Machine perfusion in abdominal organ transplantation: Current use in the Netherlands

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Abstract

Scarcity of donor organs and the increment in patients awaiting a transplant increased the use of organs from expanded criteria donors or donation after circulatory death. Due to the suboptimal outcomes of these donor organs, there is an increased interest in better preservation methods, such as ex vivo machine perfusion or abdominal regional perfusion to improve outcomes. This state-of-the-art review aims to discuss the available types of perfusion techniques, its potential benefits and the available evidence in kidney, liver and pancreas transplantation. Additionally, translational steps from animal models towards clinical studies will be described, as well as its application to clinical practice, with the focus on the Netherlands. Despite the lack of evidence from randomized controlled trials, currently available data suggest especially beneficial effects of normothermic regional perfusion on biliary complications and ischemic cholangiopathy after liver transplantation. For ex vivo machine perfusion in kidney transplantation, hypothermic machine perfusion has proven to be beneficial over static cold storage in a randomized controlled trial, while normothermic machine perfusion is currently under investigation. For ex vivo machine perfusion in liver transplantation, normothermic machine perfusion has proven to reduce discard rates and early allograft dysfunction. In response to clinical studies, hypothermic machine perfusion for deceased donor kidneys has already been implemented as standard of care in the Netherlands.
INTRODUCTION

The major obstacle in organ transplantation is the imbalance between demand and supply of suitable donor organs. In the Eurotransplant region, a total number of 14773 patients were on the active organ waiting list on 1 January 2018, while only a number of 7918 patients received a transplant from either a living or deceased donor[1,2]. Consequently, approximately 50% of the waitlisted patients did not receive an organ transplant and either remained waitlisted, became unfit for transplant or died while being waitlisted. This accentuates the urgent need to tackle organ shortage. One solution to address this problem is the increased use of suboptimal organs, such as organs from expanded criteria donors (ECD) or donation after circulatory death (DCD). However, DCD donation is not performed in several countries, mainly because of legal restrictions. Besides, ECD and DCD organs have impaired clinical outcomes based on their poor tolerance to ischemia-reperfusion injury[3]. The outcomes of DCD kidney, liver and pancreas transplantation in comparison to donation after brain death (DBD) have been previously described and are summarized in Table 1. DCD kidneys are more prone to delayed graft function (DGF) and primary non function (PNF), while graft survival is similar[4,5]. DCD livers have more frequent biliary complications, such as ischemic cholangiopathy, with corresponding inferior graft and patient survival rates[6]. For pancreas transplants from a DCD donor, the odds of graft thrombosis are 1.67 times higher compared to DBD pancreas transplants[7]. Therefore, increasing the quality of those suboptimal organs is of paramount importance.

The best strategy for organ preservation in an era where the use of ECD and DCD organs continues to increase is still a major topic of discussion. During the past decade, there has been renewed interest in the use of machine perfusion instead of static cold storage (SCS) as a preservation technique. The concept behind machine perfusion is dynamic reconditioning and repair through restoring blood flow of the donor organ by connecting it to a pump with the possibility to add oxygen and therapeutic agents. Besides this benefit of organ repair that may lead to improved organ quality, machine perfusion has the promising possibility to make initially discarded organs transplantable[8-10]. The second benefit is the possibility of pre-transplantation viability assessment of the donor organ “while on the pump” to prevent unnecessary transplantations with an organ that will never function in the recipient[11,12]. The third benefit is the possibility to extend the time until transplantation, for example in order to provide daytime surgery and to allow time for transfer of the donor organ to the recipient hospital.

The Netherlands has a continuously growing abdominal transplantation program, as shown in Figures 1-3. In the past years, there has been an extensive increase in the DCD program. For kidney transplantation, the amount of DCD organs transplanted within the deceased donor organ transplant program was 39% in 2009, and this increased up to 55% in 2018[13,14]. For the DCD liver transplant program, this was 23% in 2009, which increased up to 39% in 2018[13,14]. For pancreas transplantation, the amount of DCD grafts used increased from 0% in 2009 to 42% in 2018[13,14]. So far, many experimental studies show the potential beneficial effects of machine perfusion in various types of organ transplantation. Many clinical studies have been recently published, translating the earlier experimental work into the clinic. Standard of care concerning organ preservation in the Netherlands already changed in response to earlier published clinical studies. With this state-of-the-art review, we aim to describe the history of machine perfusion in abdominal organ transplantation, as well as the rationale behind different types of perfusion, its potential benefits and its current use in the Netherlands as one of the pioneering countries with regard to translating
Table 1 Outcomes from meta-analyses or large studies comparing donation after circulatory death to donation after brain death outcomes in abdominal organ transplantation

