The Use of the Oxygenated Airdrive™ Machine Perfusion System in Kidney Graft Preservation: A Clinical Pilot Study

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Kidney graft preservation · Machine perfusion · Clinical kidney transplantation

Abstract

*Background:* The shortage of donor kidneys has led to the use of marginal donors, e.g., those whose kidneys are donated after circulatory death. Preservation of the graft by hypothermic machine perfusion (HMP) provides a viable solution to reduce warm ischemic damage. This pilot study was undertaken to assess the feasibility and patient safety of the Airdrive™ HMP system in clinical kidney transplantation.

*Methods:* Five deceased-donor kidneys were preserved using the oxygenated Airdrive HMP system between arrival at the recipient center (Amsterdam UMC) and implantation in the patient. The main study end-points were adverse effects due to the use of Airdrive HMP. Secondary end-points were clinical outcomes and perfusion parameters. All events occurring during the transplantation procedure or within 1 month of follow-up were monitored.

*Results:* Five patients were included in this pilot study. No technical failures were observed during the preservation period using the Airdrive HMP. Mean perfusion parameters were: duration 8.5 h (3–15 h), pressure 25 mm Hg (18–25 mm Hg), flow 49.77 mL/min (19–58 mL/min), resistance 0.57 mm Hg/min/mL (0.34–1.3 mm Hg/min/mL), and temperature 8.2 °C (2–13 °C). Mean cold ischemia time (CIT) was 20.2 h (11–29.5 h). No adverse events or technical failures were observed during preservation and transplantation or during the 1-month follow-up.

*Conclusions:* This pilot study showed the feasibility of the use of the Airdrive HMP system with no adverse events in clinical kidney transplantation.
Introduction

The shortage of donor kidneys for transplantation has led to the use of marginal donors such as donation after circulatory death (DCD) [1, 2]. DCD kidneys suffer from warm ischemic damage which is associated with early and late graft loss [1, 2]. The optimization of preservation methods can play an important role in improving the quality of these donor organs.

The traditional preservation method, static cold storage (SCS), comprises washout of the graft with a cooled preservation solution, followed by storage on melting ice in the same solution [3–5]. Although this method is low in cost and easy to use, SCS reached its limits in the preservation of marginal donor organs [6]. Therefore, hypothermic machine perfusion (HMP) was reintroduced to preserve donor kidneys during transportation. HMP maintains a continuous flow through the organ’s vasculature and, at the same time, can oxygenate the perfusion fluid. Previous studies showed a reduced incidence of delayed graft function (DGF) in the recipients of donor kidneys preserved by HMP when compared to SCS [7]. Moreover, several studies showed that HMP was superior to SCS concerning the risk of DGF after kidney transplantation in recipients of donation after brain death (DBD) and DCD [8–10].

Our research group has developed a new portable, disposable, oxygenated machine perfusion apparatus called the Airdrive™ HMP system [11, 12]. This system perfuses the graft with hypothermic (8 ± 4 °C) oxygenated perfusion solution in a pulsatile fashion and at a set perfusion pressure of 25 mm Hg. In preclinical animal studies, pulsatile oxygenated perfusion using the Airdrive HMP system was shown to be biologically safe [13], and it was able to resuscitate warm ischemically damaged kidney grafts in a porcine autotransplant model [14].

The aim of this pilot study was to assess the technical feasibility and safety of the Airdrive HMP system in the clinical preservation of both human DBD and DCD kidneys prior to transplantation.

Methods

The Airdrive HMP System

The Airdrive HMP system perfuses the organ by means of an oxygen pressure-driven membrane pump. This pump system uses pressurized oxygen as the driving force for 3 purposes: (i) pulsatile displacement of perfusion fluids by a membrane pump; (ii) to pressurize oxygen in the perfusion fluid by the oxygenator; and (iii) create overpressure by venting the excess oxygen into the organ chamber to support sterility.

