

Machine perfusion in transplantation

SUMMARY

The preservation of donor organs through machine perfusion (MP) creates new opportunities in transplantation medicine for the benefit of patients. In view of the organ shortage and the increasing number of marginal organs, there is a need to establish MP in Germany in order to improve organ utilization and therapeutic outcomes. In kidney transplantation, the use of MP can significantly improve 1-year survival. MP also offers advantages in liver, heart, and

lung transplantation. As recommended by the Organ Donation Committee (KfO, Kommission für Organspende) of the German Transplantation Society (DTG, Deutsche Transplantationsgesellschaft) as well as the Permanent Committee on Organ Transplantation (StäKO, Ständige Kommission Organtransplantation), its use should be initially adopted in standard care in the form of hypothermic machine perfusion in kidney transplantation and then be further extended.

In clinical trials, machine perfusion has proven to be an effective and safe procedure that can reduce damage to donor organs and lead to improved posttransplantation outcomes. In addition, it permits a better assessment of organ quality, supports the decision making whether to accept or reject an organ for transplantation, and ultimately increases the number of transplantable organs. Available procedures include hypothermic machine perfusion (HMP), normothermic machine perfusion (NMP), and controlled oxygenated rewarming (COR) after standard cold storage. Perfusion may be initiated at the transplantation center subsequent to cold storage or may start immediately following organ procurement using portable devices. Internationally, machine perfusion is already being successfully used in clinical practice. In consideration of the shortage of donors and organs, rapid establishment in Germany would offer considerable advantages.

According to a written recommendation issued by the KfO and addressed to the German Organ Procurement Organization (DSO, Deutsche Stiftung Organtransplantation) from November 17, 2016:

“On the basis of the positive clinical experience with machine perfusion in kidney transplantation worldwide and the current ... groundbreaking results of pre-

clinical and clinical trials, there are currently no medical reasons precluding the introduction of machine perfusion of kidney allografts before transplantation. From the extensive positive clinical experience in other countries it rather follows that this progress must no longer be withheld from our patients in Germany. (...) Therefore, we recommend

- the nationwide introduction of machine perfusion ... for organ preservation as a clinical standard in kidney transplantation as soon as possible
- for this purpose, ... established systems such as the LifePort Kidney Transporter (1.0, 1.1) from Organ Recovery Systems (ORS) should be used
- in conjunction with ... the proven Custodiol® solution for preservation.”

In June 2017, StäKO also recommended considering the introduction of HMP in kidney transplantation as part of standard care. Ensuring the appropriate funding will be essential for future use in clinical routine. In terms of organisation and logistics, the implementation can be managed by the German Organ Procurement Organisation (DSO). Nationwide introduction can ensure that the full benefit of machine perfusion for the affected patients is realised and that more patients receive the urgently needed organ whilst promoting the further development of this innovative method. In the future, for instance, interventions in the preservation phase could facilitate the development of new therapies and improvement of organ quality.

The pathophysiological and experimental principles of machine perfusion as well as the benefits, methods, and current evidence for the different organs are described in detail below.

EXPERT MEETING

“Machine perfusion in transplantation” on September 28, 2017 in Frankfurt am Main, Germany.

Chair: Prof. Dr. Björn Nashan, Hamburg. Speakers: Prof. Dr. Friedhelm Beyersdorf, Freiburg, Thomas Biet, Frankfurt, Prof. Dr. Thomas Minor, Essen, Prof. Dr. Andreas Paul, Essen, Prof. Dr. Ursula Rauen, Essen, Dr. Vinzent Spetzler, Hamburg, Prof. Dr. Gregor Warnecke, Hanover

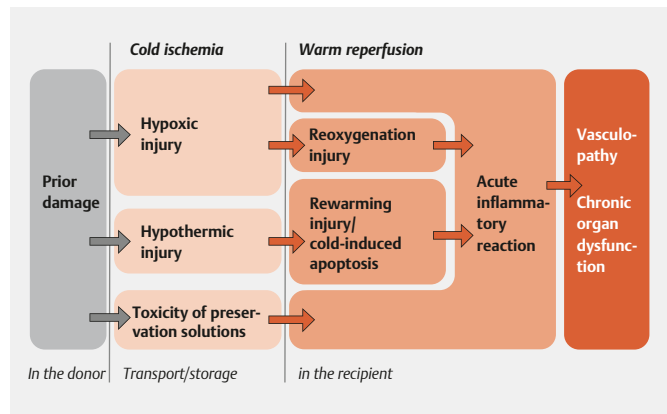
Preservation injury

The leading cause of cell damage following organ procurement is ischemia, particularly ischemic hypoxia, which leads to energy shortage and subsequent cell damage. This hypoxic cell injury occurs mainly from impairment of the cellular ion homeostasis, particularly of sodium and calcium ions [1, 2]. During reperfusion mitochondrial changes occurring in the hypoxic phase also lead to reoxygenation injury and a mitochondrial permeability transition, early elements of reperfusion injury [1–3]. Hypothermia slows the hypoxia-induced cell injury processes but on the other hand it leads to cell injury itself [1, 4]. The hypothermic injury is mediated by an intracellular increase in redox-active iron ions, followed by the increased formation of reactive oxygen species (ROS) and mitochondrial permeability transition [1, 4, 5]. Membrane-permeable iron chelators reduce hypothermic injury as well as its aggravation during rewarming [1, 5, 6]. The toxicity of preservation solutions may cause further injury [7]. During reperfusion with blood, the above-mentioned cell damage or the compounds released in the process lead to an (acute) inflammatory response, which increases tissue damage and can negatively impact the long-term course [3, 8]. ▶ **Fig. 1** displays the various elements of donor organ damage which develops in a clinical situation through cold ischemia and warm reperfusion on the basis of pre-existing organ damage.

