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Chapter

Machine Perfusion Strategies in Liver and Renal Transplantation

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Abstract

Transplantation is the only treatment for patients with end-stage renal and hepatic disease but unfortunately, it is limited worldwide due to the organ shortage. The need to expand the donor pool with the use of donors after cardiac death (DCD) and extended criteria donors (ECD) has led to major improvements in organ preservation. From cold static storage and preservation solutions to different types of machine perfusion, the possibility of successfully transplanting a marginal organ becomes reality. In this chapter, we examine the machine perfusion methods and the advantages of new technology in minimizing ischemic injury and improving the transplant outcome. The establishment of protocols with the use of biomarkers in order to assess the transplant suitability of the graft will eventually provide the ideal opportunity to intervene and improve the quality of the organ.

Keywords: machine perfusion, liver transplantation, kidney transplantation, organ preservation, hypothermic machine perfusion, normothermic machine perfusion

1. Introduction

In this chapter, after a brief introductory reference to the definition and history of machine perfusion in transplantation, their contemporary necessity is discussed. For this purpose, two important topics such as ischemia–reperfusion injury and marginal grafts are analyzed. Subsequently, the machine perfusion strategies in liver and kidney transplantation are mentioned separately.

The review of the literature was conducted using the combination of various keywords (liver transplantation, kidney/renal transplantation, machine perfusion, hypothermic/normothermic/subnormothermic machine perfusion, ischemia–reperfusion injury, marginal grafts, extended criteria donors, donors after cardiac death, cold static storage, and organ preservation) in PubMed research database. The inclusion criteria of the articles were the English language and their relevance to the topic, which was judged by the authors after studying the abstracts.

Transplantation is the only treatment for patients with end-stage renal and hepatic disease. Despite the recent U.S. milestone of 1 million transplants until 2022, the

number of patients on waiting lists remains high [1]. The great need for increment of the donor pool leads to the utilization of allografts from extended criteria donors (ECD) and donors after circulatory death (DCD). The vulnerability of these marginal grafts in ischemia–reperfusion injury (IRI) [2] revealed all the weak points of standard preservation methods and resulted in poor transplant outcomes. Moreover, the ECD and DCD kidney grafts have increased immunogenicity and as a result higher rates of rejection [3].

The combination of nonideal donors with limitations in graft evaluation results in discarded organs that further exacerbate the transplantation gap. In an attempt to find solutions, the interest of scientific community turned to preservation strategies, particularly the application of machine perfusion methods to these organs, in order to assess and make them suitable for transplantation [4, 5].

The concept of machine perfusion (MP) in the field of transplantation is not new. In 1885, the initial idea of extracorporeal circulation with the construction of a closed circulatory system [6] and 52 years later the transition from blood to chemical perfusion solutions, in order to keep organs "alive" [7], laid the foundations for the development of organ preservation. Machine perfusion in a human kidney was performed for the first time in 1967 by Belzer. The first liver transplantation in humans was performed by Starzl, with the application of a hypothermic low-flow perfusion method that used diluted blood [8, 9]. Thus, although the original concept involved room temperature and dynamic perfusion, in 1969 Collins GM changed completely the perspective, with the 12-hour preservation of canine kidneys in an iced solution, which later evolved into Collins solution with a longer preservation time [10]. Nowadays, preserving the organ in an ice box at 0–4°C, after flushing it with a cold preservation solution (usually the University of Wisconsin or Histidine-Tryptophan-Ketoglutarate solution), is the most common method worldwide. Static cold storage (SCS) has been established as the gold standard due to its simplicity, efficacy, and low cost [11]. The idea of machine perfusion was abandoned but, in the beginning of this century, gained interest again in clinical practice.

