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OPTN POLICY (K ANDREONI, SECTION EDITOR)

Promise of Normothermia

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Abstract
Purpose of this Review Normothermic ex vivo machine perfusion (NMP) is a novel preservation modality that has been investigated as a tool to preserve and protect organs from extended criteria donors (ECDs). This review summarizes the latest clinical and experimental progress in this field and tries to answer questions such as what are the future implications of NMP, what are its therapeutic potentials, and what are the limitations associated with this technology?
Recent Findings New emerging data from clinical trials with NMP devices have demonstrated the safety and feasibility of this technology as well as its ability to preserve allograft function during the preservation period.
Summary NMP provides potential solutions to limitations associated with the standard cold preservation modality. It maintains the allografts in a physiological state, prevents depletion of cellular energy sources, enables resuscitation and assessment of the ECD organ, and opens the door for future ex vivo therapeutic interventions. Hence, it should increase donor pool and positively impact transplant outcomes.

Keywords Normothermic ex vivo machine perfusion · Organ preservation · Extended criteria donors · Transplantation · Donation after circulatory death (DCD)

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Abbreviations

NMP	Normothermic ex vivo perfusion
IRI	Ischemia reperfusion injury
CSP	Cold static preservation
MSCs	Mesenchymal stem cells
ECD	Extended criteria donors
DCD	Donation after cardiac death

Introduction

Since the first human organ was transplanted in 1954, there has been significant progress in the field of transplantation regarding surgical techniques, anesthesia, post-operative care, immunosuppression, and organ preservation. Hence, with the expansion of clinical transplant centers globally and the subsequent increase in the rate of solid organ transplantation during the last five decades, the gap between the organ supply and demand has grown significantly. According to the United Network for Organ Sharing (UNOS), every 10 min, one patient is added to the national transplant waiting list and due to donor shortage, 22 patients die every day while waiting for a transplant. The donor shortage crisis and efforts to expand the donor organ pool have led to increased interests in utilizing extended criteria donors (ECDs) that are often deemed to be not suitable for transplantation.

The principal limiting factor for using ECDs (e.g., donation after cardiac death (DCD)) is the current inability to decrease graft injury acquired from anoxic conditions during cold static preservation (CSP). Therefore, ECD grafts have been associated with higher risk of post-transplant complications such as primary graft nonfunction (PNF), delayed graft function (DGF), and subsequent graft loss [1–4]. Consequently, use of ECD grafts have been linked to increased recipient morbidity, mortality, and hospital length-of-stay, while impacting

negatively on the subsequent quality of life and overall cost for this therapy for the transplant recipient [5–7]. These concerns have made transplant centers reluctant to use ECD grafts for clinical transplantation, depending on the nature of the marginal graft. However, to respond to the growing list of patients waiting for transplantation, many transplant centers have justified their criteria of accepting ECD organs to be able to increase transplant rates.

The concept of CSP is based on the significant reduction of the cellular metabolic activity and oxygen demand by hypothermic preservation at 4 °C. Combining organ flush with preservation solution (e.g., University of Wisconsin (UW) solution) with cold storage lowers the rate of ischemic injury during preservation, prolonging viability of the organ. Although cellular metabolism drops significantly at hypothermic conditions, it does not stop completely and eventually cellular energy stores such as adenosine triphosphate (ATP) continue to be depleted in organs preserved under CSP [8]. ATP depletion leads to interruption of essential cellular mechanisms that require ATP to sustain functionality. Hence, ATP depletion leads to accumulation of toxic by-products of anaerobic metabolism, NA+/K+ ATPase pump dysfunction, cell swelling, and mitochondrial injury [9]. Furthermore, organ reperfusion and brisk oxygenation under warm conditions after organ implantation lead to formation of reactive oxygen species (ROS) and activation of pro-inflammatory cytokines bringing a new additional set of biological insults to the tissues that further enhance the magnitude of ischemia-reperfusion injury (IRI) [10]. The overall impact of IRI on the transplanted organ depends on the initial quality of the allograft and the duration of cold and warm ischemia time. Hence, the IRI impact on allografts ranges from insignificant cellular injury to DGF and PNF.

