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REVIEW

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REVIEW

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.

Key words: Machine perfusion; Review; Kidney transplantation; Liver transplantation; Pancreas transplantation

Core tip: Scarcity of donor organs and the increment in waitlisted patients increased the use of organs from expanded criteria donors or donation after circulatory death donors. Due to suboptimal outcomes of these organs, there is an increased interest in dynamic preservation, such as *ex vivo* machine perfusion or abdominal regional perfusion to

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improve outcomes. This review discusses perfusion types, 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 as focus the Netherlands.

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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[56]			
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[57]			
Biliary complications (%)	26	16	< 0.001[a]
Ischemic cholangiopathy (%)	16	3	< 0.001[a]
3-yr graft survival (%)	73	74	0.01[a]
3-yr patient survival (%)	82	88	0.04[a]
Pancreas[7]			
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[a]

[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

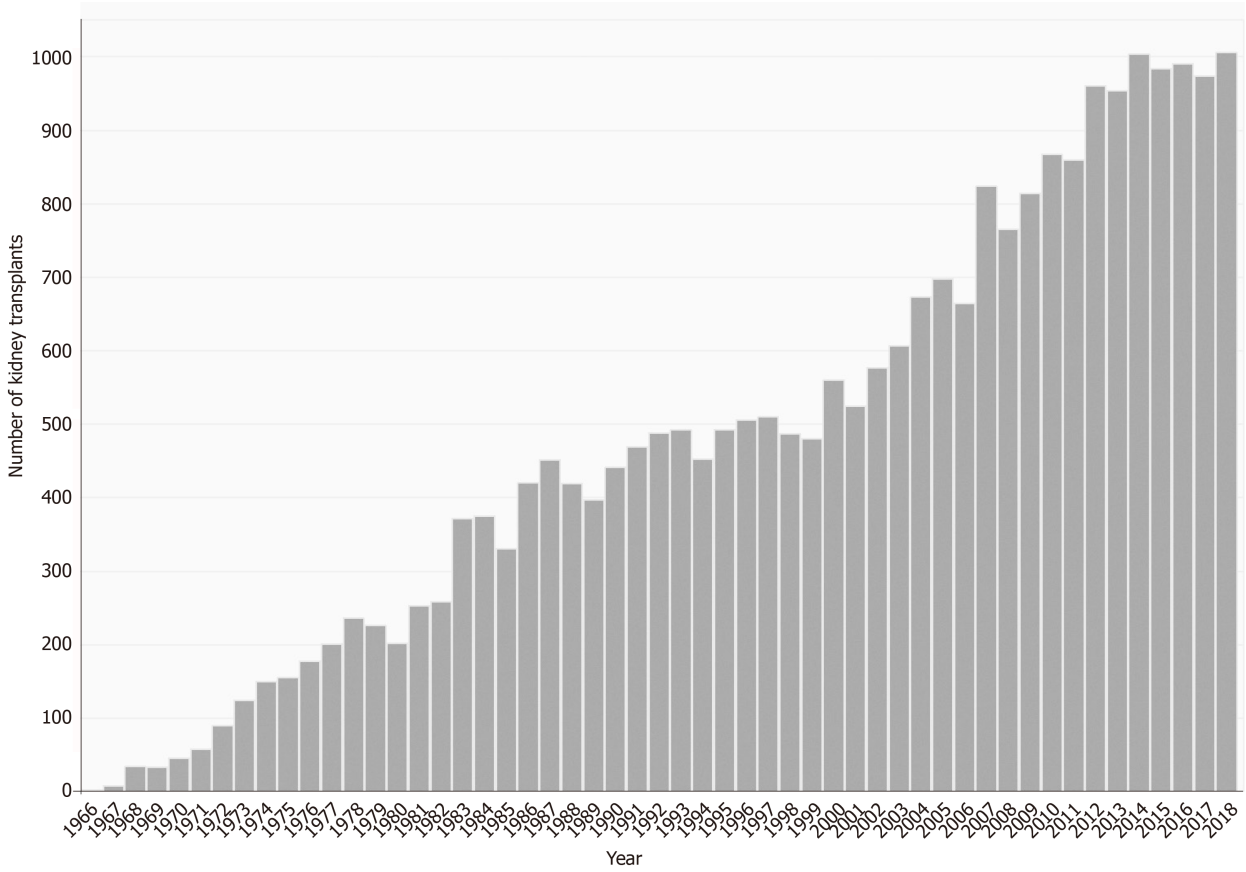

Figure 1 Number of kidney transplantations in the Netherlands per year

improves results, which was later also confirmed in a rabbit study[28,29]. In 2002, Brasile *et al*[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[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

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 *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

