Machine perfusion in organ transplantation: a tool for ex-vivo graft conditioning with mesenchymal stem cells?

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Purpose of review
Machine perfusion has emerged as a tool to evaluate pretransplant graft function more objectively during preservation. Machine perfusion also offers the possibility to recondition questionable organs and to 'immunomodulate' allografts *ex vivo*. This article aims to review the current knowledge on machine perfusion of the various solid thoracic and abdominal organs, and to discuss the new possibility of conditioning and treating grafts with mesenchymal stem cells (MSCs) during machine perfusion.

Recent findings
Different methods of machine perfusion have been described varying among organs in temperature and composition of perfusate. Commercial devices have recently become available for machine perfusion of all organs, with the largest clinical experience acquired in kidney and lung transplantation. Clinical studies are ongoing for liver, heart, and pancreas. MSC therapy in organ transplantation is now emerging with clinical studies set up to investigate its potential to attenuate ischemia/reperfusion injury (innate immunity) and to downregulate the alloimmune response (adaptive immunity) and promote engraftment after transplantation. We hypothesize that delivery of MSCs directly into the machine perfusion circuit may provide a unique opportunity to treat and immunomodulate organs prior to transplantation. To our knowledge, no study on ex-vivo delivery of MSCs during machine perfusion has been reported.

Summary
Machine perfusion of solid organs has regained much attention during the last decade. It provides a new promising tool that may allow pretransplant ex-vivo assessment, preservation, repair, and conditioning of grafts. Experimental research and clinical trials testing the administration of MSCs during machine perfusion are warranted to explore the potential benefit and mechanisms of this approach.

Keywords
ex-vivo treatment, machine perfusion, mesenchymal stem cells, organ transplantation

INTRODUCTION

Solid-organ transplantation has become a standard life-saving therapy in selected patients suffering from end-stage organ failure. In addition, organ transplantation remarkably ameliorates the quality of life. The medical community has come a long way in organ transplantation to where we are today [1]. The application of this ultimate treatment modality is only limited by the number of 'acceptable' organ donors and 'transplantable' grafts.

Static or simple cold storage (SCS) with conventional preservation solutions was designed at a time when donors were 'ideal' and preservation periods were short. In an era of donor shortage, increased use of suboptimal grafts, and organ exchange across sometimes distant geographical areas, SCS has reached its limits [2]. In the last decade, old techniques dating from the early days of transplantation have reemerged whereby organs are continuously and dynamically perfused instead of being statically

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KEY POINTS

- Machine perfusion may allow improved (and longer) preservation, ex-vivo organ assessment, repair, and conditioning.
- The use of mesenchymal stem cells to treat human diseases has gained much attention – in particular in the field of organ transplantation – because of their proregenerative, anti-inflammatory, and immunomodulatory properties.
- Machine perfusion provides a unique tool to treat organs directly with mesenchymal stem cells *ex vivo* prior to transplantation and to study their mode of action.

cold stored during their preservation. This technology has been substantially refined and new portable machines have been developed and introduced in the clinical arena to facilitate ex-vivo machine perfusion of solid organs. The purpose of this review is to summarize the current experience with machine perfusion of thoracic and abdominal organs, to give an overview of the currently available devices, and to discuss their clinical applications. In addition, the attractive but yet to be explored possibility of treating and conditioning solid organs *ex vivo* during machine perfusion with mesenchymal stem cells (MSCs) will be discussed.

MACHINE PERFUSION: CONCEPT AND METHODS

Machine perfusion consists of creating a flow through the organ generated by a pump in a circuit to recirculate a preservative solution at various temperatures through the vasculature. This continuous perfusion permits better penetration of preservation solutions within the organ, delivery of oxygen and nutrients to the parenchyma (in case the perfusate is oxygenated), and the removal of toxic metabolites (in case the perfusate is renewed or filtered). In addition to an improved preservation, machine perfusion may allow real-time monitoring of functional and biochemical performance of the graft prior to transplantation and may provide a tool to select 'transplantable' grafts, to improve their condition, to reduce the incidence of ischemia/reperfusion injury (IRI), and possibly to safely increase the preservation time.

