

Machine perfusion of thoracic organs

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Contributions: (I) Conception and design: D Van Raemdonck; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: This article summarizes recent knowledge and clinical advances in machine perfusion (MP) of thoracic organs. MP of thoracic organs has gained much attention during the last decade. Clinical studies are investigating the role of MP to preserve, resuscitate, and assess heart and lungs prior to transplantation. Currently, MP of the cardiac allograft is essential in all type DCD heart transplantation while MP of the pulmonary allograft is mandatory in uncontrolled DCD lung transplantation. MP of thoracic organs also offers an exciting platform to further investigate downregulation of the innate and adaptive immunity prior to reperfusion of the allograft in recipients. MP provides a promising technology that allows pre-transplant preservation, resuscitation, assessment, repair, and conditioning of cardiac and pulmonary allografts outside the body in a near physiologic state prior to planned transplantation. Results of ongoing clinical trials are awaited to estimate the true clinical value of this new technology in advancing the field of heart and lung transplantation by increasing the total number and the quality of available organs and by further improving recipient early and long-term outcome.

Keywords: Heart transplantation; lung transplantation; machine perfusion (MP); *ex vivo* lung perfusion (EVLP); donor after circulatory death

Submitted Jan 15, 2018. Accepted for publication Feb 25, 2018.

doi: 10.21037/jtd.2018.02.85

View this article at: <http://dx.doi.org/10.21037/jtd.2018.02.85>

Introduction

“Good morning doctor, I hope you had a good night of sleep. The organ has been fully reconditioned overnight. It has now been assessed and accepted for transplantation. We have called upon the recipient for transfer to the operating room” said the scrub nurse to the surgeon over the phone. This is a scenario every transplant surgeon would dream of to become reality during his professional career.

Heart as well as lung transplantation have become a standard life-saving therapy in selected patients suffering from end-stage heart (1) or lung (2) failure. In addition, quality of life is remarkably improved in the majority of these recipients. Selection criteria for heart (3) and lung (4)

transplant candidates have recently been reviewed by working groups within the International Society for Heart and Lung Transplantation (ISHLT). However, the application of this ultimate treatment modality is currently limited by the number of “acceptable” organ donors and “transplantable” grafts.

During the last decade, machine perfusion (MP) of solid organs has become clinical reality and offers the possibility to assess, preserve and recondition organs prior to transplantation. Previous review papers have reported on the different techniques, protocols and devices currently available for perfusion of heart (5-9) and lungs (10-21). Increasing comfort with this new technology and important clinical experience with MP was reported over the last

24 months. The purpose of this review is to summarize the recent clinical experience in the perspective of future clinical applications.

MP of thoracic organs for normothermic preservation

To slow down metabolism and reduce warm ischemic injury, organs nowadays are cooled by flushing them with organ specific preservation solutions followed by *static* cold storage (SCS). Cooling from 37 to 4 °C decreases the metabolic rate by 12- to 13-fold. This method was designed at a time when donors were “ideal” and preservation periods were short. Up to date it remains the golden standard for preservation of heart (22,23) and lungs (24,25).

In an era of donor shortage, increased use of suboptimal grafts, and organ exchange across sometimes distant geographical areas, SCS has reached its limits. Although the technique of cold storage is simple, safe, and cheap, metabolism does not cease completely. Anoxia may still occur and sodium-potassium ATPases are still inhibited with disruption of transcellular ion gradients. Primary graft dysfunction (PGD) or even primary non-function of heart (26) and lungs (27) jeopardizing the life of the recipient immediately after transplantation remains a substantial risk. Time has come to think outside the ice-box (28).

Indeed, MP has the potential to better preserve graft quality by sustaining continued metabolism dependent on the perfusion temperature, by providing oxygen, energy and nutrients, and by removing toxic waste products (in case the perfusate is regularly renewed or filtered). Over the last decade, old techniques dating from the early days of transplantation have re-emerged whereby organs are continuously and *dynamically* perfused instead of being *statically* cold stored during their preservation. This technology was substantially refined and new devices for MP of heart and lungs are being developed and introduced in the clinical arena. Portable systems will largely facilitate continuous MP preservation during transport between donor and recipient hospitals.