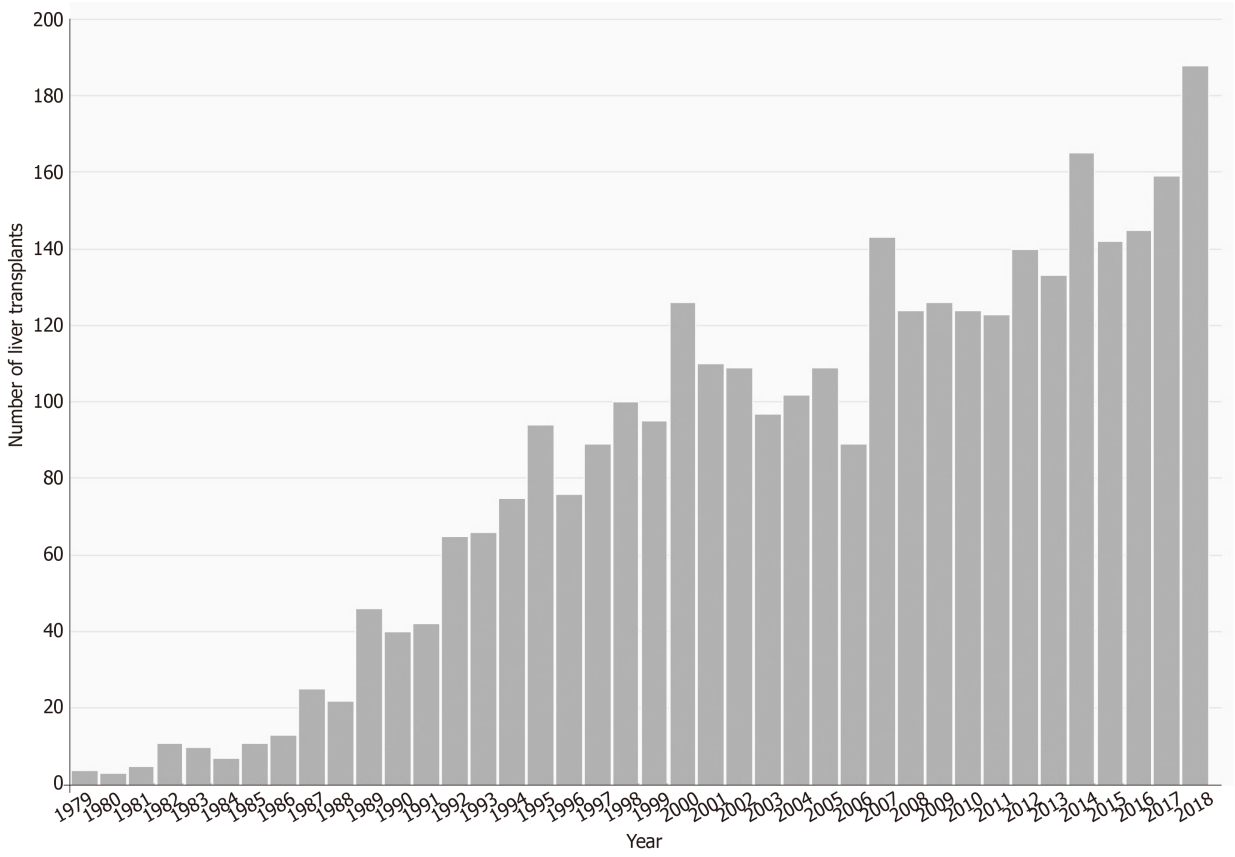

Figure 2 Number of liver transplantations in the Netherlands per year.

to the subdiaphragmatic aorta. The thoracic aorta is clamped to prevent auto-resuscitation, which has been shown to be an effective method[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*[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*[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*[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[35]. Miñambres *et al*[36] 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[36]. Also, Magliocca *et al*[37] 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

