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Machine perfusion for kidneys: how to do it at minimal cost

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Abstract Due to a shortage of organs for transplantation, many centres use marginal grafts to increase their donor pool. As kidneys from non-heart-beating donors (NHBD) have sustained initial ischaemic damage, their viability is difficult to predict. Hypothermic pulsatile perfusion has not only been used to improve the condition of such grafts, but also allows viability assessment. Suitable systems are becoming more readily available, but they are expensive. We have used existing dialysis equipment with modified sterilised inserts to create a pulsatile hypothermic perfusion system. With this system, 41 NHBD kidneys were perfused for up to 8 h; their intravascular renal resistance (IRVR), flow characteristics as well as glutathione S transferase (GST) measurements were performed to assess viability. This hypothermic pulsatile perfusion system is now an integral component of our NHBD programme.

Keywords Renal transplantation · Machine perfusion · Dialysis · Non-heart-beating donor

Abbreviations *CS* Simple cold storage · *GST* Glutathione S transferase · *HBD* Heart-beating donor · *IRVR* Intravascular renal resistance · *MPS* Machine perfusion · *NHBD* Non-heart-beating donor · *UW* University of Wisconsin

Introduction

Renal transplantation has generated debate since its inception. One of the most controversial points of contention in the early stages was how kidneys should be stored between harvesting and implantation. The initial issue was whether to apply machine perfusion (MPS) or simple cold storage (CS). The evidence of the detrimental effects of prolonged perfusion and the greater logistic involvement necessary led to a decline in the use of machine perfusion [15]. However, interest in this technique persisted particularly in the United States, where improved preservation solutions were used. In Europe, with the introduction of the brain death legislation, transplant centres have continued to use conventional cold storage systems with kidneys from Heart Beating Donors (HBD). However, over the past decade, the growing disparity in supply and demand of organs and the use of more marginal kidneys from Non Heart Beating Donors (NHBD) have renewed interest in pulsatile preservation systems. In Europe, these systems have been used for testing the quality of kidneys from such donors [9].

In Europe, the perfusion systems used were Gambro PF-3B machines, which were available commercially in the early 1970s. Their manufacture has long since ceased, due to a shift in emphasis in organ procurement away from conventional heart beating donors. At present, the only commercial perfusion system manufactured is the American Waters Medical RM3 renal perfu-

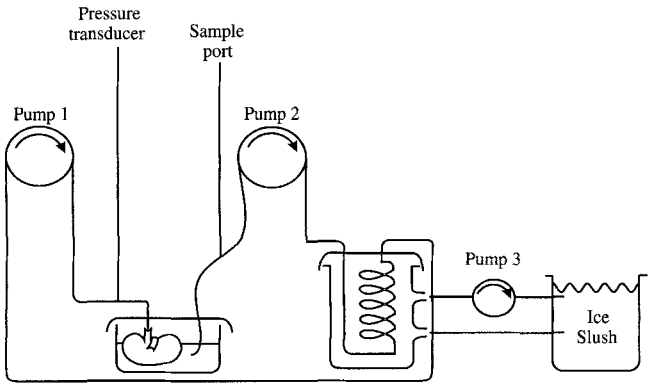

Fig. 1 The renal artery is perfused with UW solution via pump no.1, while the effluent from the vein is collected by pump no.2 and re-circulated. This forms a closed system of 500 ml of UW solution. Temperature is controlled at 4–8 C by a heat exchange system, serviced by pump no. 3. The system is maintained at 45–60 mm of Hg pressures. Sample port on 'venous' limb allows measurement of GST and proteases. Pressure transducer on 'arterial' limb enables measurement of IRVR and flow rates

sion system. In the early days of pulsatile perfusion, many centres developed their own homemade pulsatile perfusion systems [18]. Due to the limited supply of such pulsatile perfusion systems when we re-commenced our NHBD programme, we decided to improve a system that we had used in the early days of renal transplantation. By doing so, we produced a low cost systemthat allowed serial measurements to be taken of the perfusate. In addition, flow rates; pressure profiles, and intrarenal vascular resistance could be determined.