Heart

In the past several decades there has been scientific and clinical interest towards *ex situ* heart perfusion with oxygenated and nutrient enriched blood to reduce ischemic injury to the donor heart and potentially enable assessment of metabolic and mechanical function. Hypothermic MP

of heart was reported in animal experiments with long preservation times (29-33). Recent preclinical studies with hypothermic MP confirm that it provides superior donor heart preservation compared to cold static storage in terms of left ventricular function, cardiac myocyte integrity, and energy stores (34-39). Hypothermic MP devices have been developed for human heart preservation. After a set of experiments in a porcine heart transplant model reported by Steen *et al.* (33), a clinical trial in humans is now ongoing at the Skåne University Hospital, Lund, Sweden. The first human heart transplant using Stig Steen’s new heart solution and machine has been successful [Steen S (Lund, Sweden) personal communication].

Several reports have investigated normothermic MP of the donor heart to maintain a steady state of metabolism (7,40-42). An elevated lactate level at the end of MP appears to be a powerful predictor of graft failure (43). The feasibility of normothermic *ex situ* heart perfusion for 12 hours has previously been demonstrated with recovery of cardiac function and preservation of endothelial cell function (44,45). These studies have paved the way for development of clinical devices for *ex situ* heart perfusion.

The Organ Care System (OCS) is the first and only clinical platform up to date that can maintain the donor heart in a warm, beating, near-physiological state prior to transplantation (OCS™ Heart, Transmedics®, Andover, MA, USA). Institutional studies reported the successful use of the OCS in human heart transplantation (46-48). Clinical trials were started in 2007 in USA (PROCEED) (49) and in Europe (PROTECT) (50) with results presented in abstract form only. In 2015, Ardehali *et al.* reported the results of the first clinical trial (PROCEED II) in heart transplantation to assess the efficacy and safety of this new technology (51). In a prospective, open-label, multicenter, randomized non-inferiority trial (ClinicalTrials.gov, number NCT00855712) at ten heart-transplant centers in the USA and Europe, heart-transplant candidates (aged >18 years) were randomized to receive donor hearts preserved with either the OCS (n=67) or SCS (n=63) (52). Thirty-day patient and graft survival rates were 94% and 97%, respectively (P=0.45). Eight (13%) patients in the OCS group and nine (14%) patients in the SCS group had cardiac-related serious adverse events. The authors concluded that OCS yield similar short-term clinical outcomes (51). In an editorial commentary in *Lancet*, the clinical value of this new technology for standard heart preservation was however questioned. Some hearts that looked initially acceptable for transplantation were ultimately not implanted. OCS

also requires additional surgical and technical support, proprietary equipment, and appropriate transport that are inevitably more costly than those needed for cold static storage (53). However, proponents believe that the *ex situ* perfusion of the heart is able to enhance viability of donor organs by reducing time-dependent ischemic injury (54). In a single-center, non-randomized study, better outcomes with this new technology compared to SCS were reported with regard to recipient survival and incidence of PGD as well as acute rejection (46). Further studies are needed to evaluate the impact of this new preservation technology on the number of heart transplants and its outcome.

Lung

Compared to heart transplantation, the impact of the length of the cold ischemic time on the outcome after lung transplantation is less clear. Over the years several studies with inherent flaws have reported conflicting results on this topic (2,55,56). With modern extracellular-type preservation solutions, lungs preserved on ice can be safely transplanted within a time window of 8–10 hours. Yeung *et al.* from the Toronto group recently reported that the extension of graft preservation time beyond 12 hours with EVLP did not negatively affect early lung transplantation outcomes (57).

