
Executive summary

Introduction

In the early days of kidney transplantation, during the fifties and sixties, donor organs were initially obtained from both living donors and patients who died of a cardiac and circulatory arrest (the so-called '*non-heart-beating donor*' - NHBD). At that time these were the only suitable organ donors available. This changed when brain death criteria were introduced around 1968, which meant that patients in whom cerebral death was diagnosed could also be considered as potential organ donors. After 1970 the use of these '*heart-beating donors*' (HBD) became predominant. This trend is also closely linked to the development of effective immunosuppressive drugs and the progressing understanding of the importance of HLA compatibility between donor and recipient, through which the results of cadaveric donation and transplantation have improved substantially.

In this way the number of kidney transplants could be expanded considerably, and this also allowed the transplantation of other organs (e.g. heart, liver and lungs). Furthermore, the successful development of effective organ preservation methods made it possible to transport donor organs over longer distances, and in this way laid the foundation for international organ exchange organizations, such as Eurotransplant and Scandia-transplant.

In the past decades the number of organ donations and transplants in the Netherlands has been massively outstripped by the ever-increasing number of patients on the transplant waiting list. For almost every type of organ there now exists a substantial

waiting list. Also, for all organs the average waiting time till transplantation is on the increase. For instance, in 2003, the average wait for a kidney transplant was well over 1100 days, counting from the first day of dialysis treatment (which equals registration on the waiting list). The proportion of kidney patients on the waiting list being transplanted within a two-year period, has dropped since 1998 from half to less than one-third. Another result of this shortage of donor organs is the substantial mortality on the waiting list, in particular among patients waiting for a heart, liver, or lung transplant.

In all fairness one has to observe that, in the past twenty years, there has been no substantial increase in the number of cadaveric kidney transplants. This number is now around 370 per year, and shows no upward trend. The main cause for this is the gradual, and – so it appears – structural decline of the number of patients from whom organs could be retrieved following determination of brain death. Both the reduction of the number of fatal traffic accidents and the high incidence of family refusals to donate are responsible for this. One cannot but conclude that the actual development of cadaveric organ donation in the Netherlands is reason for serious concern, despite recent efforts at improvement.

These circumstances force one to consider alternative sources of donor organs besides the usual brain-dead cadaveric donor. The Minister of Health, Welfare and Sports in the Netherlands has therefore requested the Dutch Health Council to report on any available alternative sources of donor organs, and to focus in particular on living donor transplants and non-heart-beating donation. This advisory report, which has been drawn up by an expert committee of the Health Council, covers not only the medical state of the art, but also the ethical, legal and social aspects of organ donation.

Renewed interest in living donor transplantation and NHB-donation

The gradual decline in the number of cadaveric donations from heart-beating donors appears to have been partly compensated for by an increase in the number of donations from living donors and non-heart-beating donors. For the time being, this only relates to kidney transplantation. The revival of interest in the Netherlands for these types of donation has resulted in a situation where, in 2003, over 30 percent of all cadaveric donor kidneys originated from NHB-donors. In that same year, one third of all kidney transplants in the Netherlands (a total of 560) have been performed using organs from living donors.

All this justifies the conclusion that the kidney transplant program in the Netherlands is becoming more and more dependent on these ‘novel’ types of donation, in order to give patients a reasonable chance of getting transplanted. It is therefore imperative that, together with active promotion of heart-beating donation, effective measures are taken to stimulate these types of donation.

Living donor kidney transplantation

Kidney grafting using organs from living donors is in fact as old as transplantation itself. The first successful kidney transplant, in 1954, was performed with a kidney from an identical twin-brother. Justification for living donation has, up to now, rested mainly on the degree of blood relationship between donor and recipient. For medical as well as ethical reasons, it has long been assumed that living donation could only take place between persons sharing a close genetic relationship, that is: siblings or parents and children.

During the mid-nineties this view changed. Research has now shown that even kidney donations and transplants between genetically unrelated donor and recipient combinations give good results. This concerns mainly donations between spouses or unmarried partners, but also between in-laws and friends (so-called 'emotionally related' donors). These unrelated transplants are comparable in graft survival to transplants involving haplo-identical relatives (e.g. a parent or a sibling), and superior to transplants from cadaveric, HLA-matched kidney donors. The long-term results of these living donor kidney transplants can be expressed in terms of graft half-life. That is: the number of years at which 50 percent of the grafts is still functioning.