|                         | DCD                  | DBD                  | P value     |
|-------------------------|----------------------|----------------------|-------------|
| **Kidney**[^a^]         |                      |                      |             |
| PNF (%)                 | 3.2                  | 2.6                  | 0.06        |
| DGF (%)                 | 48.5                 | 24.9                 | < 0.001[^a^]|
| 1-yr eGFR[^1^]          | 47.4 (35.6-61.2)     | 48.7 (37.3-61.1)     | 0.69        |
| 5-yr graft survival (%) | 76.8                 | 78.1                 | 0.60        |
| 5-yr patient survival (%) | 86.5                | 89.4                 | < 0.001[^a^]|
| **Liver[^c^]**          |                      |                      |             |
| Biliary complications (%) | 26                   | 16                   | < 0.001[^a^]|
| Ischemic cholangiopathy (%) | 16                   | 3                    | < 0.001[^a^]|
| 3-yr graft survival (%) | 73                   | 74                   | 0.01[^c^]   |
| 3-yr patient survival (%) | 82                   | 88                   | 0.04[^c^]   |
| **Pancreas[^d^]**       |                      |                      |             |
| Graft survival          | HR 0.98 (0.74-1.31)  | Reference value      | 0.92        |
| Patient survival        | HR 1.31 (0.62-2.78)  | Reference value      | 0.47        |
| Graft thrombosis        | OR 1.67 (1.04-2.67)  | Reference value      | 0.006[^c^]  |

[^1^]: Data is presented as median and interquartile range.
[^a^]: Statistically significant. DBD: Donation after brain death; DCD: Donation after circulatory death; DGF: Delayed graft function; eGFR: Estimated glomerular filtration rate; HR: Hazard ratio; OR: Odds ratio; PNF: Primary non function.

Machine perfusion in standard of care.

**HISTORY**

In the 1960s, machine perfusion became part of clinical practice with its main goal to extend preservation time for cross-matching and transportation of the organ[^15^]. However, in the late 1980s, Folkert Belzer and James Southard[^16^-^18^] developed the University of Wisconsin solution, which improved preservation time significantly when compared to the commonly used EuroCollins solution. Because SCS was a much cheaper and simpler manner of organ preservation without compromising donor organ quality, the interest in machine perfusion decreased[^19,20^].

In the Netherlands, important research steps concerning preservation techniques started with the usage of hypothermic machine perfusion (HMP) on donor kidneys. In 1978, a study was published showing that kidneys severely damaged by ischemia were found to have a higher percentage of immediate function when preserved with HMP compared to SCS[^21^]. Five years later, an article was published wherein the clinical outcomes of 75 kidneys transplanted after HMP were compared to 2686 kidneys transplanted after SCS in the Eurotransplant region. Creatinine clearance, PNF and DGF did not differ significantly[^22^]. These studies raised the hypothesis that only kidneys that have been subjected to prolonged periods of warm ischemia might benefit from HMP in an era of mainly standard criteria donors[^22,23^]. Later on, when organ shortage forced the more frequent use of ECD donors, various clinical studies were published suggesting that HMP could result in better short-term outcomes, especially in those ECD donors[^24^-^26^]. This led to the Machine Perfusion Trial, a randomized controlled trial (RCT) executed in the Eurotransplant region with the University Medical Center Groningen as principal investigator. The results, published in 2009, showed that HMP was associated with a reduced risk of DGF and improved graft survival in the 1st year after transplantation[^27^].

Research concerning normothermic machine perfusion (NMP) started in the early eighties. Two important animal studies concerning normothermic ex vivo perfusion were carried out, also with the goal to allow longer preservation times[^28,29^]. The first study was carried out in a dog auto transplant model. Twenty-four dogs were assigned to one of four intervention groups, differing in total preservation time (96 h or 144 h) and HMP alone or interrupted with 4 h of normothermic perfusion on the animal. For both preservation times, the two groups (2 and 4) who also underwent normothermic perfusion had significantly higher creatinine clearance than the HMP only group. This suggested that interruption of HMP by normothermic perfusion
improves results, which was later also confirmed in a rabbit study\cite{28,29}. In 2002, Brasile \textit{et al}\cite{30} investigated graft function in a canine auto-transplant model using kidneys with a prolonged warm ischemia time. He found that all kidneys after NMP had direct function, in contrast to kidneys transplanted after HMP or SCS. NMP became of larger interest due the increased use of ECD organs. The hypothesis was that those organs require careful reconditioning and repair, which may not be optimal in a hypothermic environment where metabolism is suppressed. Together with the growth in the amount of ECD donors, NMP gained interest, with the first in human kidney transplantation after NMP in 2011\cite{31}. Currently, only small clinical studies have been performed concerning NMP. An RCT comparing NMP to SCS in DCD kidney transplantation is currently ongoing in the United Kingdom, with the expected results to be published in 2020/2021 (ISRCTN15821205).

