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REVIEW

Normothermic liver preservation: a new paradigm?

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Summary

Despite increasing donor numbers, waiting lists and pre-transplant mortality continue to grow in many countries. The number of donor organs suitable for liver transplantation is restricted by cold preservation and ischemia-reperfusion injury (IRI). Transplantation of marginal donor organs has led to renewed interest in new techniques which have the potential to improve the quality of preservation, assess the quality of the organ and allow repair of the donor organ prior to transplantation. If successful, such techniques would not only improve the outcome of currently transplanted marginal livers, but also increase the donor pool. Experimental evidence suggests that preservation under near physiological conditions of temperature and oxygenation abrogates IRI. Normothermic perfusion maintains the organ in a physiological state, avoiding the depletion of cellular energy and the accumulation of waste products, which occurs with static cold storage. It enables viability assessment prior to transplantation thereby reducing the risk of transplanting inherently marginal organs. Here we review the use of normothermic machine perfusion as a means of organ preservation.

Introduction

Since the first human liver transplant performed in 1963 by Thomas Starzl [1] and with decades of developmental and experimental work, liver transplantation is now fully established as the standard treatment for patients with end-stage liver failure. In 2012, 23 986 liver transplants were performed in 68 countries worldwide [2].

As the success of liver transplantation has improved, so the indications have expanded and the supply of donor organs for transplantation has not kept up with the demand. This has necessitated the use of increasingly marginal livers from extended criteria donors, (including older donors with medical comorbidities and steatotic livers) and those from donation after circulatory death (DCD) donors. These grafts are known to be more susceptible to ischaemia–reperfusion injury, leading to higher rates of primary nonfunction (PNF) [3–5]. Many innovative approaches have been developed in the quest for a new source of donor organs. These include xenotransplantation and the development of bioartificial organs. Immunological reactions currently limit the progression and development of xenotransplantation [6]. Liver bioengineering has demonstrated more promise with recent advances of decellularizing and successful grafting with liver cells in a whole organ porcine model [7]. However, none of these options is close to clinical implementation.

There has been little change in the routine clinical practice of organ preservation in liver transplantation since the introduction of University of Wisconsin solution in the late 1980s. Whilst suitable for high-quality organs, static cold storage (SCS) is a limiting factor in the viability of marginal donor organs. The need to transplant high-risk donor organs has led to renewed interest in new techniques which may improve the quality of preservation, assess the quality of the organ and even allow repair of preretrieval injury of the donor organ prior to transplantation. If successful, such techniques might not only improve the outcome of currently transplanted marginal livers, but also increase the donor pool. In this context, machine perfusion of the liver both at low temperature (hypothermic) and at physiological

temperature (normothermic) has gained prominence in the last decade.

Here we review the use of normothermic machine perfusion as a means of organ preservation.

Physiology of organ retrieval and cold preservation

The term ischaemia–reperfusion injury (IRI) describes a cascade of injuries that result from the combination of anaerobic metabolism (during cold preservation) and reperfusion (reprovision of oxygenated blood and physiological temperature). This is the primary mode of injury, which results in post-transplant dysfunction in an organ that was functioning normally in its donor prior to retrieval [8].

Oxygen drives cellular activity, allowing the production of adenosine tri-phosphate (ATP). During the retrieval process, as soon as blood flow ceases, the supply of oxygen, nutrients and cofactors stops, and the accretion of metabolic waste products begins as a consequence of anaerobic metabolism. The depletion of ATP results in disabling of sodium-potassium membrane pumps, causing a loss of electrolyte gradients and membrane integrity. This in turn causes cellular oedema, influx of free calcium and subsequent activation of phospholipases that promotes inflammation and leads to cell death [9–11]. Furthermore, where normally the products of ATP breakdown are converted to uric acid by xanthine dehydrogenase, in an ischaemic environment, xanthine dehydrogenase is converted to xanthine oxidase, which in the following reperfusion phase, in the presence of oxygen, converts the accumulated products into xanthine and free radicals causing lipid peroxidation and further cellular destruction [12,13]. In DCD organs, an initial period of warm ischaemic injury is sustained between the cessation of circulation and cold flush, resulting in a significant degree of ATP depletion prior to cooling.