Machine perfusion is an *ex-vivo* platform where organs are connected to a pump and perfused with the solution in a controlled flow, constantly, until implantation. The main purpose is to provide essential substances and remove waste products in order to maintain cellular metabolism in a predetermined way. There is variation in machine perfusion methods in terms of temperature, oxygen and nutrient supply, preservation solutions, delivery method, duration, and time-point of perfusion. Depending on the temperature, there are three types of machine perfusion: normothermic (35.5–37.5°C), hypothermic (1–8°C), and subnormothermic (20–35.5°C) temperature with the latter sought in fewer studies [12]. Also, the variation of temperatures differs slightly in the literature.

Hypothermia reduces cellular metabolism while at the same time, the preservation solution enhances ATP production [13]. Also, the addition of oxygen restores mitochondrial oxidative activity by electron transport [14]. Hypothermic machine perfusion (HMP) has the significant advantage of safety, as in case of machine failure, the graft can easily be preserved in SCS.

The aim of reducing cold ischemia time (CIT), which is an independent risk factor for delayed graft function (DGF), has led to the development of normothermic machine perfusion (NMP). During this method, the reperfusion phase after ischemia time takes place in an artificial environment as close as possible to physiological conditions (temperature and oxygen), in order to avoid the inflammatory process and the destructive injury, it causes to the graft. Normothermia has the important

advantage of assessing the graft in real-time, as bile and urine are produced by liver and kidney grafts, respectively [15]. On the other hand, it is a more complicated and costly procedure as it requires a sufficient amount of oxygen, oxygen carriers, and necessary substances for the graft function [16]. In an effort to limit the use of human blood products with red blood cells or plasma, the development of extracellular oxygen carriers began [17].

Subnormothermic machine perfusion (SNMP) is an intermediate state between hypothermic and normothermic conditions, maintaining low cellular energy demands and mitochondrial activity, while the organ is still "alive." This method is simpler than NMP as red blood cells are not necessary [18]. Although SNMP started as a promising technique, disappointing results in a porcine kidney model prevented its further clinical application. The SNMP group had increased rates of renal and tubular injury than the NMP group [19]. Currently, it is still at an experimental stage in both liver and kidney transplantation with important clinical prospects.

Controlled oxygenated rewarming (COR) is an alternative perfusion method that focuses on transitioning the graft from hypothermia to normothermia by gradually increasing the temperature (from 8–20°C). Mitochondrial function can be affected by rapid temperature change when the graft is reperfused after cold ischemic preservation. In particular, the opening of the mitochondrial permeability transition pore contributes in a destructive way to the occurrence of IRI. COR allows smooth recovery of mitochondrial function and studies have shown its feasibility in clinical application in liver and kidney transplantation [20, 21].

In the last decade, many studies have been published on different models of machine perfusion and large clinical trials in humans have been performed, changing the concept of preservation in transplantation. From procurement to transplantation, the reasons for this development, in addition to the increasing use of ECD or DCD grafts, are the comprehension of the complicated biological pathways and phenomena such as IRI.

1.1 Ischemia: Reperfusion injury

During organ procurement, the blood supply to the organs is interrupted, and after implantation or *ex-situ* normothermic machine perfusion of the grafts, it is restored. This process, defined as ischemia–reperfusion injury, leads to cell death in an oxidative environment and production of reactive oxygen species (ROS) [2].

IRI consists of three phases and each of them causes a different effect on the organ. First, it is the ischemic phase, when the blood and oxygen supply of the organ is inhibited. Dramatic depletion of ATP unregulates sodium-potassium ATPases in cell membranes, resulting in increased calcium concentration and acidic pH [22, 23]. It is of notice that the type of donor (donation after brain death or after circulatory death) plays an important role in ischemia injury to the graft [24]. Second, it is the reperfusion phase, when ischemic tissues are reoxygenated and as a result release ROS, that is mainly formed in complex 1 - mitochondrial respiratory chain [25]. Furthermore, in liver grafts, disorders in the mitochondrial permeability transition pore (MPTP) allow the release of danger-associated molecular patterns (DAMPs) from the nucleus [26], which interact with Toll-like receptors (TLRs) and activate Kupffer cells [27]. Finally, a prolonged period of inflammation is established where important liver microstructures are deranged. For example, damage to the endothelial glycocalyx or the combination of increased vasoconstrictive agents and decreased nitric oxide levels deteriorates the microcirculation and raises the risk

of early allograft dysfunction (EAD) [28, 29]. Third is the late injury phase, which follows the release of ROS and continues the cascade of cytotoxic events with the activation of resident and recruited immune cells [30].