**ABDOMINAL REGIONAL PERFUSION**

\textbf{Rationale of ARP}

The development of ARP took place in Spain among uncontrolled DCD donors in a successful attempt to increase the donor pool. Abdominal regional perfusion (ARP), depending on the temperature also called normothermic regional perfusion (NRP) or hypothermic regional perfusion (HRP), is an \textit{in-vivo} dynamic preservation technique that is performed while the organs are still in the donor. After withdrawal of life-sustaining support and circulatory arrest with a following period of no-touch, the donor is transferred to the operating room. In the non-ARP situation, the super-rapid recovery (SRR) technique is used to access all potential donor organs and cannulate the aorta to start cold flushing as quickly as possible, which ends the first warm ischemia time. Then, the donor organs will be inspected on eligibility for transplantation and the organs will be retrieved. In the ARP situation, cannulas will be placed in either the abdominal aorta and caval vein or in the femoral artery and femoral vein. The cannulas are connected to an extracorporeal membrane oxygenation-like device, which uses a pump to recover donor venous blood, oxygenate it and add substrates. Subsequently, the oxygenated blood will be returned...
Figure 2 Number of liver transplantations in the Netherlands per year.

to the subdiaphragmatic aorta. The thoracic aorta is clamped to prevent autoresuscitation, which has been shown to be an effective method\(^\text{[32]}\). Depending on the law regulations per country, cannulation into the femoral vein and artery is to be performed before cardiac arrest to reduce further warm ischemia time. However, in most countries in Europe, no pre-mortem interventions are allowed by law. Besides the hypothesis that ARP improves organ quality by minimizing warm ischemia time, there are more benefits of this technique. Because the organs are still in the donor body, this creates a more physiological environment for the organs than connected to a pump outside of the body. Also, it is possible to perform viability assessment in the donor. As a third reason, ARP modifies an urgent procedure into an elective organ recovery procedure, which could reduce organ damage and organ losses due to surgical events. Also, NRP is supposed to be more cost-effective than NMP because multiple organs are resuscitated through one procedure.

**Clinical outcomes after ARP**

**Kidney:** Literature concerning kidney transplantation after ARP is scarce, and most of the literature focuses on NRP instead of HRP. Table 2 contains the core clinical studies describing clinical outcomes of kidney transplantation after ARP. A few studies also compared ARP outcomes to either DBD outcomes or outcomes after retrieval with the SRR technique. Farney et al\(^\text{[33]}\) compared 25 kidney transplants after HRP to kidney transplants retrieved with the SRR technique. They concluded that kidney transplants after HRP had lower rates of DGF and shorter hospitalization. Lee et al\(^\text{[34]}\) investigated 31 kidney transplant outcomes after HRP and compared those to outcomes after DBD or living donor kidney transplant. He showed a higher rate of DGF in comparison to DBD but similar incidence of acute rejection and 5-year graft and patient survival rates. Valero et al\(^\text{[35]}\) described in situ perfusion with HRP and NRP. They concluded a lower incidence of DGF and PNF after NRP when compared to in situ perfusion or total body cooling\(^\text{[36]}\). Miñambres et al\(^\text{[37]}\) investigated 37 kidney transplantations after NRP and compared their clinical outcomes to DBD kidney transplant outcomes. They showed that graft survival was similar to graft survival of a DBD kidney with 5% PNF and 27% DGF\(^\text{[38]}\). Also, Magliocca et al\(^\text{[39]}\) compared the outcomes after NRP with DBD outcomes. They concluded no statistically significant differences in DGF, PNF and rejection. In conclusion, HRP could possibly reduce the incidence of DGF and hospitalization duration after kidney transplantation when compared with the SRR
technique. Graft survival after NRP resembles DBD graft survival, which has been shown to be similar to DCD kidney graft survival using the SRR technique[5]. However, NRP may reduce the incidence of DGF and PNF.