Static cold storage relies on the effect of cooling to diminish cellular metabolism and minimize the rate of ATP depletion. For every 10°C drop in temperature, metabolism is slowed 1.5-fold to twofold [11]. However, anaerobic metabolism continues even at 1°C, leading to continued ATP depletion and, upon reperfusion, the IRI cascade [11]. Cold ischaemia, therefore, primes the cells for damage, the effects of which become manifest upon reperfusion. The avoidance of ischaemia by the provision of oxygenation and other metabolic substrates for the liver is therefore a logical target for innovative preservation methods. The ideal method of organ preservation should (i) reverse the injury sustained before or during organ retrieval, (ii) avoid ischaemia during preservation, (iii) minimize reperfusion injury and (iv) enable viability testing before transplantation.

The concept underlying normothermic machine perfusion (NMP) is the recreation of a physiological environment during preservation. This requires the delivery of oxygen and nutrients at normal temperature. This should enable (i) prolonged preservation without the time-dependent damage that is caused by cold preservation, (ii) the ability of the organ to recover from some types of injury that occurred before retrieval, (iii) the opportunity to measure the function of the organ during preservation in order to predict the post-transplant outcome and allow careful selection and (iv) minimization of ischaemia–reperfusion injury by restricting hypoxia to the period of implantation rather than the entire duration of preservation.

Normothermic perfusion of the liver is not a novel concept. In the 1930s, Alexis Carrel and Charles Lindbergh first perfused various organs with normothermic, oxygenated serum and demonstrated viability for several days [14]. As liver transplantation approached clinical reality in the 1960s, canine organs were preserved at 12–15^{O}C with autologous blood using a femoro-femoral extracorporeal perfusion circuit [15]. In these experiments, perfusion was started after the cessation of natural circulation without *in situ* flushing of the organs and the resulting warm ischaemic period was presumably the reason for the failure of the subsequent 2-h perfusions, demonstrated by elevation in SGOT and bilirubin levels, and by the development of coagulation defects [15]. Kestens *et al.* [16] in 1966 successfully preserved canine livers for up to 5 h before successful transplantation using oxygenated blood at 10-18°C. Pulsatile perfusion of canine livers through the hepatic artery alone using hyperbaric oxygenated salt solution was performed in 1967, with marginal results [17]. Brettschneider *et al.* [18] subsequently perfused the portal vein and hepatic artery of canine livers with a perfusate consisting of a 50–50 mixture of autologous blood and preservation solution in a refrigerated, hyperbaric environment. Of five livers preserved for 8–9 h, four recipients of the homografts survived for more than 24 h [18]. The same group preserved human livers for 4–7 h, and all seven patients survived the first postoperative week. [19] However, the introduction of Collins solution [20] and the ease of use of static cold preservation moved the emphasis away from machine perfusion. It is only in the last decade, with increasing pressure to transplant high-risk organs, that the feasibility of machine perfusion is once again being explored. Hypothermic machine perfusion (HMP) of the liver was investigated in the setting of a Phase 1 clinical trial in 2010 [21]. Guarrera *et al.* successfully transplanted 20 human livers, which underwent HMP after a period of SCS. In 2015, the same group reported transplantation of 31 extended criteria donors (ECD) following HMP and compared these with matched controls. There were significant differences in biliary stricture rates and hospital stay; a reduction in early allograft dysfunction was not statistically significant [21,22]. This technology has not yet been subjected to a randomized clinical trial, and the question

therefore remains unresolved as to the extent to which the relatively simpler technology of HMP will be effective in the context of high-risk organs.

