



# **Donation after Cardiocirculatory Determination of Death: A Review**

**A Working Document  
Prepared for the Forum:  
Donation after  
Cardiocirculatory  
Determination of Death**

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**by**

Leonard Baron, MD  
Clinical Lecturer,  
Department of Anaesthesia  
University of Alberta  
Anaesthetist, Misericordia  
Community Hospital and  
Health Centre  
Edmonton, Alberta

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## **Executive Summary**

The first successful solid organ transplant was performed in 1954 and heralded in a new era in which critical life-threatening disease could be treated in a new and novel fashion. At the outset only renal transplantation was performed using living related donor organs, but as new techniques for tissue matching, organ preservation and supportive interim therapy such as dialysis and immunosuppression were developed, the opportunity to treat increasingly complex patients and to use cadaveric organ donation became a reality. Later, in the 1960s, determination of death by neurological criteria became more widely accepted and organs for transplantation were more often obtained from this group of patients.

Since that time, the number of patients awaiting transplantation has increased dramatically and techniques for transplanting the liver, pancreas, heart, and lungs have now been introduced into clinical practice. At the same time, the number of potential donors was insufficient to meet the demand of potential recipients. This phenomenon was observed widely across the Western world, and Canada was no exception.

Some Western nations, notably Spain, the Netherlands, and the United States, began to reconsider non-heart-beating (NHB) cadaveric organ donation in an effort to relieve the supply and demand inequity of organs for transplantation. For cultural and social reasons, Japan did not adopt criteria for neurological determination of death until recently. These nations have become the dominant leaders in the procurement and transplantation of organs from NHB donors and publications from these countries dominate the medical literature at this time.

To date, only limited efforts to introduce NHB organ donation into Canadian medical practice have been pursued. This literature review could not identify any transplant programs in Canada that were making use of NHB organ donation. Canadian physicians have, however, expressed interest in this opportunity, as is evidenced by publications from a variety of medical centers including the University of Alberta Hospital in Edmonton, Foothills Hospital in Calgary, and the University of Ottawa. Knoll identified significant barriers to introducing NHB organ donation into Canadian practice including ethical concerns amongst medical practitioners; a lack of awareness of potential benefits and risks associated with NHB organ donation; and a critical shortage of resources in emergency departments, intensive care units and surgical suites required to introduce a program of this nature and magnitude. Canada's situation should not be considered unique as similar issues have already been described in the United States by the Institute of Medicine (IOM).

The most comprehensive work on the practices and protocols relating to non-heart-beating organ transplantation identified during this review was that published by the Institute of Medicine in 2000. This document provides both scientific and ethical validation for various non-heart-beating organ transplantation protocols employed in the United States. The IOM report has also drawn attention to the fact that evidence-based support for some practices is lacking and warrants further study. This report reviews the ethical concerns and medical procedures for NHB donation including potential conflicts of interest, determination of death and confirmation of irreversibility, interventions prior to death and after consent in controlled donation and interventions prior to death and after consent in uncontrolled donation.

## **Background**

Like many Western nations, Canada has been experiencing a growing discrepancy between the number of patients awaiting organ transplantation and the supply of organs needed to address these increasing demands. Expanding wait lists, increased wait periods prior to transplantation, and deaths while awaiting transplantation are several of the inherent consequences of this disparity in organ supply and demand.

In the past several decades the Canadian medical community has derived its supply of transplantable organs from donors who have been declared dead by neurological criteria. Efforts at educating the public about the benefits of donorship and transplantation have been largely unsuccessful in achieving significant gains in organ donor rates. Increasingly, physicians have had to reconsider the traditional eligibility criteria for donation and have begun to look at potential donors who might have been considered marginal in the past. Several Canadian publications have examined this opportunity (Ploeg, van Bockel et al. 1992; Taylor, Field et al. 1996; Campbell and Sutherland 1999). In particular, these authors have given consideration to the non-heart-beating (NHB) donor (referred to as a “donor following cardiac death” in some more recent publications) as a source of additional organs for transplantation. In spite of substantial successes with NHB organ donation in many countries, including the Netherlands, Spain and Japan, the Canadian medical community has yet to generate protocols implementing similar processes in Canada. The concept of NHB organ donation in Canada has received little public attention and most Canadians remain relatively uninformed regarding this issue.