Different methods have been investigated experimentally. Techniques may vary among solid organs. Various ranges of temperature have been used from hypothermic perfusion at 4°C to normothermic perfusion at 37°C. The former method is intended to preserve the organ in a low metabolic state, while the latter will keep the organ in a more physiologic and metabolically active state with the advantage that organ repair and reconditioning may become possible. Solutions used as perfusate also vary among various organs from low potassium crystalloid solutions to blood-based solutions (full blood or packed red blood cells) mixed with colloids (dextran) and albumin. The power to circulate the perfusate through the vasculature is created by a roller pump (occlusive) or a centrifugal pump (non-occlusive) that delivers a continuous flow or a pulsatile flow mimicking the physiologic variations in systolic and diastolic pressure. Organs can be preserved in resting mode (preservation) or functioning mode (assessment). With normothermic perfusion, organs will resume their function. Kidneys will excrete urine and clear creatinine, and the liver will produce bile and coagulation factors and will clear metabolites. Hearts can be perfused while fibrillating or beating building up pressures. Lungs can be perfused in an atelectatic state or while ventilated, allowing gas exchange.

During machine perfusion, different physiological parameters specific to the organ can be measured and various biochemical markers released in the perfusate or excreted (in urine or bile) can be analyzed to assess the viability and the functional state of the graft. The exact value of these markers to decide whether to accept or to decline an organ and to predict its functional performance after transplantation is not clear yet and needs to be further investigated. For the kidney, vascular resistance correlates with delayed graft function, but the predictive value is low [3]. For the liver, the vascular resistance does not seem to correlate with viability [4]. In normothermic machine perfusion, the group of Friend at Oxford University has shown that the capacity of the liver to correct metabolic acidosis during machine perfusion correlates well with its function after transplant [5]. For the lung, oxygenation capacity taken alone may be misleading in assessing the ex-vivo lung. Other parameters like pulmonary vascular resistance, compliance, and airway pressures are equally important [6].

Several smaller and transportable commercial devices for machine perfusion have recently become available for all organs facilitating the clinical application of this new technique in the daily transplant practice. Randomized clinical trials with these devices have been completed (kidney), are ongoing (lung, heart), or are planned (liver). Costeffectiveness of machine perfusion needs to be analyzed for every organ in order to justify reimbursement by health authorities and insurance companies. Machine perfusion of kidney – by reducing the need

for dialysis after transplant and improving graft survival – has already been shown to be costeffective [7▪▪].

Further research in all solid organs is ongoing with regard to the optimal perfusion technique and solutions.

MACHINE PERFUSION: EXPERIENCE AND DEVICES FOR CLINICAL USE

A thorough review summarizing current experimental knowledge and clinical experience with pretransplant graft viability assessment during machine perfusion for all solid organs was recently published [8▪▪].

Machine perfusion of kidneys historically has gained the largest interest as a prototype machine was developed in the late 1960s by Belzer. Several clinical studies including a large randomized trial [9,10,11▪], but not all [12], have shown a reduced rate of delayed graft function and better graft survival after hypothermic machine perfusion versus SCS. Machine perfusion is now believed to be the preferred method for preserving kidneys at higher risk originating from expanded criteria donors [13], donors older than 65 years [14], and donors after circulatory death [15]. The predictive capacity of machine perfusion parameters (vascular resistance and perfusate biomarkers) is not sufficient to be used as a sole indicator to accept or discard a given kidney [16–18]. Successful outcome following normothermic machine perfusion using a red-cell-based solution has been recently published by the team of Leicester [19,20]. Several companies have now marketed commercial devices for clinical kidney perfusion (Fig. 1): LifePort Kidney Transporter (Organ Recovery Systems, Des Plaines, Illinois, USA); RM3 (Waters Medical Systems, Birmingham, Alabama, USA); and Kidney Assist (Organ Assist, Groningen, The Netherlands).