Experimental evidence for the efficacy of NMP of the liver

A landmark study by Schön *et al.* [23] in 2001 using a porcine model of transplantation demonstrated that NMP is feasible as a means of liver preservation and enabled successful transplantation of donor livers that had been subjected warm ischaemia. When exposed to 1 h of warm ischaemia time (WIT), all six animals undergoing 4 h NMP prior to transplantation survived, compared to five of six transplanted without preservation, and none of six survived with 4 h static cold storage prior to transplantation. At around the same time, the feasibility of prolonged normothermic liver perfusion (72 h) was demonstrated, as well as the potential benefits of NMP with respect to synthetic and metabolic function [24–26]. Simulating the context of a DCD donor in a pig liver reperfusion model, the same group demonstrated that following 60 min of *in situ* warm ischaemia, livers undergoing NMP for 24 h demonstrated superior synthetic function and less cellular damage compared to livers in cold storage for 24 h [27].

There has been much debate as to whether the benefits of normothermia can be delivered by a brief period of perfusion following static cold storage (normothermic reconditioning) or requires the complete avoidance of cooling (normothermic preservation). In a clinical context, this has important practical implications with respect to whether the perfusion device must be made transportable (to the donor hospital). To address this question, porcine livers were subjected to 60 min of WIT followed by either immediate normothermic perfusion or cold storage for 4 h followed by NMP, with a total preservation time of 24 h in both groups. All livers were then reperfused for 24 h, as a surrogate for transplantation. Livers transferred directly to normothermic perfusion with no cold ischaemic period showed significantly superior bile production, acid–base control and transaminase release [28]. However, this experimental setting with no period of cold ischaemia is not compatible with clinical application. A shorter cold ischaemia time (CIT) of 1 h (to simulate *in situ* cold flush, explantation and benchwork (organ cannulation etc.) showed no difference between the two groups. This implied that a 1-h period of cooling is an acceptable approach to take forward into clinical practice [29].

In a transplant (rather than reperfusion) model of DBD and DCD liver transplantation, the Oxford group investigated the effects of 5 and 20 h preservation times. In the 5-h preservation group, there was no difference between SCS and NMP in the DBD model. However, there was a significant difference between SCS and NMP in the 20-h preservation experiments for both DBD and DCD livers. In the DBD group with 20-h preservation times, six of seven NMP transplants survived compared to two of seven SCS transplants. With the introduction of 40 min of WIT prior to organ retrieval (a model of DCD donation), none of the four animals transplanted with SCS-preserved livers survived compared to four of five of the NMP transplant recipients [30]. This suggested that NMP might be able to resuscitate livers that had undergone a degree of warm ischaemic injury prior to retrieval that would not be survivable with cold preservation [30].

NMP in combination with normothermic regional perfusion

The NMP concept of delivering oxygenated normothermic blood is essentially the same as that which underpins normothermic regional perfusion (NRP), which provides reoxygenation of DCD organs during a shorter period of *in situ* perfusion rather than a longer period of *ex situ* perfusion. Fondevila *et al.* in 2011 reported a study in which the two approaches were studied to look for additive (or synergistic) effects. In a porcine model, NRP was instituted immediately upon cardiac arrest in the donor; livers were then retrieved and stored by NMP, before transplantation. After 90 min of circulatory arrest, porcine livers were allocated to three groups (each of six livers). In one group, livers were preserved immediately with cold storage. In the other two groups, donors underwent 60 min of NRP followed by either SCS or NMP. Livers were preserved for 4 h and then transplanted into recipient pigs. There were no 5-day survivors with immediate cold storage, 83% in NRP + SCS and 100% in NRP + NMP [31]. The authors concluded that in this very rigorous model, the combination of NRP and NMP is able to achieve successful liver transplantation reliably following 90 min of circulatory arrest. If this reflects what could be achieved in the clinical situation, then this would have a major effect on the utilization not only of organs from DCD Category III donors ('controlled') but also those in DCD Category II ('uncontrolled') donors.