Normothermic ex vivo machine perfusion (NMP) is a novel preservation modality that provides full oxygenation and optimized physiological conditions for organs before transplantation. Growing interest in utilizing NMP for the preservation of the ECD grafts is based on studies that have shown the superiority of oxygenated perfusion of the suboptimal allografts over CSP [11]. During NMP, toxic waste products are being cleared from the tissue and the organ is supplied with nutrients and oxygen; therefore, cellular ATP is maintained at physiologic ranges keeping the allograft at its optimum functionality [12–14]. Furthermore, utilization of optimized perfusion solutions that do not contain coagulation factors, platelets, leukocytes, or pro-inflammatory cytokines minimizes the cell-mediated injury phase of IRI. Diminishing the extent IRI and protection against cellular death mechanisms provide an opportunity for suboptimal grafts to start cellular regenerative pathways [9].

After several years of research on pre-clinical models, NMP has finally become a more realistic option in clinical transplantation. In this communication, we review the major recent technological advancements and clinical experiences in the field of normothermic perfusion and describe the potential of NMP technology for future applications.

Advantages of Normothermic Perfusion

Viability Assessment

One of the most significant benefits of normothermic systems over the CSP method is the ability to evaluate the functionality of the allografts before transplantation. Ongoing metabolism during normothermic preservation period allows for measuring key metabolic elements specific for each organ, evaluating the allograft viability and deciding about its implantation into the recipient accordingly. Several studies have validated the specific viability markers for each organ in large animal transplant models [15–18]. If current ongoing clinical trials validate these markers and prove their ability to predict allograft function post-transplantation, one of the pivotal challenges of utilizing ECD organs will be addressed. In this scenario, when an ECD organ becomes available and is being deemed unsuitable for transplantation, it will be placed on NMP device for a certain amount of time and viability parameters will be measured continuously. If the results indicate a nonfunctioning graft, the organ will be discarded and vice versa. This valuable approach will not only decrease the risk of post-transplant complications associated with the use of ECD grafts but also should reduce the number of discarded organs, thereby increasing the donor pool.

Pharmacological Reconditioning

Induction/reduction of gene expression and manipulation of protein synthesis require the presence of active cellular metabolism that is severely altered at hypothermic conditions [19, 20]. Moreover, induction of gene expression is feasible with NMP, but not for cold static storage [13]. NMP systems provide an ideal environment to repair, optimize and treat allografts with targeted injury-specific therapies before transplantation. Supplementing the NMP system with pharmacological compounds does not affect the procurement phase nor other organs from the donor, making NMP systems an ideal platform for clinical purposes. Several compounds have been tested experimentally for different organs and have shown promising results.

The combination of ischemia and subsequent reperfusion injury has deleterious effects on ECD allografts. Hence, efforts have been made to protect suboptimal organs by supplementing the perfusion circuit with different solutions/compounds. It has been shown that supplementing β2-adrenoreceptor agonists during normothermic perfusion of DCD dog lungs attenuates lung injury and protects allografts

against IRI [21]. In a porcine heart-beating liver transplantation model, Goldaracena et al. added anti-inflammatory agents (alprostadil, sevoflurane, carbon monoxide, and n-acetylcysteine) to the perfusion solution during the ex vivo preservation and showed that the inflammatory signaling pathway can be reduced by this protocol and improve outcomes after transplantation [22]. Furthermore, our group and others have demonstrated that reduction of steatosis is possible during NMP of steatotic grafts with the help of either prolonged NMP or addition of defatting agents to the perfusate [23••, 24, 25].

It has been shown that IRI can be attenuated by prevention of apoptosis and induction of protective genes during the preservation period. In particular, induction of members of the heat shock protein family (HO-1) is possible with warm perfusion and can protect the organ against IRI [26]. In the kidney, Nicholson et al. showed that ex vivo administration of erythropoietin during NMP of isolated porcine kidney allografts augments inflammatory cell apoptosis and drives the apoptotic cell into tubular lumens. They further demonstrated that this effect leads to reduction of inflammation, protection of renal grafts, and remodeling of renal tissue through IL-1β and caspase-3 [27]. In the lung, it has been shown that supplementation of DCD porcine lungs before or shortly after death with nebulized N-acetyl cysteine attenuates inflammatory pathways and thus decreases IRI post-transplantation [28]. Although this study did not involve an NMP system during the experiments, the same protocol can be used during NMP of DCD lungs.