IRI is globally independent risk factor in transplantation and is related to acute rejection, postreperfusion syndrome, DGF, and primary non-function (PNF) [31]. The standard static cold storage was an inferior preservation method for kidneys [32] and failed to protect marginal livers from the effects of ischemia–reperfusion injury [33], so the need for a different strategy was imperative. Continuous machine perfusion circulation of metabolic substances and removal of inflammatory products, such as toxins and cytokines [34], reduce the degree of graft injury, for example, to the liver's deep peribiliary glands and stroma [35].

1.2 Marginal grafts

As already mentioned, the use of suboptimal grafts is constantly increasing due to the transplant gap between the donor pool and the recipient waiting list. Marginal liver grafts are organs with an increased chance of failure or PNF after transplantation. Also, the definition includes cases where diseases can be transmitted from the donor to the recipient [36]. Usually, high risk liver grafts come from donors with factors such as: liver macrosteatosis, cardiac death, advanced age, long stay in the intensive care unit, infections and malignancies.

Macrosteatosis is not a prohibitive factor for transplantation if the percentage is <30% but the fatty liver is considered to have worse postoperative outcomes than grafts without steatosis [37]. DCD livers due to prolonged warm ischemia time are susceptible to ischemic-type biliary lesions. Microcirculation disorders, during IRI, cause damage to the arterial plexus of the biliary tree, so there is high risk of biliary strictures after the transplantation [38]. Advanced age has negative effects on liver reserves, so injury after reperfusion is more serious and increases the risk of post-transplant complications [39].

Machine perfusion techniques appear to benefit these borderline livers most, with characteristics such as macrosteatosis >30%, DCD donors, donors >60 years old, cold ischemia time > 8-10 h, warm ischemia time > 30 min, insufficient *in situ* perfusion, prolonged organ procurement, and generally discarded grafts due to eliminated transaminases or any nonvascular problem [40, 41].

Different scoring systems have been developed to predict graft survival: Survival outcomes following liver transplantation (SOFT), donor risk index (DRI), Eurotransplant-DRI, etc. Clinical parameters (cardiac arrest >15 min, age > 55 years, BMI >30), laboratory results (AST, ALT, HBV, and HCV), ICU conditions (days, drugs, and infections) and of course histology after biopsy are included and considered in the transplant decision. Finally, nonheart beating and DCD donors are ECDs by definition [42].

The definition of borderline kidneys, which actually includes donor risk factors for kidney transplants, is derived from living donors, as in the early stages were mainly associated with risks to the recipient [43]. The Kidney donor risk index (KDRI) is a practical tool for predicting the posttransplant outcome. Factors such as weight, height, race, history of diabetes, hepatitis C status, and DCD are included [44]. The OPTN-approved criteria for ECD kidneys consider the following donor parameters: age, cerebrovascular accident as the cause of death, history of hypertension, and creatinine level [45].

Also, acute kidney injury or extracorporeal membrane oxygenation (ECMO) prior to organ retrieval significantly affects the graft quality [46, 47].

2. Machine perfusion of the liver

2.1 Hypothermic machine perfusion

During hypothermic machine perfusion, the liver graft is perfused with a preservation solution, mainly University of Wisconsin (UW) or Vasosol (modified UW), usually at 4–11°C. In this way, the graft takes essential substances and eliminates waste products [40, 48]. The pO2 level is 20 kPa, as no additional oxygen is provided. HMP clinical series was first published in 2010, as a safe and effective perfusion system by James Guarrera [49].

In hypothermic conditions, deceleration of cellular metabolism and cryoprotection, prepare the liver graft for the time of reperfusion. HMP provides protection to the graft in a complicated and not completely clarified way, as far as ischemia–reperfusion injury is concerned. Studies have shown that it has positive effects on mitochondrial complexes and increases cellular energy, leading to metabolism of molecules such as succinate [50, 51].