Steatotic livers

An increasing proportion of donor organs have fat deposition within hepatocytes (steatosis). There is good evidence that macrovesicular steatosis involving greater than 30% of hepatocytes is associated with poorer outcome [32]. It has been hypothesized that NMP may have benefits with respect to the transplantation of steatotic livers in a number of ways: (i) the avoidance of cooling – the compliance of steatotic liver tissue alters considerably as the temperature falls and it is possible (although not proven) that this is one

mechanism to explain the poor immediate postoperative recovery of such organs;[33] (ii) reduction of ischaemia–reperfusion – steatotic livers are known to be very sensitive to ischaemia–reperfusion injury and reduction in this may be of particular benefit in such livers;[34,35] (iii) mobilization of fat and reduction of intracellular fat during NMP and[36,37] (iv) pharmacological strategies to increase fat metabolism[36]. In 2009, Nagrath *et al.* [36] used a NMP circuit with perfusate exchange and the addition of a cocktail of 'defatting' agents to demonstrate a 65% reduction in triglyceride levels in a steatotic rat model. In a porcine model of steatosis, with prolonged NMP alone, without perfusate exchange or defatting agents, the degree of steatosis was reduced, suggesting that the liver fat is mobilized very rapidly [37]. Experimental work on the impact of NMP on steatotic liver is needed; this reflects the difficulty in obtaining a reliable reproducible and clinically relevant animal model of steatosis (as well as an agreed method to classify and quantify steatosis).

Clinical experience of normothermic machine perfusion

With promising results from large animal model experimental work, NMP moved into discarded human liver research. Recently, op den Dries *et al.* have reported results from discarded human livers. Four discarded DCD human liver grafts were normothermically perfused on the Liver Assist (OrganAssist) device for 6 h after 12-17 min of warm ischaemia followed by cold preservation of 4.5–9.5 h [38]. This demonstrated feasibility of NMP in human livers with well-perfused livers, continuous bile production, falling lactate levels and preservation of liver morphology on histological examination [38].

A Phase 1 clinical trial (ISRCTN 14355416) of normothermic liver perfusion has been conducted (as yet unpublished) and recruitment to a Phase 3 randomized controlled clinical trial recently commenced (ISRCTN39731134); this compares normothermic machine perfusion to static cold storage.

Implementations of normothermic perfusion of the liver

Most of the NMP circuits that have been developed for experimental or clinical purposes have been constructed using components developed for cardiopulmonary bypass: pumps, oxygenators and heat exchangers. Although hypothermic perfusion systems have been developed that perfuse only the portal vein, all the clinical devices that operate at normothermia perfuse both portal venous and arterial circulations. Some implementations achieve this by means of two pumps and parallel circuits [38,] whereas others achieve the necessary dual circulation (with differential pressures and flows) using a single pump [30]. In general, centrifugal pumps are preferred because of lower levels of haemolysis and preferable pressure/flow characteristics. Some circuits allow free drainage of venous blood from the inferior vena cava (IVC) into an open reservoir (OrganAssist) [38,] whereas others use a fully cannulated (i.e sealed) circuit. The relative merits of these two design features remain a matter for debate.

There has been much discussion over the preferred perfusion solution. Most groups recognize the need for a specialist oxygen carrier, although dissolving enough oxygen in a simple solution is theoretically possible using hyperbaric conditions [39]. Specialist oxygen carriers that have been considered include perfluorocarbon molecules, [40,41] but increasingly the consensus is to use erythrocytes. Blood-based perfusates have been the basis of the majority of recent publications in this area [24,30,31,38].

Similarly, there is a range of published experience with respect to the additives that have been used to maintain metabolic function during perfusion. These include nutrition (amino acids, insulin and glucose), drugs to prevent thrombosis and microcirculatory failure (heparin and prostacyclin), antibiotics and other agents to reduce cellular oedema, cholestasis and free radical injury [24]. Porcine liver perfusions demonstrated a reduction in bile production with histological evidence of cholestasis after about 10 h of normothermic perfusion, thought to be due to depletion of bile salts because of the absence of the enterohepatic circulation. An infusion of taurocholate was shown to resolve this issue [42]. The Oxford group uses a combination of heparin, insulin, prostacyclin and a bile salt (taurodeoxycholic acid). The need for nutrition is less well evidence based, but is based on the argument that a functioning liver is likely to become energy substrate-depleted within 24 h in the absence of nutritional input – a combination of carbohydrate and protein is given by infusion; lipid is avoided [43].