O₂ administration (oxygenation) during cold storage reduces hypoxic and reoxygenation injury, but it can enhance ROS-dependent cold injury processes. Particularly under cold, aerobic conditions, effective protection against iron-dependent cold injury therefore appears necessary. A modified preservation solution (Custodiol-N*) demonstrated advantages over HTK solution and KPS-1 solution in experimental models [10, 11], and was also used clinically for reconditioning [12]. In addition to limiting the preservation injury, machine perfusion may in the future offer the opportunity for therapeutic interventions in the preservation phase, which are still to be investigated in detail, and could potentially improve organ quality.

Ischemia as well as hypothermia and some preservation solutions cause donor organ damage. Organ preservation must strive to minimize the injury (or to counteract it by specific measures) and ideally to create during this phase the necessary conditions for cellular repair processes.

* Currently in clinical testing



▶ **Fig. 1** Tissue injury by cold ischemia and warm reperfusion; mod. acc. to [1, 9].

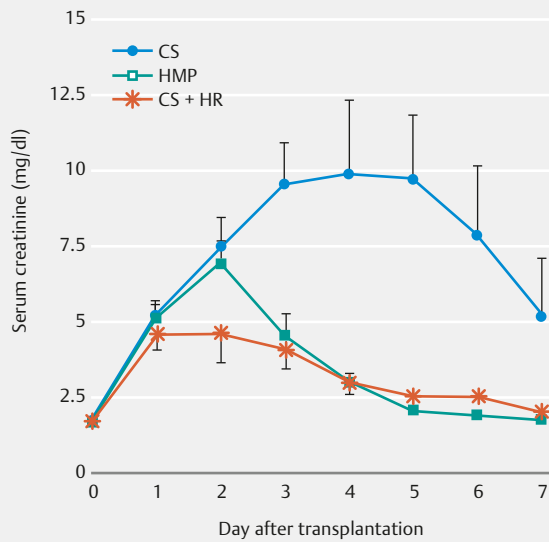
Experimental approaches

Experimental approaches examine the influence of various parameters, such as oxygenation, temperature, and the duration of perfusion in the different organ perfusion and reconditioning techniques. They generate evidence regarding the optimal clinical procedure and potential clinical benefits.

In organ cold storage, oxygen is the first substrate to be lacking. As a result, acidosis and energy deficiency develop. Administering 100% O₂ as part of the HMP of rat livers almost completely eliminated hypoxic lactate rise and bile production was good. With 20% O₂, the effect on bile production was minor [13]; oxygenation during HMP did not improve renal function of ideal organs (porcine kidneys), but significantly fewer ROS formed during reperfusion [14].

Surface endothelial molecules of the rat liver such as ICAM1 (intercellular adhesion molecule 1) and MHC class II (major histocompatibility complex) were more strongly expressed following cold storage (CS) than following HMP [15]. Inflammatory upregulation in the rat liver 12 hours after transplantation was less pronounced following HMP than after NMP [16]. With regard to renal function, in a porcine model a short HMP (hypothermic reconditioning) for 2 hours following 19 hours of CS was as effective as longer HMP for 21 hours [14] (▶ **Fig. 2**).

Both in healthy and in ischemically injured porcine livers, NMP was associated with advantages over cold storage in terms of survival following transplantation as well as organ function (transaminases) and structure (histology). The advantages were particularly pronounced in livers with prior injury and in those from non-heart-beating donors (NHBD) [17].



► **Fig. 2** Autograft function after transplantation in porcine kidneys preserved by 21 h of cold storage (CS), 21 h of hypothermic machine perfusion (HMP), or by 19 h of CS + 2 h of hypothermic reconditioning (HR) (CS + HR); mod. acc. to [14].

In cold stored kidney and liver allografts, the rewarming injury must be considered: Porcine livers exhibited significantly better bile flow after (slow) controlled oxygenated rewarming (COR) than after CS or HMP [18].

In animal models, even hybrid solutions, i.e. transport in CS followed by in-house reconditioning using machine perfusion, demonstrated advantages over cold storage alone. During the transition from cold storage to reperfusion, a slow temperature increase (COR) was favourable.

Kidney transplantation

HMP in kidney transplantation was first described in 1968 [19]. Because of organ shortage and the growing percentage of extended criteria donors (ECD) [20], there is renewed interest in machine perfusion. Currently, several portable systems are available for HMP



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► **Fig. 3** Systems for machine perfusion of the kidney: a) LifePort Kidney Transporter, b) Kidney Assist, c) Kidney Assist Device (Organ Assist, Netherlands), d) Waves.