Also, livers perfused under hypothermic conditions had less of the ultrastructural effects seen in SCS. The number of CD68+ macrophages and, in general, inflammatory injury agents were significantly decreased, as shown by measurements at the end of preservation and after graft reperfusion [51, 52].

During hypothermic oxygenated machine perfusion (HOPE), the pO2 level is 60–100 kPa, and in this technique additional perfusate oxygen is provided to the graft. Oxygen is diluted in the perfusion fluid so there is no need for oxygen carriers [53]. Oxygenation in hypothermic conditions restores mitochondrial function and promotes metabolic activity. As a result, the reduction of ROS and succinate does not lead to further damage in mitochondrial function [54, 55].

HOPE was initially used in a clinical setting in 2014, where Maastricht Type III-DCD liver grafts were treated and subsequently assessed [56]. A matched case analysis of DCD livers compared HOPE treatment with standard SCS. 25 HOPE livers had fewer biliary complications and better 1-year graft survival than 50 SCS livers, but with longer cold ischemic time in the last group [57]. HOPE-DCD livers showed a reduced risk of acute rejection and improved 5-year graft survival in a recent study with the same comparators (94% in HOPE DCD vs. 78% in SCS DCD). They also have better laboratory results (INR and lactates on the first day) and fewer postoperative complications [58]. Moreover, HOPE treatment proved beneficial in macrosteatotic livers and has a positive impact on graft function and survival compared to the unperfused group [59]. Similarly, grafts from donors with advanced age seem to have good results with HOPE treatment. In two transplantations with octogenarian grafts, this perfusion technique promoted the recovery process after IRI and reduced hospitalization [60].

The hypothermic machine perfusion uses either the portal vein alone or the portal vein and hepatic artery together. The dual perfusion with oxygen is called dual flow hypothermic oxygenated perfusion (D-HOPE) and attempted to optimize the oxygenation of the biliary system. D-HOPE DCD livers had low peak ALT and bilirubin levels compared with SCS, but no difference in patient and 1-year graft survival. Perfusion pressure is also a technical detail of great importance during machine perfusion. High pressure leads to additional damage at endothelial cells, so the desired levels are 20–30 mmHg in the hepatic artery and 3–5 mmHg in the portal vein during HMP [61].

A meta-analysis of 12 studies comparing HMP and SCS in liver grafts showed the superiority of HMP in reducing posttransplant AST and ALT serum levels, early allograft

dysfunction, total biliary complications, and ischemic cholangiopathy. No statistical significance was observed in outcomes for primary nonfunction, hepatic artery thrombosis, postreperfusion syndrome, patient survival, and liver graft survival (1 month, 6 months, and 1 year) [62]. An additional advantage of HMP is that in case of pump failure, the organ can be stored in cold static conditions, so it is a safe perfusion method.

The viability assessment during HMP is challenging because of metabolic deceleration and absence of bile production. However, there is a growing interest in the literature for potential markers during HMP and HOPE. Peak AST after transplantation was found to be associated with AST and LDH levels after 2 h of perfusion [49]. Also, cellular ATP concentration during D-HOPE appears to be related to liver posttransplant function at a biochemical level [61]. A recent study by Muller et al. discovered a new mitochondrial biomarker that can be counted by spectroscope after 30–45 min of HOPE. Flavin mitochondrial mononucleotide (FMN) is easily detected in HOPE perfusate and can predict graft function and possible complications before implantation [63].

2.2 Normothermic machine perfusion

Normothermic machine perfusion uses temperatures between 35 and 38°C and components from blood products such as erythrocytes. Oxygenators are necessary and dual perfusion (portal and arterial) is performed. The aim is to mimic the physiologic environment so that the metabolism and function of the liver graft being maintained. The first clinical introduction was in 2016 when a phase-1 clinical trial was published [64]. Minimizing clod ischemia time enables long preservation of the liver graft without injury. In fact, a recent protocol described a metabolic, active, and functional human liver after 7 days of NMP [65].