Liver: Only incidental cases have been described concerning liver transplantation after HRP[33,38,39]. The outcomes of those transplants are not discussed separately. The results from liver transplantation after NRP are summarized in Table 3. One study by Hessheimer et al[40] compared 95 controlled DCD liver transplant outcomes after NRP to the outcomes of liver transplantation after retrieval with the SRR technique. They showed a significant decrease in favor of the NRP group for graft loss (NRP: 12%, SRR: 24%), biliary complications (NRP: 8%, SRR: 31%), ischemic cholangiopathy (NRP: 2%, SRR: 13%) and retransplantation rates (NRP: 5%, SRR: 9%). Miñambres et al[36] and Fondevila et al[41] described NRP-DCD liver transplant outcomes in comparison to DBD outcomes. They concluded that graft and patient survival after NRP-DCD liver transplantation is comparable to DBD liver transplantation. In conclusion, NRP decreases the incidence of biliary complications, ischemic cholangiopathy, graft loss and retransplantation rates when compared to the SRR technique. Graft and patient survival rates are comparable to those after DBD liver transplantation.

Pancreas: There is scarcity of studies about pancreas transplant outcomes after the use of ARP. Two aforementioned studies for kidney and liver transplant outcomes after NRP also described some anecdotal cases of pancreas transplant outcomes after NRP. Oniscu et al[42] described two combined kidney-pancreas transplants and one islet transplant after NRP, all with primary function. Miñambres et al[36] described one combined kidney-pancreas transplant after NRP, also with primary function. Butler et al[43] described two pancreas transplants after 120 minutes of NRP, both with primary function.

Current practice in the Netherlands
In October 2018, the first liver transplantation after NRP was successfully performed in Erasmus Medical Center, Rotterdam, The Netherlands. This transplantation was part of the NRP project, a collaboration between organ retrieval team West (consisting of Leiden University Medical Center and Erasmus Medical Center) and subsidized by
Fourteen kidneys were transplanted in 11 recipients. Therefore, clinical outcomes are calculated in the 11 recipients.

Table 2  Clinical studies published about kidney transplant outcomes after abdominal regional perfusion

| Study                  | n  | DCD type | Rejection, % | DGF, % | PNF, % | Graft survival, % | Patient survival, % |
|------------------------|----|----------|-------------|--------|--------|------------------|---------------------|
|                         |    |          |             |        |        |                  |                     |
| HRP                    |    |          |             |        |        |                  |                     |
| Valero et al[43], 2000 | 8  | II       | -           | 75     | 0      | -                | -                   |
| Koyama et al[45], 2002 | 46 | III/IV   | -           | 87     | 6.5    | 88.3             | -                   |
| Lee et al[39], 2005    | 31 | II/III/IV| 35.5        | 41.9   | 0      | 100 - 88.4       | 100 - 100           |
| Sánchez-Fructuoso et al[40], 2006 | 320 | I/II    | 4.4        | 60.9   | 4.4    | 87.4 - 82.1          | 95 - 90             |
| Farney et al[41], 2011 | 25 | III      | 16          | 21     | 0      | 88 - 88           | -                   |
|                         |    |          |             |        |        |                  |                     |
| NRP                    |    |          |             |        |        |                  |                     |
| Valero et al[43], 2000 | 8  | II       | -           | 12.5   | 0      | -                | -                   |
| Magliocca et al[39], 2005 | 24 | III      | 0           | 8.3    | 0      | -                | -                   |
| Reznik et al[44], 2011 | 20 | II       | 10          | 70     | 10     | -                | -                   |
| Hessheimer et al[38], 2015 | 158 | II    | -           | 65     | 9      | 88               | -                   |
| Oniscu et al[36], 2014 | 32 | III      | -           | 40     | 6      | 87.5 - 96.8      | -                   |
| Butler et al[40], 2014 | 14 | III      | -           | 18.2   | 9.1    | -                | -                   |
| Rojas-Peña et al[35], 2014 | 29 | III      | -           | 31     | 3.5    | -                | -                   |
| Demiselle et al[37], 2016 | 19 | II       | -           | 53     | 5.3    | 94               | -                   |
| Mihámbres et al[38], 2017 | 37 | III      | -           | 27     | 5      | 91.8             | -                   |

1Fourteen kidneys were transplanted in 11 recipients. Therefore, clinical outcomes are calculated in the 11 recipients;
2Outcomes were only mentioned from their own center. DCD: Donation after circulatory death; DGF: Delayed graft function; HRP: Hypothermic regional perfusion; NRP: Normothermic regional perfusion; PNF: Primary non function.

