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Cold but not too cold: advances in hypothermic and normothermic organ perfusion

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Transplantation is the method of choice and, in many cases, the only method of treatment for patients with end-stage organ disease. Excellent results have been achieved, and the main focus today is to extend the number of available donors. The use of extended-criteria donors or donors after circulatory death is standard, but is accompanied by an increased risk of ischemia reperfusion injury. This review presents newly developed machine perfusion techniques using hypothermic, subnormothermic, or normothermic conditions, with or without oxygenation. Possibilities for treatment and quality assessment in decision-making about organ acceptability are also discussed.

Keywords: Organ donation; Organ protection; Cold storage; Normothermic machine perfusion; Ischemic reperfusion injury

INTRODUCTION

With the very first transplantations in clinical medicine [1], discussions started about how best to protect organs from damage, how to keep them alive and functioning, and how to preserve them over an extended period of time [2]. Knowing that a decrease in temperature slows all biological processes and reactions, simple cold storage was the basis of organ preservation over many decades. Cold storage and perfusion with cold solutions to wash out the blood from small vessels in order to avoid clotting were used with quite good success over many years [3].

In this context, scientific discussions focused on the composition of the perfusion fluids to establish an equilibrium of electrolytes similar to that in a physiologic environment, with a high concentration of intracellular potassium and a normal concentration of extracellular sodium. To establish such an equilibrium, cell membranes need to be intact and to work at least on a low level. This type of work in the cell needs energy and produces substances such as lactate, the accumulation of which changes the pH, causing further cell damage.

Several perfusion solutions are available, and some of them are effective in the wash-out of blood and cells, such as Ringer solution and EuroCollins [4]. In particular, EuroCollins and its modifications have been used over many years as a cheap and effective perfusion solution making it possible to keep kidneys viable over up to 24 hours.

However, with the increasing number of liver transplantations and transplantations of other organs, several experimental trials were conducted to find better solutions for organ protection. These efforts led to the development of two solutions, which are widely accepted and are still in use all over the world. Both have different underlying principles. Histidine-tryptophan-ketoglutarate (HTK) solution, developed by Brettschneider in Germany [5,6], is solely intended to keep the pH value stable through a very potent buffer system [7]. In contrast, the University of Wisconsin (UW) solution supplies cells with a number of substances delivering energy to the cell [8].

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HIGHLIGHTS

- **To establish good graft function Ischemia reperfusion injury (IRI) must be reduced as much as possible.**
- **Normothermic machine perfusion (NMP) is currently the best method to avoid IRI.**
- **NMP is specifically important in heart transplantation and is the standard procedure in DCD.**
- **More sophisticated perfusion technique allows evaluation and even treatment of organs for transplantation.**

UW solution was developed at the University of Wisconsin by Southard and Belzer with the intention of keeping cells alive and working [9]. HTK was already in use as a cardioplegic solution in heart surgery and was well known to clinicians, but it had not been tested for the extended storage and protection of organs. HTK was used as a whole-body perfusion solution for all abdominal organs, including the pancreas and small bowel, and for the heart and lungs. UW solution was only used for abdominal organs. The combined use of both solutions made it necessary to encircle and clamp the abdominal aorta directly below the diaphragm when both retrieval teams (thoracic and abdominal) were ready to start perfusion.

While UW solution can be used in small volumes, sometimes even after precooling and wash-out of blood with Ringer solution, HTK solution is used with a high volume (e.g., 20 L or more) depending on the body weight to establish a stable buffer system. Some publications reported inferior outcomes with the use of HTK solution [10]; however, this was often only due to the use of inadequate volume for perfusion.

Several trials compared both solutions [11-14]. Not all of them reached statistical significance. However, when using a reduced incidence of delayed graft function (DGF) as a surrogate for good organ protection, there are data showing superiority of both HTK and UW solutions in comparison to others such as EuroCollins, Marshall, and Celsior [15].

The extended analysis done by Opelz and Döhler [16] with data from the Collaborative Transplant Study (CTS) registry demonstrated that in kidney transplantation, all solutions were safe and effective when the ischemia time was restricted to 18 hours. Only with the extension of ischemia time to more than 36 hours was there reduced graft survival at 3 years, specifically in the very small group of HTK-perfused kidneys.