Living donor transplants with a full HLA-match between related donor and recipient result in a half-life of 26 years; in case of a haplo-identical tissue match the half-life is around 13 years. The same goes for the half-life of grafts from an unrelated live donor. Finally, the half-life of cadaveric grafts is approximately 10 years (Har00). And even where the results of cadaveric grafting have improved considerably in recent years, the superior outcome of living donor transplants remains.

An important aspect of living donor kidney transplants is the opportunity to avoid dialysis treatment. Research has shown that transplantation prior to the start of dialysis (so-called pre-emptive transplant) has a beneficial effect on long-term graft survival. This is of special importance in paediatric transplantation, since dialysis treatment is known to cause growth retardation.

Much research effort has gone into establishing the risk of living donation. The risk of peri-operative morbidity (less than 2 percent serious complications), and even mortality (around 0,03 percent) is small, but should not be played down when giving information to the potential donor. The risk of adverse consequences to the health of the living donor (e.g. hypertension or impaired kidney function) has also been shown to be small: living kidney donors have a normal life expectancy. Finally, one should not ignore the fact that living donor transplants are financially cost-saving by reducing (or even avoiding) expensive chronic dialysis treatment. All in all the benefits of living donor kidney transplants more than outweigh the possible disadvantages to the donor.

An important recent development is the laparoscopic method for donor nephrectomy. Instead of removal through classical 'open' surgery, in this procedure the kidney is removed via a minimally invasive procedure using an endoscope. The advantages to the donor are claimed to be: a smaller scar and less pain, a shorter period of hospitalisation, and rapid rehabilitation. This new technique requires further standardization and assessment.

These past years a debate has started concerning the limits of living kidney donation. In addition to family donation, involving genetically related donors, donation by emotionally related donors (in particular spouse/partner) has now been widely accepted. This is much less the case for donation by persons who are more distantly related to the recipient (e.g. friends or in-laws), or donation by persons who share no relationship at all with the recipient (the unrelated anonymous donors). Also, different types of cross-exchange between donor and recipient pairs, who are unable to donate directly because of ABO-incompatibility or the presence of reactive antibodies against the donor, now offer realistic possibilities (so-called paired kidney exchange or crossover donation).

It is important also to find adequate medical and moral justification for these new types of living donation. The Health Council concludes that genetically unrelated living kidney donors (emotionally related as well as unrelated anonymous donors) do not run greater risk to their health than genetically related living donors. In addition, the Council has established that the relevant Dutch legislation (the Organ Donation Act of 1996) does not present any obstacle to this type of donation. Again, from an ethical perspective, there are no conclusive arguments to exclude these novel types of unrelated living donation beforehand. However, in these cases it seems justified to do a careful assessment of the motives and background of the potential donor. Paid or commercial donation is rejected by the Health Council (as far as the situation in the Netherlands is concerned).

The Council thinks it is feasible in the coming years to increase the number of living donor kidney transplants in the Netherlands up to 250 per year. An important precondition is that the actual bottlenecks in the capacity of the centres are removed.

Transplantation of extra-renal organs from living donors

The persistent shortage of cadaveric donor organs is the reason that today the possibilities of living donation of extra-renal organs are explored in practice. Donation of part of the liver from parent to child has been performed since 1990 and gives excellent results. The risk to the donor's health, although not negligible, can be justified in the light of the beneficial outcome of these – lifesaving – procedures in often very young children.

A even more complex issue is the donation and grafting of part of the liver from an adult donor to an adult recipient. Because adequate liver function in the recipient requires the removal of a substantial portion (at least 50 to 60 percent) of the donor's

liver, the risk of severe complications and even death is considerable (0.5 to 1.5 percent mortality, 15 to 20 percent complications). This risk should be balanced against the prospects of the recipient: a favourable outcome of the transplant and the possibility of dying on the waiting list. One should also take into account that over ten percent of the transplanted patients face a possible re-transplant in the short run, which puts pressure on the whole liver transplant programme. For the moment, the Health Council considers living donor liver transplantation justified only in a highly select group of adult liver patients.

A special type of liver donation from a living donor is the 'domino transplant'. This concerns patients with hereditary metabolic disease (such as familial amyloidotic polyneuropathy - FAP) for whom a liver transplant is indicated and planned. After removal the native liver of the patient is in turn transplanted to a second, often older, patient in urgent need of a donor liver. As symptoms of the disease become manifest only after a long period of time, and since they will not primarily affect the liver function, no substantial problems have been reported so far in recipients of a domino-liver.