Ex vivo lung perfusion (EVLP) was reported in historical papers as a method to assess the quality of the graft (58) and as preservation technique during distant thoracic organ procurement (40). The first successful transplant after EVLP was published by Steen and colleagues in 2001 (59). Much experimental work on the technique for prolonged EVLP was carried out at the Universities of Lund (60) and Toronto (61). The attention of most research groups was mainly focused on the value of EVLP as a tool to assess the quality of non-standard lungs prior to acceptance for transplantation (13–21). Because of the comfort and the good outcome with SCS, little clinical interest was shown in this technology as a potential tool for normothermic lung preservation (62). A prospective, international, multicenter, randomized controlled, non-inferiority clinical study (Inspire trial) was recently completed comparing normothermic portable *ex vivo* machine preservation with the OCS Lung™ (Transmedics®, Andover, MA, USA) to SCS of standard donor lungs (ClinicalTrials.gov number NCT 01630434) (63). A total of 320 patients were randomized to both treatment arms. This is the largest clinical and randomized trial in lung preservation performed to date. The primary effectiveness end-point was a

composite of patient and graft survival at day 30 and absence of PGD grade 3 within the first 72 hours. The final results were presented at the 2016 annual ISHLT meeting (64). The study showed that the OCS group met the non-inferiority test as compared to the SCS group in the per protocol population. Of notice, the incidence of PGD grade 3 within 72 hours after transplantation in that population was significantly lower ($P=0.015$) in the OCS group. The investigators stated that this finding might have an impact on the development of chronic rejection and long-term survival, but this will need further study follow-up. The full paper reporting study results is still awaited.

While normothermic *dynamic* preservation of donor lungs on the portable OCS Lung™ device in the Inspire trial already commenced in the donor hospital and continued during transport to the recipient hospital, other groups have looked at the value of normothermic *static* preservation after a first cold ischemic period prior to transplantation. In a pig lung transplant model, the Toronto group previously investigated the impact of prolonged (12 hours) normothermic EVLP following a first period of 12 hours cold ischemia. Recipient animals did better in terms of superior oxygenation and less edema when compared to recipients of lungs that were stored cold for 24 hours (62). In a recent study using the same transplant model, this group investigated the impact of a second cold ischemic period (2 and 10 hours) following a first 10-hour period of cold storage and then 6 hours of normothermic EVLP. After 4 hours of reperfusion in the recipient animal, oxygenation function, acute lung injury score, inflammatory markers, and cell death pathway markers were similar between the 2- and 10-hour groups. Of notice, both EVLP groups demonstrated better oxygenation compared to the control group with 24 hours cold static preservation without EVLP (65). A prospective, single-center clinical trial was conducted by the Vienna lung transplant team randomizing 80 patients transplanted with cold stored lungs immediately upon arrival versus similar lungs that were first evaluated for 4 hours with normothermic static EVLP using the Toronto technique (66). Short-term clinical outcomes in recipients did not differ between both groups. Patients remained intubated (1.6 *vs.* 1.6 days, $P=0.67$), in the intensive care unit (6 *vs.* 6 days, $P=0.76$), and in the hospital (23 *vs.* 19 days, $P=0.42$) for a comparable period of time. The 30-day survival was 97.1% *vs.* 100% ($P=0.46$). Of note, the incidence of PGD more than grade 1 was lower in the EVLP group at all-time points compared to the control group, but this difference failed to reach statistical

significance (24 hours, 5.7% *vs.* 19.5%, $P=0.10$). Likewise, the need for post-operative prolonged extracorporeal membrane oxygenation was lower in the EVLP group (5.7% *vs.* 12.2%, $P=0.44$).

Further studies are needed to evaluate the impact of this new preservation technology and its best timing in the total preservation process on the outcome after lung transplantation.

MP of thoracic organs for transplantability assessment

In addition to the potential of safely replacing and prolonging the preservation period, MP creates a “window” between procurement and transplantation during which real-time functional performance, metabolic need, and viability of the graft can be evaluated under optimal conditions. Data collected during this preservation period may provide information that can help clinicians to predict the risk of PGD and that can assist them in deciding to accept or discard a given organ for transplantation. This new platform, therefore, may provide a tool to select “transplantable” grafts of the best quality in an effort to increase the thoracic donor organ pool. In a retrospective database analysis of declined lung donors, our group identified a large potential (>20%) for EVLP to further increase the donor pool in a transplant center where the majority of donor lungs are already fulfilling extended criteria (67). Similarly, MP of heart is expected to significantly increase the total number of hearts accepted for transplantation (5,54).