The technical properties of the Airdrive system were described by Dirkes et al. [12] in 2013. Briefly, medical-grade oxygen is provided by a standard 1-L, 300-bar pressurized cylinder with a single reducing valve to reduce the pressure to 1.6 bar (Medidis, Lelystad, The Netherlands). As shown in Figure 1, a 2-way solenoid valve further reduces the 1.6 bar to 0.10–0.15 bar. Pressure sensor P1 indicates sufficient oxygen gas pressure from the oxygen cylinder. The vascular resistance (VR) of the organ is measured by a second pressure sensor (P2), which coordinates a second solenoid valve (V2). This valve controls filling of the bottom part of the pump. Pressure sensor P3 indicates the presence of perfusion fluid in the organ chamber by static column pressure on the draining part towards the upper side of the pump. A rolling diaphragm, which is impermeable to gases and fluid, acts as a barrier between the gas chamber and the fluid circulation. By alternating the inlet of oxygen gas sequentially, the membrane moves up and down, thereby perfusing the organ in a pulsatile fashion. The redundant pressurized oxygen from the lower part of the pump is subsequently led through a semipermeable tubing system (the oxygenator), forcing oxygen into the perfusion fluid, after which the oxygen-rich perfusate passes an expansion chamber and a bubble trap. After each completion of the pumping cycle, excess oxygen from the lower part of the pump is further vented into the organ chamber to induce overpressure. The oxygen dissipates through 2 filter patches.
(Porex, UK) positioned in the organ chamber cover, through which air escapes gradually, maintaining sterility. A temperature sensor on top of the pump measures the temperature of the perfusion fluid passing through the pump.

During preservation, the perfusion flow, system pressure, intra-organ VR, temperature, and preservation time are continuously displayed on the electronic control system and stored. All components are embedded in a polystyrene transporter box (Hordijk, Delft, The Netherlands) to provide optimal isolation. Four pre-cooled packs with an optimal phase exchange of 0–1 °C (stored at –20 °C) are placed underneath the organ chamber inside the transporter box for temperature control.

**Patients**

Patients older than 18 years with end-stage renal disease planned to receive a deceased-donor kidney were enrolled in this pilot study. Patients younger than 18 years were excluded as well as those scheduled to receive a kidney from a living donor.

**Preservation**

After arrival at the Amsterdam University Medical Center (UMC), donor kidneys were removed from the preservation apparatus that was used during transport, i.e., SCS, or other HMP systems like KidneyAssist®, and connected to the Airdrive HMP system. Kidneys were washed out using Belzer® UW machine perfusion solution (UW-MPS) to remove preservation solution used during transportation (i.e., Belzer cold storage solution [UW-CS] when transported by SCS and UW-MPS when transported in other machine perfusion systems). Wash-out was performed on sterile ice to maintain the low temperature. After the wash-out, the renal artery of the graft was connected to the Airdrive HMP system, and perfusion with oxygenated Belzer UW-MPS was started. Total cold ischemia time (CIT) was calculated from start of in situ cold perfusion in the donor until the end of preservation in the Airdrive HMP system at the time of transplantation.
Primary and Secondary Outcomes
Postoperatively, the recipient patients were evaluated during 1 month of follow-up. Side effects possibly related to the use of Airdrive HMP were set as primary outcome measures: cardiovascular events, hematological abnormalities and postoperative infections. Secondary outcome measures were: postoperative renal function, dialysis treatment, histological outcome of the reperfusion biopsy, and the preservation parameters of the Airdrive system.

Results

Baseline Characteristics
Five patients who were planned to receive a deceased donor kidney at the Amsterdam UMC were included in this study. Baseline characteristics are shown in Table 1. On arrival at the Amsterdam UMC, the kidneys were preserved by SCS (n = 4) or HMP (n = 1) (KidneyAssist device). After the recipient patients gave oral and written consent, the donor kidneys were connected to the Airdrive HMP system and perfused until the start of the transplantation procedure. Total machine perfusion time per inclusion varied between 3 and 15.5 h. Mean total CIT was 20.2 h (11–29.5 h).
Table 2. Primary and secondary outcomes

