Postgraduate Medical Journal

The Journal of Continuing Medical Education

REVIEWS

Use of non-heart-beating donors in renal transplantation

R M Kimber, M S Metcalfe, S A White, M L Nicholson

Abstract

The rate of renal transplantation has plateaued and is now limited by the number of donor organs available. In the past all donor kidneys came from living donors or controlled non-heart beating donors. It was not until the introduction of brainstem death criteria that cadaveric heart beating donors became the main source. Recently, there has been renewed interest in non-heart beating donors, who have already suffered cardiorespiratory arrest. Kidneys from these donors have a unique set of problems associated with increased duration of warm ischaemia. To minimise this, the kidneys are cooled in situ using an intra-aortic balloon catheter and are perfused with cold hyperosmolar citrate. Retrieval can then proceed in the normal fashion. Despite a higher level of delayed graft function, the results from non-heart beating renal transplantation are good, with long term function comparable to cadaveric organs. If used safely, they enable significant expansion of the donor pool. Techniques in the future, such as machine perfusion preservation, may further improve the results from non-heart beating programmes.

(*Postgrad Med J* 2001;77:681-685)

Keywords: non-heart-beating donors; renal transplantation

There continues to be a shortage of kidneys suitable for transplantation in the UK. Figures from June 2000 indicate that there are still 4782 patients on the active national kidney transplant waiting list and this number rises each year (UK Transplant Services Authority (UKTSSA) data). The number of transplants

being performed falls a long way short of the demand. For example in 1999 only 1468 cadaveric renal transplants were performed (UKTSSA 1999 data). In recent years, heart beating, brainstem dead, cadaveric donors have been the main source. The majority of these are from road traffic accidents and cerebral catastrophes, however the introduction of seat belt legislation and routine hypertensive screening has reduced death rates from both of these conditions. Cadaveric donors suffering fatal cerebrovascular accidents are generally older, and organs from such patients would be considered "marginal". In addition, the reduction in intensive care unit and neurosurgical beds available has reduced the number of suitable ventilated patients. At present the only alternative sources of kidneys for transplantation include living donors of which there are a limited number, and non-heart beating donors.

What are non-heart beating donors?

Conventional cadaveric renal transplants are retrieved from intensive care unit patients who fulfil the criteria for brainstem death. These patients remain ventilated and have a beating heart at the time of the organ retrieval. This minimises the length of time the kidneys spend at body temperature without oxygen supply (warm ischaemic time). Non-heart beating donors represent an alternative source of organs. These donors have already suffered cardiorespiratory arrest. These have a longer warm ischaemic time due to the inevitable delay between circulatory arrest and organ preservation. It must be emphasised that death must be pronounced before non-heart beating donation can commence. This is therefore very different from patients remaining ventilated after brainstem death.

Department of Surgery, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK

R M Kimber
M S Metcalfe
S A White
M L Nicholson

Correspondence to:
Miss Kimber
rkimber@doctors.org.uk

Submitted 15 December 2000
Accepted 2 April 2001

Box 1: Leicester protocol for non-heart beating donors

- Age <60 years.
- Warm ischaemic time <40 min.
- No known renal impairment.
- No malignancy (except primary central nervous system tumours).
- No systemic sepsis.
- No complicated diabetes mellitus.
- No uncontrolled hypertension.

There are four categories of non-heart beating donors defined by a group in Maastricht.¹

- I. Dead on arrival.
- II. Unsuccessful resuscitation.
- III. Awaiting cardiac arrest.
- IV. Cardiac arrest when brain dead.

Controlled and uncontrolled donors

An important distinction needs to be made between controlled and uncontrolled non-heart beating organ donation. Before the introduction of legislation defining brainstem death criteria, all cadaveric kidney transplants were performed using controlled non-heart beating donors. This involved the withdrawal of ventilation leading to cardiac arrest and the subsequent retrieval of organs. The important point, which defines the controlled donor, is that the cardiac arrest is expected. This allows kidneys to be removed with warm ischaemic times of less than 10 min. The controlled non-heart beating donors represent categories III and IV. In the uncontrolled donor, cardiac arrest occurs suddenly and is unexpected. The commonest example would be a myocardial infarction complicated by an arrhythmia. If resuscitation efforts fail, and death is pronounced, then non-heart beating organ donation may be considered. The warm ischaemic

time from these uncontrolled non-heart beating donors (categories I and II) is likely to be much longer when compared with the controlled non-heart beating donors.