Devices currently in clinical or preclinical testing

Liver assist

The Liver Assist is a CE-marked pressure-controlled device that provides pulsatile flow through the hepatic artery and continuous flow through the portal vein. For this, it uses a dual system of rotary pumps and hollow fibre membrane oxygenators. Temperature settings are not fixed and can be manually altered by the user. These are displayed on the screen in real time. The liver is cannulated via the coeliac artery or aorta and portal vein. The inferior vena cava is left open and drains into the reservoir. The cystic duct is ligated and the common bile duct is catheterized. As the device is not transportable, livers are cold preserved from

the retrieval centre to the transplant centre before being placed on the device. The Liver Assist can be used in hypothermic, subnormothermic or normothermic modes (Fig. 1). This enables slow rewarming after cold storage, which has been shown to be beneficial [43].

OrganOx metra

The OrganOx Metra is a mobile normothermic perfusion device. It provides continuous flow through the hepatic artery and portal vein, using a single pump delivering blood to the artery directly and to the portal vein via a reservoir. The system is fully cannulated and maintains physiological pressures and flows by a process of 'auto-regulation'. The OrganOx system is almost fully automated, with built-in blood gas analysis and algorithm-controlled regulation of arterial pressure, gas delivery, temperature, as well as bile output measurement: the system is designed to perfuse a liver for up to 24 h. The device is transportable to the donor hospital (Fig. 2).

Transmedics liver preservation

The TransMedics Organ Care System[44] includes NMP devices for the heart, lung and, most recently, liver. These devices are transportable to donor hospitals and initial publications of the heart and lung devices confirm the feasibility of their use in the clinical environment [45,46].