Living donation of lung lobes, and of intestinal segments is still in an early phase of development. However, the prospects of satisfactory long-term graft function seem favourable. Transplantation of a pancreatic segment from a living donor is also performed in some centres. The risk to the donor in this operation is however considerable, whereas the outcome of these transplants is not superior to that of an organ from a cadaveric donor.

Non-heart-beating kidney donation

In the non-heart-beating donor death is determined according to cardiopulmonary criteria: irreversible apnoea and circulatory arrest following cardiac arrest. In the early days of kidney transplantation these NHB-donors have already been used, since there were at that time no scientific grounds for a precise determination of death on neurological criteria (brain death). After the (almost) universal acceptance of brain death criteria in 1968 (Harvard criteria) the use of NHB donors was discontinued in the seventies. However, the acute shortage of cadaveric donors has rekindled the interest in this type of donation. In the Netherlands use has been made of NHB-donors since 1980 (in the Maastricht centre). As of 2000 all transplant centres in the Netherlands perform NHBD procedures and at present around 30 percent of all transplantable donor kidneys come from NHB donors.

Although determination of death on cardiopulmonary criteria is considered to be the 'classical' method, the Health Council has observed that nevertheless some substantial differences in opinion exist concerning the steps to be followed and the due caution that should be exercised. In fact, proper robust scientific foundation of the criteria for irre-

versible circulatory arrest is lacking, and at present no specific procedures are outlined in the Organ Donation Act (in contrast to the procedure required for brain dead patients, as outlined in the Brain Death Protocol).

The Health Council holds the view that the death of a potential donor can be assumed with certainty, if a situation of irreversible circulatory arrest has been existing during at least five minutes. After this period all cerebral functions are irretrievably lost as well. After observing this five minute no-touch interval, one may start preservation of the organs, in particular cooling of the kidneys inside the body (in situ preservation) using hypothermic perfusion. To preserve organs from NHB-donors several methods have been developed: preservation on ice (simple cold storage), the already mentioned in situ preservation, and preservation of kidneys outside the body with the help of machine perfusion. To assess the viability of these organs before they are implanted, several techniques have recently been developed. However, a truly reliable and validated test is still not available.

The most important issue, however, is the outcome of non-heart-beating donor transplants. Although NHBD kidneys usually show delayed graft function after implantation, when compared to kidneys from heart-beating donors, there is in the long run no real difference in graft survival and graft function between these kidneys. The Health Council therefore concludes that NHBD kidneys should no longer be considered 'marginal' or second best.

The NHBD procedure has some aspects that carry special ethical and legal importance. Besides the procedure for the determination of death, this concerns the timely start of organ preserving measures and getting consent for the removal of organs. When a patient dies in hospital after a decision has been taken to withhold or withdraw further life-prolonging treatment (ventilator switch-off procedure), it is usually known beforehand whether the donor or the relatives consent to donation, and proper arrangements can be made for the final goodbye to the deceased.

However, if the situation concerns a patient who dies in the Emergency Care department after an unsuccessful resuscitation effort, or a patient who is found to be dead on arrival, the NHBD-procedure has to be carried out under great time pressure. Problems arise when consultation of the national Donor Register shows that the deceased has left the decision to donate to his relatives or has not taken the step to register his will at all. Often in these cases, the relatives are not present in the hospital to give their consent, and preservation of the organs can no longer be postponed, because of the risk of decay and loss after they have suffered a prolonged period after warm ischaemia. The Dutch legislator has provided for this situation by stating in the Organ Donation Act that physicians are allowed to take the necessary organ preserving measures, while they are awaiting consent for organ retrieval. In this way the option of donation is kept open to the relatives.

NHB-donation is now practised in all university centres, and is increasingly being introduced in general hospitals. The Health Council is convinced that further development of non-heart-beating donation in these hospitals will contribute significantly to the increase of the number of transplantable donor kidneys.

NHB-donation of extra renal organs

Internationally there is only limited experience with NHB-donation of extra renal organs. Most expertise has been gained with NHB-donation and implantation of the liver. It has been shown that livers from patients who die in hospital after a planned decision has been taken to withdraw life-support (ventilator switch-off procedure in category III NHB donors), are viable for transplantation. The outcome of these transplants does not differ significantly from liver transplantation using an organ from a heart-beating donor (at least not in the short run). In 2001, NHBD liver donation has started in some centres in the Netherlands.