The short-term objective of this review is to document the medical issues pertaining to NHB organ donation. Having reviewed these issues and discussed the ethical and legal considerations pertaining to NHB organ donation, the long-term goal of this undertaking is to establish practical guidelines for the introduction of NHB organ retrieval in order to benefit Canadian society.

# **1. A Brief History of Solid Organ Transplantation**

## **Early transplantation**

The first recorded successful solid organ transplant was that of a living kidney donation between identical twins in 1954 (Merrill, Murray et al. 1956). Several attempts at kidney transplantation involving NHB cadaveric donors had preceded this success but all earlier transplants had ultimately failed. In retrospect, the failure of these early attempts at solid organ transplantation is of little surprise as techniques for organ preservation and modulation of host immune response were unknown at the time. Early efforts at solid organ transplantation focused on minimizing organ rejection, which had been anticipated, through the use of living related organ donation, which eliminated the need for organ preservation while minimizing potential for immune-related rejection.

Living related organ donation was not always practical however. During the 1960s organ transplantation from unrelated donors began to gain wider acceptance as early generations of immunosuppressive agents including azathioprine and corticosteroids were administered. Despite these new modes of therapy, the greatest likelihood for success in transplantation still depended on the use of a living related donor. Prior to 1963, fewer than 10% of kidney transplant recipients survived for more than three months when transplanted organs were derived from cadaveric donors (Starzl 1964).

Early efforts at kidney transplantation though were more successful than liver and heart transplantation because, unlike the liver and the heart, the kidneys are paired organs allowing for live donation. This technique of kidney transplantation remained preferred for some time while procurement of a non-paired organ was clearly impossible prior to established cardiorespiratory death of the donor. Cadaveric transplantation of unpaired organs relied heavily upon improved organ preservation techniques that were subsequently developed.

Well into the 1960s, solid organs for transplantation were derived from both living donors and NHB donors. The first reported kidney transplant from a donor whose brain had apparently ceased functioning while on artificial mechanical support was performed in Sweden in 1964 (Louisell 1966). Informed consent for kidney procurement was obtained from the patient's family prior to the patient's demise. As the concept of brain death was yet to have been introduced into clinical practice, the donor was declared dead using traditional cardiorespiratory criteria two days following kidney donation. This case resulted in extensive public deliberations regarding the acceptability of defining death by neurological criteria alone. What emerged was a controversy of such magnitude that Sweden became one of the last countries in the Western world to adopt legislation defining neurological criteria for death.

In the interim, Dr. Christian Barnard became the first surgeon to perform a heart transplant using a donor heart obtained from a young woman who had been declared "brain dead" by her neurosurgeon. He was able to follow this course of action because the legal definition of death at that time was imprecise in South Africa. It is noteworthy that Barnard chose to delay heart procurement until such time as the donor's heart had ceased beating spontaneously, reputedly in order to minimize any controversy related to the concept of brain death.

## **Advances in transplantation**

By today's standards early attempts at organ transplantation were primitive. Several advances have contributed to improved patient outcomes. These included the following: 1) the introduction of improved techniques for tissue typing, ensuring more appropriate matching of donors to prospective organ recipients, 2) improved technologies for sustaining patients temporarily when organ function failed, such as renal dialysis, 3) continued improvements in immunosuppressive therapy, 4) enhanced organ preservation techniques, and 5) improved surgical techniques. Today research continues in many of these areas and the emergence of pre-transplant viability testing may further enhance the possibilities in solid organ transplantation.