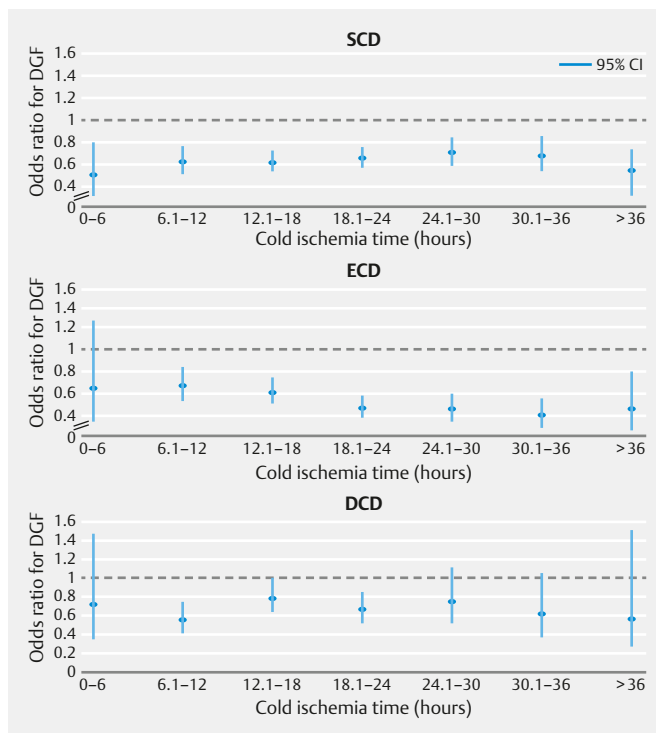
of the kidney (► **Fig. 3**): LifePort Kidney Transporter (Organ Recovery Systems, USA), Kidney Assist (Organ Assist, Netherlands), Waves (Waters Medical Systems, USA), and Airdrive (QRS Healthcare, Netherlands). They differ in various parameters, such as temperature, flow (pulsatile, continuous), systolic pressure, oxygenation, and monitoring functions.

In the largest international, randomized controlled clinical trial of HMP in kidney transplantation completed to date [21], the outcomes for 672 transplanted kidneys were analyzed. From each of 336 consecutive deceased donors, one kidney was transplanted following HMP with the LifePort Kidney Transporter and the other following cold storage. The primary endpoint of delayed graft function (DGF) with need for dialysis occurred in 70 patients receiving an HMP-treated organ and in 89 patients receiving a cold stored organ (adjusted odds ratio [AOR] 0.57; $p = 0.01$). HMP was moreover associated with lower serum creatinine levels in the first 14 days after transplantation (median AUC of serum creatinine 1456 vs. 1787; $p = 0.01$).

One-year graft survival was significantly higher with HMP than following cold storage (94 vs. 90%; $p = 0.04$). This large study demonstrated for the first time that HMP of the kidney is associated with improved graft survival.

Two retrospective analyses of registry data confirmed these results: In the analysis of the Scientific Renal Transplant Registry [22], which included over 10,000 patients who received an organ following pulsatile HMP, DGF occurred less frequently in both recipients of DBD (donation after brain death) and DCD (donation after circulatory death) kidneys than following CS. The AOR for DBD kidneys was 0.56 (95% CI 0.53–0.6), for DCD kidneys 0.7 (95% CI 0.61–0.8). A recent analysis [23] showed that pulsatile perfusion is associated with a lower risk of DGF independent of cold ischemia time and donor type (► **Fig. 4**). The analysis also revealed the growing importance of machine perfusion: in 2011, it was used in 25% of standard criteria donors (SCD), more than 50% of ECD, and more than 70% of DCD (US data).

NMP is technically far more complex and currently has the additional disadvantage of no portable system being available. In kidney transplantation, it is therefore only used at the recipient center. A clinical trial [24] compared NMP (1 hour of perfusion at the end of preservation, average temperature 34.6 °C, $n = 18$) and



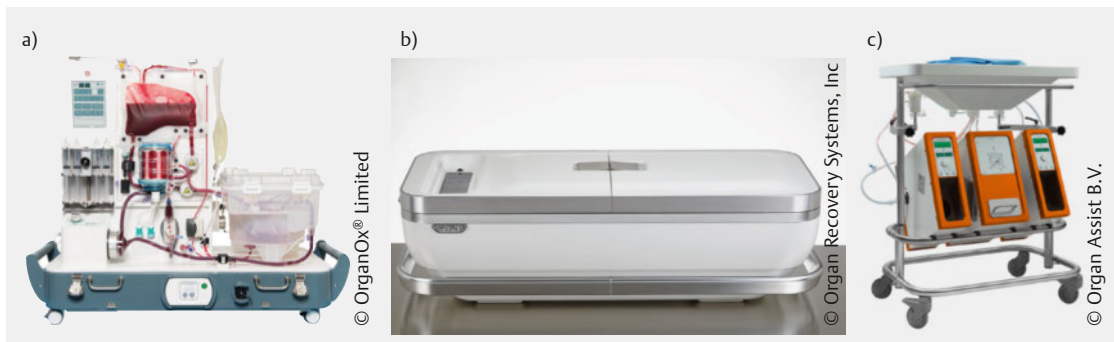
► **Fig. 4** Adjusted odds ratios for delayed graft function (DGF) after pulsatile perfusion vs. cold storage by cold ischemia time for SCD, ECD, and DCD transplants; mod. acc. to [23].

CS ($n = 47$). DGF occurred less frequently following NMP (5.6 vs. 36.2%; $p = 0.014$), but a significantly larger number of these patients were transplanted before dialysis. A multicenter, randomized trial [25] with 400 patients receiving a DCD kidney is still in progress; in one arm, the organ is reconstituted using 1 hour of NMP following cold storage.