NHB-donation of lungs is at present still in an experimental phase. The short term results look promising, but there is still uncertainty over the outcome in the long run. NHB-donation of the pancreas is presently being performed – in small numbers – in some American and Japanese centres. This procedure usually involves transplanting the pancreas simultaneously with the kidney. Immediately after implantation the kidney function is somewhat compromised when compared to transplantation with a heart-beating donor kidney. In the long run however, both the kidney and the pancreas function satisfactorily.

Recommendations

Based on a thorough analysis of the scientific state-of-the-art in living donor transplantation and non-heart-beating donation, the Dutch Health Council puts forward the following recommendations.

Organ donation in general

- 1 The number of cadaveric donations in the Netherlands has reached a plateau, and structurally falls short of the ever-increasing number of patients on the transplant waiting list. In the past five years this decline has been partly compensated for by an increase in both living donations as well as non-heart-beating donations. The Health Council recommends that a three-track policy be followed: cadaveric donation (from heart-beating donors) should be promoted by a broad approach (legislation, additional funds, education); at the same time specific measures should be taken to promote further increase of both living donation and non-heart-beating donation.

Living donor kidney transplantation

- 2 Living donor kidney transplantation generally offers patients the optimal prospects of long-term rehabilitation and improvement of their quality of life. Living donation is also justified by the limited risk to the health of the donor.
- 3 The option of living donation should be brought more actively to the attention of kidney patients and their relatives (but without creating a sense of obligation).
- 4 In the Netherlands there is scope for increasing the annual living donor transplant activity; on the basis of the present waiting list a target of 250 transplants per year seems feasible.
- 5 Living kidney donation from genetically unrelated, but emotionally involved persons (spouses, partners, in-laws, close friends) can be justified on both medical and ethical grounds.
- 6 In certain cases, living donation by an individual who is neither genetically nor emotionally related to the recipient (so-called altruistic stranger or Good Samaritan donor) can be considered. This situation requires strict preservation of the anonymity of both donor and recipient. The donor kidney should be allocated following the usual rules of allocation.
- 7 Cross-exchange donation between pairs of spouses/partners with ABO blood group incompatibility or existing reactive antibodies (positive cross-match) is acceptable on both medical and ethical grounds and should be facilitated by national or international organ exchange institutions.
- 8 There is no place for paid or commercial organ donation in the Netherlands.
- 9 The option of pre-emptive kidney transplantation deserves more attention, especially in children.
- 10 Laparoscopic nephrectomy is likely to have important advantages to the donor, but better standardization of this method and careful assessment of the outcome should be undertaken.
- 11 Follow-up data on living donors should be entered in a national registry.

Living donor liver transplantation

- 12 Living donation of liver segments by an adult to benefit a child recipient is justified, according to the Health Council, on both medical and ethical grounds.
 - 13 Living donation of liver segments to benefit an adult recipient involves substantial risk to the donor, but this procedure can be justified for a select group of patients under exceptional circumstances.
 - 14 The Health Council recommends that alternative options for liver donation (such as non-heart-beating liver donation) should also be assessed.
 - 15 Domino transplantation of the liver offers to patients a worthwhile chance of rehabilitation.
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Living donation of other extra-renal organs

- 16 Living donation of lung lobes and of intestinal segments is at present still in a developmental phase. Living donation of a pancreatic segment does not offer superior outcome over cadaveric donation.

Non-heart-beating donation

- 17 Non-heart-beating donation of kidneys and other organs offers an important additional source of transplantable donor organs, and should be actively promoted.
- 18 The expansion of NHB-donation to both university centres and peripheral hospitals should be facilitated through reaching a national consensus over relevant guidelines.
- 19 The procedure for determination of death on cardiopulmonary criteria for use in NHB-donation should be outlined in an updated protocol.
- 20 When determining the death of a potential NHB-donor, an interval of at least five minutes of circulatory arrest should be observed, during which no handling of the body or interventions should take place. Following this five-minute no-touch period organ preserving measures can be started.
- 21 The option of NHB-donation deserves better attention in the information offered to both the patient and the general public.

NHBD kidney transplantation

- 22 The results of kidney transplantation from non-heart-beating donors (in terms of graft survival and kidney function) are comparable in the long run to those of kidneys from heart-beating donors. NHBD-kidneys, in the view of the Health Council, should no longer be considered as marginal or second-best organs.

NHBD transplantation of extra renal organs

- 23 NHB liver donation offers a potentially important source of transplantable donor organs and should now be actively promoted, among others by developing a uniform protocol.
- 24 NHB-donation of the lungs and the pancreas is for the moment still an experimental procedure.