Machine perfusion of livers was first attempted in the late 1960s by Bretschneider and Starzl. More recently, hypothermic and normothermic machine perfusion of the liver have been investigated in an experimental setting [5,21–28]. So far, only one clinical study has been published comparing 20 adult liver recipients after hypothermic machine perfusion with a historically matched group of recipients after SCS with a reduction in early allograft dysfunction (5% versus 25%; respectively; $P = 0.08$) [29,30]. Feasibility of normothermic liver machine perfusion in man has yet to be proven. Several companies have now marketed commercial devices for clinical liver perfusion (Fig. 2): Metranormothermic perfusion (OrganOx Ltd, Oxford, UK); LifePort Liver Transporter (Organ Recovery Systems); Liver Assist (Organ Assist).

Machine perfusion of pancreas has remained largely unexplored. The majority of studies aimed to optimize the preservation of pancreata in order to increase the islet yield after cold preservation [31,32]. In a very small human study, machine perfusion of pancreata resulted in better islet yield and viability compared with SCS [33]. The same devices currently available for kidney perfusion can be used and adapted for the perfusion of human pancreata.

Ex-vivo lung perfusion (EVLP) was studied in historical studies as a method to assess the quality of the graft [34] and as a preservation technique during distant thoracic organ procurement [35]. The first successful transplant after EVLP was published by Steen *et al.* [36] in 2001 stimulating many research groups worldwide to further investigate the technique in animal models [37–40] and in discarded human lungs [41–43]. Much experimental work was carried out at the University of Toronto [44,45].

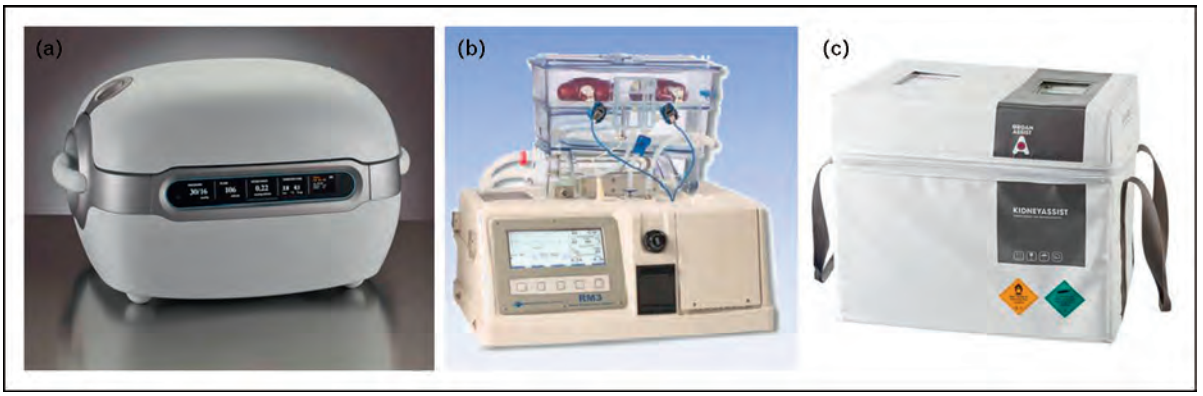

FIGURE 1. Devices for kidney machine perfusion: (a) LifePort Kidney Transporter (Organ Recovery Systems, Des Plaines, Illinois, USA), source: www.organ-recovery.com; (b) RM3 (Waters Medical Systems, Birmingham, Alabama, USA), source: www.wtrs.com; and (c) Kidney Assist (Organ Assist, Groningen, The Netherlands), source: www.organ-assist.nl.