Methodology

The pump perfusion system

We utilised a BELLCO BL 760 blood pump module, its use for haemodialysis having ceased in 1988. The two pumps were connected in series, with the first triggering the second at set pressures. The second peristaltic pump delivered a pulsatile flow into the kidney (arterial limb). After perfusing the organ, the perfusate was sucked up by the peristaltic action of the first pump (venous limb). Between the two pumps, the tubing conveyed the perfusate to a heat exchanger. Thus, the cycle was completed, enabling a closed system of perfusion. (Fig.1)

Disposable tubing

This was custom made by Associated Hospital Supplies (Perthshire, UK), and delivered sterilised at a cost of ≤ 5 per pack. A sample port was incorporated in the venous limb to allow serial sampling for Glutathione S transferase (GST) in order to assess organ viability.

Cooling system

This was incorporated to maintain a working temperature of 4–8 °C. The heat exchanger was a sterilisable stainless steel coil obtained from a LUCAS Mark 2 dialysis machine. This was incorporated into the circuit between the two serial rotor pumps. The coil itself was encased in a waterproof container through which a separate, simple, self-priming pump (HOZELOCK Cascade 1000) circulated ice melt water via a separate non-sterile circuit.

Organ chamber

An anaesthetic humidifier chamber was suitable for the purpose and could be sterilised and re-used.

Flow rates

These were calculated by measuring the amount of perfusate pumped by the 'arterial' pump per minute at various dial settings on the Bellco machine. After calibrating the machine and producing a graph of rotor speed against volume, the flow rates could be determined from the graph at a given rotor speed.

Perfusate

The Newcastle modification of University of Wisconsin (UW) solution [11] was used. This was of a lower cost than the commercially available solution. Of this solution, 500 ml was placed in the organ chamber, the lines being primed from this point.

Monitoring

Pressure

A standard arterial pressure transducer was connected to a port on the arterial tubing. The pressure changes were monitored on an oscilloscope which was a standard patient monitor (Datascope 2000 I). The systolic and diastolic pressures were demonstrated and read on the monitor. The resistance was calculated by dividing the mean pressure by the flow rate.

Temperature

An infrared temperature probe (CHY 610 LC) was used for this purpose. The laser marker was aimed at the kidney through the organ chamber to obtain readings. The mean temperature variation is shown in Figure 2.

Results

This system was tested on kidneys not suitable for transplantation. The machine was run continuously for 48 h and the attrition to the tubing (inserts) was noted (though no fractured tubing occurred). There was no significant change in flow rates or delivery volumes over the prolonged experimental perfusion. The cooling capacity of the pump and the heat exchanger were eval-

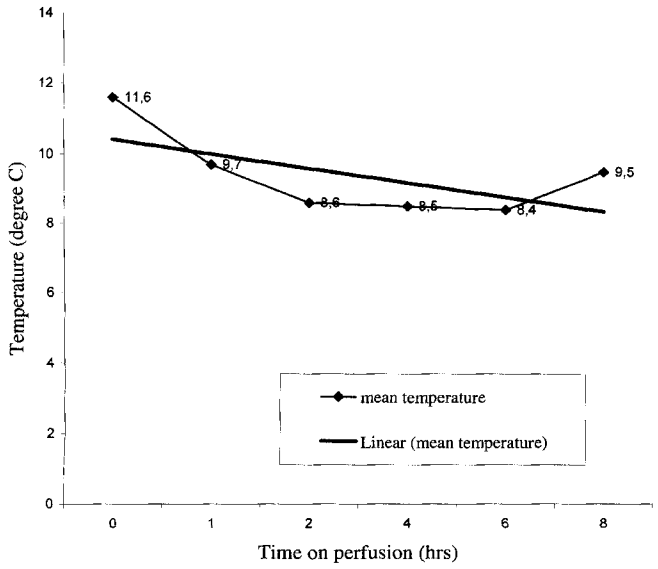

Fig. 2 Mean temperature variation on perfusion

uated, and microbiological tests were run on the system. The temperature remained steady at 5–10 °C with this system, and cultures taken from the perfusate remained sterile. Table 1 shows the cost for each kidney machine perfused on this system. These costs have to be added to the cold storage costs, as in all cases the kidneys were initially cold stored prior to transportation and machine perfusion.

The encouraging results from these experimental studies prompted ethical approval, which was granted for clinical studies. A protocol was established for viability testing, using this pulsatile preservation system for all NHBD kidneys at our centre. Viability parameters were a maximum of 200 U/L for total GST, complimented by an intrarenal vascular resistance below 0.7, with a flow rate above 40 ml/min of 100 g kidney weight.