|                      | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|----------------------|-----------|-----------|-----------|-----------|-----------|
| **Primary outcomes** |           |           |           |           |           |
| Technical problems   | No        | No        | No        | No        | No        |
| Cardiovascular events| No        | No        | No        | No        | No        |
| Hematological        | No        | No        | No        | No        | No        |
| abnormalities       |           |           |           |           |           |
| Postoperative        | No        | UTI       | No        | No        | No        |
| infections           |           |           |           |           |           |
| **Secondary outcomes** |         |           |           |           |           |
| Kidney function      | Good      | Good      | Good      | Good      | Good      |
| DGF                  | Serum creatinine: too high during whole follow-up | Serum creatinine: too high during whole follow-up | Serum creatinine: too high during whole follow-up | Serum creatinine: too high during whole follow-up | Serum creatinine: too high during whole follow-up |
| Urea                 | too high during whole follow-up | too high during whole follow-up | too high during whole follow-up | too high during whole follow-up | too high during whole follow-up |
| PNF                  | Serum creatinine: too high during whole follow-up | Serum creatinine: too high during whole follow-up | Serum creatinine: too high during whole follow-up | Serum creatinine: too high during whole follow-up | Serum creatinine: too high during whole follow-up |
| DGF, DD ATN          | Serum creatinine: too high during whole follow-up | Serum creatinine: too high during whole follow-up | Serum creatinine: too high during whole follow-up | Serum creatinine: too high during whole follow-up | Serum creatinine: too high during whole follow-up |
| Potassium level      | increased | increased | increased | increased | normal |
| Dialysis             | No        | Yes, directly after NTx until end of follow-up | Yes, directly after NTx until end of follow-up | 4× after NTx, stopped on day 12 | No |
| Histology            | no abnormalities | RTE + atherosclerosis | microangiopathy + ATN, day 24 combined rejection | no adequate reperfusion biopsy | no adequate reperfusion biopsy |
| Machine perfusion parameters | good | good | good | good | good |
| Appearance of kidney graft upon arrival at the UMC | Good | No macroscopical abnormalities: 1 angiolipoma and 1 cyst | No macroscopical abnormalities, but not equally colored | No macroscopical abnormalities | No macroscopical abnormalities |
| Reperfusion color kidney graft | equally red color | equally red color directly after reperfusion | purple color | equally red color | equally red color |

ATN, acute tubular necrosis; DD, deceased-donor; DGF, delayed graft function; NTx, kidney transplant; PNF, primary nonfunction; RTE, reactive tubular endothelium; UTI, urinary tract infection.
Primary Outcomes

Outcome parameters are presented in Table 2. Except for 2 patients who developed a urinary tract infection which was effectively treated with antibiotics, no major side effects as stated in the protocol (cardiovascular events, hematological abnormalities, or postoperative infections), occurred during the 1-month follow-up. During machine perfusion of all 5 donor kidneys, no serious technical abnormalities were observed related to the Airdrive HMP system, except for differences in temperature.

Secondary Outcomes

Secondary outcomes concerning renal function and histological parameters differed among patients (Table 2). Overall, serum creatinine and urea levels decreased after kidney transplantation compared to preoperative levels; in patient 1, the serum creatinine level decreased to a physiological level.

Patients 2, 4, and 5 were diagnosed with DGF and patient 3 was diagnosed with primary non-function (PNF). Additional dialysis was required in three patients temporarily, only for patient 3 until the end of follow-up (Table 2).

Fig. 2. Machine perfusion parameters of the Airdrive system during perfusion of the donor kidneys. Only the clinical relevant parameters of the machine are shown on a display which is visible next to the upper cover of the organ chamber. Of the kidneys that were preserved in the Airdrive were received by the 5 patients included in the study, perfusion parameters were as follows. a Vascular resistance during machine perfusion. b Perfusion flow of UW-machine perfusion solution through the donor kidney and the system measured in the tubing during machine perfusion. c Temperature changes during machine perfusion measured in the tubing.
Histological outcomes of reperfusion biopsies differed between kidneys; with no abnormalities in patient 1 and reactive tubular endothelium in patients 2 and 3. In the latter, reactive parenchyma was also seen with a combined rejection pattern at day 24 postoperatively. The reperfusion biopsies of patient 4 and 5 were inadequate for histological analysis.