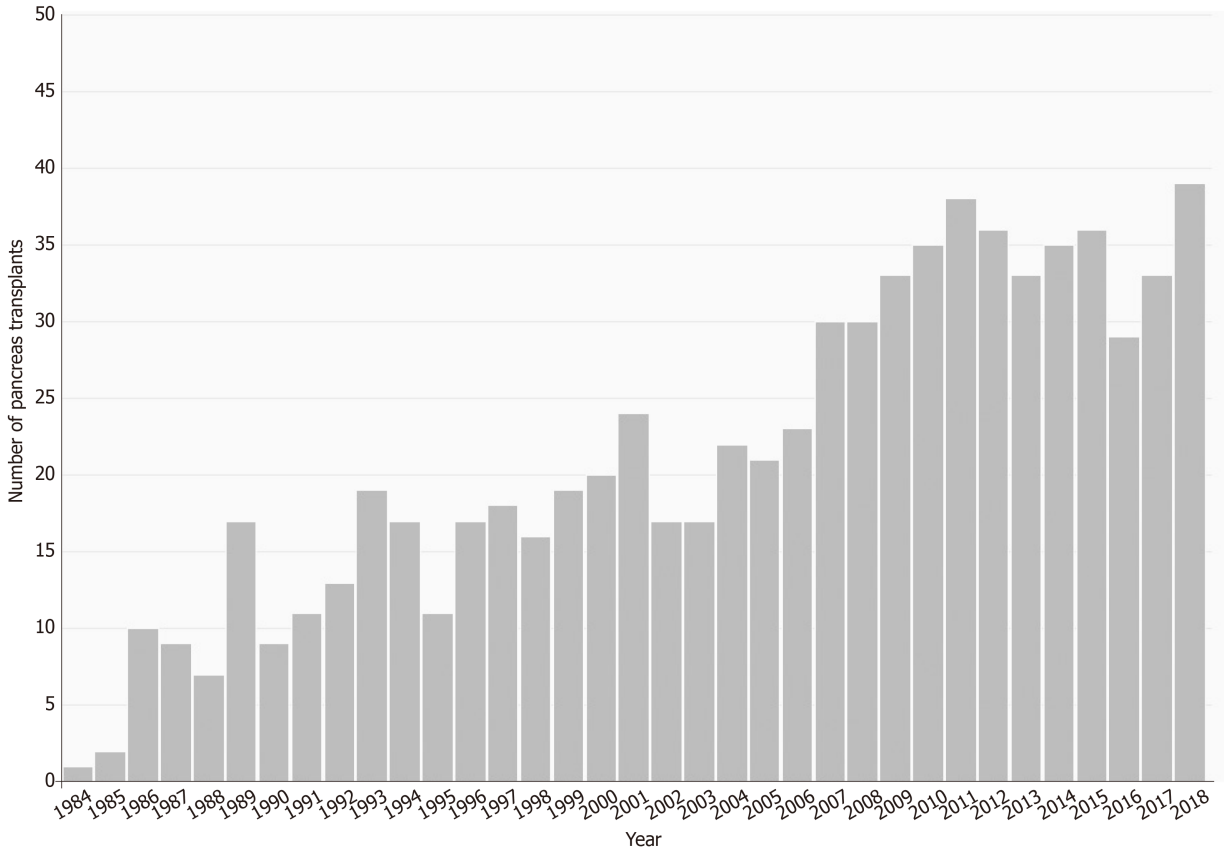

Figure 3 Number of pancreas transplantations in the Netherlands per year.

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

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

Study	*n*	DCD type	Rejection, %	DGF, %	PNF, %	Graft survival, %			Patient survival, %		
						1	3	5	1	3	5
HRP											
Valero *et al*[35], 2000	8	II	-	75	0	-	-	-	-	-	-
Koyama *et al*[58], 2002	46	III/IV	-	87	6.5	88.3	-	-	-	-	-
Lee *et al*[34], 2005	31	II/III/IV	35.5	41.9	0	100	-	88.4	100	-	100
Sánchez-Fructuoso *et al*[59], 2006	320	I/II	4.4	60.9	4.4	87.4	-	82.1	95	-	90
Farney *et al*[33], 2011	25	III	16	21	0	88	88	-	-	-	-
NRP											
Valero *et al*[35], 2000	8	II	-	12.5	0	-	-	-	-	-	-
Maglioccaet *al*[37], 2005	24	III	0	8.3	0	-	-	-	-	-	-
Reznik *et al*[60], 2011	20	II	10	70	10	-	-	-	-	-	-
Hessheimer *et al*[61], 2015	158	II	-	65	9	88	-	-	-	-	-
Oniscu *et al*[42], 2014	32	III	-	40	6	87.5	-	-	96.8	-	-
Butler *et al*[43], 2014	14[1]	III	-	18.2	9.1	-	-	-	-	-	-
Rojas-Peña *et al*[62], 2014	29[2]	III	-	31	3.5	-	-	-	-	-	-
Demiselle *et al*[63], 2016	19	II	-	53	5.3	94	-	-	100	-	-
Miñambres *et al*[36], 2017	37	III	-	27	5	91.8	-	-	-	-	-

[1]Fourteen kidneys were transplanted in 11 recipients. Therefore, clinical outcomes are calculated in the 11 recipients;
[2]Outcomes 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 PaO_2 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.

