischemic livers. Subsequently, we address the critical establishment of objective donor organ indices of viability to be evaluated during perfusion. Finally, major challenges are discussed regarding translating MP into the clinical environment.

2. BACKGROUND ON MACHINE PERFUSION

2.1. Basic Design Elements

MP dates back to the mid-1800s [7, 8] when it was used to increase understanding of organ pathophysiology [9–11]. With remarkably little change in components over the decades, MP is evolving into a long-term organ preservation modality, providing treatment to damaged organs, and serving as an objective and dynamic diagnostic device. The basic principle of MP is that it functions as an artificial body for the isolated organ. Perfusate, a blood supply that may be wholly or partially artificial in content, is continuously cycled through the organ by one or more pumps, the “heart” of the device (Figure 1). Prior to entering the organ, the perfusate is typically oxygenated by the “lungs”, large-surface-area arrangements made of silastic tubing or dialysis membranes that are exposed to balanced gas mixtures. A heat exchanger can be used to control the perfusion temperature, filters can be used to remove particulate matter, and bubble traps can be positioned immediately prior to the organ to minimize air embolisms from entering the vasculature. Upon exiting the organ, the perfusate may be directed through a dialyzer for the renal and enteric functions of toxin dilution and nutrient replenishment from a perfusate reservoir.

2.2. System Standardization

As typical as the MP components are, perfusates and perfusion systems are far from being standardized. The enormous clinical potential of MP lies in administering highly specialized treatment regimens to an isolated organ. Multiple perfusates have been designed to optimize marginal organs and recover otherwise discarded donor organs for transplantation. There is particular emphasis being placed on reversing ischemia, which afflicts the majority of disqualified donor organs, since it requires oxygen and nutrients, augmented by vasodilators and antioxidants [15–19]. Defatting of steatotic organs is currently being attempted using perfusate compositions that increase the catabolism of lipids and improve microcirculation with vasodilators [20–22]. Perfusate is specific to treatment of liver tumors [23, 24], inoculation of donor organs against further viral damage upon transplantation into hepatitis-positive recipients [25, 26], and preconditioning donor organs to better tolerate downstream ischemia [27].

The construct of MP is presently research group-dependent, with species and perfusion temperature the two primary parameters influencing design choices. For example, in an attempt to minimize damage to the biliary epithelium, which has an

Figure 1. MP design increases in complexity when the oxygen requirements of the organ cannot be met by the oxygen dissolved in perfusate, necessitating additional oxygen carriers. (A) High metabolic demand during normothermic MP (37°C) required the use of red blood cells as oxygen carriers in experiments conducted by Tolboom, et al. [12]. A dual-circuit system was designed to sustain a high hematocrit in a low-volume primary circuit directly supplying the liver, while communicating with a large nutrient reservoir through a dialyzer impermeable to red blood cells in the secondary circuit. (B) Perfusion at temperatures $\leq 20^{\circ}\text{C}$ [13, 14] reduces the oxygen requirements of the organ, which can be met with a single circuit that pumps perfusate from the organ chamber/reservoir through an oxygenator and bubble trap to the organ.

arterial blood supply, human-size livers (700–1500 g) have preferential dual vessel circulation [28, 29]. Rat livers (7–15 g) however, are routinely perfused via the portal vein only, avoiding the technically challenging cannulation of the small hepatic artery and the addition of a secondary circuit to accommodate dramatically different arterial flow parameters [12, 30, 31]. Livers also appear to tolerate perfusion at a wide range of temperatures. Organs perfused at low temperatures have reduced metabolic rates and require very little oxygen. Some systems simply circulate a reservoir of cooled perfusate through the organ with a pump, relying on dissolved oxygen in the perfusate [32, 33]. Room temperature perfusions use oxygenators to dissolve more oxygen in the perfusate, but require no temperature control [14, 34, 35] (Figure 1B). By contrast, normothermic perfusions require additional oxygen carriers, such as whole blood or isolated and washed erythrocytes [30, 31, 36]. Though simpler methods are being investigated [37], normothermic MP designs are complex arrangements, as seen in Schön et. al. who used seven pumps, three temperature regulators, and dialysis for perfusion of porcine livers [28], and Tolboom et. al. who used three pumps and dialysis

for rat livers (Figure 1A) [12]. Developing a standardized system that is both effective and logistically feasible is a prominent challenge in the translation of animal to human MP, and a prerequisite for obtaining reliable and meaningful organ-performance data.