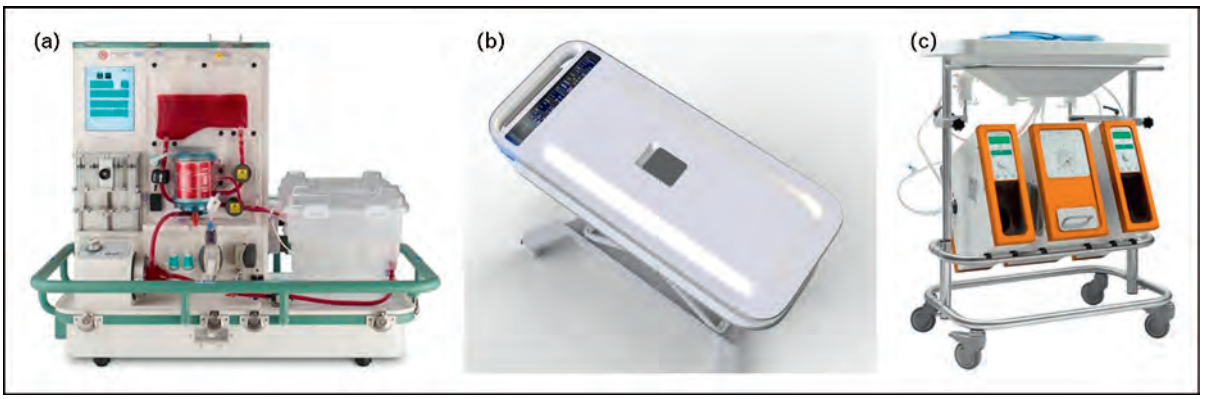

FIGURE 2. Devices for liver machine perfusion: (a) Metranormothermic perfusion, OrganOx Ltd, Oxford, UK) source: www.organox.com; (b) LifePort Liver Transporter (Organ Recovery Systems, Des Plaines, Illinois, USA), source: www.organ-recovery.com; and (c) Liver Assist (Organ Assist, Groningen, The Netherlands), source: www.organ-assist.nl.

Successful transplantation of questionable lungs after EVLP has recently been reported by different groups worldwide [46–52,53▪]. Results of an international multicenter trial (Inspire) randomizing standard donor lungs to be preserved with SCS versus machine perfusion are awaited [54]. Several companies have now marketed commercial devices for clinical lung perfusion (Fig. 3): OCS Lung (Transmedics, Andover, Massachusetts, USA); Vivoline LS1 (Vivoline Medical, Lund, Sweden); Lung Assist (Organ Assist); and XPS (XVIVO Perfusion AB, Göteborg, Sweden).

Hypothermic machine perfusion of heart was reported in animal experiments [55–58]. Left ventricular function seems better preserved after hypothermic [59–61] and normothermic [62,63] machine perfusion compared with SCS. Clinical trials were started in 2007 in USA (PROCEED) [64] and Europe (PROTECT) [65], with only preliminary data reported so far. One company has marketed a commercial device for clinical heart perfusion (Fig. 4): OCS Heart (Transmedics).

EX-VIVO RESUSCITATION OF ORGANS

As discussed above, experimental and clinical data have already shown that machine perfusion creates a 'window' between procurement and transplantation during which functional performance and viability of the graft under optimal conditions can be evaluated. Data collected during this period of ex-vivo preservation may provide information that can help clinicians to predict the risk of dysfunction after transplantation and that can assist them in