The combination of HOPE and NMP versus NMP in nontransplanted livers was studied by the Birmingham group. The HOPE/NMP livers showed lower indicators of inflammation and better recovery of their metabolic rate [66]. According to the first prospective multicenter randomized controlled trial, the use of NMP (121 livers) instead of SCS (101 livers) increases the utilization of grafts by 50%. NMP despite the longer preservation time (11.9 vs. 7.7 h) reduced the grade of graft injury as seen by the low levels of AST and EAD, in both DCD and DBD livers. However, there was no superiority of NMP in PNF, biliary complications, ischemic cholangiopathy, graft, and patient survival [67].

The great advantage of NMP is the ability to evaluate the graft during preservation time. Observation of liver parameters such as bile production with laboratory test results, such as transaminases, lactate, glucose, and pH, have created scoring systems to aid in the transplant decision. Perfusate lactate, bile production, vascular flows, and liver appearance of five rejected livers were evaluated during NMP (after SCS), and finally transplanted with good outcomes [68]. In a study in 23 human livers, biochemical parameters of bile were examined after 6 hours of NMP and compared with the grade of bile duct injury. Biliary bicarbonate, pH, glucose, and bile/perfusate glucose ratio were identified as potential biomarkers of posttransplant cholangiopathy [69].

2.3 Subnormothermic machine perfusion

Subnormothermic machine perfusion is a method that uses temperatures between HMP and NMP, usually 21–25°C, and an oxygenated preservation solution such as HOPE. This subphysiologic temperature, on one hand, reduces the metabolic rate but, on the other hand, the graft is warm enough to allow viability assessment [70].

Three hours of SNMP in seven discarded human livers showed satisfactory bile production and liver function [71] but the study did not include posttransplant outcomes in order to determine the favorable effect of SNMP.

2.4 Controlled oxygenated rewarming

In an experimental animal study, a gradual raise in temperature (up to 20°C) with simultaneous oxygenated perfusion was performed for 90 min after a period of end-ischemia HMP. Posttransplant peak transaminase level was lower, and 6 months of patient survival was higher in the COR group compared with the control group [72]. Combined protocols, such as DHOPE-COR-NMP used in discarded livers, have significantly increased the number of transplantable grafts [73].

2.5 Therapeutics in machine perfusion methods

During machine perfusion, in addition to the standard enrichment of the preservation solution (glucose, heparine, insulin, antibiotics, maybe oxygen, and nutrients), agents targeting graft recondition can be added. Machine Perfusion therapeutic agents aim to improve the marginal graft to follow a successful transplantation. The unique advantage of this *ex vivo* procedure is that the agents are washed out of the graft and cannot interact with the recipient's immune system. Defatting cocktails that increase lipolysis, vasodilators with vascular protective effects, and gene therapies with specific targets and without side effects are just several possible treatments for a marginal liver graft.

2.5.1 Defatting agents

In a porcine model, 48 h of NMP in steatotic livers resulted in higher metabolism (triglyceride, glucose, and urea in the perfusate) and less lipid detection in the tissue (histologically demonstrated) [74]. In another rodent model with steatotic grafts, 3 hours of NMP with the addition of a defatting cocktail showed a reduction of lipids in the cells with a raise in lipid mobility at the gene level [75]. The defatting cocktail was tested on discarded human grafts with good outcomes compared to the control group. Triglycerides accumulation and the grade of macrovesicular steatosis were significantly reduced [76].

2.5.2 Vasodilators

Prostaglandin E1 is a vasodilator with fibrin clot dissolution activity, which has been shown to meliorate microcirculation injury. Rodent studies where PGE1 is used in NMP verified the beneficial effect on treated livers. The levels of aspartate and alanine aminotransferase were decreased and the bile production was higher [77, 78]. Nitroglycerin and prostaglandin E1 were contained in the Vasosol solution used in the first clinical trial of HMP in human livers [79]. Apart from PGE1, prostacyclin had the same advantages in treated porcine livers [80]. Another porcine transplant study researched the effect of BQ123 and verapamil as vasodilators and noticed that treated livers had better flow in the hepatic artery [81].