3. PRESERVATION OF HEALTHY DONOR ORGANS

3.1. Static Cold Storage

Today's definition of an optimal standard criteria donor (SCD) is a young, previously healthy person who developed fatal brain injury due to causes such as head trauma, intracranial hemorrhage, or stroke. These donors after brain death (DBD) can retain cardiopulmonary function thereby sustaining organs with an oxygenated blood supply until a decision is made to withdraw life support. Transplantable organs are then procured for static cold storage (SCS) on ice (0°C–4°C) [38]. By reducing organ temperature from 37°C to 0°C, Van't Hoff's rule predicts a 12- to 13-fold temperature-induced reduction in metabolic activity, which also slows the progression of ischemic damage [39, 40] buying the organ finite storage time [41, 42]. Since organs can generally tolerate an hour of warm ischemia (WI), they should theoretically be able to tolerate 12 hours of cold ischemia [43]. Calne et al. demonstrated this in kidneys that retained function after 12 hours of preservation in cold blood [44]. Specially-designed preservation solutions [45–47] have fundamentally changed this correlation, with University of Wisconsin (UW) solution being the first to prolong liver storage in dogs to 48 hours [48, 49] and up to 30 hours in humans [50, 51]. However, in the absence of objective measures of organ ischemic damage during storage, clinical data indicate that transplantation success rates fall from 92% to 59.5% if storage exceeds 12 hours [52]; hence, longer storage times are generally avoided [41, 53–55].

3.2. Hypothermic Machine Perfusion

One goal, and an important test of the validity of MP, is to enhance organ storage conditions for healthy donor organs by minimizing ischemic time. A simple and successful proof of this concept has been demonstrated in the kidney, where SCS has been shown to be inferior to continuous recirculation of cold storage solution in the organ [56]. Hypothermic machine perfusion (HMP) reduces delayed graft function, increases storage time, and improves survival rates compared to SCS [57–59], justifying the increase in graft treatment expense [60]. HMP of the kidney is now performed routinely in certain clinical practices, particularly for marginal organs [56]. Still in the experimental phase, animal studies in the liver have shown that HMP is at least as good as SCS if not better [61, 62]. In one such study, a porcine model comparing 12 hours of SCS and HMP showed both had comparable post-transplantation alanine aminotransferase (ALT) levels, total bilirubin levels, and 5 day survival rates [33]. Pienaar *et al.* were able to extend storage of canine livers to 72 hours using HMP through portal perfusion only, which were then successfully transplanted [63]. Sufficiently high-powered studies comparing SCS with HMP have yet to be conducted in human livers [64, 65], but recently, Guarrera *et al.* demonstrated that 4 hours of HMP is well tolerated by human livers after an average 5 hours of SCS.

Overall graft and patient survival were comparable to SCS-only treatment at 1 year, with functional parameters, duration of hospital stay, and assessed quality of life in favor of SCS+HMP treatment [66]. By proceeding to firmly establish MP as a storage modality for the liver to minimize transplantation exigency and optimize organ usage, the road will be paved for the consistent use of MP as a therapeutic device for suboptimal organs [57, 67].

4. RECOVERY OF ISCHEMIC DONOR ORGANS WITH MACHINE PERFUSION

The application of MP to the recovery of ischemic organs, in particular those deriving from donors after cardiac death (DCD), is of greatest interest not only because this group represents the largest source of unused donor organs presently available, but also because the treatment regimen may be as simple as the restoration of oxygen and nutrients to the organ in a non-inflammatory perfusate. DCDs were phased out of use in the 1960s because of higher success rates with DBD organs [68, 69]. Today, DCDs are categorized as (1) dead on arrival, (2) unsuccessful resuscitation, (3) awaiting cardiac arrest after ventilator switch off, and (4) cardiac arrest while brain-dead. For DCDs in categories 1 and 2, the ischemic time cannot be accurately determined and these organs are rarely used. DCDs in categories 3 and 4 who have a controlled ischemic period [6, 70] less than 30 minutes may be considered for transplantation. Experimental MP conducted in a wide range of temperature has shown that the recovery of ischemic livers with up to 60 minutes of WI is possible. Further, MP can provide three valuable pieces of information about DCD organs, particularly those from categories 1 and 2, by: (1) assessing the extent of ischemic damage, (2) predicting graft function after transplantation, and (3) recovering viability parameters to a state in which the organ has a high chance of successful implantation and long-term function.