Machine perfusion parameters were comparable and remained within the limits of the manufacturer’s settings (Fig. 2), except for kidneys 1 and 3 in which the temperature exceeded 1 °C above the maximum and 2 °C below the minimum manufacturer’s setting of 8 ± 4 °C, respectively. Mean perfusion parameters were as follows: duration of perfusion 8.5 h (3–15 h), pressure 25 mm Hg (18–25 mm Hg) (only < 25 mm Hg at the start of perfusion), flow 49.77 mL/min (19–58 mL/min), resistance 0.57 mm Hg/min/mL (0.34–1.3 mm Hg/min/mL), and temperature 8.2 °C (2–13 °C). In all of the kidneys, the temperature slowly increased over time, with a mean increase of 0.46 °C/h (Table 3).

Resistance started high showing values of: 1, 0.69, 0.41, 1.3, and 0.94 mm Hg/min/mL in kidneys 1–5, respectively, but decreased over time during perfusion to: 0.34, 0.44, 0.52, 0.49, and 0.43 mm Hg/min/mL, respectively. Simultaneously, the flow rate increased over time in all kidneys.

The kidney received by patient 3 had been connected to the KidneyAssist device prior to inclusion. The perfusion parameters at the start of perfusion of the donor kidney in the Airdrive were comparable to those recorded for the KidneyAssist device (Table 4).

**Discussion**

In this first clinical pilot study, the oxygenated Airdrive HMP system proved to be technically feasible and safe. No serious adverse events related to the device were observed during the 1 month follow-up. The Airdrive HMP system consists of a flow-driven pump that operates by oxygen pressure [13]. The system oxygenates the UW-MPS and also ensures pulsatile flow, thereby creating an overpressure in the organ chamber to maintain sterility. The Airdrive HMP is portable and disposable. The oxygen-driven, positive-displacement pump ensures
autoregulation of perfusion pressure and flow, which potentially reduces the risk of increased pressure and pathological shear stress, especially in damaged kidneys retrieved from extended-criteria donors and older circulatory-death donors. A meta-analysis showed that HMP is associated with a significantly lower incidence of DGF, when compared to SCS [10]. However, the numbers needed to treat (NNT) to prove that DGF can be prevented was 13.6 for DBD kidney recipients and 7.26 for DCD kidney recipients. The present pilot study, which was primarily set up as a safety study, included a lower number of patients (1 DCD and 4 DBD kidney recipients). Due to the low power of our pilot study, no relation can be concluded to the incidence of DGF or PNF and the use of the Airdrive. A randomized controlled trial (RCT) will be needed to show the advantages of Airdrive HMP compared to SCS and other HMP systems.

Limitations

A limitation of the study was the small number of included patients. We aimed to include 7 patients. Unfortunately, only 5 were included due to organizational issues associated with the availability of a surgical room and team when other lifesaving emergency procedures had priority. The minimum time (2 h) that the donor kidney needed to be perfused using the Airdrive according to the study protocol made it difficult to include more cases in this study.

Advantages and Disadvantages of the Airdrive HMP versus Other Machine Perfusion Systems

An advantage of the Airdrive system is the ability to adjust its flow velocity and pump rate to the intra-organ vascular resistance which protects it from high pressure, thereby preventing potential endothelial damage.

Another advantage of the Airdrive system over LifePort® and KidneyAssist is that it is completely disposable, it can be used as a stand-alone device, and it incurs lower costs.