2.5.3 Gene modulation agents

Antisense oligonucleotides (ASOs) and siRNA are auspicious gene agents that can have specific targets without the need for viral convection. Silencing of miRNA-122

by ASO resulted in reduced HCV activity in a porcine study [82]. Despite the fact that antiviral medication is widespread and efficient, this finding is important in the evolution of MP therapeutics. siRNAs can have multiple targets such as Fas pathway, p53, RelB, TNF-a, and proapoptotic caspases. All these targets are associated with different aspects of IRI and can potentially protect livers, as shown in animal models under normothermic or hypothermic conditions [83–85].

2.5.4 Others

Anti-inflammatory agents (alprostadil, n- acetylcysteine, carbon monoxide, and sevoflurane) used under subnormothermic or hypothermic conditions, especially the NLRP3 inflammasome inhibitor mcc950 [86], enkephalin, which is a Δ-opioid agonist treated rat livers under NMP [87], and human liver stem cells in an extracellular form [88], significantly reduced IRI markers.

3. Machine perfusion of the kidney

3.1 Hypothermic machine perfusion

HMP has been established as a safe and effective preservation method with benefits in kidney transplantation. In one of the first RCTs with 336 deceased donors, nonoxygenated HMP was superior to CSC in reducing DGF and increasing 1-year graft survival, regardless of donor type [32]. This publication integrated HMP into daily clinical practice. Afterward, the good short-term results (DGF and 1-month kidney function) of HMP were also confirmed in DCD kidneys. Regarding long-term outcomes, the 164 kidney transplants (82 HMP vs. 82 SCS) had no significant difference in 1-year graft survival [89].

The addition of oxygen and the development of HOPE showed promising results. Application of HOPE in a rodent study significantly decreased markers of reperfusion injury (IL-6, ENO, and TNF-alpha) after kidney transplantation [90]. In a recent meta-analysis, PNF and DGF were significantly reduced in HMP kidneys compared with SCS, but no difference in acute rejection was observed. Also, one-year graft survival was longer in the HMP group [91].

Although the benefit of HMP over SCS has been proven, a large randomized clinical trial COPE-POMP, which evaluated ECD kidneys stored on ice and then perfused in oxygenated hypothermic conditions for 2 hours before implantation, showed no advantages in graft survival (3 months and 1 year) and function (PNF and DGF). These results may be associated with the use of HMP in different centers [92]. Another recent RCT, COPE-COMPARE, compared oxygenated HMP with nonoxygenated HMP in Maastricht III DCD kidneys (50 years and older). The first group improved renal function while decreasing posttransplant complications and acute rejections [93].

The ideal duration and timepoint of HMP are under research, with most studies using end-ischemia time. This phase is practical as the graft is transported on ice and assessed prior to transplantation. In a clinical study of 66 ECD kidneys subjected to end-ischemic perfusion for 369 minutes, the percentage of DGF was 0 versus 9.3% in the contralateral kidneys preserved in SCS [94].

Several potential biomarkers for graft assessment have been studied. The levels of glutathione S-transferase (GST), N-acetyl-beta-D- glucosaminidase (NAG),

heart-type fatty acid-binding protein (H-FABP), or LDH measured in the perfusate during MP and are related to DGF [95–97]. Parameters in HMP, such as resistance and flow, are used in scoring systems to assess kidney quality and risk of DGF [98]. It is noteworthy that CIT, as an independent risk factor in graft function after transplantation, increases the percentage of DGF as hours of cold ischemia pass. As the study of the data from the "Machine Perfusion Trial" showed, if CIT was above 10 hours, DGF was not reduced by HMP [99].