4.1. Hypothermic Machine Perfusion (HMP)

Since HMP is becoming a conduit of oxygen and nutrients for healthy SCD organs, evaluating whether it can also recover DCD organs is logical [71–73]. The quantity of oxygen that should be delivered to DCD livers was investigated in rat livers with 30 minutes of WI perfused hypothermically with histidine-tryptophan-ketoglutarate solution (HTK) for 18 hours while being gassed with 0%, 20% (ambient) or 100% oxygen [74]. It was determined that 100% O₂ was superior in minimizing ALT release both during perfusion and reperfusion. Interestingly, this treatment also resulted in reduced oxygen free radical-mediated lipid peroxidation upon warm reperfusion with enhanced activation of the 5' adenosine monophosphate-activated protein kinase (AMPK) salvage pathway, and upstream activation of protein kinase A. Moreover, only livers receiving the 100% O₂ treatment showed recovery of bile production. In a different model of rat liver transplantation, SCS exacerbated 30 minutes of warm ischemic damage causing graft failure, while 5 hours of HMP enabled graft recovery resulting in recipient survival for five days [75]. Porcine studies determined that even a short 1–2 hours of oxygenated HMP after 60 minutes of WI and 6 hours of cold

ischemic storage mitigated damage [76–78], though after transplantation of these organs, the studies were terminated within 24 hours since the animals were not thriving.

The impact of oxygenation on the recovery of ischemic organs was observed through a separate, novel method that enhanced the delivery of oxygen during HMP without affecting normal flow through the liver [79]. Oxygen persufflation, a method by which oxygen is inflated in a retrograde fashion through the liver and allowed to escape from capsular pin-pricks, was found to provide some benefits over regularly dissolved oxygen in perfusate by minimizing organ damage and restoring organ function [80, 81]. In particular, persufflation appeared to restore tissue adenosine triphosphate (ATP) content above normal values [82], which is known to be correlated with improved graft function and survival [83]. Minimizing oxidative damage during this process can be promoted by the prior cold-flushing of the organ with antioxidants such as superoxide dismutase (SOD) or n-acetylcysteine [84], and has been used in the successful recovery and transplantation of DBD human livers that experienced up to 60 minutes of WI within 48 hours prior to procurement of the donor organ [85]. Further investigations into the efficacy and safety of this technique applied to DCD livers are necessary.

HMP evidently provides some benefits to WI livers, however there are no compelling long-term results post-transplantation yet. Further, it is believed that hypothermia contributes to ischemia reperfusion injury (IRI) [86]. The degree of IRI is directly correlated with duration of cold storage [87] and is responsible for 10% of acute and chronic rejection events [88]. MP during the hypothermic phase can reduce oxidative stress and pro-inflammatory cytokine expression compared to SCS [66, 89]; however, non-parenchymal cells, the endothelium in particular, demonstrate increased sensitivity to cold flow-induced damage [90–92], which negatively impacts the microvasculature [93].

4.2. Normothermic Machine Perfusion (NMP)

To counter hypothermia-induced damage, perfusion of the organ at physiological temperatures has been advocated [94, 95]. This method provides the added advantage of being able to evaluate organ status by comparing normothermic machine perfusion (NMP) data to known *in vivo* parameters [96]. NMP has demonstrated superior graft function compared with SCS porcine livers [18, 97] and has preserved SCD livers stably for up to 72 hours [29]. NMP successfully recovered livers exposed to 60 minutes of WI for transplantation in both rat and porcine models, with follow-up continuing beyond 4 weeks post-procedure in the rat model [12, 29, 98, 99]. The principle of NMP has proven to be critical in the recovery of uncontrolled DCD livers, which currently contribute a significant fraction of donor organs in Spain [100–104]. Donor livers in these circumstances are perfused *in situ* with the donor's blood supply circulated via an extracorporeal membrane oxygenator (ECMO).