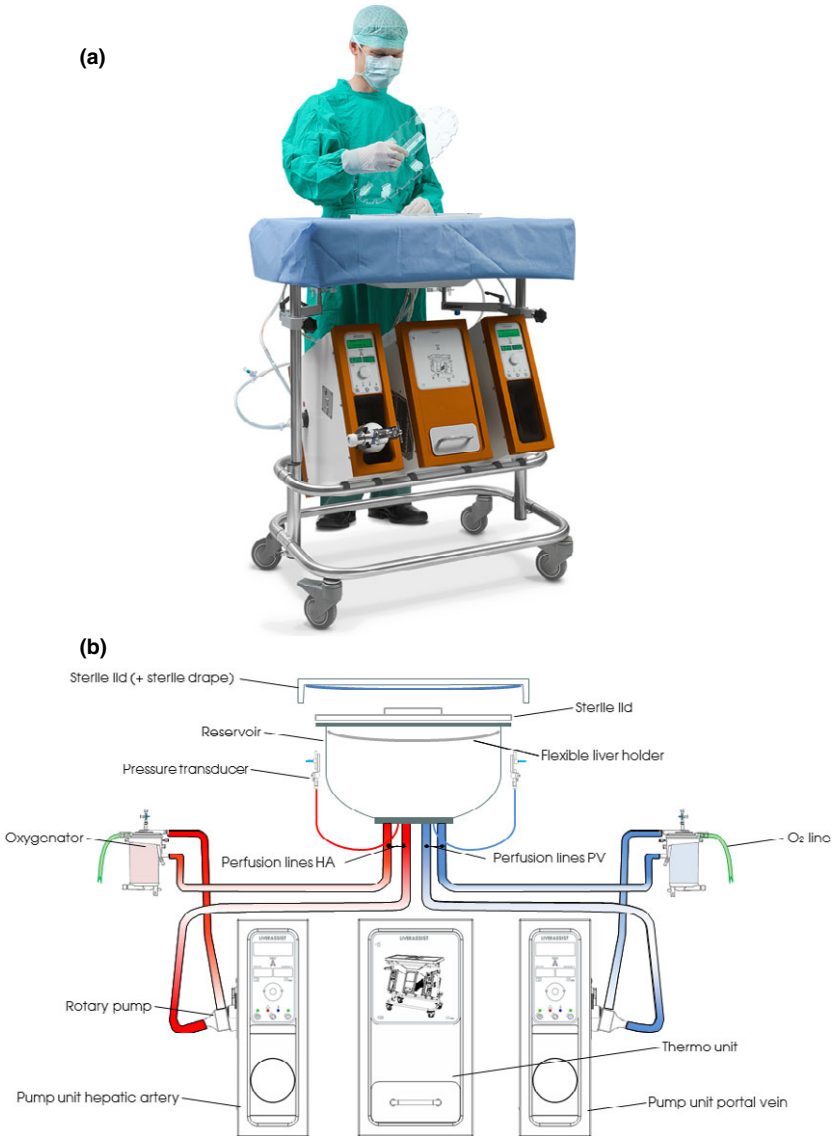

Figure 1 A photograph (a) and a schematic drawing (b) of the Liver Assist device (Organ Assist, Groningen, the Netherlands).

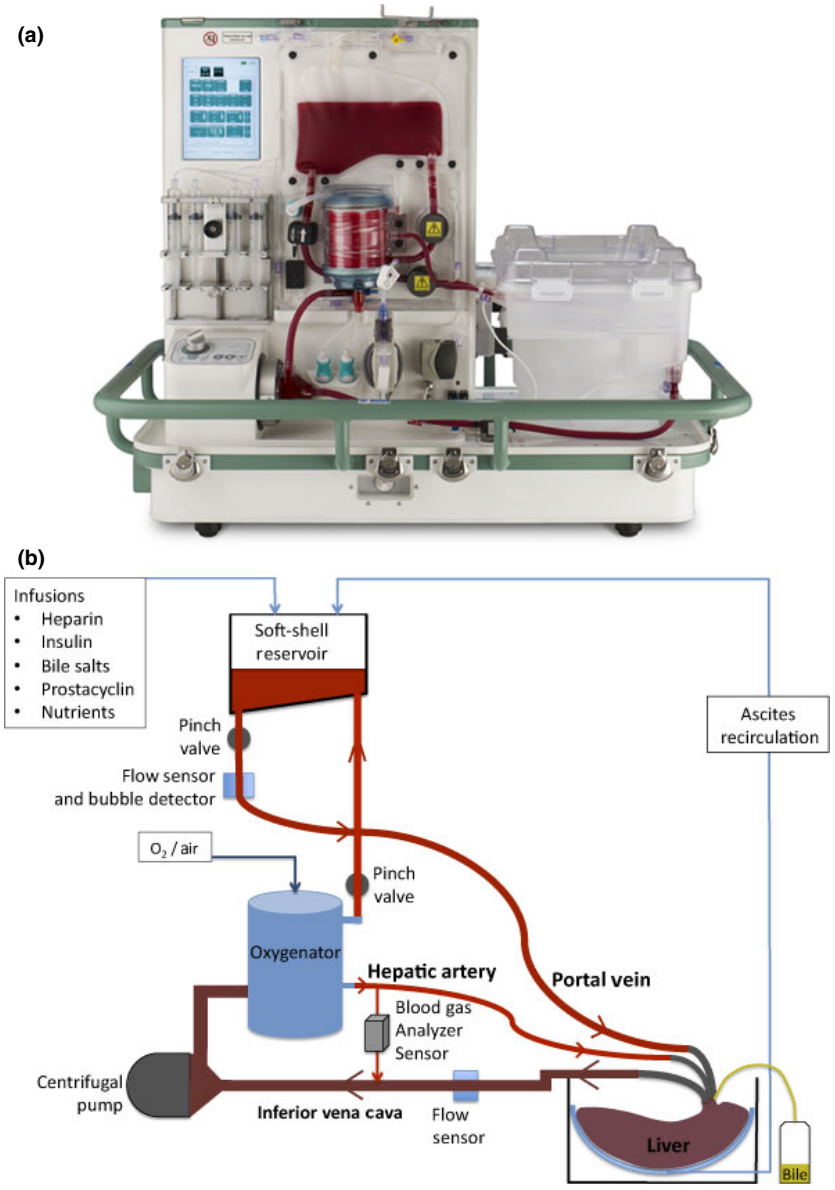

Figure 2 A photograph (a) and schematic drawing (b) of the OrganOx Metra mobile perfusion device (OrganOx, Oxford, UK, www.organox.com).