The Ministry of Health, Welfare and Sport. The goal of this project is to increase the number of transplantable organs and to improve organ quality. NRP can be carried out in every potential DCD donor, but within the Dutch project it is currently only carried out within DCD type III donors. Different protocols exist in the literature for pump parameters during NRP. In the Dutch NRP project, a pump flow of 2-3 L per minute is pursued with a temperature starting at 33 °C that is slowly increased to 37 °C. For oxygen, a mix between air and oxygen is used with the aim to reach a PaO2 of 110-150 mmHg. Loss of volume is supplemented by adding red blood cells concentrate, albumin and Ringer’s lactate. The circuit is primed with heparin to prevent the blood from clotting. Bicarbonate is added in case of acidosis to keep the pH within a physiologic range. For the liver, the following issues are considered to determine suitability for transplantation: (1) Aspartate aminotransferase (ALAT) less than 4 times the upper limit at the end of NRP; (2) ALAT reaches its plateau phase between first and second hour; (3) Lactate below 5 mmol/L at the end of NRP; (4) Glucose doubles at the end of NRP in comparison to the start of NRP and (5) Glucose is above 10 mmol/L at the end of NRP. After 2 years, results of this project will be analyzed to see whether this technique should be implemented nationwide in the Netherlands.

**EX VIVO MACHINE PERFUSION**

**Rationale of ex vivo machine perfusion**

Whereas the goal of preserving an organ on SCS is slowing down deterioration of the donor organ, the goal of ex vivo machine perfusion is sustaining organ viability, organ repair and organ preconditioning. This all takes place in the period between procurement and transplantation of the donor organ with the main goal to optimize outcomes of the graft when transplanted in the recipient. In comparison to ARP, ex vivo machine perfusion takes place after organ retrieval, and it may also be used in case of a DBD donor organ. During ex vivo machine perfusion, the donor organ is connected to an often pressure-controlled perfusion device that pumps perfusate solution continuously through the organ vasculature. Ex vivo machine perfusion can be performed at different temperatures: Hypothermia, normothermia and subnormothermia. In comparison to SCS, HMP may be a more efficient way of cooling of the donor organ while metabolic and toxic waste products are washed out.
During NMP, the temperature is within physiologic range, which increases metabolic activity and allows for active repair and reconditioning. Therefore, NMP may be more beneficial in donor organs that require reconditioning, such as ECD organs.

As normothermia leads to metabolic activity, an oxygenated perfusate is essential. Therefore, a blood-based perfusate is often used, containing washed and leukocyte-depleted red blood cells. Another option is to use an acellular perfusion solution containing a hemoglobin-based oxygen carrier. No studies have investigated which of the two is preferred. In practice, the blood-based perfusate is more popular, probably because this option is less expensive. For NMP, additional substances are added to provide the best circumstances for active repair. The composition and number of additives in the perfusate differs. In general, antibiotics, vitamins, prostaglandins, bicarbonate and heparin to prevent thrombosis are added. Currently, there is no evidence favoring one perfusate solution over another. For HMP, kidney perfusion solution-1 is used as the standard solution for clinical machine perfusion, without additional substances.

### Clinical outcomes of ex vivo machine perfusion

**Kidney:** In abdominal organ transplantation, most clinical research concerning ex vivo machine perfusion is carried out in kidney transplants. Currently ongoing RCTs or clinical trials involving discarded kidneys are mentioned in Table 4. There is conclusive evidence for the benefits of HMP over SCS. In 2009, the aforementioned Machine Perfusion Trial of the Consortium for Organ Preservation in Europe (COPE) was published, showing that non oxygenated HMP offers a graft survival benefit in comparison to SCS and a decrease in DGF in all deceased donor kidneys[27]. Subsequently, the COPE-COMPARE trial was initiated, investigating the possible beneficial effects of adding oxygen to HMP. The preliminary results as presented on the American Transplant Conference 2019 showed that oxygenated HMP shows a significant benefit for graft survival and 1-year graft function, which is possibly mediated through a lower risk of BPAR[44]. The results from other studies, as mentioned in the Table 4, have not been published yet.