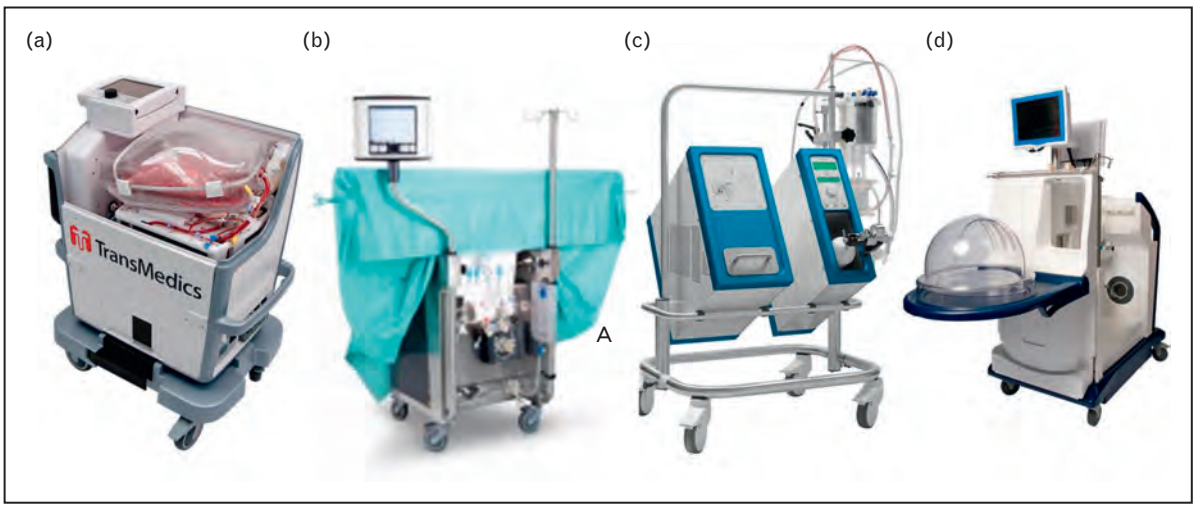

FIGURE 3. Devices for lung machine perfusion: (a) OCS Lung (Transmedics, Andover, Massachusetts, USA) source: www.transmedics.com; (b) Vivoline LS1 (Vivoline Medical, Lund, Sweden), source: www.vivoline.se; (c) Lung Assist (Organ Assist, Groningen, The Netherlands), source: www.organ-assist.nl; and (d) XPS (XVIVO Perfusion AB, Göteborg, Sweden), source: www.xvivoperfusion.com.

FIGURE 4. Device for heart machine perfusion: OCS Heart (Transmedics, Andover, Massachusetts, USA), source: www.transmedics.com.

deciding to accept or discard a given organ for transplantation. Also, machine perfusion has the potential to better preserve the quality of the graft by sustaining continued metabolism (at higher temperatures and with oxygen), providing energy and nutrients, and removing toxic waste products (in case the perfusate is regularly renewed). In the future, machine perfusion may offer a tool for ex-vivo repair of the organs and improvement of their quality prior to transplantation and perhaps for 'immunomodulation' of these organs in order to protect them from innate immune responses (IRI) and adaptive immune responses (acute and chronic rejection) in the recipient.

Many organs, excluding those with fixed structural damage related to previous injuries or life-style habits such as smoking or alcohol abuse, are currently declined because of acute – albeit recoverable – injuries. Potential grafts may get injured by several hits during the whole transplantation process in the transition phase from donor to recipient: the initial insult leading to brain damage, resuscitation maneuvers with intubation and ventilation, autonomic storm and systemic inflammation following brain-stem death, warm ischemia in donors after circulatory death, organ manipulation and surgical trauma during procurement and organ extraction, the cold preservation period, the implantation process, and finally the reperfusion phase. Altogether, organ damage may result from direct mechanical trauma and contusion, hemorrhage, inflammation, and infection.

Once the organs are recovered from the deceased body, ex-vivo treatment during machine perfusion becomes possible. Normothermic perfusion providing oxygen and other metabolic substrates under physiological conditions appears to be the way forward to improve the viability of suboptimal grafts. Research is ongoing for all organs to look for ways to administer agents with the potential to reduce the injury and to restore organ functionality. The easiest strategy to deliver drugs directly to the organs is by including them into the perfusion solution or by injecting them into the afferent tubing running to the vasculature of the graft. Theoretically, different drugs according to the type of injury or even a combination of them (cocktail approach) could be administered at intervals during machine perfusion: antibacterial, antiviral, and antifungal agents to treat infection, anti-inflammatory molecules to block proinflammatory responses, vasodilating agents to improve perfusion of the microvasculature, fibrinolytic agents to dissolve microthrombi, high osmotic agents to remove interstitial edema, etc. An advantage of this isolated machine perfusion setting is that these drugs could be given at higher doses than *in vivo* as there is no risk to harm other organs. A restriction, however, may be that certain drugs cannot be metabolized in the ex-vivo circuit and therefore active components would have to be given. On the other hand, toxic metabolites may accumulate over time. Therefore, repeated renewal of the perfusate or insertion of filters in the ex-vivo circuit may become necessary. Finally, machine perfusion also offers the possibility of direct and targeted genetic intervention by using viral vectors or silencing RNA technology.