Warm ischaemia is known to be a major determinant of renal function after kidney transplantation. None the less, the amount of reversible warm ischaemic injury that the human kidney can sustain is still not known with any certainty. Some animal studies have shown that kidneys have the capacity to recover from 120 min of warm ischaemia,^{2,3} however, most human non-heart beating programmes would exclude kidneys with such prolonged warm ischaemia. The period of warm ischaemia is usually defined as the time between cardiac arrest and the start of cardiopulmonary resuscitation; however, lesser degrees of warm ischaemia occur at other times. This may occur in the terminal phase before death or during inadequate cardiopulmonary resuscitation, for example.

Which patients are suitable for non-heart beating organ donation?

In Leicester, a protocol exists to facilitate the identification of potential organ donors by accident and emergency staff and the transplant coordinator. The donor must fulfil all of the criteria (box 1). The total acceptable duration of circulatory arrest is often not known but the generally accepted upper limit is 30–40 min.^{4,5} (Most of these criteria are similar to those required for cadaveric organ donation.)

What happens next?

After death is pronounced, time is of the essence in order to minimise warm ischaemic

Figure 1 Schematic diagram showing the position of the double balloon triple lumen aortic catheter.

Figure 2 Plain abdominal radiograph showing the two aortic balloons filled with radio-opaque contrast.

injury to the kidneys. Cardiopulmonary resuscitation must be stopped for a period of 5–10 min. This ensures that an equivalent situation to brain death has been reached. After this time cardiopulmonary support is restarted using a ventilator with 100% oxygen and a mechanical cardiac compression device. This allows the accident and emergency staff to be released to perform other duties. The kidneys must be cooled as soon as possible to reduce oxygen consumption by inhibition of the temperature dependent sodium potassium pump. This is achieved by in situ kidney perfusion/cooling using a double balloon triple lumen aortic catheter (fig 1).⁶ The technique involves making a 5 cm transverse groin incision to allow exposure and control of the femoral vessels. This causes minimum disturbance to the cadaver. The double balloon triple lumen catheter is introduced into the aorta via the common femoral artery. The two balloons are then inflated using radio-opaque contrast medium. The upper balloon occludes the aorta at the level of the diaphragm and the lower balloon at the level of the aortic bifurcation. An abdominal radiograph is taken to confirm the position of the balloons and allows repositioning if necessary (fig 2). The kidneys can then be perfused continuously with hyperosmolar citrate at 4°C. The loins of the cadaver quickly cool in comparison to the surrounding tissues. A Foley catheter is placed in the femoral vein to allow drainage. Perfusion can then be continued while consent for organ retrieval is obtained from the relatives. In some areas of the UK, the coroner has the authority to grant transplant teams permission to perform in situ kidney perfusion in the absence of the relatives. This is very important because even a small delay at this point can lead to irreversible ischaemic damage.

Obtaining consent

Consent is usually obtained from the next of kin by the transplant coordinator. The use of non-heart beating donors is a unique situation in which the relatives are newly bereaved. The task of obtaining consent for organ retrieval must be approached carefully and sensitively. Despite the situation, experience has shown that permission for organ retrieval is obtained in a high proportion of cases. At this stage the coroner, if not already involved, must be informed. Corneas and bones from non-heart beating donors may be suitable for transplantation and the appropriate retrieval teams are contacted. After this the donor is transferred to the operating theatre for organ retrieval and the kidneys are stored in hyperosmolar citrate solution on ice. However, there is much research in the area of renal preservation, and other techniques such as pulsatile machine perfusion are being developed which may have advantages for kidneys from non-heart beating donors. Recipient selection and operative technique are the same as for cadaveric transplantation. However, immunosuppressive regimens are modified to avoid compounding the warm ischaemic renal insult, with the additional

insult of a high dose calcineurin inhibitor (for example, cyclosporin and tacrolimus).