Gene Therapy

In addition to targeting specific metabolic and synthetic pathways, the unique access to the whole organ during NMP enables therapeutic gene alterations. Thus, this approach prevents the systemic exposure of the recipient's other organs to the potential harmful properties of the vector system. Also, due to constant monitoring and assessment of the organ during NMP, organs successfully modified by this system can be selected from those that failed to exert the envisioned modifications. Achievable gene therapies using NMP systems include targeted manipulation of cytokine expression, modulation of apoptotic and costimulatory pathways, and manipulation of leukocyte recruitment signaling pathways [29]. Recently, in a porcine lung transplant model, Keshavjee and colleagues showed that intratracheal delivery of E1-, E3-deleted adenoviral vector encoding either IL-10 or a fluorescent protein to porcine lungs during NMP decreases inflammation and leads to superior post-transplant lung function [30].

MSC Therapy

The immunomodulatory effects of mesenchymal stem cells (MSCs) make them a promising tool for cellular therapy in the field of organ transplantation [31, 32]. Emerging interests include utilizing MSC therapy in mitigation of IRI and reduction of acute and chronic rejection by induction of tolerance [33]. NMP, in this regard, provides a unique platform for the selective administration of MSCs directly to the allografts while the organs are being kept under physiological conditions in an isolated system. This approach bypasses the challenge of trafficking of the MSCs to desired tissues.

Although no experimental data has been published on ex vivo treatment of an organ by administration MSCs, in vivo studies have shown promising results. Administration of MSCs in the murine model of acute renal failure, modulated IRI, and improved early renal function [34]. Interestingly, in a clinical study, Ricordi and colleagues showed that the administration of MSCs at reperfusion phase and 2 weeks later diminishes the acute rejection rate, lowers infection, and improves graft survival 1 year post-transplantation when compared to IL-2 receptor antagonists [35]. These beneficial effects were further investigated in a rodent model of hepatic IRI and showed that systemic administration of MSCs accelerates the recovery from IRI [36]. Furthermore, donor infusion of MSCs prior to heart transplantation has been shown to generate regulatory T cells and thus improve recipient survival in a semi-allogeneic murine model [37].

With the development of advanced NMP systems, the use of MSCs for ex vivo treatment and recovery of organs is now becoming feasible. As aforementioned, to date, there has not been any published study on ex vivo administration of MSCs for the purpose of recovery of declined organs making them suitable for transplantation. The only study describing the use of MSCs during NMP was published in 2009. Lee et al. demonstrated that addition of allogeneic human MSCs during NMP of human lung injured by *E. coli* endotoxin leads to attenuation of acute lung injury [38]. This approach led to restoration of alveolar epithelial fluid transport mechanisms and significant reduction in pulmonary edema. Hence, to test these promising potentials, further research is needed.

Prolonged Preservation

Marginal organs are known to have increased sensitivity to cold storage. Current standard cold preservation does not allow extended solid organ preservation period, making organ transplantation an emergency procedure. Thereby, preservation times are restricted by the organ-specific safe cold ischemia times and often transplantation operations have to be performed outside the regular working hours. Needless to mention that the unpredictable nature of donor availability creates interdisciplinary challenges that exerts more pressure on the entire surgical team and hospital staff.

With the use of NMP, however, extended and potentially unlimited duration of perfusion is theoretically feasible. This

potential benefit can make transplantation procedure an elective operation positively impacting patient's costs and decreasing risks that are associated with out-of-hour surgeries [39, 40]. Furthermore, maximizing the preservation period would allow optimized recipient selection, preparation, assessment, and tissue matching that may lead to better outcomes. Prolonged preservation, also theoretically, may allow long-distance organ sharing between transplant centers.

Combined NMP and In Vivo Normothermic Recirculation

Normothermic recirculation methods for nonheart-beating donors were first described by the Barcelona group in the late 1990s [41]. The aim was to reverse warm ischemia injury by employing an extracorporeal machine oxygenator (ECMO) at 37 °C once the donor had been declared deceased. This period of recirculation would enable assessment of the potential donor organs, especially the liver. The rationale of normothermic recirculation lies in rapid restarting of the donor blood circulation to reverse depleted cellular energy sources that occur following cardiac arrest. Hence, this approach is most useful in the case of donors from Maastricht categories I, II, and IV when cardiac arrest is unpredictable.