A direct comparison between the effectiveness of NMP and HMP has not been conducted, though two separate studies by Dutkowski [105] and Tolboom [106] investigated the response of rat livers exposed to 45 minutes of WI (29°C and 34°C, respectively). In the first study, livers were treated with 5 hours of SCS and 1 hour of

HMP, while in the second, livers were treated with 2 hours of SCS and 4 hours of NMP. In both groups, transaminase release was reduced, and transplantation was successful. From an efficacy perspective, it is unclear how long Dutkowski et al. monitored the animals post-transplantation, and what fraction of the animals that were not treated with HMP also survived. By contrast, all control animals in Tolboom et al.'s study died potentially because the WI temperature was more severe, while all recipients survived > 30 days. From a practical perspective, Dutkowski's approach was simpler and more clinically feasible; the longer SCS time simplifies organ transportation with autonomous organ recovery occurring in a shorter period of time.

Complexity is the major limitation to the use of NMP. At 37°C, the perfusate requires an oxygen carrier. Red blood cells are most effective but are also a source of considerable variability within the perfusate, requiring constant adjustments to sustain hematocrit as cells die or fluid levels change during dialysis. Multiple pumps and dialyzers to separate perfusate reservoirs are usually required, making the system immobile and cumbersome to use. While NMP may avoid hypothermia-induced damage, a simpler and consistent methodology would be more suitable for clinical use.

4.3. Subnormothermic Machine Perfusion (SNMP)

Operating perfusion systems at room temperature may represent the best of both HMP and NMP designs, while being ultimately simpler and more effective than either. It is known that the act of cooling an organ retards not only the metabolic progression of ischemia, but also many destructive enzymes. Phospholipases, normally active at 37°C, for example, are inactivated in livers stored at 21°C and 4°C regardless of the preservation solution used [107]. Similarly, reperfusion injury was minimized equally in organs stored at 26°C and 4°C, showing no change in sinusoidal perfusion index, leukocyte attachment, hepatic architecture or transaminase release [108]. At 20°C–21°C, restoration of energy charge was more rapid, bile production higher, portal venous resistance lower and glycogen content better recovered than at lower temperatures [34, 109].

We recently performed a series of transplantations that demonstrated successful recovery of rat livers exposed to 60 minutes of WI with subnormothermic perfusion (SNMP) at either 30°C or 20°C [110]. The technique used a sanguineous perfusate, identical to that used in the complex NMP system in a previous study [12], but operated at room temperature ($20 \pm 2^\circ\text{C}$). To investigate the possibility of removing the need for oxygen carriers at room temperature, we subsequently repeated the experiments using the same perfusate but without the addition of blood components (red blood cells and plasma), relying instead on the oxygen dissolved in Williams Medium E to support the liver. The perfusion system was significantly simplified to a single pump, a reservoir, an oxygenator and a bubble-trap, resembling that of HMP systems without the need for temperature control. Transplantation of the livers after such treatment was successful, showing excellent survival rates 1 month post-procedure [14]. The ability to avoid cold-induced damage while retaining some metabolic activity with which to evaluate organ viability, and significantly simplifying the perfusion system by removing the need for temperature control and oxygen carriers, makes perfusion at room temperature a valuable proposition [35]. A comparison of the preservation methods discussed above can be found in Table 1.