The majority of these cases involve sudden death and a postmortem examination is usually required in order to determine the exact cause.

Results

GRAFT SURVIVAL

Early non-heart beating graft survival is encouraging with studies showing a one year graft survival of 73%–91%,^{7–13} and a five year graft survival of 54%–80%.^{7 8 11 12 14 15} These are comparable to cadaveric renal transplant results (fig 3).

GRAFT FUNCTION

Non-heart beating donor kidneys can achieve a good level of function in the long term. Some studies show a significantly higher serum creatinine in non-heart beating kidneys, however 55% of non-heart beating kidneys achieve normal post-transplant renal function.^{7 8 13} Another observation after non-heart beating kidney transplantation is that delayed graft function (an episode of post-transplant dialysis) is particularly common with rates ranging from 67%–100%.^{7–9 12–15} This is compared with a delayed graft function rate of 19%–35% in cadaveric heart beating donor kidneys.^{7 8 12 13} The rate of permanent (primary) non-function in non-heart beating donor kidneys is also relatively high (6%–14%) compared with 1%–8% in cadaveric renal transplant kidneys.^{7–9 12–15} Primary non-function in heart beating cadaver grafts is thought to be due, in the majority of cases, to cortical ischaemic necrosis. The increased rate of permanent non-function in non-heart beating donor kidneys may represent irreversible warm ischaemic damage. There is a great deal of research currently being directed towards developing a reliable method of predicting renal viability before transplantation, to allow identification of kidneys from non-heart beating sources, that are unlikely to function.

ACUTE REJECTION AND COMPLICATION RATES

Acute rejection rates for cadaveric and non-heart beating kidneys are similar ranging from 31%–47% for cadaveric transplants.^{7 8 12 16} and

Figure 3 Comparison of renal transplant graft survival from three donor sources (NHBD = non-heart beating donor, LD = live donor, HBD = heart beating donor).⁸

24%–51% for non-heart beating transplants.^{7 8 12 15 16} Vascular and urological complication rates are similar for both groups.⁸

FACTORS INFLUENCING OUTCOME OF NON-HEART BEATING DONOR KIDNEYS

Factors thought to influence the success of non-heart beating donor kidneys include donor age, donor mode of death, and warm ischaemic time. Several studies have shown an increase in acute tubular necrosis, a reduction in graft survival, and higher mean creatinine concentrations with non-heart beating donors over the age of 55 years.^{17 18} Other studies comparing donor mode of death have shown reduced graft survival when the donor died of cerebrovascular disease compared with kidneys from donors who died from other causes such as trauma or anoxia.¹⁹ Studies examining the effect of warm ischaemic times on outcome in non-heart beating renal transplantation have shown reduced three and five year graft survival when the duration of warm ischaemia exceeds 30 min.²⁰ Recipient factors linked with inferior graft survival include uncontrolled recipient hypertension and one or more previous renal transplants.¹⁹

Ethical considerations

The circumstances surrounding sudden death in accident and emergency departments can pose ethical difficulties in the situation of non-heart beating organ donation. Once the decision has been made to abandon cardiopulmonary resuscitation, the patient is pronounced dead. It is only after this that organ donation should be considered otherwise this exposes the clinician to a conflict of interest. This emphasises the importance of a resuscitation protocol that should be followed in all cases before resuscitation can be pronounced unsuccessful.

The other main ethical consideration surrounds the insertion of the aortic catheter before consent has been obtained from the relatives. Different countries vary widely on their policy for this issue. Some states in the USA prohibit perfusion before family consent. However, in Australia, Columbia, Spain, and Holland the existence of presumed consent legislation allows in situ cooling to go ahead.^{21 22} This is clearly a grey area. In the UK the policy varies from region to region, with some coroners authorising insertion of the catheter and some refusing.