One could ask, is it necessary to further extend the ischemia time? There are several reasons for doing so. First, with the introduction of human leukocyte antigen (HLA) typing and the allocation of organs on the basis of a good HLA match, the time for organ transportation has increased due to longer distances between the donor hospital and recipient center. Second, there are increasingly many donors not only for kidney donation, but also for liver and pancreas donation. The liver and pancreas are less tolerant of ischemia than the kidney. With the limited number of trained transplant surgeons and organs allocated to donor centers, liver transplantation is performed as the first procedure, followed by kidney transplantation, making it necessary to extend the storage time of the kidneys. Third, time is necessary for an advanced evaluation of donors to prevent the transmission of infectious diseases from the donor to recipient [17].

With the intention to allow longer storage time, some centers have continued to use the technique of machine perfusion. Belzer [3] was one of the pioneers in the field. As early as the 1960s, he published a 17-hour preservation time on a machine followed by successful transplantation. However, simple cold storage with EuroCollins solution or other solutions had the advantage of being very simple and cost-effective. The disadvantage of this technique was the accumulation of metabolites and the change in pH, leading to ischemia reperfusion injury (IRI), DGF, and reduced graft survival of the transplanted organ [18]. These effects were more evident with the use of organs with extended donor criteria (ECD) or donors after circulatory death (DCD) [19]. In the 1970s and even 1980s, trauma was the main cause of brain death. This is no longer the case. The donor age has increased enormously, and the majority of cases now involve brain death as a consequence of stroke and cerebral bleeding. Moreover, many donors have a long history of hypertension, diabetes, and other diseases affecting organ quality [20,21]. ECD and organs from DCD are widely used. In many countries, these are the only categories of donors with increasing numbers, as the numbers of standard criteria donors (SCD) and living donors (LD) are stabilizing or even decreasing. Of course, when using organs from ECD and DCD, the risk of developing IRI is elevated [22]. This issue has prompted a renewed discussion on how to avoid IRI by using pump machines or supplying nutrients or oxygen.

Machine perfusion also makes it possible to evaluate the quality of an organ and to decide whether it is accept-

able. It has even become feasible to supply organs with substances that improve organ quality [21]. Thus, discussions about whether to keep an organ on the machine and use the time to achieve better organ function or to perform transplantation as quickly as possible to avoid damage have started again.

The current state of the discussion is reviewed below, with a main focus on abdominal organ perfusion, preservation, and protection.

KIDNEY PRESERVATION

Simple cold perfusion and cold storage remains the method of choice for SCD kidneys if the ischemia time is not extended to more than 18 to 24 hours. In practice, this means that transplantation should be performed as soon as possible, even in the middle of the night if necessary [23]. However, this is no longer feasible in several countries, including the Netherlands, as restrictions in working time and hours of personnel have made it necessary to postpone kidney transplantation to the regular schedule of the next day. These regulations have resulted in longer preservation times. The question of whether machine perfusion is superior to cold storage and allows a longer preservation time was first addressed in a randomized trial published by Moers et al. [24,25].

This trial included donors from the Netherlands, Belgium, and the federal state North Rhine-Westphalia in Germany with one kidney of the same donor transplanted after cold storage and the other perfused on a kidney pump provided by Organ Recovery Systems. This landmark publication showed that machine perfusion was associated with a significant decrease in graft loss at 1 year. The number of cases with DGF was reduced in the machine perfusion group, without reaching statistical significance. However, a subgroup analysis of ECD kidneys in the same trial showed a significantly reduced risk of DGF, implying that this methodology at least has advantages in the protection of non-SCD kidneys [26].

With the background of this publication, several perfusion systems and machines were either developed or modified. It is difficult to compare these machines and the published results because they differ in terms of the temperature used, oxygen and nutrient supply, duration of perfusion, and technical details such as pulsatile or non-pulsatile perfusion, automation and monitoring. No scientific trials have directly compared the use and efficacy of one apparatus to that of another [27-31].