Large animal models show that normothermic recirculation leads to partial restoration of ATP and reduced glutathione (GSH) in the liver and kidney subjected to 30 min of warm ischemia. It is known that the beneficial effects of normothermic recirculation are mediated through ischemic preconditioning [42]. Thus, this method leads to reduced IRI in the liver and other organs. The first clinical trial of this approach with DCD livers was carried out by Fondovilla et al. and showed that this technique is safe and feasible [43]. However, due to the risk of ischemic cholangiopathy and the low number of grafts that have been transplanted with this methodology, it has been suggested that the combination of NMP with normothermic recirculation can optimize the effectiveness and safety of the entire procedure [44]. The combination of both techniques would allow minimizing or even eliminating cold ischemia time. Therefore, organs with longer warm ischemia time can be successfully procured, preserved, and finally transplanted.

NMP as Bioreactor

In the search for novel methods for addressing the donor shortage and increasing functional organs, promising approaches have emerged in the recent years. Development of organ and tissue scaffolds by decellularization of allogeneic or xenogeneic organs such as liver [45], lung [46–48], and heart [49] has opened a new window in the field of tissue bioengineering. Decellularization techniques consist of isolating the extracellular matrix of an organ or tissue from its natural inhabiting cells by specific protocols such as physical decellularization (sonication, freeze/thaw), enzymatic decellularization (trypsin, endonucleases), and chemical decellularization (Triton X-100, sodium dodecyl sulfate) [50]. This technique provides a natural three-dimensional biologic scaffold that can be potentially repopulated with either stem cells or functional parenchymal cells. Preliminary experiments in rodent models have shown the formation of biocompatible scaffolds that have satisfactory functionality in short-term models [50, 51].

The potential role of NMP systems in this novel approach is acting as a bioreactor for decellularization, recellularization, and regeneration of the organs [52–55]. Various temperature ranges have been investigated so far, and the consensus is that the normothermic (or near-normothermic) temperatures are likely to provide the most optimized physiological conditions for recellularization of three-dimensional organ scaffolds [50]. It is well known that cellular growth, attachment, and self-assembly is tightly dependent on the physiological temperatures. Therefore, NMP would provide an optimized physiological environment for the decellularized scaffold making recellularization process feasible. NMP systems provide an ideal platform for delivery of nutrients and other treatments to the cells inside the scaffold and also remove the harmful/waste by-products of cellular metabolism from the tissue. Furthermore, NMP ability to deliver oxygen to highly vascularized tissues with high metabolic function can solve a poor oxygen delivery problem as one of the most critical challenges of tissue engineering of such tissues [56].

The greatest challenge of utilizing NMP systems as bioreactors, however, is the duration of perfusion that these systems can provide. As a preservation modality, NMP of solid organs is limited in duration, with reports of successful preservation of organs from 1 [57] up to 72 h [58]. Although 72 h of organ preservation is considered "prolonged preservation" in the field of transplantation, by no means do current NMP systems offer required perfusion durations for recellularization purposes. With current technology, recellularization of entire scaffolds and developing functional organs occur over a few weeks to months [59], a duration that is far from the reach of current NMP systems' capabilities. Moreover, some cell lines tend to dedifferentiate in culture conditions. For example, mature hepatocytes dedifferentiate within a few weeks in the culture environment [60], adding more complexity to the whole concept of organ engineering. Therefore, further technological advances in the oxygen carriers and perfusion solutions are needed in this field for the NMP bioreactors to become a reality.

Clinical Experience with NMP

Although machine perfusion has played a minor role in the field of solid organ transplantation so far, it has been

continuously investigated in preclinical studies and clinical trials [16–18, 21, 22, 23••, 57, 61–64, 14, 65–69, 70••, 71–80]. Multiple NMP systems with different approaches have been developed by various research groups for the liver, heart, lung, and kidneys.