► **Table 1** Criteria for ECD liver, marginal or high-risk liver grafts; mod. acc. to [27, 28].

- Donor age >65 years
- High BMI, steatosis
- Intensive care unit stay >7 days, hypernatremia
- >3-fold normal values of AST, ALT, γ GT, bilirubin
- Hepatitis B/C positive
- Split liver transplantation
- Malignant tumor (in case history)
- Alcohol and/or drug abuse
- Sepsis, meningitis
- Cold ischemia time >8/12 h

AST = aspartate aminotransferase, ALT = alanine aminotransferase, BMI = Body Mass Index, γ GT = γ -glutamyl transferase

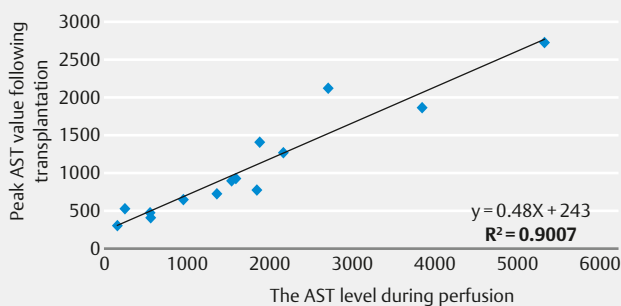


► **Fig. 5** Systems for machine perfusion of the liver: a) OrganOx® metra™ (OrganOx Ltd, United Kingdom; transportable, NMP); b) LifePort® Liver Transporter (Organ Recovery System, USA; transportable, HMP); c) Liver Assist (Organ Assist, Netherlands; mobile, HMP, COR and NMP).

In kidney transplantation HMP is associated with a reduced risk of DGF and higher 1-year graft survival, and it is already clinically established. NMP is still in the clinical trial phase.

Liver transplantation

The organ donation situation in Germany has led to an increased interest in machine perfusion in liver transplantation as well: There is an organ shortage, along with a high proportion of expanded criteria donors (► **Table 1**). Clinically, ECD livers are associated with the risk of primary delayed function (PDF) and primary nonfunction (PNF) and hence graft loss. Particularly in organs of marginal quality, it is difficult to assess this risk in advance, which frequently means that the organ offer is declined for transplantation. This is where machine perfusion offers two major advantages: Machine perfusion permits the evaluation of



► **Fig. 6** Correlation of AST values during perfusion with AST peak values after liver transplantation ($p < 0.001$); mod. acc. to [12]. AST= aspartate aminotransferase, R^2 = coefficient of determination (square of correlation coefficient).

future organ function as well as reconditioning of the organ before transplantation [26].

► **Fig. 5** shows systems for liver perfusion.

The first clinical case series on HMP in liver transplantation [29] compared HMP and CS, with 20 patients in each group. Early allograft dysfunction (EAD) was less common following HMP at 5 vs. 25% ($p = 0.08$). Graft and patient survival of both groups were equal. For ECD livers, the results following HMP ($n = 31$) vs. CS ($n = 30$) were as follows [30]: EAD (19 vs. 30%), PNF (3 vs. 7%) and 1-year patient survival (84 vs. 80%) were numerically, but not significantly, better following HMP. However, with HMP, significantly fewer patients suffered biliary complications (13 vs. 43%; $p = 0.001$), resulting in a significantly shorter hospital stay (13.6 vs. 20.1 days; $p = 0.001$).

Normothermic ex-vivo machine perfusion (NMP) with OrganOx® metra™ (► **Fig. 5a**) was first examined in a matched pairs analysis [31]. Twenty patients underwent liver transplantation following NMP, the control group of 40 patients following CS. The median peak AST value in the first 7 days was significantly lower in the NMP group (417 vs. 902 U/l; $p = 0.03$). EAD (15 vs. 23%), 30-day graft survival, and 6-month patient survival (100 vs. 97.5% in both cases) were comparable.

In a preliminary analysis of an ongoing randomized controlled trial comparing continuous NMP and CS, results were shown for DBD and DCD livers [32]. Early graft function, measured using the surrogate parameters of peak AST value and EAD, was better in the NMP group than in the CS group despite longer ischemia time and longer preservation time.

The studies also showed that the AST and ALT levels in the perfusion medium correlate with postoperative values and are predictive for EAD. The use of machine

perfusion thus permits the evaluation of future organ function [12, 29] (► Fig. 6).

The data on HMP in liver transplantation show good outcomes. Continuous NMP is associated with a lower incidence of EAD. The preservation time can be extended with NMP. More organs are transplantable following machine perfusion, which could considerably improve the situation in liver transplantation.

Lung transplantation

In lung transplantation machine perfusion is always performed under ventilation. Since ventilation at low temperatures may harm the organ, normothermic machine perfusion (at 35–37 °C) is used, either following 4–6 hours of cold storage (using a stationary device) or soon after organ procurement (with a portable device). Portable ex-vivo lung perfusion (EVLP) has the advantage of significantly shortened ischemia time, immediate lung reconstitution, and continuous monitoring of pulmonary function. Available systems include XVIVO (XVIVO Perfusion AB, Sweden), VIVOLINE (Vivoline Medical AB, Sweden), Lung Assist (Organ Assist, Netherlands), and the portable OCSTM Lung System (TransMedics, Inc., USA). Steen's solution or OCS (Organ Care System) lung solution are used as perfusion solutions.