## **Development of the neurological determination of death**

As early as 1966, Daube addressed several important issues pertaining to the use of NHB cadaveric organs to advance the needs of the living (Daube 1966). Although he argued that withdrawal of futile supportive therapy was inherently reasonable, he was equally adamant that interference with the dying patient prior to established death was unacceptable. These values are still widely held to be true throughout the medical community today and may have contributed to the "dead donor rule" which remains a basic principle in organ donation to this day.

In 1968, a committee was convened at Harvard University in order to develop neurological criteria for death in the presence of irreversible coma. The introduction of newer and more intensive supportive medical technologies had created previously unseen burdens on families of critically ill patients, medical caregivers and upon society as a whole. In an effort to attenuate these pressures, the committee sought to develop acceptable neurological criteria for death. The medical literature remains somewhat unclear as to whether development of these criteria might also have been intended to address the issue of obtaining organs for transplantation. What is clear, however, is that this new means of defining and diagnosing death had a direct impact upon the availability of organs for transplantation inasmuch as physicians would now be able to procure perfused organs from a subset of patients who had not been considered "legally dead" up to this point in time.

It took some time for neurological determination of death to become an established practice and acceptance of these criteria was not without controversy. As late as the mid-1970s some argued that the work of the Harvard committee was simply an attempt "to declare death to achieve practical ends" and that the committee's conclusions were unethical and unacceptable. Others countered that the Harvard committee's position was ethically consistent, arguing that organs should not be removed until a reliable diagnosis of death had been established. This principle is now often referred to as the "dead donor rule" which states that a donor must be dead before organs can be procured and that the process of procurement cannot, in any way, contribute to the death of the donor.

## **Impact of the neurological determination of death**

At the same time as acceptance of the neurological criteria for death widened, interest in living organ donation waned when concerns about possible donor coercion and commercialization of organ donation surfaced. Initially, the additional organs provided from this new donor pool met the needs of patients. However, over the years, the demand for solid organ transplantation once again outstripped the available supply. The earlier poor outcomes associated with NHB organ donation had been largely overcome by improved preservation technologies, improved techniques to assess organ viability and enhanced immunosuppressive therapy.

As late as 1993, an unofficial moratorium on the use of NHB organ donors existed in many countries. Japan was a notable exception to this phenomenon, as cultural and social issues precluded the wide adoption of determination of death by neurological criteria. Japan had become a world leader in NHB organ transplantation largely of necessity; while other countries such as the Netherlands, Spain, Latvia and the United States sought to resolve organ supply and demand problems by implementing policies and procedures for NHB organ procurement. Many other countries, Canada among them, have yet to resume transplantation using NHB donors.

## **2. Clinical Classification of NHB Donors**

Following the First International Workshop on NHB organ donation, the Maastricht classification for NHB donors was published (Table I). This classification has become the standard by which NHB donors are described. (Table I) (Kootstra 1995; Kootstra, Daemen et al. 1995; Kootstra, Kievit et al. 1997).

**Table I: Maastricht classification of non-heart-beating donors**

| <b>Category</b> | <b>Status</b>                          | <b>Condition</b> | <b>Frequency of Utilization</b> |
|-----------------|----------------------------------------|------------------|---------------------------------|
| I               | Dead on arrival                        | Uncontrolled     | Rare                            |
| II              | Unsuccessful resuscitation             | Uncontrolled     | Frequent                        |
| III             | Awaiting cardiac arrest                | Controlled       | Less frequent                   |
| IV              | Cardiac arrest in a brain dead patient | Uncontrolled     | Rare                            |

### **Category I – Dead on arrival**

Category I patients include all patients presenting “dead on arrival,” including those patients found dead at the scene of attempted resuscitation. As the exact time of death may be unknown, the duration of warm ischemic time (WIT) is often indeterminate (see below). Precise information on the time of cardiorespiratory arrest is required if a Category I patient is to be considered for NHB organ donation. WIT criteria frequently exclude Category I patients from becoming NHB donors. For example, Kootstra has suggested that the time from circulatory arrest to institution of cooling should not exceed 45 minutes (Kootstra, Daemen et al. 1995). Similarly, Steen recommends a 60-minute window for NHB lung procurement interventions to commence (Steen, Sjöberg et al. 2001). Establishing contact with surviving family members may be problematic and obtaining timely consent for organ retrieval may be difficult. There is limited time available to assess the donor and access to surgical suites for organ retrieval, when necessary, may be difficult. With all of these inherent limitations, Category I patients are seldom considered for organ donation in many Western countries at this time. However, continuing work on viability testing techniques may render this group of patients eligible for NHB organ donation to a greater extent in the future.