In contrast to HMP, clinical studies concerning the use of NMP in kidney transplantation are still in its infancy. This is possibly because NMP may be more hazardous because potential failure of NMP leads to harmful additional warm ischemia time. In 2011, the first human kidney transplant after ex vivo NMP was performed in the United Kingdom with good post-transplant outcomes[31]. Currently, there is no evidence from RCTs yet that NMP may be beneficial. However, experimental studies have already shown the benefits of NMP over HMP[44]. A phase II, multi-center RCT is currently recruiting to assess the efficacy of 1 h ex vivo NMP compared to SCS only in DCD III and IV kidney transplantation (ISRCTN15821205). However, this RCT does not answer the question whether the addition of NMP has beneficial effects in comparison to HMP only. Another study from the Cambridge group is assessing the use of NMP in discarded kidneys, with the primary aim to make them transplantable.

### Table 3 Clinical studies published about liver transplant outcomes after normothermic regional perfusion

| Study                  | n | DCD type | Rejection, % | BC, % | IC, % | PNF, % | Graft survival, % | Patient survival, % |
|------------------------|---|----------|--------------|-------|-------|--------|--------------------|---------------------|
| Otero et al[36], 2004  | 14| II       | 22           | -     | 28    | 28     | 43                 | 71                  |
| Fodevila et al[37], 2007| 10| II       | -            | 10    | -     | 10     | 50                 | 70                  |
| Jimenez-Galanes et al[40], 2009 | 20| II       | -            | -     | 5     | 10     | 80                 | 85                  |
| Fodevila et al[37], 2012| 34| II       | -            | 12    | 8     | 4.3    | -                  | -                   |
| Oisco et al[41], 2014  | 11| III      | -            | 18.2  | 0     | 9.1    | 87.5               | 96.8                |
| Butler et al[42], 2014 | 3 | III      | -            | 0     | -     | -      | -                  | -                   |
| Rojas-Peña et al[43], 2014| 13| III      | -            | 14.3  | 14.3  | -      | 85.7               | -                   |
| Hessheimer et al[44], 2015| 42| II       | -            | -     | 10    | -      | 73                 | -                   |
| De Carls et al[45], 2016| 7 | II/III   | 14.3         | 14.3  | 0     | 0      | -                  | -                   |
| Miñambres et al[46], 2017| 11| III      | -            | 0     | 0     | 9.1    | 90.9               | -                   |
| Hessheimer et al[47], 2019| 95| III      | -            | 8     | 2     | 2      | 88                 | 93                  |

BC: Biliary complications; DCD: Donation after circulatory death; IC: Ischemic cholangiopathy; NRP: Normothermic regional perfusion; PNF: Primary non function.

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- **Clinical outcomes of ex vivo machine perfusion**

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Liver: Currently, there are many ongoing clinical trials for liver ex vivo machine perfusion. Table 5 summarizes all ongoing RCTs and non-randomized trials in discarded livers. Oxygenated HMP, better known as HOPE in the liver transplantation field, is currently under investigation together with RCTs investigating dual hypothermic oxygenated machine perfusion (DHOPE). The results from these RCTs are expected to follow in 2020. A case control study from the Groningen group in 10 patients found a higher graft survival, a two-fold lower peak ALAT and bilirubin in livers treated with DHOPE.

There is conclusive evidence for NMP over SCS in donor livers. In 2018, a RCT among all deceased liver donors was published comparing SCS to NMP with a minimal duration of 4 h. This study showed a 49.4% reduced peak ASAT during the first 7 d post-transplant in both DCD and DBD livers. Early allograft dysfunction was 74% lower than in the SCS arm. Discord rates were higher in the SCS group (24.1% vs 11.7%). However, there were no differences in biliary complications, ischemic cholangiopathy, incidence of PNF or graft and patient survival at 1 year. A recently published study in discarded livers combined the use of DHOPE with recently published study in discarded livers combined the use of DHOPE with

Pancreas: Machine perfusion of pancreas grafts is still in its infancy because of lower incidence of pancreas transplants. Besides, machine perfusion may increase edema of the pancreas due to its low-flow state. The use of machine perfusion in the pancreas is currently still in the pre-clinical experimental phase. Studies in the earlier years have favored SCS over HMP in preservation failure and post-transplant survival rates. However, in more recent studies, results have been superior in machine perfusion. No large data are yet available concerning the use of machine perfusion in pancreas transplantation.