Heart

The Harefield group reported on the successful use of OCS to assess heart quality in transplantation from donors with an adverse profile (e.g., left ventricular ejection fraction <50%, left ventricular hypertrophy, donor cardiac arrest, alcohol/drug abuse, coronary artery disease) (68). The International Expand Heart Pivotal Trial (ClinicalTrials.gov number NCT 02323321) is currently investigating this potential with donor hearts that do not meet current standard acceptance criteria (69). Results of the trial are awaited.

After intensive research in large animal models (70-75), recent success with clinical heart transplantation from donors dying after circulatory arrest (DCD) has boosted the interest in normothermic *ex situ* heart perfusion as a tool to

assess cardiac recovery after hypoxic arrest and subsequent functional performance prior to transplantation (7,76). The groups in Sydney (77-79), Cambridge (80,81), and Harefield (68) have now reported case series of DCD heart transplantation with excellent early survival. A new method to assess performance of the heart recovered from a DCD was recently reported by the group at Papworth Hospital, Cambridge, UK. Extended thoracoabdominal normothermic regional perfusion (NRP) in the deceased donor with the aid of venoarterial extracorporeal membrane oxygenation allows metabolic and functional recovery and subsequent assessment of the arrested heart *in situ*. In their opinion, donor hearts that fail post-NRP assessment can be discarded avoiding the use of expensive material for *ex situ* functional evaluation (82). The authors speculate that thoraco-abdominal NRP may become the new gold standard for DCD organ retrieval in the future.

Lung

Equally, MP allows quality assessment of the pulmonary graft prior to transplantation. The first successful transplant after EVLP in 2000 was with a lung recovered from an uncontrolled DCD (59). More interest in EVLP was noticed for pulmonary grafts that initially did not meet standard lung criteria. Successful transplantation of questionable lungs after EVLP has now been reported by several groups in Europe and North America with good clinical outcome (83-99). The overall lung yield after EVLP across all reported series is around 80% (17).

The role of EVLP for secondary assessment of questionable donor lungs is being investigated in several clinical trials (100). The first clinical trial was conducted in Canada by the Toronto Lung Transplant Group. In the *HELP* trial (Human *Ex Vivo* Lung Perfusion), high-risk lungs that otherwise would not be used, were assessed with EVLP. Eighty six percent of the lungs that originally did not meet acceptance criteria from both DBDs and DCDs, were ultimately transplanted after EVLP and resulted in equivalent recipient outcome compared to those of contemporary standard control donor lungs. Rates of PGD grade 3 at 72 hours after transplantation were reported to be low (2% in EVLP lungs versus 8.5% in control lungs) (84,88). More than 100 clinical lung transplants have now been performed in Toronto with a 5-year survival of 70% in the EVLP cohort compared to 63% in controls (100). Functional outcome and quality of life are equivalent to

conventional lung transplants (101). The *DEVELOP*-UK trial including all five lung transplant centers in the UK (Controlled Trials.com number ISRCTN44922411) was designed to compare one-year recipient survival between standard-criteria (SCD) versus extended-criteria (ECD) donor lungs after EVLP reconditioning according to the Lund protocol using the Vivoline[®] LS1 device (XVivo Perfusion AB, Göteborg, Sweden) (102). The trial started in April 2012, but was prematurely stopped after some fatalities. Results have been reported recently (103). Overall, one-third of donor lungs subjected to EVLP were deemed suitable for transplant. Estimated survival over 12 months was lower than in the standard group, but the data were also consistent with no difference in survival between groups. Patients receiving these additional transplants experienced a higher rate of early graft injury and need for unplanned ECMO support, at increased cost. Three multicenter trials are still ongoing. The *NOVEL* trial (Clinical Trials.gov number NCT 01365429) is a prospective, non-randomized, controlled, clinical study in 104 recipients in eight U.S. centers comparing 30-day post-transplant mortality as primary end-point between SCD versus ECD lungs after EVLP reconditioning according to the Toronto protocol using the XPS[™] device (XVivo Perfusion AB, Göteborg, Sweden) (104). The trial was started in May 2011 and is still recruiting patients. Preliminary results were updated at the 2014 annual ISHLT Meeting (105). The *Expand Lung Trial* (Clinical Trials.gov number NCT 01963780) is a prospective, international, multicenter, non-randomized, single-arm clinical study that examines the safety and effectiveness of the OCS[™] Lung perfusion device for recruiting, preserving, and assessing ECD lungs for transplantation (106). Preliminary results on the first cases were presented at the 2014 (107) and 2016 (108) annual ISHLT meetings. The trial is now completed and final results are awaited. Finally, the *Perfusix* trial (Clinical Trials.gov number NCT 02234128) in the US is looking at extending preservation and assessment time of donor lungs using the Toronto EVLP System[™]. Retrieved lungs will be shipped to a dedicated EVLP facility (109).