### **Category II – Unsuccessful resuscitation**

Category II encompasses the bulk of patients considered eligible as NHB donors in Europe and Japan. Typically this group consists of patients who are either brought to emergency departments in cardiac arrest with full resuscitation having already been instituted or who arrest in the emergency department itself. A small subset of Category II patients includes those who experience cardiac arrest while in hospital (referred to as Category V in some articles published after 2003). WIT is more readily determined in these instances and surviving family members are often more readily identified or may already be with the patient. The family may be able to provide important medical information regarding the premorbid health status of the dying

patient, thereby facilitating evaluation for NHB organ donation. Consent for organ donation is often more easily obtained in Category II patients. In countries that have adopted presumed consent legislation, insertion of cooling catheters may proceed. Some centers bridge the time until consent is obtained with reinstitution of cardiopulmonary resuscitative measures.

### **Category III – Awaiting cardiac arrest**

In some instances, critically ill patients who are expected to die are being aggressively managed in the intensive care environment or, less often so, in an emergency department or post-anesthesia care unit. While these patients characteristically do not fulfill neurological criteria for death, continuing medical care may be considered futile and death is anticipated to occur imminently upon withdrawal of life-sustaining treatment. This group of patients may include both patients who are ventilator dependent and those who are under intensive supportive care without ventilation. These patients are designated Category III and they currently constitute the greatest proportion of identifiable NHB donors in North America. The family is frequently already in attendance or readily available and discussions with the family may permit withdrawal of life-sustaining therapy in a more controlled fashion following fully informed consent. The systematic withdrawal of therapy in a controlled environment allows the recovery of not only the kidneys, but also the liver, pancreas, lungs and possibly the heart. This may be contrasted to uncontrolled organ retrieval that, at this time, essentially limits recovery to the kidneys and lungs alone.

### **Category IV – Cardiac arrest in a brain dead patient**

Category IV describes the small number of patients who suffer unanticipated cardiorespiratory death during or following neurological determination of death. Resuscitative efforts may be attempted but are unsuccessful. In this case, clinicians may proceed with instituting NHB organ donation protocol procedures when applicable.

### **Controlled vs. uncontrolled donors**

From a practical clinical perspective it may be more useful to classify NHB donors into two subgroups: uncontrolled and controlled. The distinction between these two subgroups depends upon whether the patient experiences a spontaneous cardiorespiratory death first or whether treatment is first withdrawn and a cardiorespiratory death ensues.

The majority of uncontrolled NHB organ donors worldwide are Category II patients. Category IV patients are the fewest in number. They too are considered uncontrolled inasmuch as the cardiorespiratory death of these patients is unanticipated and not related to withdrawal of therapy. Maastricht Category III patients are characteristically already treated in an environment where intensive life-sustaining resuscitative measures have already been established. Although critically ill, these patients may be relatively well stabilized and, hence, are referred to as controlled patients. The decision to withdraw treatments precedes identification of the patient as a potential organ donor.

### **3. International Perspectives on Organ Donation and the Impact of NHB Donor Programs**

Scarcity of transplantable organs has become a serious issue for physicians from many Western nations. As early as 1993 DeVita et al documented supply and demand inequities in organ availability for transplantation (DeVita, Snyder et al. 1993). As this disparity has increased, medical communities have had to become increasingly more innovative in finding the means to provide the greatest benefit for those patients requiring organ transplantation.