### Table 4 Currently ongoing clinical trials concerning ex vivo machine perfusion in kidney transplantation

| Name of study | Registration number | Design | PI | n | Primary outcome | Intervention | Included donors | Results |
|---------------|---------------------|--------|----|---|----------------|-------------|-----------------|--------|
| Unknown       | ISRCTN913152        | Non-randomized | Cambridge | 90 | Graft function | 1 h NMP | Discarded kidneys | November 2019 |
| COPE-POMP     | ISRCTN638525        | RCT    | COPE Essen | 262 | Graft survival 1 y | Short period HMP vs SCS only | ECD-DBD | July 2019 |
| COPE-COMPARE  | ISRCTN329679        | RCT    | COPE Leuven | 162 | Kidney graft function 1 y | HMP with oxygen vs HMP without oxygen | DCD III ↓ risk BPAR ↑ 1-y eGFR | Augustus 2018 |
| PIO           | NCT03031067         | Case control | Bologna | 20 | Graft function | 2 h HMP vs SCS | ECD-DBD | February 2018 |
| PREDICTION    | NCT0205950          | Case control | Bergamo | 60 | Kidney function | HMP vs SCS | ECD-DBD | Augustus 2018 |
| Unknown       | NCT03837197         | RCT    | Bologna | 260 | DGF | 2 h oxygenated HMP vs SCS | ECD-DBD | December 2021 |
| IMPULSION     | NCT0170910          | RCT    | Lyon | 162 | DGF | 6-8 h HMP vs SCS | ECD | August 2016 |
| Machine perfusion trial | ISRCTN838763 | RCT    | COPE Groningen | 654 | Non-oxygenated HMP vs SCS | DCD III and DBD | DCD III and IV | January 2021 |
| Unknown       | ISRCTN158212        | RCT    | Cambridge | 400 | DGF | 1 h pre-transplant NMP vs SCS | DCD III and IV | |

BPAR: Biopsy proven acute rejection; COPE: Consortium for Organ Preservation in Europe; DBD: Donation after brain death; DCD: Donation after circulatory death; DGF: Delayed graft function; ECD: Expanded criteria donor; eGFR: Estimated glomerular filtration rate; HMP: Hypothermic machine perfusion; HR: Hazard ratio; NMP: Normothermic machine perfusion; OR: Odds ratio; PI: Principal investigator; RCT: Randomized controlled trial; SCS: Static cold storage.
Table 5  Currently ongoing clinical trials concerning ex vivo machine perfusion in liver transplantation

| Name of study | Design | PI | n | Primary outcome | Intervention | Included donors | Results |
|---------------|--------|----|---|----------------|-------------|-----------------|---------|
| DHOPE DCD    | RCT    | Groningen | 156 | % NAS | 2 h end-ischemic DHOPE | DCD III | October 2019 |
| HOPE          | RCT    | Zurich   | 170 | Postoperative complications | 1-2 h HOPE | DBD | July 2019 |
| HOPE ECD-DBD | RCT    | Aachen  | 46  | Peak ALT | 1-2 h HOPE | ECD-DBD | June 2019 |
| DHOPE-COR-NMP| Non-randomized | Groningen | 16 | Graft survival | DHOPE, gradually rewarming, NMP | Discarded livers (DCD and DBD) | 11 livers transplanted 100% patient/graft survival, 9.1% ischemic cholangiopathy |
| PIO           | Case control | Bologna | 20 | Graft function | 2 h HOPE | ECD livers | February 2018 |
| VITTAL        | Non-randomized | Birmingham | 22 | Patient survival | 4 h NMP | Discarded livers (DCD and DBD) | March 2020 |
| Liver WP2     | RCT | Oxford COPE | 220 | Peak AST | Minimally 4 h NMP | All deceased donors | 49.4% ↓ peak AST[8] |
| CORNET        | RCT | Essen   | 40  | Peak AST | 1,5 h COR until 20 degrees (dual perfusion) | ECD | February 2021 |
| DHOPE         | Case control | Groningen | 10 | Graft survival 6 mo | At least 2 h DHOPE | DCD III | ↑ graft survival (P = 0.052), ↓ peak ALT (P = 0.006), ↓ bilirubin (P = 0.044) |
| Unknown       | RCT    | Bologna | 260 | Early allograft dysfunction | Minimally 1 hour of HOPE | ECD-DBD | December 2021 |

ALT: Alanine aminotransferase; AST: Aspartate transaminase; COR: Controlled oxygenated rewarming; COPE: Consortium for Organ Preservation in Europe; DBD: Donation after brain death; DCD: Donation after circulatory death; DHOPE: Dual hypothermic oxygenated perfusion; DCD: Donation after circulatory death; ECD: Expanded criteria donor; HOPE: Hypothermic oxygenated perfusion; NAS: Non-anastomotic strictures; NMP: Normothermic machine perfusion; PI: Principal investigator; RCT: Randomized controlled trial

Viability assessment

One of the benefits of machine perfusion is the possibility of viability assessment. However, rules concerning viability assessment are not set in stone. It still remains highly difficult, as often no highly predictive cut-offs of liver or kidney markers have been identified that could lead to either acceptance or rejection of the donor organ. Especially for HMP, viability assessment is largely unexplored.