Moreover, there is growing interest in using different techniques sequentially, such as starting with cold perfusion and storage followed by rewarming before implantation [32-34]. Depending on the availability of techniques in the donor hospital, the most frequently used models involve starting with simple cold storage followed by cold perfusion at a dedicated (usually university-based) procurement center, followed by rewarming either with or without oxygen shortly before transplantation. A number of different methods for organ perfusion have been recurrently discussed (Table 1) [35]. The idea of pulsatile normothermic perfusion is not new at all. The very first attempts of organ preservation tried to mimic physiologic conditions as much as possible [36]. In the 1960s, Belzer et al. [3] introduced the method of hypothermic perfusion of the kidneys, which was simpler than normothermic machine perfusion (NMP). However, the simpler the better. The breakthrough in simple cold storage came when Collins et al. [4] introduced specific solutions for cold organ preservation.

Nonetheless, even in conditions of reduced metabolism under cold conditions, there is an accumulation of metabolites leading to IRI. The increasing number of ECD and even the use of high numbers of DCD in several countries led to growing interest in the revival of a more physiologic environment during perfusion and storage [37,38]. This requires advanced technology, ideally with NMP from the donor hospital to the transplant center [39]. Other perfusion solutions can be used, adding different nutrients. In general, normothermic perfusion enables normal cellular metabolism, specifically when adding oxygen [40]. It could even allow repair of injuries and more sophisticated testing of functionality and viability [21,41]. The need to add oxygen for organ perfusion was already discussed in the 1970s. Several experimental and clinical studies were published

Table 1. Methods of organ preservation currently in use

Method
• Cold (hypothermic) perfusion and storage
• Hypothermic machine perfusion
• Hypothermic oxygenated machine perfusion
• Subnormothermic machine perfusion
• Normothermic machine perfusion
• Normothermic oxygenated machine perfusion
• Normothermic regional perfusion in donors after circulatory death

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using oxygen and measuring oxygen pressure on the surface of transplanted kidneys [42]. However adding oxygen requires an oxygen carrier, which ideally would be blood. Other carriers or the simple use of oxygen as an additive to the solution did not show meaningful effects [43-46].

In general, the results of kidney transplantation are very good when using sophisticated protocols of immunosuppression and patient monitoring. These protocols and HLA matching as the basis for the allocation of kidneys have helped to achieve these good results. However, it was demonstrated years ago by the CTS that the difference in graft function at 3 years between cases with zero mismatches and those with a full-house match was not as large as the difference based on the simple and subjective impression of the transplant surgeon regarding whether a kidney was good or suboptimal [47].

Thus, to further improve the results of kidney transplantation, the focus is on organs that are suboptimal or originate from ECD or DCD. The Kidney Donor Risk Index, preimplantation biopsy, analysis of pump and perfusate parameters, and other parameters might help to distinguish between high-quality and suboptimal kidneys [48-52]. As a very sophisticated method, the use of nuclear magnetic resonance imaging to measure the adenosine triphosphate content of cells in a kidney ready for implantation showed close correlations with outcomes [53,54]; however, this technique has never been introduced into clinical practice. These parameters are not sufficiently exact or reproducible to determine whether to discard a kidney. Furthermore, research is needed to evaluate whether the improvement of kidney function using pump techniques is detectable. The study by Moers et al. [24] introduced hypothermic machine perfusion (HMP) without oxygenation and excluded the effect of all donor parameters by allocating one kidney from the same donor to HMP and the other to static cold storage (SCS). The donors were consecutive cases from the Netherlands, Belgium, and North Rhine-Westphalia in Germany, all above the age of 16. In total, 359 donors were enrolled, and 336 in the HMP group and 336 in the SCS group could be assessed. In the analysis of the whole study population, there was a significant difference concerning DGF, but only in the subgroup analysis of ECD, and in further studies with DCD the advantage of the HMP could be demonstrated very clearly [26,55]. Further analysis revealed that “traditional” risk factors such as cold ischemia time (CIT), time on dialysis, and the origin of kidney disease had an even higher impact on graft survival. It is well known that CIT is an important risk factor. A reason for the good results in LD is the extremely short ischemia time of only a few hours, or even shorter at some centers. To reduce CIT, NMP should be used, not HMP as in the Moers et al.’s study [24]. This technique was introduced by a group from Cambridge and evaluated in different settings, most often starting with a period of SCS followed by NMP, either as pre-warming before transplantation or over the whole time of storage and transportation [35,56]. Other studies with the same approach have been conducted in DCD. The evaluation is done using a specific newly developed scoring system. However, the authors warned not to use this scoring system alone as the basis for deciding whether to discard kidneys [57]. The parameters used include macroscopic appearance, blood flow, und urine output.