Table 1. Comparison of liver preservation modalities

	SCS (0°C–5°C)	HMP (0°C–5°C)	SNMP (20°C–30°C)	NMP (37°C)
Perfusate	<ul style="list-style-type: none"> • IGL-1 	<ul style="list-style-type: none"> • Vasosol 	<ul style="list-style-type: none"> • Modified Krebs 	<ul style="list-style-type: none"> • Whole blood
Examples [91, 95]	<ul style="list-style-type: none"> • UW • Celsior • HTK • Custodiol-N • Euro Collins • Marshalls 	<ul style="list-style-type: none"> • Custodiol-N • Polysol • HTK • UW-Gluconate • Starch-free UW 	<ul style="list-style-type: none"> • Henseleit • UW-Gluconate • Lifor • Williams Medium • E with and without blood components 	<ul style="list-style-type: none"> • (ECMO) • L-15-based artificial blood • Williams Medium • E with blood components
Method [28, 34, 35, 109, 111, 112]	Single flush under gravity then stored on ice.	Continuous circulation before, during, or after transportation. (0.1–1.0 ml/min/g)	Continuous circulation before, during, or after transportation (1.6–4.0 ml/min/g)	Continuous circulation before, during, or after transportation (0.6–1.8 ml/min/g)
Applications	Established in humans	<ul style="list-style-type: none"> • Not routinely used in humans • Porcine • Rat 	Rat	<ul style="list-style-type: none"> • Established in humans (ECMO) • Porcine • Rat
Human Liver Storage (hrs)	< 12	< 4	NA	< 4
Typical Components	<ul style="list-style-type: none"> • 1–2L bag • Ice 	<ul style="list-style-type: none"> • Roller Pump • Bubble trap • Oxygenator/Persufflation • Heat exchanger • Reservoir 	<ul style="list-style-type: none"> • Roller Pump • Bubble trap • Oxygenator • Reservoir 	<ul style="list-style-type: none"> • Centrifugal Pump • Bubble trap • Oxygenator • Heat exchanger • Oxygenator • Dialyzer (optional) • Reservoir
Isolated/En Bloc	En bloc	Isolated	Isolated	Isolated
Mobility	Ice box	Immobile - Device needed	Immobile - Device needed	Immobile - Device needed
DCD Treatment	No	Yes	Yes	Yes

5. INDICES OF VIABILITY

Organ transplantability is presently determined by the empirical correlation of recipient outcome with donor characteristics and is strongly specific to centers or regions [87]. Age, for example, is frequently cited as either having an impact on donor organ function [113, 114], or not [115–117] provided there is very strict adherence to additional

selection criteria. Other assessments of organ status depend on non-specific serum markers in the donor prior to explantation and the visual interpretation of graft macro- and microscopic appearance after explantation [118–121].

A major advantage of MP lies in providing real-time, organ-specific data to support these decisions quantitatively, ensuring minimal disqualification of donor organs. We recently analyzed 25 metabolites measured hourly over 6 hours for 11 WI and 7 fresh rat livers during NMP using multi-way principle component analysis (MPCA) [122]. MPCA provided an index that accurately specified the extent of ischemic injury in donor organs, identifying whether a given perfused liver was ischemic or fresh with >98% specificity. Used on organs with minimal patient history (such as uncontrolled DCDs), the extent of ischemia can be diagnosed and, combined with its rate of approach to “fresh” status, the likelihood of recovery to a transplantable state can be estimated.

This hypothesis-free data-intensive approach to evaluating organs in perfusion will reveal the parameters that are critically correlated with organ viability. These parameters may provide useful insights into the specific mechanisms of ischemic organ recovery in MP that are presently associated with the restoration of oxygen and nutrients. Further, by correlating the parameters with graft outcomes post-transplantation, algorithms can be developed that inform positive intervention strategies and predict graft outcome. A simple example comes from a recent study using an NMP perfusion model of warm ischemic rat livers comparing 26 metabolites and liver transaminases. ALT was found to be highly predictive of graft outcome within 30 minutes of reperfusion (100% classification accuracy and 100% average relative accuracy) [123]. Usefully, liver transaminases are rapidly measurable parameters that are already well-known to correlate with graft survival [119, 124, 125]. By contrast, oxygen uptake rate had a cross-validated classification accuracy of only 57%, suggesting that while the supply of oxygen is an important component to ischemic organ recovery, restoring cellular integrity is critical.

However, a single non-specific marker of cell damage to evaluate cellular integrity would be insufficient for developing a robust automated feedback control of perfusion. For instance, it has been determined that non-parenchymal cells are more sensitive to ischemia than hepatocytes [126]. By measuring creatine kinase and hyaluronic acid, both markers of endothelial damage that precede hepatocellular enzyme release [127, 128], evaluation timeliness and specificity is improved, while better informing the treatment approach. Similarly, biliary endothelial damage, presently evaluated with alkaline phosphatase or gamma-glutamyl transpeptidase [129], and biliary function, assessed by total bilirubin production and bile acid content [119, 130], are critical measurements for DCD organs, which are known to have high incident of biliary complications [131–133]. It is also important to perform this modeling directly in human livers to avoid species-dependent differences, particularly in biliary dysfunction which will adversely impact automation of any proposed treatment strategies [134, 135].