Compared with kidney, liver, heart, and pancreas, the lung can be considered as a privileged organ as it not only carries a vascular, but also a bronchial tree providing direct access to the entire parenchyma. In that way, active drugs can be delivered to the pulmonary graft by instillation or nebulization via the airway as already practiced nowadays *in vivo*. Also, the liver is different from other solid organs in that it carries a dual vascular system allowing drug delivery to the parenchyma by perfusion via either the hepatic artery (that preferentially vascularizes the biliary tree which is

particularly susceptible to ischemia) or the portal vein (that preferentially vascularizes the liver parenchyma) or both. Flow competition between these two systems has been observed experimentally by researchers from our group [66]. The potential relevance of this finding for drug administration warrants further study.

The aforementioned treatment possibilities during machine perfusion are currently hypothetical and only very few papers have been published on organ therapy during machine perfusion.

In the kidney, Nicholson of the Leicester group investigated the effect of adding erythropoietin to the perfusion solution in a porcine model of isolated normothermic hemoperfusion. The authors found that erythropoietin promotes inflammatory cell apoptosis, drives inflammatory and apoptotic cells into tubular lumens. This eventually leads to inflammation clearance, renoprotection, and tissue remodeling through caspase-3 and IL-1β [67].

In the liver, our group has demonstrated in a pig transplant model (of donation after circulatory death) that a multifactorial biological modulation (cocktail approach) including administration of streptokinase and epoprostenol in the donor and administration of glycine, alpha1-acid glycoprotein, MAP kinase inhibitor, alpha-tocopherol, glutathione, and apotransferrin to the recipient eliminates primary nonfunction, improves liver function, and increases survival. Biochemically, TNF-alpha and redox-active iron were suppressed and biliary bile salt toxicity was reduced [68]. Furthermore, inflammation-regulating genes were suppressed [69]. It will be interesting to test the administration of this type of treatment (and others) not only in donors and recipients, but also directly to the graft ex-vivo during machine perfusion. Here too, normothermic liver perfusion may reveal superior to hypothermic perfusion as many of these interventions may require an active metabolism to operate.

In the lung, our group has previously investigated the role of the antioxidant N-acetyl cysteine nebulized in nonheart-beating donor pig lungs subjected to 3 h of warm ischemia. Functional performance [70] and inflammatory response [71] assessed during EVLP was attenuated compared to the nontreated control group. Aerosolized N-acetyl cysteine, therefore, has great potential to attenuate inflammation during EVLP. The Zurich group investigated the role of surfactant administration to porcine lungs injured by acid aspiration. Ex-vivo administration of surfactant via lavage resulted in improved graft function when compared with a control group [72]. The same group found that adding the fibrinolytic drug urokinase to the reperfusion solution resulted in improved graft function with decreased pulmonary vascular resistance and better oxygenation [73]. In a series of human donor lungs determined to be unsuitable for transplantation by the Toronto group, five lungs were subjected to 12 h of normothermic EVLP and treated by transbronchial gene therapy with the anti-inflammatory interleukin 10. Improvement in pulmonary function, restoration of alveolar–blood barrier integrity, and attenuation of lung inflammation were noticed [74].