Kidney:

For NMP, Hosgood et al[8] developed a quality assessment score based on macroscopic perfusion, renal blood flow and urine output during NMP. The total amount of urine produced during NMP has proven to be significantly less in kidneys deemed unsuitable for transplantation[8]. It is unknown whether parameters during perfusion, such as flow and intrarenal resistance, may predict post-transplant outcomes.

Liver:

For HOPE, flurometric analysis of released mitochondrial flavoproteins was shown to have a high predictive value of liver graft function after transplantation with an area under the curve of 0.926 for 90-day graft loss[53]. During NMP, liver viability can be assessed using a combination of transaminase release, glucose metabolism, lactate clearance and maintenance of acid-base balance[54]. Evaluation of bile pH may predict post-transplant biliary complications, such as ischemic cholangiopathy[54]. No correlation has been found for hepatic artery/portal vein resistance and hepatocellular damage[54]. Also, there was no difference in hepatic artery/portal vein resistance between non-transplanted livers and transplanted livers and transplanted and non-transplanted livers[54]. Liver enzymes, lactate and bile production has shown not to be sufficient for prediction of liver graft failure in the
recipient\(^{44}\). The following criteria have been described as being associated with successful transplantation of a normothermically perfused liver\(^{44}\): (1) Maximum bile pH > 7.5; (2) Bile glucose concentration ≤ 3 mmol/L or ≥ 10 mmol less than perfusate glucose; (3) Able to maintain perfusate pH > 7.2 without >30 mmol bicarbonate supplementation; (4) Falling glucose beyond 2 hours or perfusate glucose under 10 mmol/L which, on challenge with 2.5 g glucose, does subsequently fall; (5) Peak lactate fall ≥ 4.4 mmol/L per kilogram per hour; and (6) ALAT < 6000 iU/L at 2 h.

Current practice in the Netherlands

After publication of the results of the Machine Perfusion Trial in deceased donor kidneys, a committee was established in the Netherlands to implement this technique as standard of care. As a result, since January 2016, the Netherlands is the first country where HMP is standard of care for all deceased donor kidneys. Several studies, both experimental and clinical, are carried out in the Netherlands concerning the possible additional benefits of NMP in donor kidneys. In March 2018, the first kidney transplantation after NMP in the Netherlands was performed successfully in Erasmus Medical Center in Rotterdam. It was the start of a pilot study, the POSEIDON study, to assess the feasibility of kidney transplantation after NMP in the Eurotransplant Senior program. Because of the poor results of kidney transplantation in this program, the hypothesis was that those patients may benefit the most from an effort to improve organ quality by NMP\(^{45}\). The results from the NMP patients will be compared to a historical cohort of Eurotransplant Senior Program patients that have been treated with HMP. The study finished its inclusion, and the results are expected in the beginning of 2020. Furthermore, various experimental studies are currently carried out in discarded human kidneys and porcine kidneys concerning the best perfusion parameters to use when performing NMP. One of them is the PROPER study, a collaboration between Erasmus Medical Center, Leiden Medical Center and Groningen Medical Center, with the goal to improve discarded kidneys to make them transplantable. For liver ex vivo machine perfusion, the aforementioned DHOPE, DHOPE-DCD and DHOPE-COR-NMP studies are led by Groningen Medical Center. Various experimental studies on discarded livers or animal livers are currently carried out, and the results of those are about to follow.

CONCLUSION

Since the renewed interest in machine perfusion, major steps have been made by translating experimental research into clinical studies. For NRP, there is no evidence from RCTs yet. The currently available evidence suggests especially beneficial effects for improving outcomes of liver transplantation by reducing the incidence of biliary complications and ischemic cholangiopathy. For ex vivo machine perfusion in kidney transplantation, HMP has proven to be beneficial over SCS in an RCT, while NMP is currently under investigation. For ex vivo machine perfusion in liver transplantation, NMP has proven to reduce discard rates and early allograft dysfunction. Multiple RCTs, such as the DHOPE, are ongoing from which the results are awaited. In response to clinical studies, NRP and HMP for deceased donor kidneys have already been implemented as standard of care in the Netherlands.

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