3.2 Normothermic machine perfusion

The first clinical application of NMP (35 min after 11 hours of SCS) in human kidney transplantation was in 2011 with good postoperative results [100]. A larger clinical study compared 18 ECD kidneys that underwent NMP (for approximately 63 min) with matched ECD kidneys that were preserved on ice. DGF was lower in the NMP group (5.6 vs. 36.2%) but 1-year graft survival was comparable in both groups [101].

The advantages of preserving a kidney in normothermic conditions are many. Cold ischemic injury is minimized as aerobic metabolism and renal functions are restarted [102]. The preservation time is investigated in the literature. In a recent study, discarded human kidneys underwent 24 h of NMP using urine recirculation with stable or slightly better tubular function after histopathological assessment [103].

The observation of the graft is feasible and provides the opportunity for assessment.

Parameters, such as total urine output, renal blood flow, and macroscopic perfusion during NMP, are used in score systems to evaluate the graft quality and "transplantability" [104]. Of course, therapies and agents that improve the condition of the graft prior to transplantation are feasible in normothermic preservation. A functional organ in NMP is more easily modified than in hypothermic conditions where cellular mechanisms are under-functioning.

3.3 Therapeutics in machine perfusion

3.3.1 Hypothermic conditions

Mesenchymal stem cells (MSC) and their extracellular vesicles, which have been used in a rat model where the kidneys underwent HMP, have a potential protective role in the perfusion process. The results showed increased activation of enzymes related to cell metabolism and membrane permeability [105]. Carbon monoxide-releasing molecule 401 (CORM-401) decreased IRI markers and improved graft function [106]. Anticoagulative agents, such as thrombalexin and heparin conjugate, have been tested to improve microcirculation, with positive outcomes in the kidneys [107, 108].

3.3.2 Normothermic conditions

Application of MSCs to NMP had a suppressive role in the inflammatory process, in human kidneys [109]. Erythropoietin and its derivative, cyclic helix B peptide (CHBP), can reduce inflammatory agents, such as caspase-3 and IL-1β, providing renoprotection against IRI and improving urine production of the kidney. Recently, a mouse kidney model defined the role of endoplasmic reticulum stress (ERS) in IRI and pointed out the therapeutic potential of CHBP with CHOP (an indicator of ERS) as a biomarker

[110–112]. Also, nanoparticles can be used as drug-delivered agents in blocking or preventing events of inflammation at a molecular level. For example, a possible target is the vascular cells of the graft's endothelium that are mainly damaged by IRI and performed antidonor antibodies. Nanoparticles, with the presence of anti-CD 31 antibodies, can target endothelial cells and deliver therapeutic agents during NMP [113].

4. Conclusion

Banking organs on a worldwide scale after quality tests would be the ideal method of organ preservation in order to select the perfect-match recipient and then proceed to scheduled surgery [114]. This goal has been achieved in stem cell transplantation and important achievements are taking place in solid organ transplantation, through the development of organ preservation with machine perfusion. Starting with animal experiments and, subsequently, with human clinical studies and randomized controlled trials, machine perfusion is an alternative that still has a lot to offer in solid organ transplantation.

The advantages of MP in short-term outcomes of transplantation are dependent on the preservation method but also the beneficial effects in long-term organ function are continuously demonstrated. It is a platform where, beyond quality, the immunogenicity of the graft could be studied and modified according to the profile of the recipient [103]. The specific targets and the lower dosages, which can be achieved using MP therapeutics agents compared to conventional systemic pharmacological agents, open a new chapter in marginal graft utilization. This may in the future help change the transplant process to a more personalized medicine approach.

New MP technology reveals new perspectives in transplant logistics. Graft evaluation leads to more transplantable organs perhaps in more complex recipients. The prolonged time of preservation provides the opportunity for preoperative planning and elective surgery in day time.

"*Which perfusion technique enables the highest utilization rate of otherwise discarded livers with the best available outcomes*, *regarding complications*, *graft- and patient survival*" [115]. This question, which could concern the kidney as well, remains to be answered. So far, there is no evidence of the superiority of a preservation strategy. Randomized clinical trials with combined perfusion protocols may provide the answer to the ideal approach in solid organ transplantation.

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