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, %		
							1	3	5	1	3	5
Otero *et al*[64], 2004	14	II	22	-	28	28	43	-	-	71	-	-
Fondevila *et al*[41], 2007	10	II	-	10	-	10	50	-	-	70	-	-
Jiménez-Galanes *et al*[65], 2009	20	II	-	-	5	10	80	-	-	85	-	-
Fondevila *et al*[66], 2012	34	II	-	12	8	4.3	-	-	-	-	-	-
Oniscu *et al*[42], 2014	11	III	-	18.2	0	9.1	87.5	-	-	96.8	-	-
Butler *et al*[43], 2014	3	III	-	-	0	-	-	-	-	-	-	-
Rojas-Peña *et al*[62], 2014	13	III	-	-	14.3	14.3	85.7	-	-	-	-	-
Hessheimer *et al*[61], 2015	42	II	-	-		10	73	-	-	-	-	-
De Carlis *et al*[67], 2016	7	II/III	14.3	14.3	0	0	-	-	-	-	-	-
Miñambres *et al*[36], 2017	11	III	-	0	0	9.1	90.9	-	-	-	-	-
Hessheimer *et al*[40], 2019	95	III	-	8	2	2	88	88	-	93	93	-

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

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[45]. 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 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	ISRCTN91315246	Non-randomized	Cambridge	90	Graft function	1 h NMP	Discarded kidneys	November 2019
COPE-POMP	ISRCTN63852508	RCT	COPE Essen	262	Graft survival 1y	Short period HMP *vs* SCS only	ECD-DBD	July 2019
COPE-COMPARE	ISRCTN32967929	RCT	COPE Leuven	162	Kidney graft function 1 y	HMP with oxygen *vs* HMP without oxygen	DCD III	↓ risk BPAR ↑ 1-y eGFR[44]
PIO	NCT03031067	Case control	Bologna	20	Graft function	2 h HMP *vs* SCS	ECD -DBD	February 2018
PREDICTION	NCT02055950	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	NCT01170910	RCT	Lyon	162	DGF	6-8 h HMP *vs* SCS	ECD	August 2016
Machine perfusion trial	ISRCTN83876362	RCT	COPE Groningen	654	DGF	Non-oxygenated HMP *vs* SCS	DCD III and DBD	↓ risk of DGF (OR 0.57) ↓ risk of graft failure (HR 0.52) ↑ allograft survival (94 *vs* 90%, P = 0.04)[27]
Unknown	ISRCTN15821205	RCT	Cambridge	400	DGF	1 h pre-transplant NMP *vs* SCS	DCD III and IV	January 2021

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.

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[46].

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[47]. This study showed a 49.4% reduced peak ASAT during the first 7 d post-transplant in both DCD and DBD livers[47]. Early allograft dysfunction was 74% lower than in the SCS arm. Discard rates were higher in the SCS group (24.1% *vs* 11.7%)[47]. However, there were no differences in biliary complications, ischemic cholangiopathy, incidence of PNF or graft and patient survival at 1 year[47]. A recently published study in discarded livers combined the use of DHOPE with subsequently controlled oxygenated rewarming and NMP[48]. From the 16 livers perfused according to the protocol, 11 were considered transplantable, which was decided based on pre-defined viability criteria. The authors conclude that the attributable percentage of transplantable livers in their center was increased 20% by using the DHOPE-COR-NMP protocol. This would have a major impact on the amount of transplantable livers if applied worldwide.

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[49-51]. However, in more recent studies, results have been superior in machine perfusion[52]. No large data are yet available concerning the use of machine perfusion in pancreas transplantation.

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	NCT02584283	RCT	Groningen	156	% NAS	2 h end-ischemic DHOPE	DCD III	October 2019
HOPE	NCT01317342	RCT	Zürich	170	Postoperative complications	1-2 h HOPE	DBD	July 2019
HOPE ECD-DBD	NCT03124641	RCT	Aachen	46	Peak ALT	1-2 h HOPE	ECD-DBD	June 2019
DHOPE-COR-NMP	NTR5972	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[48]
PIO	NCT03031067	Case control	Bologna	20	Graft function	2 h HOPE	ECD livers	February 2018
VITTAL	NCT02740608	Non-randomized	Birmingham	22	Patient survival	4 h NMP	Discarded livers (DCD and DBD)	March 2020
Liver WP2	ISRCTN39731134	RCT	Oxford COPE	220	Peak AST	Minimally 4 h NMP	All deceased donors	49.4% ↓ peak AST[47]
CORNET	ISRCTN94691167	RCT	Essen	40	Peak AST	1,5 h COR until 20 degrees (dual perfusion)	ECD	February 2021
DHOPE	NTR4493	Case control	Groningen	10	Graft survival 6 mo	At least 2 h of DHOPE	DCD III	↑ graft survival (P = 0.052) ↓peak ALT (P = 0.006) ↓bilirubin (P = 0.044)[46]
Unknown	NCT03837197	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, fluometric 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[48]. Liver enzymes, lactate and bile production has shown not to be sufficient for prediction of liver graft failure in the

recipient[54]. The following criteria have been described as being associated with successful transplantation of a normothermically perfused liver[54]: (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[55]. 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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