EX-VIVO CONDITIONING OF ORGANS WITH MESENCHYMAL STEM CELLS

MSCs are multipotent self-renewing cells isolated from whole bone marrow. A paradigm shift has occurred in our concept of how cell therapies utilizing MSCs mediate their beneficial effects. It is now appreciated that, although MSCs can be described as having differentiation potential, their effector function is based less on in-situ differentiation, transdifferentiation, or fusion and more on paracrine effects and cross-talk with other cells within diseased tissues. Mechanistic hypotheses of MSCs as cell-based therapy are postulated on their immunomodulatory properties (interaction with the innate immunity and suppression of T-cell responses) and their ability to secrete soluble factors [75]. These properties of MSCs make them particularly interesting for use as a cellular therapy in solid-organ transplantation [76,77] and in tissue-engineered organ replacement [78] for currently intractable conditions. Experience with MSCs therapy in transplantation is emerging for all solid organs in an attempt to attenuate the severity of IRI, to help recovery from reperfusion injury, and to promote graft acceptance by reducing acute and chronic rejection. Machine perfusion offers a unique platform to selectively administer these MSCs directly into the donor organ, overcoming the issues of homing, trafficking, and safety. Especially, allogeneic MSCs are attractive because of their wide availability at the time of organ harvest. Autologous stem cells might be of less interest to modulate acute donor organ injury during machine perfusion as the isolation steps take longer time intervals and can never be planned in advance when a potential donor becomes available.

In kidney, it has been shown that administration of MSCs enhances recovery from ischemia–reperfusion-induced acute renal failure in rats [79]. Operating mechanisms are not known with certainty, but seem to involve anti-inflammatory properties and facilitation of tissue repair, and this through endocrine and paracrine interactions and cellular crosstalk between MSCs and dendritic cells, macrophages and other cell types. On the basis of their renoprotective properties and their capacity

to promote tissue repair after injury, MSCs are considered as a new therapeutic tool in patients with acute kidney injury and ongoing trials are testing their effect [80]. The role of autologous MSCs as an induction therapy to promote graft acceptance has also been studied in a randomized controlled trial after living-related kidney transplantation. This landmark study demonstrated a lower incidence of acute rejection, a decreased risk of opportunistic infection, and a better estimated renal function at 1 year compared with the IL-2 receptor antibody treatment group [81].

In liver, MSCs have also been shown to accelerate recovery from IRI in rodents [82]. In liver transplantation, the role of MSCs as immunomodulators to reduce rejection is currently being investigated [83]. A phase I safety and feasibility trial is set up at the University Medical Center Regensburg in recipients receiving two doses of third-party multipotent adult progenitor cells (MAPCs) at day 1 and 3 after liver transplantation, in addition to a calcineurin-inhibitor-free immunosuppressive regimen with basiliximab, mycophenolic acid, and steroids [84]. Results are awaited before a phase II/III trial will be conducted to assess their clinical efficacy.

In intestine too, it has been shown that MSCs can help to control IRI in rodents [85]. This property of MSCs in addition to their protolerogenic properties makes them a particularly attractive strategy to improve outcome after intestinal transplantation, a procedure still defeated by a profound IRI and a vigorous rejection response.

In lung, much research was done by the group of Matthay at the University of California San Francisco in a model of acute lung injury comparable to donor lung injury. In cultured human alveolar type II cells damaged by a mixture of cytokines, these investigators demonstrated the ability of allogeneic human MSCs to restore the epithelial permeability that is needed to limit edema formation after lung transplantation [86]. In one study from the same research group, allogeneic MSCs were administered to human donor lungs declined for transplantation. In an isolated reperfusion model, MSCs were administered directly into the airways to study their treatment potential in acute lung injury [87]. Several basic anti-inflammatory and antibacterial properties have been attributed to MSCs that may be beneficial to restore lung injury in patients with acquired respiratory distress syndrome [88]. The spectrum of possible MSC-based therapies for acute lung injury includes both targeted intrapulmonary and intravascular administration during EVLP.

In heart, pretransplant donor infusion of MSCs has been shown to prolong the survival of a semi-allogeneic heart transplant in a mouse model through the generation of regulatory T cells [89].