Whether prolonged NMP can help restore or even improve kidney function is not yet clear. The promising results from Kaths et al. [58] in an experimental setting using porcine kidneys from donation after brain death (DBD) or DCD showed that NMP was at least equivalent to SCS in terms of tubular injury and kidney function. Studies with long-term preservation involving 24-hour NMP showed that the kidneys were well preserved and functional. This proves that NMP for over 24 hours is possible. However, these results are not that very surprising, since several cases have been published wherein SCS alone and CIT for over 36 to 48 hours were followed by successful transplantation. Nevertheless, there is certainly a place for NMP in kidney preservation when it comes to ECD and DCD. A further study (the HOPE study) focused on the question of whether NMP with additional oxygen could improve kidney function [59]. The results are promising, with a clear advantage of NMP over SCS. Other studies, such as the COPE, POMP, COMPARE have not yet been finished [60].

HMP opens the possibility of evaluating kidney function with the intention to increase the number of available organs from ECD and DCD. NMP could be effective for the repair of kidneys either alone or by administration of various drugs [61]. Even immune modulation and other methods to reduce organ damage, such as the use of anti-inflammatory drugs, can be introduced. Early and specific immunosuppression becomes feasible. These new developments are excellently summarized in a review published by Hamelink et al. [62].

REGIONAL NORMOTHERMIC PERFUSION

With the introduction of extracorporeal membrane oxygenation in intensive care, a method became available that also seemed to be suitable for regional perfusion of organs after death declaration. A number of questions have been answered concerning maintenance of the permanence principle for death during in situ regional perfusion [63]. However, there is no international agreement about the use of DCD.

In the overwhelming majority of scientific publications, death in DCD is defined as the permanent cessation of brain circulation [64]. In countries where DCD is legally not prohibited, methods have been developed to start regional perfusion of abdominal organs and even restart heart beating without reperfusion of the brain. These techniques have been extensively discussed by a number of expert groups in the UK, Canada, and other countries [63]. After confirmation of death in DCD and before starting normothermic regional perfusion (NRP), it is considered appropriate to perform surgery to ligate or divide the aortic arch vessels for cases with thoracic NRP or to occlude the descending aorta for abdominal NRP [65]. Opening the vessels of the supra-aortic arch to the atmosphere ensures that there is no reperfusion to the brain. The details of the underlying principles and the methodology have been described in detail by Manara et al. [63] as a result of an international working group defining death [64,66].

With strict compliance with these regulations not to restore perfusion of the brain, NMP offers a unique opportunity to maintain physiological conditions through oxygen and nutrient delivery. Moreover, it provides enough time to evaluate the suitability of organs for transplantation, and the possibility of treating an organ and restoring complete function is even apparent.

The first results of NRP in DCD were published in 2014 from a group in the UK [67]. Thirty-two kidney transplants, 11 liver transplants, two combined pancreas-kidney transplants, and three double lung transplants were successfully performed. In a second trial, 43 livers were transplanted after NRP from DCD and compared to a historical group of livers after cold storage [68]. The IRI decreased significantly. Another group from Spain obtained similar results.