The routine or selective use of EVLP for controlled DCD lung evaluation is still controversial as good outcome has been reported without EVLP (110,111). The Toronto group compared the outcome after DCD lung transplantation with and without EVLP. Survival was comparable although EVLP cases had a shorter length of ventilation and hospital stay (112). The authors concluded that EVLP helped to safely increase their DCD lung

utilization. In our own experience, controlled DCD lung transplantation with a short (<30 min) total warm ischemic time results in excellent short- and long-term outcome without using EVLP (113). EVLP can be performed in case of any doubt of graft quality (112,114). For uncontrolled DCD, however, EVLP is indispensable to evaluate graft quality since there is no clinical information available before the arrival of the retrieval team. Also, the incidence of PGD grade 3 is expected to be higher after transplantation as previously reported by the Madrid group (115,116). Other groups have followed a similar policy of pre-transplant lung assessment from such donors (117,118).

MP of thoracic organs for repair and reconditioning

As discussed above, MP creates a “window” between procurement and transplantation during which functional performance and viability of the graft can be evaluated. If prolonged dynamic preservation (>12–24 hours) of thoracic organs proves to be feasible and safe, MP may offer a tool for *ex vivo* repair and quality improvement prior to transplantation, thereby not forgetting the importance of *in vivo* optimization prior to organ procurement (119). 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—damage. Thoracic organs may get injured by several hits during the whole transplantation process in the transition phase from donor to recipient. Altogether, organ damage may result from direct trauma, inflammation, infection, brain death and the agonal phase and warm ischemia in a DCD setting.

Once the organs are recovered from the deceased body, *ex situ* treatment during MP theoretically becomes possible (120,121). Intravascular perfusion providing oxygen and other metabolic substrates under physiological conditions appears to be the way forward to improve the viability of suboptimal grafts and may already be sufficient to recover intrinsic repair mechanisms. Additional specific treatments targeting different pathways to interfere with the organ have been suggested (100). The easiest strategy would be to deliver drugs directly to the organs by including them into the perfusion solution or by injecting active agents into the afferent tubing running to the vasculature of the graft. Theoretically, pharmacological interventions could be targeted according to the type of injury or even given in combination as a “cocktail” at intervals during MP:

anti-bacterial, anti-viral, and anti-fungal agents to treat infection (122,123), anti-inflammatory molecules to block pro-inflammatory responses (124-126), cytoprotective and anti-ischemic metabolic agents (127-129), agents initiating or enhancing ischemic postconditioning, vasodilating agents to improve perfusion of the microvasculature, fibrinolytic agents to dissolve microthrombi (130), dehydration of tissue with perfusate with high oncotic pressure, etc. An advantage of this isolated MP setting is that these drugs could be given at higher doses than *in vivo* since there is no risk to harm other organs. A restriction, however, may be that certain drugs cannot be metabolized in the 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, hemofiltration, or insertion of filters and membranes in the circuit may become necessary for removal of harmful and toxic waste products (blood clots, neutrophils, inflammatory cytokines). Finally, MP also offers the possibility to interfere at the genetic level by using viral vectors (131) or silencing RNA technology. The aforementioned organ repair strategies during MP are currently experimental and only very few clinical papers have been published so far. In the future, organ reconditioning hubs may appear to be an efficient method of delivering this service to all transplant centers (132).

Heart

Beside the series reporting on MP to evaluate the quality of DBD hearts (68) or to resuscitate DCD hearts (77,81), the authors are not aware of any clinical study or case report whereby an initially unacceptable cardiac allograft was first rehabilitated *ex situ* during MP prior to transplantation.