FUTURE RESEARCH

Many issues related to MSCs therapy remain unresolved and warrant further research: precise operating molecular and cellular mechanisms, influence of the timing and the site of administration, effect of various type of cells (autologous versus donor-specific versus third party versus xenogenic), trafficking of these cells and their homing to particular organs and their transendothelial migration in the parenchyma, and the influence of local inflammation on this process.

With the development of advanced organ regenerative strategies, the use of molecular and cellular treatments to repair organs *ex vivo* is now becoming conceivable. Machine perfusion provides a unique tool to deliver these therapies directly to the organs while they remain physiologically perfused and metabolically active in an isolated circuit *ex vivo*.

From an experimental point of view, direct administration of MSCs to an organ during machine perfusion in an isolated circuit *ex vivo* provides a unique experimental platform to study the potential therapeutic effects of these cells and their operating mechanisms. Perfusing an organ directly with MSCs may allow to better study the trafficking of these cells and their homing to particular organs and the factors influencing this process, their effect on the immunogenicity of the perfused organ (MHC expression, effect on endothelial cells and passenger antigen-presenting cells), their effect on intragraft innate immunity and local inflammation (cytokine, adhesion molecule, chemokine expression, cellular infiltration etc.), and their mode of action. Administration of MSCs during machine perfusion carries exciting potentials: first, the possibility to promote repair of damage endured prior to preservation because of donor-related injury and second, the possibility to downregulate local intragraft inflammation and reduce graft immunogenicity in order to make grafts less vulnerable to IRI and to rejection in the recipient.

To our knowledge, no experimental data on ex-vivo treatment with MSCs during machine perfusion to improve graft quality have been published so far. Similarly, to our knowledge, there are no reported data on the possibility to administer MSCs cells during machine perfusion to render organs more resistant to IRI and to diminish acute or chronic rejection after transplantation. To explore these possibilities, further research testing the effect of the direct administration of MSCs during ex-vivo organ perfusion is urgently needed. If the above

would prove to be possible, this may revolutionize the practice of solid-organ transplantation by increasing the number of transplantable grafts and by improving their function and facilitating their acceptance after transplant, thereby reducing the need for immunosuppression and its attending complications (toxicity, infection, and malignancies) [90,91]. Access to transplantation would increase and results of transplantation would improve.

CONCLUSION

Machine perfusion of solid organs has regained much attention during the last decade. In addition to better preservation, it provides a promising tool that may allow ex-vivo assessment, repair, and conditioning of donor organs prior to transplantation. The largest clinical experience accumulated so far has been obtained in kidney and lung transplantation. It is hoped that this new technique in the near future will contribute to maximize the number of available organs for transplantation, to decrease the risk of primary graft dys(non)function after transplantation, and to improve long-term graft and patient survival. Further technological developments and research on the optimal technique and preservation solutions for long-term, ex-vivo organ perfusion are needed before it will become an established technique for all organs in the daily transplant practice.

The use of MSCs to treat human diseases has gained much attention because of their proregenerative, anti-inflammatory, and immunomodulatory properties. This is an emerging field and further experimental research and clinical trials are warranted. Early experience in the field of transplantation suggests that MSCs – when they are administered *in vivo* – ameliorate IRI by downregulating innate immunity, favor tissue repair at sites of inflammation, and may promote graft acceptance by downregulating the adaptive immunity. Machine perfusion provides a unique experimental platform to better study the function and properties of MSCs and a unique therapeutic tool to directly 'treat' an organ while it is perfused and maintained in a metabolically active state in an isolated ex-vivo circuit. Further studies are warranted to determine whether this strategy may favor repair of higher risk grafts that have been damaged prior to preservation and may condition and protect grafts from subsequent inflammatory and immune insults after transplantation (e.g. IRI and rejection).

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Conflicts of interest

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 115).

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This review summarizes the past and present evidence, and provides important background for clinicians and investigators using the ex-vivo lung perfusion/isolated perfused lung system.

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