Two other machine perfusion systems are currently in use: LifePort (organ recovery) and KidneyAssist (organ assist). The KidneyAssist device is comparable to the Airdrive HMP system except for the pump. KidneyAssist and LifePort both consist of a roller pump [15, 16]; the KidneyAssist pump generates a pulsatile flow. The LifePort and KidneyAssist both use melting ice for cooling and perform at low temperatures within the range 2–4 °C [15, 16]. The ice is placed in a separate chamber close to the organ chamber. However, in order to keep the temperature stable, the ice needs to be replaced manually, thereby requiring opening of the top cover.

A disadvantage of Airdrive is the recorded instability of the perfusate’s temperature. As shown in this study, the temperature increased gradually over the time of perfusion to a mean value of 8.2 °C, with a maximum value of 13°C. In the case of kidney 1, this was due to insufficient provision of sterile ice during preparation of the kidney’s artery before connecting it onto the Airdrive HMP system. In kidney 3, the starting temperature was 2 °C below the minimum, possibly due to the low temperature in the KidneyAssist device in which the kidney was preserved during transport.

The perfusate in the Airdrive is cooled using 4 cold-packs placed in a separate, foam-insulated space that is in contact with the bottom part of the organ chamber. Improvement of the cooling capacity of the cold-packs will better maintain the perfusion temperature.

Nevertheless, it is not yet clear which temperature and oxygenation setting do most benefit and do less harm the donor kidney. During hypothermia (4–10 °C), especially at 4 °C, only 10% [17] of the metabolism remains active and only 40% of chemical reactions still take place, compared to 37 °C [18]. In recent years, several preservation techniques were studied to elucidate the optimal temperature and oxygenation settings. It was found that controlled oxygenated rewarming (COR) improved post-transplantation renal function [19]. COR is a
method in which the donor kidney is perfused with oxygen-rich perfusion fluid that is rewarmed from hypothermic (4–10 °C) up to subnormothermic temperatures (20 °C) before implantation. The gradual temperature increase observed in our study may therefore not be harmful according to the COR principle. However, this needs to be confirmed in further research studies using controlled temperature increase.

Besides the Airdrive, the KidneyAssist has been designed to oxygenate the perfusion fluid by using a combination of 100% medical oxygen and a hollow-fiber oxygenator (390 cm²), reaching a maximum oxygen pressure of 600 mm Hg in the perfusate [20]. A recent RCT, which compared oxygenated HMP with non-oxygenated HMP, showed a 1-year graft survival benefit for transplanted DCD kidneys preserved by oxygenated HMP [21]. This suggests that oxygenation of the perfusion fluid may also be an advantage of the Airdrive HMP.

In conclusion, the results of this pilot study showed the feasibility of the Airdrive HMP system and no adverse events in clinical kidney transplantation. Larger-scale studies are needed to assess the advantages of the Airdrive HMP compared to SCS and other currently available HMP systems.

Statement of Ethics

The study protocol (ref. No. NL5270401815) was approved by the local hospital medical ethics review board and conducted according to the Dutch law for performing medical research with human patients, as stated in the Declaration of Helsinki. Each patient who met the inclusion criteria of this study was orally informed by a physician of the kidney transplantation team. Each patient got sufficient time to read the patient information document. Each patient that wanted to participate gave oral and written consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.H.E.H. wrote the protocol, managed the supply of materials received from the company and the storage of these materials in the operating rooms, patient selection and recruitment, registration of data, data analysis, and played a leading role in writing the manuscript. S.D.H. was responsible for the study design and set-up of the study protocol for approval from the medical ethics committee of the Amsterdam UMC and contributed to writing the manuscript. I.C.J.H.P. performed patient selection and recruitment, surgical handling for connection of the kidney donor graft into the Airdrive machine perfusion system and the kidney transplantation and contributed to writing the manuscript. M.M.I. was responsible for the study design, and performed patient selection and recruitment, surgical handling for connection of the kidney donor graft into the Airdrive machine perfusion system and the kidney transplantation and contributed to writing the manuscript. F.J.B. was responsible for the study design, contributed to writing the manuscript, and was the leading medical practitioner for the patients who participated in the study. T.M.v.G., the principal investigator, was responsible for the study design, study facilities, and contributed to writing the manuscript.
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