► Fig. 7 Organ Care System OCS Lung (TransMedics Inc., USA), portable system for machine perfusion of the lung; OCS Heart and OCS Liver are also available.

The organ shortage also puts a greater focus on the use of ECD organs in lung transplantation. However, this increases the risk of PGD (primary graft dysfunction), which is associated with higher 90-day and 1-year mortality as well as more frequent chronic rejection (BOS, bronchiolitis obliterans syndrome) [33, 34].

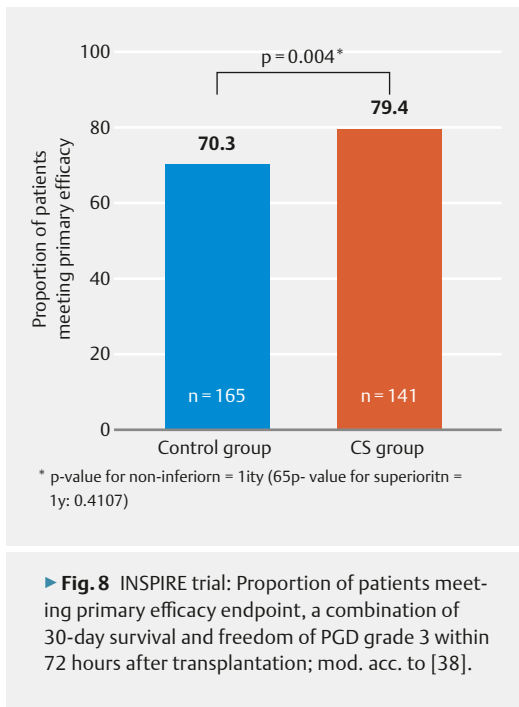
ECD lungs treated with EVLP were compared to a control group (116 SCD lungs without EVLP) [35]. After 4 hours of perfusion, 20 of 23 lungs were transplantable. The incidence of PGD 72 hours after transplantation was numerically, but not significantly, lower in the EVLP group compared to the control group (15 vs. 30% in the control group, $p = 0.11$). No significant differences were found in the secondary endpoints and no severe adverse events related to EVLP occurred.

In the multicenter, non-randomized, controlled NOVEL trial [36], 42 of 76 ECD lungs were transplantable (utilization rate of 55%) following EVLP (after CS, stationary, 3–6 hours). The survival rate was comparable to the control group (SCD organs) after 30 days (41 vs. 42%) and 1 year (38 vs. 40%).

After a pilot study [37] with 12 patients confirmed that portable EVLP (OCS system with Steen's solution) can be safely performed and all lungs were successfully implanted in high-risk recipients, the multicenter, prospective, randomized INSPIRE trial was initiated [38] (► Fig. 7). Non-inferiority of NMP was demonstrated for the primary efficacy endpoint, a combination of 30-day survival and freedom from PGD grade 3 in the first 72 hours after transplantation (► Fig. 8). The primary safety endpoint was also met: Lung graft-related serious adverse events occurred at comparable rates in both arms (37 in the OCS arm and 48 in the control arm, $p = 0.02$ for non-inferiority).

In the EXPAND trial [39], the use of NMP in ECD grafts using the OCS Lung System is currently being evaluated.

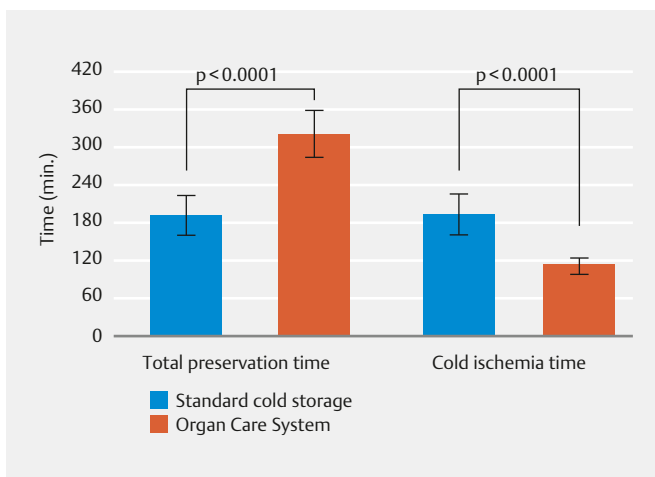
Preservation of lung grafts with NMP (EVLP) is a safe procedure. In particular, it can be used to evaluate ECD lungs and recruit them for transplantation. The indication-specific use of NMP in lung transplantation is urgently needed to increase the proportion of transplantable organs and make transplantation available to more patients.



► **Fig. 8** INSPIRE trial: Proportion of patients meeting primary efficacy endpoint, a combination of 30-day survival and freedom of PGD grade 3 within 72 hours after transplantation; mod. acc. to [38].

Heart transplantation

In heart transplantation, ischemia time plays a particularly prominent role. If the ischemic time is > 3 hours, the risk of early graft failure (EGF) rises sharply [40]. Beyond 3 hours, each additional 5 minutes of total ischemia time equates to one more day in ICU [41]. Since, moreover, survival rate and time of heart transplant patients depend on the ischemia time [42], reducing the latter is of great prognostic import.



► **Fig. 9** Significantly longer total preservation time and significantly shorter cold ischemia time with Organ Care System (OCS preservation) vs. cold storage; mod. acc. to [43].