There are additional highly sensitive and dynamic markers of the liver’s overall biosynthetic capacity and cellular integrity. ATP is a good indicator of the degree of ischemic damage sustained, dropping off exponentially with ischemic time [136]. It can

be measured directly or as a function of its breakdown products hypoxanthine and xanthine [137]. The ischemic liver's ATP content is correlated with organ viability, providing a quantitative measure of cellular recovery during perfusion and a measure of graft transplantability [138]. Other routinely-measured biosynthetic processes of the liver include albumin synthesis, clotting factor production [97] and urea synthesis [139, 140]. Hepatic clearance of drugs like lidocaine, which is measured through its conversion to monoethylglycinexylidide (MEGX) within the hepatic cytochrome P450 system, is also useful in evaluating graft function [141–143]. MP enables the measurements of all the above-mentioned parameters in serum, while data-mining and visualization tools will identify [83, 144] and standardize the fewest necessary to rapidly and accurately diagnose organ status, and prognose and guide organ recovery [83, 144].

6. TRANSLATIONAL CHALLENGES

An estimated 5,000 uncontrolled and 1,000 controlled DCD livers could be added to the U.S. donor pool per year [145], essentially doubling the available organ supply, by initiating a 24-hour donor organ procurement team as is presently available in Spain [102, 128]. However, instead of relying on the Spanish model of ECMO to recover the organs, MP may provide a more convenient approach to organ-specific treatment [15]. Still in the experimental phase, the translation of MP technology to humans is dependent on carefully controlled clinical trials that will verify MP's safety and efficacy.

Further, the logistical question of how to introduce MP into the current donor procurement process remains unanswered. Presently a donor's organs are flushed en bloc with a cold storage solution, initiating a period of cold ischemia, after which specific organs are recovered. While SCD organs are subsequently stored and transported on ice, ischemic donor organs will require optimization via MP first, involving backbench preparation of the inflow vessels for cannulation, which increases an additional hour of cold ischemic time. The exact tolerance of organs to a combination of extended warm and then cold ischemia prior to MP will have to be determined [17, 106, 146]. Then the choice will have to be made between perfusing the organ prior to, during, or post transportation. Perfusion prior to transportation is based on the hypothesis that restoring the organ's ATP levels and glycogen content to normal will enable it to withstand a second, longer round of SCS during transport [147]. The advantage of this approach is that the MP setup does not have to be portable and perfusion can be conducted under the best conditions (temperature, dialysis, perfusate, oxygenation). The organ could also be reperfused after cold storage to optimize it for transplantation. The disadvantage of a non-mobile perfusion approach is that it adds several hours to the procurement process. Lengthy procurements can be avoided by perfusing the organ during transportation; however, the design must be simple, robust and able to withstand pump failure. Such design considerations would also do well to heed the lessons learned from the renal perfusion systems, particularly as they impact the future cost effectiveness of MP [148–150].

The challenges ahead are significant, but pursuing the ultimate goal of perfusing all donor livers to evaluate their viability and likelihood for optimization is a worthy endeavor. It will better ensure that every donor organ will be used for transplantation, cell isolation [151, 152], or decellularized scaffold procurement [153], and will have a significant impact on increasing the availability of treatment options for patients with end stage liver disease.

7. CONCLUSIONS

Despite a critical shortage of viable livers for transplantation, only a fraction of the available donor livers is used. MP functions as a therapeutic window that allows objective evaluation of organ viability, improvement of long-term organ storage conditions, and rendering transplantable the large fraction of organs that would otherwise be discarded. Though many challenges remain in realizing the potential afforded by this technique, its value in treating donor organs strongly favors endeavors to incorporate MP into routine donor organ care.

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CONFLICT OF INTEREST

The authors have no financial conflicts of interest.

NOMENCLATURE

ALT	Alanine aminotransferase
AMPK	5' Adenosine Monophosphate-Activated Protein Kinase
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
DBD	Donor after Brain Death
DCD	Donors after cardiac death
ECMO	Extracorporeal Membrane Oxygenator
HMP	Hypothermic Machine Perfusion
IRI	Ischemia Reperfusion Injury
MPCA	Multi-way Principle Component Analysis
NMP	Normothermic Machine Perfusion
SCD	Standard Criteria Donor
SCS	Static Cold Storage
SNMP	Subnormothermic Machine Perfusion
SOD	Superoxide Dismutase
UW	University of Wisconsin
WI	Warm Ischemia

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