NMP of the liver is currently undergoing clinical trials in Europe with promising preliminary clinical outcomes [68, 70••, 81]. It appears that NMP has been able to modify ischemic injury as one of the primary limitations associated with the use of ECDs. Investigational device exemption trials have been planned for two companies that produce NMP systems for the liver. Moreover, the Consortium for Organ Preservation in Europe (COPE) has enrolled more than 200 patients in a clinical trial, and the data are currently being analyzed [82]. It is still a subject of debate whether machine perfusion is going to have a significant role in the field of liver preservation or will it be limited to specific situations (steatotic, DCD) in coming decades [83]. There is general agreement that with rapid development of novel technologies in the field of ex vivo machine perfusion, NMP systems will have a bold impact in addressing the donor shortage problem.

The clinical use of NMP devices for lungs has gained much more momentum recently. Pioneered studies and clinical trials led by the Toronto group has proved that selected donor ECD lung allografts can be used for clinical transplantation after NMP [76, 84••]. Due to the recent introduction of NMP systems for lung, the long-term follow-up data are not available yet; however, after 4 years of experience with NMP system for lungs, the Toronto group have shown that there is no significant differences in survival or complication rates among the recipients of NMP perfused lungs or conventional lungs [76]. It has also been demonstrated that the incidence of post-transplant complications such as infection episodes and death are similar between recipients of NMP perfused lungs and conventional donor lungs after 12 months of transplantation [85]. Moreover, a recently published study by Tikkanen et al. has shown that parameters such as functional performance, freedom from chronic lung allograft dysfunction (CLAD), and allograft survival were similar between the recipients of NMP perfused and conventional donor lungs after 5 years of transplantation [84••]. Therefore, NMP of discarded lungs is not associated with increased morbidity or mortality of the recipients. The impact of NMP systems on the incidence of chronic rejection, however, is yet to be investigated.

The experimental research on NMP for kidney has been led mainly by two groups (Brasile and Nicholson). From the mid-1990s through 2010, Brasile et al. carried a series of experiments on a warm perfusion system for kidney with the use of an acellular perfusion solution [26, 86–95]. Although this system showed promising results in the canine models and preclinical studies, eventually the system was not used for clinical renal transplantation. Nicholson and colleagues worked on a different NMP set up that was based on a pediatric cardiopulmonary bypass system with the addition of a membrane oxygenator, centrifugal pump, a heat exchanger, and venous reservoir [65–67, 96–99]. Priming this system with a crystalloid solution as well as mannitol, prostacyclin (vasodilator), and nutrients developed an optimized and stable environment for the kidneys. After showing promising results in the porcine models of renal transplantation, this system has entered the clinical stage for ECD kidneys. The first report of clinical transplantation of NMP perfused kidneys was published in 2011 by Nicholson group showing safety and feasibility [97]. The first clinical trial of NMP for marginal kidneys was published in 2013 by the same group [100]. Although there was no difference in the graft or recipient survivals between NMP perfused and cold stored ECD kidneys, the rate of delayed graft function was significantly lower in the recipients of NMP perfused kidneys.

To date, the only commercially available NMP device for heart has been designed and manufactured by TransMedics Inc. under the name of Organ Care System (OCS). The first clinical trials (PROTECT I, II) with standard donors with OCS system were carried out in Europe between 2006 and 2008 showing safety and feasibility [61]. Subsequent clinical trial (PROCEED I) in the USA with a small number of patients was carried out between 2007 and 2008. Due to promising results from European PROTECT I and II as well as PROCEED I, the FDA approved a second randomized clinical trial (PROCEED II) with larger patient size. PROCEED II was carried out internationally between 2010 and 2013, and the results were published in 2015 showing adequate preservation of the heart allografts with the OCS system with similar short-term outcomes as hearts preserved with CSP [101]. While the beneficial effects of OCS system in ECD are currently being investigated in ongoing clinical trials in Europe and Australia, a porcine model of DCD heart transplantation with 30 min of warm ischemia demonstrated viability of the allografts pre- and post-transplantation [16].