There are no published reports yet relating to the liver device in either experimental or clinical settings.

Viability assessment

One of the biggest limitations of SCS preservation in transplantation in the era of high-risk donor organs relates to the need to predict post-transplant function. Primary nonfunction of a liver transplant is a disaster. Therefore, if there is real uncertainty as to the viability of an organ, the surgeon is ethically bound (unless the condition of the patient is such that they would be unlikely to survive long enough receive another offer) to reject the offer in the best interests of the individual patient (who is likely to receive a subsequent and lower-risk offer). The lack of objective predictors of function inevitably results in viable organs being turned down. Current (partly subjective) methods of organ assessment, including donor history, pre-operative biochemistry, visual inspection and histology, do not reliably predict those livers that will fail after transplantation [47,48]. If DCD and other marginal donors are to have a major impact on transplantation, more reliable means of predicting post-transplant outcome are necessary.

Machine perfusion provides a platform to assess organ viability before transplantation as the liver is maintained in a physiological metabolic state [49]. Several groups have demonstrated the ability to assess liver viability *ex vivo* [38,50–55]. Most recently, Sutton *et al.* [56], on the evidence of discarded liver perfusions, suggest that that bile output and other metabolic parameters may differentiate viable from nonviable livers. It should be noted, however, that until large-scale clinical studies are carried out, none of these viability markers should be regarded as validated.

Perfusion parameters

Physiological flows in the hepatic artery and portal vein indicate good perfusion of the organ with normal vascular resistance. Portal pressure and portal venous resistance are thought to be able to discriminate viable from nonviable livers within 4 h of NMP [30,57]. Brockmann *et al.* [30] showed that 'failing' porcine livers were noted to have portal pressures significantly greater than those that functioned, where portal pressures were maintained at physiological values of 2.5 mmHg. This difference became apparent at no later than 4 h after the onset of perfusion. In addition, the ability of the liver to main acid–base homeostasis has been demonstrated to be a good predictor of postoperative function [55]. When comparing cold stored and normothermically perfused porcine livers, St Peter *et al.* [55] found whilst the mean pH in both groups fell in the first 2 h, the normothermically perfused livers were able to correct this within 4 h whilst cold stored livers were unable to reverse the acidosis. In a study of discarded human livers, Sutton *et al.* [56] demonstrated that a rising perfusate bicarbonate level indicated a viable liver. The minimum perfusion period required to determine viability is as yet unclear with some reports suggesting 4 h as the minimum perfusion period and other suggesting just over 2 h.

Perfusate markers

Aspartate transaminase (AST) and alanine transaminase (ALT) have been the most commonly used markers of hepatocellular damage. Glutamate dehydrogenase (GLDH) is a further marker of hepatocellular injury, which persists in serum [58]. Beta-galactosidase, a group of enzymes located within lysosomes, is released during Kuppfer cell activation or death. Serum levels of beta-galactosidase rise early to high levels in livers injured by ischaemia and can be a useful measure of damage specifically related to Kuppfer cells [54]. However, the routine biochemical markers of liver function are simpler and probably more cost-effective to use whilst providing accuracy in reporting. Factor V levels have also been shown to be higher in normothermically perfused livers as a marker of synthetic and metabolic function [55]. These markers have all been studied in experimental settings; in the clinical setting, it is likely that only 'real-time' parameters (blood flow, blood gases, bile output) will be available to inform the rapid judgments needed to decide whether to transplant a particular organ.