NMP enables the preservation of donor allografts in a warm, heart-beating condition and therefore offers essential advantages:

- Significant reduction of ischemia time
- “Quality control” of the donor organ before transplantation, increasing recipient safety
- Optional treatment of the donor heart during transport.

In heart transplantation, NMP is typically performed using the portable Organ Care System (OCS, TransMedics Inc., USA). The multicenter, prospective, randomized PROCEED-II trial [43] compared the clinical outcomes of 67 patients following OCS preservation and 63 patients following CS. Total preservation time was longer with OCS, but crucially cold ischemia time was shorter (► **Fig. 9**). The short-term clinical outcomes were similar: The primary endpoint, patient and graft survival after 30 days, was 94 % with OCS and 97 % with CS ($p = 0.45$). Cardiac-related serious adverse events occurred in 13 % of patients in the OCS group and in 14 % in the CS group.

In the United Kingdom, OCS is predominantly used if long ischemia time is expected or if a high-risk recipient, for instance a patient with prior heart surgery or LVAD (left ventricular assist device) is to undergo transplantation. A monocentric trial [44] investigated the use of OCS in heart transplantation with a high-risk donor or recipient profile. Of 30 hearts preserved with the OCS, 26 (86.7 %) were transplantable. Only one patient (3.8 %) died after transplantation, and in 92 %, graft function was preserved (median follow-up of 257 days).

OCS preservation was also compared with CS in recipients with LVAD ($n = 15$ per arm) [45]. OCS was associated with a shorter cold ischemia time (89 min vs. 204 min), and patients required mechanical circulatory support significantly less frequently (26.7 vs. 66.7 %; $p = 0.021$). Of particular note: Following perfusion with OCS, 30-day survival was significantly higher, at 100 vs. 73.3 % ($p = 0.03$).

In heart transplantation, cold ischemia time can be considerably reduced using ex vivo organ perfusion or NMP. NMP permits treating the donor organ during transport as well as performing quality control before implantation. It is a safe procedure offering results that are at least equivalent to those of cold storage. In addition, organs which would previously be declined can be transplanted. It can also support successful heart transplantation in high-risk patients.

Organizational and financial aspects

Establishing machine perfusion in Germany is an additional aspect in organ procurement, preservation, and transport, and it requires close coordination between procuring hospitals, procuring surgeons, and transplantation centers. In general, the coordination and funding of organ transportation is a fundamental responsibility of the DSO, this principally also applies to the transport of perfusion machines. If machine perfusion is only started at the transplantation center, it is the responsibility of the center. In detail, coordination by the DSO as part of the overall process would include: national logistics management of the machines (potentially also their provision, depending on the funding model) and the consumables required, transport of the machines to the donor hospitals, transport with the organs to the transplantation centers, collection at the transplantation centers, as well as maintenance. GPS tracking could facilitate the timely communication between all involved parties. An initial logistical test was successfully conducted in 2015.

In order to implement machine perfusion it is crucial that there is a medical need and funding is secured. Machine perfusion should be first introduced for kidney transplantation. According to initial calculations, the annual cost of nationwide implementation in kidney transplantation is EUR 3–4 million (as of 2015), which would need to be included in the DSO budget. Therefore, an important step towards implementation is an agreement on funding between the statutory health insurance funds (“GKV”) and the DSO as soon as it has been decided to establish machine perfusion.

In the German Operation and Procedure Code (OPS) version 2018 [46], OPS codes were added for organ perfusion (to be coded centrally under 5–939, ▶ **Fig. 10**). Coding the performed procedures, including machine perfusion, in the OPS code creates the transparency required as a basis for financial accounting and quality assurance. In the longer term, calculations for center-specific or indication-specific funding could be made from these data. This is, for instance, conceivable for thoracic organs.

Machine perfusion has its individual aspects for each organ – but is needed for all. Machine perfusion is already widely used in international clinical practice, and on the strength of the available evidence and its associated advantages, it should be established in Germany as well. It can increase the number of transplantable organs, offering patients a chance of survival, particularly in view of the existing organ shortage.

The standard procedure for **kidney transplantation** is HMP, which achieves significantly improved 1-year survival and should therefore be used nationwide as widely as possible.

The evidence for **liver transplantation** also shows that machine perfusion is effective and safe and offers advantages over cold storage. In general, all procedures have been used successfully; therefore initially, the current state of research should be analyzed. On this basis, a consensus should be reached regarding the best suited procedure.

5-50 Liver Surgery

5-504 Liver transplantation

Excluding: Allogeneic hepatocyte transplantation (8–862 et seq.)

Note: In case of ABO-incompatible transplantation, code 5-930.21 must also be specified. The preservation method for allografts must be coded separately (5–939 et seq.)

5-555 Kidney transplantation

Note: In case of ABO-incompatible transplantation, the code 5-930.21 must also be specified. The preservation method for allografts must be coded separately (5–939 et seq.)

5-939 Preservation method for organs for transplantation/Note:

The respective type of organ transplantation must be coded separately.

Organ preservation may be normothermic or hypothermic. Ex-vivo perfusion may be pulsatile or non-pulsatile.

5-939.0 Organ preservation, without use of ex vivo perfusio

5-939.1 Organ preservation, with use of continuous ex vivo perfusion and without monitoring of organ function

5-939.2 Organ preservation, with use of continuous ex vivo perfusion and with monitoring of organ function

5-939.x Other

▶ **Fig. 10** OPS codes (Operation and Procedure Code) for coding organ perfusion in OPS, version 2018; mod. acc. to [46].