LIVER PERFUSION

The first randomized trial comparing SCS with NRP in liver procurement was published in 2018 [69]. Most recently, in January 2022, a randomized multicenter trial (PROTECT) compared 293 patients that received livers, of whom 151 were in the Organ Care System (TransMedics, Andover, MA, USA), while 142 were transplanted after cold storage [70]. The primary endpoint was a significant decrease in early allograft dysfunction, which occurred in 27 out of 151 (18%) livers in the Organ Care System arm and in 44 out of 142 (31%) livers in the cold storage arm. The livers in the Organ Care System group showed a significant reduction of IRI. The use of livers from DCD increased significantly. There was a significant reduction of ischemic-type biliary lesions in the Organ Care System group. These results indicate that the use of machine perfusion, at least for livers from ECD or DCD, will be the standard in the future. However, a number of questions remain open: (1) The distinction between SCD and ECD, (2) Assessment of the liver on the machine, (3) time on the machine, (4) cold perfusion in the donor followed by NMP or NRP, (5) possibilities of treating the liver (e.g., a steatotic liver), (6) Treatment of hepatitis C-positive donor livers, (7) Changes in the immune status of the liver cells to avoid rejection. These questions need to be addressed in randomized trials.

The results of the trials published to date have made it possible to increase the number of livers for transplantation, specifically from ECD [71-73]. Assessment of the liver and its function is critical for further increasing the number of available livers. Researchers from both Birmingham and Cambridge have been working on this question [74]. Lactate clearance, glucose metabolism, level of transaminases, bile production, und pH stability during NMP are suitable parameters for predicting outcomes after transplantation. However, a further analysis of bile composition with bile pH, glucose, and bicarbonate is needed to predict ischemic-type biliary lesions. The work of this group proved a number of parameters to be of predictive value (Table 2) [35]. The validity of these parameters was even challenged by a study by the Birmingham group [75]. Livers that were declined by seven transplant centers were perfused and, if the above criteria were fulfilled, transplanted with good 90-day patient survival.

In many cases, the reason to classify a liver as an ECD organ is steatosis. Some centers have reported that 13% to 28% of livers were steatotic, while others have reported far more, with rates exceeding 60% depending on the

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Table 2. Cambridge criteria of variables associated with successful transplantation of NMP livers [35]

Criteria
• Maximum bile pH >7.5
• Bile glucose concentration <3 mmol/L or >10 mmol/L less than perfusate glucose
• Ability to maintain perfusate pH >7.2 without >30 mol bicarbonate supplementation
• Falling glucose beyond 2 hours or perfusate glucose under 10 mmol/L, which on challenge with 2.5 g of glucose, does fall subsequently
• Peak lactate fall >4.4 mmol/L/kg/hr
• Alanine aminotransferase <6,000 U/L at 2 hours

NMP, normothermic machine perfusion.

grade of steatosis and whether the fat is accumulated in the liver cells in micro- or macro-bubbles. Several experimental attempts have been made to reduce fat in the liver. While the approach of using NMP seems to be quite successful in reducing the fat in liver cells in animal experiments, the same approach has not been that successful in clinical settings [76-78]. Even the addition of defatting agents showed only a minimal reduction [79,80]. It is not clear whether an even more extended perfusion time is necessary to reduce fat, or whether other approaches such as lipid aphaeresis are needed. There is certainly an advantage of NMP versus HMP when looking at approaches to reduce fat in the liver [81].

Other approaches are possible and subject to clinical trials. Adding antiviral substances such as miravirsen to the perfusion could reduce reinfection with hepatitis C virus. The downregulation of pro-inflammatory cells, gene therapy, and immune modulation using CTLA4-Ig are other approaches. Most of these have only been tested in experimental studies in animals.

Few studies have directly compared NMP and HMP. Instead, the addition of oxygen to either method is a promising approach. Dutkowski et al. [82] showed good results in DCD livers concerning graft survival and reduction of ischemic-type biliary lesions when adding oxygen in comparison to cold storage [83-85]. This was also confirmed by a number of other investigators. However, few cases were studied and some of the studies only compared the results with historical groups.

There is a need to systematically evaluate HMP versus NMP, both with and without the addition of oxygen. Subnormothermic machine perfusion (SMP) has also been studied, but not directly compared with cold storage [86].