Bile production

The use of a T-tube in liver transplantation has been shown to predict at an early stage which grafts will go on to develop primary nonfunction [59]. It is logical to deduce that bile production during normothermic perfusion would be similarly valuable. Graft failure has been shown to occur when a fall in serum bile acids after reperfusion does not occur following the rise seen in the anhepatic phase [60,61]. In a porcine model of transplantation, Brockmann *et al.* [30] showed that functioning livers had a significantly greater bile output than failing livers. In a study discarded human liver grafts, Sutton *et al.* [56] found that bile production of >30 g during 6 h of NMP was associated with significantly lower perfusate transaminase and potassium levels as well as histological evidence of less venous congestion and hepatocellular necrosis, compared to livers with a low cumulative bile output. Bile production is an easy, noninvasive surrogate for graft viability and has to date been shown to be the most important viability marker.

Clinical application

Liver machine perfusion is now entering the stage of clinical application [62]. Whilst correctly criticized as being technically and logistically complex, nonetheless the body of scientific evidence is growing from large animal models and discarded human liver studies [24,26–30,38]. However, if this technology is to translate effectively into mainstream clinical practice, it has to fulfil certain criteria:

Safety to the donor organ

Any use of technology carries with it an inherent risk of technical failure. A medical grade device will need to demonstrate reliability and, probably, a back-up mechanism in the event of problems. This may include methods to remove the organ from the circuit and convert to cold storage in an emergency. Cannulation of the organ and subsequent perfusion must be shown not to damage the endothelium of the vessels and bile duct.

Transportability and logistic simplicity

Although experimental data suggest that prolonged cold ischaemia prior to machine perfusion is detrimental

[28,29,31], the issue of transportability remains a technical variable. On the one hand, transportability means that the cold ischaemia time can be minimized; on the other hand, a nontransportable device avoids the need to change the logistics of organ retrieval. In order for NMP to be widely used, it needs to be user-friendly and to require minimal input once the liver is on board.

Clinical and health economic data to confirm benefit

However encouraging experimental and early clinical experience may be, the real test of NMP will come from the evidence of randomized controlled trials, comparing NMP against the current standard of care (static cold storage). The increased cost and complexity will need to be shown to be outweighed by the benefits in terms of outcome and organ utilization.

Increasing the organ donor pool

This is the important potential contribution that NMP may make to liver transplantation. With the increasing number of patients added to liver transplant waiting lists worldwide, the ability of this new technology to push back the boundaries of organ acceptance is paramount. The use of steatotic livers, DCD livers with lengthy warm ischaemic times (possibly including DCD Category II) and from older DBD donors will need to be investigated. If NMP is to succeed, its value will need to be shown in the context of improved utilization of these high-risk organ groups.

Future applications

Normothermic perfusion may be complementary to other modes of organ resuscitation and may even function as a vehicle for the delivery of drugs for organ optimization [63].

Experimental strategies have demonstrated, in principle, the potential to defat steatotic liver with drugs delivered via NMP [36]. Immunomodulation to induce tolerance (for example using adenoviruses expressing CTLA4Ig) in has been achieved through a direct infusion into the portal circulation of a rat; this could further be investigated using a NMP device [64]. NMP could also be used to deliver gene therapies, which induce cytoprotection against ischaemia–reperfusion injury, such as myr-Akt [65]. There is increasing interest in the use of mesenchymal stem cells (MSC) in transplantation. NMP may provide an appropriate vehicle for the targeted delivery of these cells.

Conclusion

Static cold storage has proved an effective and reliable method for the preservation of better quality donor livers for many years. However, the increasing demand for donor organs and the need to extend utilization to those organs that would previously been discarded provide a challenge that current static cold storage cannot match and, indeed, may be beyond the theoretical limit of any cold storage technology. Normothermic machine perfusion provides a potential solution to these limitations. It maintains the organ in a physiological state, avoids the depletion of cellular energy and accumulation of waste products, and it enables the resuscitation of organs that have sustained injury prior to retrieval. It enables viability assessment prior to transplantation thereby reducing the risk of transplanting inherently high-risk organs by identifying reliably those that should be discarded. It provides a platform for organ optimization strategies. Although much remains to be performed, NMP appears to offer the potential to enable significant expansion of the organ donor pool.

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