Although hypothermic perfusion of the pancreas has been long investigated, the field of NMP for the pancreas is not as mature as it is for the other solid organs [102]. The first experiment with discarded human pancreas and NMP was published by Barlow et al., and this demonstrated feasibility [103]. NMP provided stable perfusate pH and blood flow to the pancreases, and all allografts produced insulin during normothermic perfusion. To our knowledge, there has not been any published study comparing outcomes of transplantation of NMP perfused to cold preserved pancreases. The reason lies in the inherent difficulties in the anatomy of organ's blood supply that makes it prone to hemorrhage and small vessel venous thrombosis. Since graft thrombosis is responsible for up to 70% of technical failures during preservation of the pancreas [104], careful monitoring of parameters such as low perfusate pressure and flow should be carried out while ensuring meeting graft's metabolic demands. Hence, although

NMP of pancreas is technically challenging, the beneficial effects observed in other solid organs may apply to pancreas as well. Therefore, further investigation is warranted in this field.

Limitations

Despite the promising results of using NMP systems in preclinical and early clinical studies, there are several limitations of this methodology that need to be considered before broader application in the clinical settings. First and foremost, additional clinical research is needed for proving safety in recipients. Second, the superiority of NMP over CSP should be determined appropriately, and more research is required to determine the areas that NMP can provide superior benefits. Also, it is crucial to carry out intention-to-treat analyses comparing NMP for different organs with CSP modality for an unbiased interpretation. It is also important to consider the cost-effectiveness of NMP protocols and determine the criteria for its utilization for different organ donation situations. Organs from standard donors will not be placed onto the NMP device, and this system will be primarily used for ECD organs [83]; therefore, it is reasonable to determine the specific situations that NMP systems will be utilized in clinical settings to avoid overwhelming costs to the patient and hospital.

It is pivotal to determine the complications during preservation with NMP devices and discuss the number of allograft losses during normothermic preservation. While research groups have focused extensively on the successful preservation with the NMP systems, unfortunately, they fall short when it comes to reporting the incidence of complications during normothermic preservation. Accidents such as cannula perforation, cannula disconnection, mechanical failure of the device, and eventual organ loss have not been discussed broadly in the literature. In 2012, the University Clinic Freiburg in Germany suspended its participation in the PROTECT trial (mentioned above) for several months because a heart allograft was lost during NMP with the OCS device [9]. Technical and mechanical failures do occasionally happen during the use of cardiopulmonary bypass systems. Therefore, these challenges should be expected during the clinical trials and planned ahead for proper and immediate response.

The organ is at full functional activity during the NMP; hence, the use of oxygen carriers is mandatory. The use of RBCs for this purpose and their sensitivity to hemolysis during extracorporeal perfusion [97] represents a system limitation. Hence, nonblood-based perfusion solutions such as perfluorocarbons [105] and hemoglobin-based oxygen carriers [106] have been investigated with acceptable outcomes. However, more research is warranted to ensure the ability of these novel solutions to oxygenate highly vascular organs.

Conclusion

Despite the long history of efforts for ex vivo perfusion of organs for transplantation [107–111], they never gained widespread attention due to concerns about logistical constraints of these techniques. Subsequent introduction of cold preservation solutions and successful organ preservation under cold storage moved the clinical transplant focus away from extracorporeal machine perfusion. Due to the rising number of waiting list candidates, transplant centers have lowered their threshold for accepting ECD organs to increase the donor pool and number of transplants performed. In the search for novel strategies to recover marginal allografts and make them transplantable, the transplant community is making a U-turn and NMP has been rediscovered during the last two decades. NMP solves the limitations associated with CSP, minimizes warm and cold ischemic injury, and offers the assessment of quality, viability, and function of marginal organs before transplantation. It also provides the opportunity for organ conditioning including repair therapy, genetic manipulation, and stem cell therapy.

Preliminary clinical trials with a relatively small number of patients have shown safety and feasibility of normothermic perfusion demonstrating promising results. The real limitations and benefits of NMP are currently being evaluated in larger clinical trials. Thus, normothermic ex vivo perfusion has opened a new window in the field of organ preservation and has the potential to increase donor pool in the future.

Compliance with Ethical Standards

Conflict of Interest Babak Banan declares no conflict of interest. William Chapman reports personal fees from Pathfinder Therapeutics, personal fees from Novartis Pharmaceuticals outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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