In **heart and lung transplantation**, machine perfusion is already being used by some centers for certain indications and is currently funded by the centers themselves. In the future, indication-specific or center-specific reimbursement is conceivable for thoracic organs (e. g., through “innovative diagnosis and treatment methods” [NUBs]). Particularly for thoracic organs, the small number of transplantations limits the opportunity to prove superiority in randomized controlled trials due to insufficient sample size. The results of the available clinical trials sufficiently prove that NMP is safe and at least equivalent to cold storage and that the number of transplantable organs can be increased. For certain indications, it has shown advantages over cold storage.

There is no doubt that the future belongs to machine perfusion. Increasing clinical experience and additional targeted trials can further optimize its application. The objective must be to facilitate its use in clinical routine as soon as possible by providing appropriate logistical support and funding so that its full potential can be utilised for the benefit of patients. When a technical solution for making transplantation available to more patients on the waiting list becomes available, as in the case for machine perfusion, it is imperative to take that opportunity.

Literature

- [1] Rauen U, de Groot H. New insights into the cellular and molecular mechanisms of cold storage injury. *J Investig Med* 2004; 52: 299–309
- [2] Halestrap AP. Mitochondria and reperfusion injury of the heart – a holey death but not beyond salvation. *J Bioenerg Biomembr* 2009; 41: 113–121
- [3] de Groot H, Rauen U. Ischemia-reperfusion injury: processes in pathogenetic networks: a review. *Transplant Proc* 2007; 39: 481–484
- [4] Rauen U, Petrat F, Li T et al. Hypothermia injury/cold-induced apoptosis – evidence of an increase in chelatable iron causing oxidative injury in spite of low O₂/H₂O formation. *FASEB J* 2000; 14: 1953–1964
- [5] Rauen U, Kerkweg U, Weisheit D et al. Cold-induced apoptosis of hepatocytes: mitochondrial permeability transition triggered by nonmitochondrial chelatable iron. *Free Radic Biol Med* 2003; 35: 1664–1678
- [6] Huang H, He Z, Roberts LJ 2nd et al. Deferoxamine reduces cold-ischemic renal injury in a syngeneic kidney transplant model. *Am J Transplant* 2003; 3: 1531–1537
- [7] Rauen U, de Groot H. Inherent toxicity of organ preservation solutions to cultured hepatocytes. *Cryobiology* 2008; 56: 88–92
- [8] Land WG. The role of postischemic reperfusion injury and other nonantigen-dependent inflammatory pathways in transplantation. *Transplantation* 2005; 79: 505–514
- [9] Rauen U, Paul A. „Transportschäden“ von Transplantaten. Zellulärer Energiemangel, „ranzige“ Membranen und zerstörte Zellkraftwerke – und was man dagegen tun kann. *Unikate (Universität Duisburg-Essen)* 2013; 44: 92–104
- [10] Stegemann J, Hirner A, Rauen U, Minor T. Use of a new modified HTK solution for machine preservation of marginal liver grafts. *J Surg Res* 2010; 160: 155–162
- [11] Minor T, Paul A, Efferz P et al. Kidney transplantation after oxygenated machine perfusion preservation with Custodiol-N solution. *Transpl Int* 2015; 28: 1102–1108
- [12] Hoyer DP, Paul A, Minor T. Prediction of hepatocellular preservation injury immediately before human liver transplantation by controlled oxygenated rewarming. *Transplant Direct* 2016; 3: e122
- [13] Lürer B, Koetting M, Efferz P et al. Role of oxygen during hypothermic machine perfusion preservation of the liver. *Transpl Int* 2010; 23: 944–950
- [14] Gallinat A, Paul A, Efferz P et al. Hypothermic reconditioning of porcine kidney grafts by short-term preimplantation machine perfusion. *Transplantation* 2012; 93: 787–793
- [15] Minor T, Manekeller S, Sioutis M et al. Endoplasmic and vascular surface activation during organ preservation: refining upon the benefits of machine perfusion. *Am J Transplant* 2006; 6: 1355–1366
- [16] Schlegel A, Kron P, Graf R et al. Warm vs. cold perfusion techniques to rescue rodent liver grafts. *J Hepatol* 2014; 61: 1267–1275
- [17] Brockmann J, Reddy S, Coussios C et al. Normothermic perfusion: a new paradigm for organ preservation. *Ann Surg* 2009; 250: 1–6
- [18] Minor T, Efferz P, Fox M et al. Controlled oxygenated rewarming of cold stored liver grafts by thermally graduated machine perfusion prior to reperfusion. *Am J Transplant* 2013; 13: 1450–1460
- [19] Belzer FO, Ashby BS, Gulyassy PF et al. Successful seventeen-hour preservation and transplantation of human-cadaver kidney. *N Engl J Med* 1968; 278: 608–610
- [20] OPTN/SRTR 2016 Annual Data Report Kidney. <https://unos.org/about/annual-report/2016-annual-report/> (Besucht: 25.2.2018)
- [21] Moers C, Smits JM, Maathuis MH et al. Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med* 2009; 360: 7–19
- [22] Lodhi SA, Lamb KE, Uddin I et al. Pulsatile pump decreases risk of delayed graft function in kidneys donated after cardiac death. *Am J Transplant* 2012; 12: 2774–2780
- [23] Gill J, Dong J, Eng M et al. Pulsatile Perfusion Reduces the Risk of Delayed Graft Function in Deceased Donor Kidney Transplants, Irrespective of Donor Type and Cold Ischemic Time. *Transplantation* 2014; 97: 668–674