To date, there is no scientifically proven way to decide which method of perfusion should be used in different types of donors. Machine perfusion is certainly more challenging from a technical standpoint. Even with the Organ Care System liver perfusion system from TransMedics, which is the simplest device on the market, there is a need for training personnel to avoid mistakes and casualties in the beginning. In many cases, it might be suitable in the management of the donor to simply perfuse a liver with cold solution, transport it to a procurement center, and decide which method of NMP should be used, with the addition of whichever substances are deemed to be necessary in a specific case [87]. Organ perfusion and protection have become more difficult and challenging. The use of these techniques may even be possible in split liver procurement [88]. This possibility would involve the creation of dedicated and well-equipped procurement centers dealing with the optimal perfusion of different organs, assessment of function, evaluation of outflow parameters, allocation of each organ to a specific recipient, and subsequent transfer to the transplant center.

The improvement in perfusion and preservation techniques is very important. However, in most recently published studies, the simply calculated parameters of donor hepatectomy time and implantation time have also shown significant impacts on early graft dysfunction [89,90]. Therefore a skilled and well-trained surgeon is still the best way to improve transplant results.

PANCREAS AND ISLET CELLS

Major problems in pancreas transplantation are the development of posttransplant pancreatitis, steatosis in the organ, and non-function or insufficient function of insulin producing β-cells. Only a few studies have directly compared SCS with either HMP or NMP [91]. Insulin secretion was detectable during machine perfusion, but with very reduced or limited exocrine function. It is not clear whether the use of machine perfusion would increase the number of available organs from ECD or reduce IRI. A study used discarded organs with oxygenated HMP over 6 hours [92]. There were no signs of cell oedema, and the islet cells could be isolated with good viability and function. However, no data on the success rate of whole-organ transplantation have been published. A prolonged CIT seems to be detrimental for pancreatic transplantation. The only option

to reduce the CIT, of course, is NMP. Barlow et al. [93] has implemented this approach, showing good function and results, but with a small number of cases so far. Before introducing this technique as standard in the organ donation process, further evaluation and studies are needed. Monitoring exocrine function during perfusion is certainly a good way to evaluate the organ. Which type of perfusion solution and which treatment should be used to restore good function must also be evaluated [94].

HEART AND LUNG PERFUSION

The situation of heart transplantation is completely different from that of abdominal organ transplantation. CIT must be limited to 4 hours, or at most 6 hours. With longer CIT, heart transplantations fail in most circumstances. With such a short CIT compared to kidneys, the risk of IRI is far lower. Therefore, the approach of cardiac surgeons to optimize perfusion systems is driven by purposes other than reducing the CIT. First, there is the need to increase the number of available hearts for transplantation by using ECD and even DCD, and second, perfusion systems prolong the time available for transportation and storage. This gives more time for the transplant team to prepare the recipient for implantation despite often having a history of several operations involving the implantation of multiple ventricular assist systems, valve replacements, and so on. Third, a perfusion system allows well-monitored reconditioning of the heart, evaluation of biological parameters (especially lactate concentration), and evaluation of functional pump parameters (e.g., by changing the preload and afterload of the heart) [95,96]. Even an assessment of the heart on the machine by coronary angiography is possible. Treatment of the heart is possible, and gene therapy could be tested in the future.

Evidently, several factors make life easier for the heart surgeon, the most important of which is prolonging the time between the first cold ischemia and the second cold ischemia, when the heart is off the machine and sewed into the recipient.

The development of these machines was not driven primarily by a scientific approach, but by the idea of making certain options technically possible. The first such machine ready for clinical use is the Organ Care System [97]. The use of this machine and its attachment for the heart needs experience and training. Most trials so far have set the primary endpoint as non-inferiority compared to simple cold storage [98]. Some trials failed and were stopped mostly because centers did not have enough experience and training to run the system. Other single-center trials, however, showed significant improvements in early and late outcomes [99,100]. Many more ECD and even DCD organs were used and transplanted successfully [101-104]. The first PROTECT trial in Europe reported a 30-day graft survival rate of 100% using SCD organs [105]. The first trial in the United States, named PROCEED [97] reported a 30-day patient survival rate of 93% [106]. In both trials, the combined primary and secondary CIT was significantly reduced to 60 to 80 minutes, but with a prolonged machine preservation time.