Financial considerations

Although renal transplantation remains the most cost effective form of renal replacement therapy, the transplantation itself and the subsequent immunosuppression represent a major expenditure. Increased rates of delayed graft function seen with kidneys from non-heart beating donors will increase the length of hospital stay and mean continued dialysis, both of which may increase the cost of transplantation considerably.

Summary

- Organ shortage is the limiting factor for transplantation programmes.
- Non-heart beating donors allow expansion of the donor pool by up to 20%.
- Kidneys from non-heart beating donors have longer periods of warm ischaemia than cadaveric organs.
- After death is pronounced, the kidneys must be cooled by an intra-aortic balloon catheter in order to minimise warm ischaemic insult to the kidneys.
- There are increased rates of delayed graft function and primary non-function in non-heart beating kidneys, but long term function is good.
- Donors must be pronounced dead before organ donation is considered to prevent conflict of interests.
- The legislation surrounding consent for in situ cooling needs to be clarified.
- New preservation techniques such as machine perfusion may increase graft function and allow viability testing.
- Future research is being directed towards interleukin-2 receptor monoclonal antibodies and new immunosuppression regimens.

Clinical considerations

The increased rate of primary non-function has major implications for the recipient. The procedure of renal transplantation is not without mortality and morbidity. Prolonged periods of delayed graft function mean continued dialysis and close monitoring. Many centres advocate regular renal transplant biopsies in cases of delayed graft function to exclude the presence of treatable rejection. This requires a well motivated patient. Recipients of non-heart beating donor kidneys should be consented and informed of the higher incidence of delayed graft function and primary non-function. Recipients should be given the opportunity to decline an organ from a non-heart beating donor, however in the authors' experience this is rarely a problem.

Future prospects for non-heart beating organ donation

Research into new preservation techniques such as machine perfusion may help to minimise or even ameliorate the warm ischaemic injury that occurs in these organs. Prospective studies on non-heart beating kidneys comparing machine perfusion with simple cold storage demonstrated significantly less postoperative dialysis requirements and a significantly higher rate of immediate function when non-heart beating kidneys were stored by machine perfusion compared with cold storage.^{23 24} In addition to this, pulsatile perfusion allows the measurement of pulsatile pressure, flows and thus renal resistance. More recent evidence has linked perfusion characteristics such as poor flow, high pressures, and high intrarenal resistance with increased delayed graft function.²⁵

Newer immunosuppressive agents that are non-nephrotoxic, such as mycophenolate mofetil and sirolimus (Rapamycin), have not been sufficiently studied in the context of non-heart beating renal transplantation. These may show themselves to be useful.

Further research has been undertaken on interleukin-2 receptor monoclonal antibodies (daclizumab and basiliximab). These block the high affinity interleukin-2 receptor found on alloreactive T cells, thus causing more selective immunosuppression. There is already evidence to suggest that these drugs can significantly reduce the level of acute rejection in the first six months after cadaveric renal transplants.²⁶ These have yet to be studied in non-heart beating kidneys, but they may well prove to be beneficial in kidneys that have suffered a considerable degree of warm ischaemia.