Research is ongoing to investigate the best conditions in terms of perfusate and active agents during MP of the heart (133,134).

Lung

Compared to other solid organs, 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, drugs or gases can be delivered to the pulmonary graft by instillation or inhalation (100). *Ex situ* administration of surfactant via lavage was demonstrated to improve graft function of acid-injured lungs in a porcine EVLP model (135). In a recent study by

our group, no beneficial effect of ventilation with the inert gas argon during EVLP could be demonstrated in a porcine model (136). Ventilation of the pulmonary allograft with an inhaled bronchodilator during EVLP improved lung graft function after transplantation in a canine model (137).

Debate continues about the best conditions for EVLP with regards to cellular versus acellular composition of the perfusate (138-141), the importance of left atrial pressure (138,142), positive versus negative pressure ventilation (143), the use of leucocyte (144) or cytokine filters (145,146) in the circuit, the oxygenation level of the perfusate (147), and the role of hemofiltration (148). Research is ongoing to identify clinical biomarkers in the perfusate such as cytokines (149), endothelial markers (150), adhesion molecules (151), metabolomics (152) and to investigate imaging techniques (153,154) before and after EVLP that may be predictive of graft function after transplantation.

Few clinical case reports on successful transplantation of rehabilitated pulmonary grafts have been published so far. Sanchez *et al.* reported successful outcome after transplantation of a salvaged lung that was first reconditioned during MP for neurogenic pulmonary edema (155). Both the Zurich group (156) and the Toronto (157) reported on a case of pulmonary thrombolysis during MP followed by successful lung transplantation.

MP of thoracic organs to downregulate allograft immunity

Beside *ex vivo* repair and quality improvement, MP may offer a tool for “immunoregulation” of thoracic organs in order to protect them from responses related to the innate (ischemia-reperfusion injury) and adaptive (acute and chronic rejection) immunity developing in the recipient.

Heart

To the authors’ knowledge, no studies have been reported so far that investigated the role of MP to improve immune tolerance of the heart in the recipient after transplantation.

Lung

Two interesting studies exploring the impact of donor passenger antigen-presenting leucocytes on immunogenicity were reported recently. In a first study by Stone *et al.*, passenger leukocyte migration from donor lungs into the

recipient and the effects of donor leukocyte depletion during EVLP were investigated in a gender-mismatched porcine lung transplant model. Donor leukocyte transfer into the recipient and migration to recipient lymph nodes were markedly reduced in the group receiving EVLP lungs compared to a control group transplanted with standard lungs. In addition, recipient T cell infiltration of the donor lung was significantly diminished in the study group (158). In another study by Noda *et al.*, the role of circulating leukocytes in lungs and their relationship with circulating pro-inflammatory cytokines on ischemia-reperfusion injury was investigated in a rat lung transplant model (159). Lung function was significantly better in lung grafts on EVLP with a leucocyte filter in the circuit compared to a control group without. Interleukin-6 levels in pulmonary grafts and in perfusate were also significantly lower after EVLP in the study group. After transplantation, graft function was better and inflammatory response was less. From both studies, it appears (I) that passenger donor leucocytes play an important role in the innate and adaptive alloreactivity; and (II) that EVLP including a leucocyte filter in the circuit may be a therapeutic approach to reduce the immune response. Interestingly, in a retrospective analysis of the clinical experience with EVLP in Toronto, the authors reported that EVLP assessed lungs from brain-dead donors (DBD) developed less chronic rejection (101).

Another interesting approach to condition the graft may be the use of mesenchymal stem or stromal cells (MSCs) during MP (160). These cells 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, trans-differentiation, 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 immunoregulatory properties (interaction with the innate immunity and suppression of T-cell responses) and their ability to secrete soluble factors or microspheres (161). These properties of MSCs make them particularly interesting for use as a cellular therapy in solid-organ transplantation (162,163). MP offers a unique platform to selectively administer these MSCs directly into the donor organ overcoming issues of homing, trafficking and safety. Especially allogeneic MSCs are attractive due to their wide availability at the time of organ harvest. Autologous stem

cells might be of less interest to modulate acute donor organ injury during MP since the isolation steps take longer time intervals and can never be planned in advance when a potential donor becomes available.