- [24] Nicholson ML, Hosgood SA. Renal transplantation after ex vivo normothermic perfusion: the first clinical study. *Am J Transplant* 2013; 13: 1246–1252
- [25] Hosgood SA, Saeb-Parsy K, Wilson C et al. Protocol of a randomised controlled, open-label trial of ex vivo normothermic perfusion vs. static cold storage in donation after circulatory death renal transplantation. *BMJ Open* 2017; 7: e012237
- [26] Van Raemdonck D, Neyrinck A, Rega F et al. Machine perfusion in organ transplantation: a tool for ex-vivo graft conditioning with mesenchymal stem cells? *Curr Opin Organ Transplant* 2013; 18: 24–33
- [27] Blok JJ, Braat AE, Adam R et al. European Liver Intestine Transplant Association Eurotransplant Liver Intestine Advisory Committee; Eurotransplant Liver Intestine Advisory Committee. Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. *Liver Transpl* 2012; 18: 112–119
- [28] Braat AE, Blok JJ, Putter H et al. European Liver and Intestine Transplant Association (ELITA) and Eurotransplant Liver Intestine Advisory Committee (ELIAC). The Eurotransplant donor risk index in liver transplantation: ET-DRI. *Am J Transplant* 2012; 12: 2789–2796
- [29] Guarrera JV, Henry SD, Samstein B et al. Hypothermic machine preservation in human liver transplantation: the first clinical series. *Am J Transplant* 2010; 10: 372–381
- [30] Guarrera JV, Henry SD, Samstein B et al. Hypothermic machine preservation facilitates successful transplantation of “orphan” extended criteria donor livers. *Am J Transplant* 2015; 15: 161–169
- [31] Ravikumar R, Jassem W, Mergental H et al. Liver Transplantation After Ex Vivo Normothermic Machine Preservation: A Phase 1 (First-in-Man) Clinical Trial. *Am J Transplant* 2016; 16: 1779–1787
- [32] Nasralla D, Friend P. Outcomes from a Multinational Randomised Controlled Trial Comparing Normothermic Machine Perfusion with Static Cold Storage in Human Liver Transplantation. *ILTS 2017 (O-9)*
- [33] Whitson BA, Prekker ME, Herrington CS et al. Primary Graft Dysfunction and long-term Pulmonary Function After Lung Transplantation. *J Heart Lung Transplant* 2007; 26: 1004–1011
- [34] Diamond JM, Lee JC, Kawut SM et al. Lung Transplant Outcomes Group. Clinical risk factors for primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med* 2013; 187: 527–534
- [35] Cypel M, Yeung JC, Liu M et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. *N Engl J Med* 2011; 364: 1431–1440
- [36] Sanchez PG, Davis RD, D’Ovidio F et al. The NOVEL Lung Trial One-Year Outcomes. *J Heart Lung Transplant* 2014; 33: S71–S72 [www.jhltonline.org/article/S1053-2498\(14\)00240-X/fulltext](http://www.jhltonline.org/article/S1053-2498(14)00240-X/fulltext) (Besucht: 7.12.2017)
- [37] Warnecke G, Moradiellos J, Tudorache I et al. Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lung before bilateral transplantation: a pilot study of 12 patients. *Lancet* 2012; 380: 1851–1858
- [38] Warnecke G, Van Raemdonck D, Smith MA et al. Normothermic ex-vivo preservation with the portable Organ Care System Lung device for bilateral lung transplantation (INSPIRE): a randomised, open-label, non-inferiority, phase 3 study *Lancet Respir Med* 2018 Published Online April 9, 2018
- [39] Loor G, Warnecke G, Smith M et al. The OCS Lung EXPAND International Trial Interim Results. *J Heart Lung Transplant* 2016; 35: S68–S69
- [40] Lund LH, Edwards LB, Kucheryavaya AY et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Heart Transplantation Report–2015; Focus Theme: Early Graft Failure. *J Heart Lung Transplant* 2015; 34: 1244–1254
- [41] Rylski B, Berchtold-Herz M, Olschewski M et al. Reducing the ischemic time of donor hearts will decrease morbidity and costs of cardiac transplantations. *Interact Cardiovasc Thorac Surg* 2010; 10: 945–947
- [42] Goldsmith KA, Demiris N, Gooi JH et al. Life-years gained by reducing donor heart ischemic times. *Transplantation* 2009; 87: 243–248
- [43] Ardehali A, Esmailian F, Deng M et al. PROCEED II trial investigators. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. *Lancet* 2015; 385: 2577–2584
- [44] García Sáez D, Zych B, Sabashnikov A et al. Evaluation of the organ care system in heart transplantation with an adverse donor/recipient profile. *Ann Thorac Surg* 2014; 98: 2099–2105
- [45] García Sáez D, Zych B, Mohite PN et al. LVAD Bridging to Heart Transplantation With Ex Vivo Allograft Preservation Shows Significantly Improved: Outcomes: A New Standard of Care? *Journal of Heart and Lung Transplantation* 2015; 34 (Suppl): S95
- [46] OPS-Code 2018. www.dimdi.de/static/de/klassi/ops/kodesuche/onlinefassungen/opshtml2018/ (Besucht: 25.2.2018)