However, the management of the apparatus is complex. A substantial amount (1 to 1.5 L) of donor blood is needed and rapidly taken from the donor via aortic cannulation within 40 seconds prior to aortic clamping. Abdominal retrieval teams do not favor this procedure because of the rapid fall in blood pressure. Moreover, the requirement for blood to be used in different machines is even higher when NMP for the lung, liver, and kidneys is considered as well.

At Harefield Hospital in London, García Sáez et al. [98] has reported a high number of Organ Care System cases. Thirty donors were evaluated, and the hearts were attached to the machine with the target of a coronary artery flow of 900 to 1,000 mL/min. If function deteriorates on the machine or the heart does not return to sinus rhythm, manual massage in the apparatus is possible as well as defibrillation shock. Every 30 minutes, lactate is measured together with electrolytes and other parameters. Lactate should stay stable at a level of <5 mmol/L and always be less on the venous side than on the arterial side. With increasing lactate levels, the risk of non-function after implantation is high. With more experience with the system, even hearts with a runtime on the machine of 10 to 11 hours were used [107]. Nonetheless, there was still a reduction in combined CIT. Heart transplantation using DCD hearts has become feasible. Despite the high costs of the machine and the one-time usable material, the use of Organ Care System has become the standard at many centers.

In lung transplantation, *ex vivo* lung perfusion (EVLP) was developed to evaluate lungs specifically from DCD before implantation. The Ontario group demonstrated that the treatment of ECD lungs is possible to bring them to a status good enough for transplantation [108,109].

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However, the greatest number of additional donors can be reached by consequently using every single case of DCD [110]. Different apparatuses have been developed, not all of which are portable. The Organ Care System produced by TransMedics is the system used most widely. The flow in the machine is 2–2.5 L/min, and air is ventilated into the lung from outside. The device allows monitoring of various parameters, such as pulmonary artery pressure, pulmonary vascular resistance, and peak airway pressure. The introduction of EVLP was followed by an increase in the number of available organs for transplantation. A study has shown that the results were more or less the same when comparing DBD lungs with DCD lungs [111]. Some very preliminary data show that standard cold perfusion and storage can be used initially, followed by attachment to an EVLP system. This could make it easier for a procurement team in a small rural hospital to start with cold perfusion, followed by quick transport to a specialized perfusion center and transplantation after a period of treatment and evaluation on the machine.

CONCLUSIONS

Organ transplantation is a very successful treatment modality, and in many cases, it is the only therapy for end-stage organ diseases. In recent decades, the main focus of scientific investigations and research has been on ways to improve immunosuppression. Numerous protocols have been compared and numerous substances are licensed and available. The protocols for studies to compare or to prove superiority have become extremely difficult. Specifically, a large number of cases is required to reach statistical significance. Donor criteria have changed enormously, as well as recipient factors.

The main focus now is to increase the number of donors, which is only possible by using more ECD or even organs from DCD. Therefore, there is increasing interest in methods of evaluating and improving the function and quality of organs. To improve function means first to exclude all damaging factors and second to use methods for treatment.

CIT is certainly the most important factor for IRI. Several approaches to reduce CIT have been evaluated, such as regional machine perfusion, NMP, SMP, and others. The results of ongoing studies might provide insights on how to decide, how to proceed, and which method to choose. The limiting factor for the use of NMP systems in several organs (e.g., the heart, lungs, liver, and kidneys) is the amount of blood available from a single donor. Other oxygen carriers need to be evaluated. Further improvement is feasible using better oxygen delivery to the organ, drugs for the repair of cells, or gene therapy to make the organ less susceptible to rejection. Other methods, such as supercooling and storage at temperatures below 0°C, remain on the horizon of scientific work, but need further evaluation [112].

The costs for organ perfusion increase with the use of machines. However, there are clear advantages at least for normothermic and subnormothermic techniques for regional or single organ perfusion of the heart, lung, and liver is concerned.

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Conflict of Interest

Guenter Kirste is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

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