- 1 Kootstra G, Daemen JHC, Oomen APA. Categories of non-heart beating donors. *Transplant Proc* 1995;27:2893-4.
- 2 Mompugo E, Rigotti P, Calpalbo M, et al. Transplantation of warm ischaemia damaged kidneys: an experimental study in pigs. *Ren Fail* 1993;15:581-5.
- 3 Mompugo E, Rigotti P, Ancona E. Is warm ischaemia the main limiting factor in the use of non-heart beating donors in renal transplantation? *Transplant Proc* 1993;25:1509.
- 4 Kootstra G, Wijnen R, van Hooff JP, et al. Twenty percent more kidneys through a non-heart-beating program. *Transplant Proc* 1991;23:910-11.
- 5 Varty K, Veitch PS, Morgan JDT, et al. Response to organ shortage: kidneys retrieval programme using non-heart-beating donors. *BMJ* 1994;308:575.
- 6 Garcia-Rinaldi R, Lerar EA, Defore WW, et al. In situ preservation of cadaver kidneys for transplantation. *Ann Surg* 1975;182:576-84.
- 7 Metcalfe MS, Butterworth PC, White SA, et al. A case-control comparison of the results of renal transplantation from heart beating and non-heart beating donors. *Transplantation* 2001;71:1556-9.
- 8 Nicholson ML, Metcalfe MS, White SA, et al. A comparison of the results of renal transplantation from non-heart beating, conventional cadaveric and living donors. *Kidney Int* 2000;58:2585-91.
- 9 Varty K, Veitch PS, Morgan JDT, et al. Kidney retrieval from asystolic donors: a valuable and viable source of additional organs. *Br J Surg* 1994;18:1459.
- 10 Wynen RMH, Booster M, Speatgens C, et al. Long-term follow up of transplanted non-heart beating donor kidneys: preliminary results of a retrospective study. *Transplant Proc* 1993;25:1522-3.
- 11 Valdes F, Pita S, Alonso A, et al. Comparative study of the use of systolic and asystolic kidney donors between 1981-1995 in La Coruna, Spain. *Transplant Proc* 1997;29:3565-6.
- 12 Wijnen RMH, Booster MH, Stubenitsky BM, et al. Outcome of transplantation of non-heart-beating donor kidneys. *Lancet* 1995;345:1067-70.
- 13 Butterworth PC, Taub N, Doughman T, et al. Are kidneys from non-heart-beating donors second class organs? *Transplant Proc* 1997;29:3567-8.
- 14 Yokoyama I, Uchida K, Hayashi S, et al. Marginal kidney graft function from non-heart-beating donors. *Transplant Proc* 1997;29:3574.
- 15 Tanabe K, Oshima T, Tokumoto T, et al. Long-term renal function in non-heart-beating donor kidney transplantation. *Transplantation* 1998;66:1708-13.
- 16 Castela AM, Grino JM, Gonzalez C, et al. Update of our experience in long-term renal function of kidneys transplanted from non-heart-beating cadaver donors. *Transplant Proc* 1993;25:1513.
- 17 Matsuno N, Sakurai E, Kubota K, et al. Evaluation of the factors related to early graft function in 90 kidney transplants from non-heart-beating donors. *Transplant Proc* 1997;29:3569-70.
- 18 Koffman CG, Bewick M, Chang RWS, et al. Comparative study of the use of systolic and asystolic kidney donors between 1988 and 1991. *Transplant Proc* 1993;25:1527-9.
- 19 Hattori R, Ohshima S, Ono Y, et al. Long-term outcome of kidney transplants from non-heart-beating donors: multivariate analysis of factors affecting graft survival. *Transplant Proc* 1999;31:2847-50.
- 20 Shiroki R, Hoshinaga K, Higuchi T, et al. Prolonged warm ischaemia affects long-term prognosis of kidney transplant allografts from non-heart beating donors. *Transplant Proc* 1998;30:111-13.
- 21 Alvarez-rodriguez, del Barrio-Yesa R, Navarro-izquierdo A. Legal aspects of non-heart beating donors: the Madrid solution. *Transplant Proc* 1995;27:2933-4.
- 22 Bos MA. Legal issues concerning the use of non-heart beating donors. *Transplant Proc* 1995;27:2929-32.
- 23 Matsuno N, Sakurai E, Tamaki I, et al. The effect of machine perfusion preservation versus cold storage on the function of kidneys from non-heart beating donors. *Transplantation* 1994;57:293-4.
- 24 Henry ML. Pulsatile preservation in renal transplantation. *Transplant Proc* 1997;29:3575-6.
- 25 Kozaki K, Sakurai E, Kubota K, et al. Prediction of kidney nonfunction after transplantation with machine perfusion preservation. *Transplant Proc* 2000;32:275-6.
- 26 Nashan B, Light S, Hardie IR, et al. Reduction of acute renal allograft rejection by daclizumab. Daclizumab Double Therapy Study Group. *Transplantation* 1999;67:110-15.