Since August 1998, the Newcastle perfusion system has been utilised to perfuse and assess kidney viability in 41 NHBD kidneys, the outcome of which has been described [3]. In summary, 28 NHBD kidneys were transplanted locally and 11 discarded for the following reasons: 2 due to positive serology for syphilis in the donor, 4 had raised tGST, 1 did not perfuse on retrieval, and 4 had poor flow characteristics. Another 3 kidneys were exported to other centres (1 wasted, 2 used). The outcome of transplanted 28 NHBD kidneys is tabulated in Table 2.

Table 1 Cost of Newcastle machine perfusion system

Non disposable equipment costs	
Roller pump	No cost (old equipment)
Oscilloscope (Datascope 2000I)	No cost (old equipment)
Heat exchange coil	No cost (old equipment)
Cooling pump x 2	≤ 134
Atraumatic vascular clamp	≤ 200
Total	≤ 334
Expenditure per kidney	
Newcastle modified UW	≤ 57
Pressure transducer	≤ 7.70
Tubing (inserts)	≤ 5
Total	≤ 69.70

Table 2 Outcomes of pulsatile preservation system

Number of NHBD kidney recipients	28
Delayed graft function (%)	84.6%
Primary non function	3.8%
Mean rate of decline of S Creat over 1 month (n = 24)	17.9
One-month graft survival	92.3%
Mean 4 h tGST (U/l)	86 U/l
Mean flow rate at 4 h (ml/100 g per min)	71

Discussion

The two methods of kidney preservation are cold storage (CS) in ice slush and hypothermic pulsatile perfusion preservation (MPS). There is an ongoing debate as to the effectiveness of pulsatile perfusion systems. Some studies have failed to show any advantage of MPS [8,14,19]. Opelz and Terasaki in their study of HBD kidneys in 1981 concluded that there was no longer any benefit in machine perfusing such kidneys. [16] In the following years, the simplicity of cold storage preservation and the ease of transportation replaced MPS. Especiallythe advent of brain death legislature played a vital role in providing organs which had minimal primary warm ischaemic damage. Since then, improved preservative solutions have become available, one being University of Wisconsin (UW) solution. In earlier comparisons of CS and MPS, other preservation solutions.were used. When UW solution was used, excellent results were obtained with both CS- [17] and MPS [15] kidneys.

Due to increasing numbers of patients on waiting lists, combined with the falling rates in organ donation, many centres are increasing their organ procurement rates with "marginal" donors. This includes non-heart beating donors. Some centres have shown an increase in donor numbers from 8.6–20% [7,10] by using such donors. As the primary warm ischaemic times are longer with such donors, viability assessment and organ modulation is carried out by machine preservation of the NHBD kidneys before implantation [1,6]. Machine perfusion has been shown to improve the graft function

in cases of marginal kidneys as well as for those with prolonged cold ischaemic times [20]. The mechanism of the beneficial affect of MPS is not certain and is thought to be due to a dilatation of renal vessels and a decrease in the renal vascular resistance over the first 6–8 h. The catabolic substances accumulating in the interstitial spaces are diluted, and the intercellular fluid composition is better maintained in response to reperfusion [13].

Many studies are reported comparing CS and MPS showing generally lower rates of delayed graft function due to less acute tubular necrosis [1,12,21]. This therefore offers a potential for improved short- and long term success rates. Burdick, in a large retrospective study of 60,827 kidney transplants, stated that the need for 1st week dialysis was 2.31 times greater with CS than with MPS [5]. The logistic regression model showed that the 1 year graft survival as a response to variable showed that only the interactions between preservation methods and donor age had a significant impact on the outcome. Pulsatile perfusion was associated with an overall improvement in early kidney function in this large series, when adjusted to known risk factors. Furthermore, this paper proposed that the transplant community should consider a formal programme for MPS for all kidneys [5]

Machine perfusion systems are costlier than cold storage, however the cost has been shown to be offset by lower dialysis requirements after transplantation [5]. One study estimated a hospital saving of $ 21,604 per recipient if MPS, as opposed to CS, was used to preserve the kidneys . [13] The use of MPS is increasing, especially in cases of 'marginal' organs as well as for those with a prolonged cold ischaemia. MPS allows improvement of the graft condition as well as facilitating evaluation of viability parameters to allow selection of optimal grafts. The initial cost of commercially available machine perfusion systems is high, though the cost should be offset against potential savings from reduced dialysis. Though the system described here is not portable, it is potentially available to all dialysis units. This means that machine perfusion is possible at a fraction of the costs, opening these developments to all.

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