In lung, much research was done by the group at the University of California at San Francisco (164,165). Several basic anti-inflammatory and anti-bacterial properties have been attributed to MSCs and their extracellular vesicles that may be beneficial to restore epithelial and endothelial permeability in patients with acute lung injury from trauma or sepsis comparable to donor lung injury after reperfusion (166).

The spectrum of possible MSCs-based therapies for donor lung injury includes both targeted intrapulmonary and intravascular administration during EVLP. This was investigated in two recent studies using a porcine EVLP model. In a first study on the optimal route and dose for administering MSCs reported by the Toronto group, intravascular administration of 50×10^6 MSCs was associated with significant and sustained retention of MSCs in lung parenchyma, whereas intra-bronchial administration was not. Intravascular administration of 150×10^6 MSCs was the optimal tolerated dose and was associated with increased concentrations of human vascular endothelial growth factor in lung biopsies and decreased concentrations of pig interleukin-8 in the perfusate during 12 hours of EVLP (167). In another study by the Leuven group, the immunoregulatory capacities of multipotent adult progenitor cells (MAPC) on PGD were investigated in a lung injury model when administered via the airways. Although physiologic parameters during 6 hours EVLP were not different between both study groups, neutrophilia in bronchoalveolar lavage (BAL) fluid was significantly reduced in the MAPC group compared to controls, accompanied with a significant decrease in TNF- α , IL-1 β and IFN- γ in the BAL (168).

Many issues related to MSCs therapy in transplantation (cell type, timing and route of administration, trafficking and homing) remain unresolved and warrant further research. MP provides a unique tool to deliver these therapies directly to thoracic organs while they remain physiologically perfused and metabolically active in an isolated circuit.

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 post-transplant thereby reducing the need for immunosuppression and its attending complications (toxicity, infection and malignancies) (169-171).

Conclusions

MP of thoracic organs has gained much attention during the last decade. So far, clinical research has been focused on MP for prolonged preservation of standard hearts and lungs as a tool to increase the cross-clamp time and to reduce early graft dysfunction in the recipient. In addition, MP of heart has become an essential tool to resuscitate and to evaluate the quality of the cardiac allograft from a DCD. The largest clinical experience with MP of lung was reported as a tool to evaluate functional performance of questionable lungs prior to transplantation. MP prior to transplanting lungs from a controlled DCD with a short total warm ischemic time is probably not essential, but MP is indispensable to evaluate lung graft quality from an uncontrolled DCD. Clinical experience with MP to repair and treat previously unacceptable lungs is limited to case reports. The use of MP as an immunoregulating tool for inducing better tolerance of the thoracic organ in the recipient after transplantation is exciting and hopeful.

Further research is needed to establish the best method and preservation solutions for long-term MP. The jury is still out if MP will have an impact on long-term survival in addition to the current promising short-term results. The outcome of ongoing clinical studies is awaited to delimit the proper indications before MP will become a routine method in our daily transplant practice.

Acknowledgements

D Van Raemdonck was a senior clinical investigator supported by a grant from the Research Fund for Flanders (FWO-Vlaanderen). A Neyrinck, F Rega, and S Rex have been supported individually by a grant from the Clinical Research Fund by the University Hospitals Leuven. S Rex has been supported by a grant from the Department of Cardiovascular Sciences of the KU Leuven University, and by an unrestricted research grant from AirLiquide Belgium and France.

Footnote

Conflicts of Interest: D Van Raemdonck was a principal investigator for the Inspire Trial and for the Expand Trial; both trials were sponsored by Transmedics® (Andover, MA, USA). F Rega receives research grants from Medtronic and is a consultant to Atricure Europe (Amsterdam, the Netherlands) and LivaNova Belgium (Zaventem, Belgium). The other

authors have no conflicts of interest to declare.

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Cite this article as: Van Raemdonck D, Rega F, Rex S, Neyrinck A. Machine perfusion of thoracic organs. *J Thorac Dis* 2018;10(Suppl 8):S910-S923. doi: 10.21037/jtd.2018.02.85