Since the latter part of the 1960s the supply of transplantable organs in the Western world has largely originated from patients declared brain dead. However, in Japan, neurological criteria for determination of death have only been recently adopted as religious and cultural philosophies have limited acceptance of brain death (Moroika 2001). As late as 1985, Japanese physicians were indicted on murder charges when they removed organs from a brain dead woman. Because NHB organ donation has become the norm in Japan, the Japanese medical community has published extensively in this field and Japanese physicians are amongst the leaders in NHB organ procurement issues.

#### **Variations in internationally reported donor rates**

Of all Western nations, Spain has reported the highest organ donation rate at 35 per million population (Ferriman 2000). In contrast, both the United States and Canada have been unable to achieve this rate of donation and the supply of donor organs has not met demand (Evans, Orians et al. 1992). Since 1990 American organ procurement organizations (OPOs) have witnessed the number of patients awaiting kidney transplant approximately triple while those awaiting liver transplant have increased ten-fold. In the meantime, donations of both organs have yet to double in magnitude (United Network of Organ Sharing).

One potential explanation for the variability in donation rate between Spain and North America may lie in Spanish legislation which embodies the concept of presumed consent for organ donation. North American legislators have been reluctant to enact presumed consent legislation. Proponents have argued that such policies would dramatically increase organ availability as physicians would be granted the opportunity to procure organs without the impediment of prior consent from the deceased's family. This might be particularly useful when dealing with Maastricht Category I and II NHB donors where obtaining timely consent for organ retrieval may be difficult, if not impossible. In spite of this, many medical caregivers question the ethics of proceeding with organ retrieval without formal informed consent. Despite Spain's having adopted such legislation, prior consent for organ donation is still often sought in an effort to maintain a strong relationship between medical caregivers and the community at large. Alienation of potential donors could only further undermine efforts to provide donor organs for potential recipients.

## **Feasibility and potential of NHB organ donors**

The management of NHB donor patients is complex and involves coordinated efforts involving numerous stakeholders in the medical community including emergency departments, critical care units, laboratories, surgical suites and consulting physicians. The demands of orchestrating a transplant, from identification of a potential donor to completion and recovery from transplantation, are such that many transplantation programs have established organ procurement organizations or OPOs. These organizations play a particularly important role in the early stages of the transplant process as expedient interventions render organs which are more optimally maintained for transplantation. The consequence of this is improved recipient recovery and, hopefully, prolonged transplant functioning in the long term.

In 1994 the Leicester Royal Infirmary reported their one-year experience in kidney retrieval from NHB donors who died in emergency wards following cardiopulmonary arrest or blunt trauma. NHB donor organs accounted for 38% of transplanted kidneys in their one-year clinical experience with an adequate short-term functional outcome in 88% of solid organ recipients (Varty, Veitch et al. 1994). D'Alessandro et al. reported their experience with procurement of both kidneys and extrarenal organs from controlled NHB donors in 1995 (D'Alessandro, Hoffmann et al. 1995). Critical organ shortages forced them to re-examine their organ donation criteria and to use organs that had once been considered marginal for transplantation. While D'Alessandro et al. suggested that organ donation from uncontrolled NHB donors should be considered, they cautioned that efforts to increase the potential organ donor pool using NHB donors must be accompanied by efforts to ensure public support for such endeavors.

Wisner and Lo examined the feasibility of organ donation in blunt trauma patients in the belief that this was a substantial potential organ donor pool (Wisner and Lo 1996). They concluded that injuries often precluded in situ preservation techniques. This study also raised several significant ethical questions: 1) Is it appropriate for physicians involved in the declaration of death to also be involved in the subsequent placement of in situ vascular catheters? and 2) Is post-mortem placement of in situ perfusion catheters appropriate in the absence of consent from next of kin? In spite of these challenges, Wisner and Lo achieved a potential donor yield of one NHB donor per month in a busy Level I trauma unit. Evers and Lewis performed a retrospective review of death records from a large urban Level I trauma center and determined that, over a two-year period, 23 patients suitable for NHB donor could be identified, a rate comparable to that published by Wisner and Lo (Evers and Lewis 1999).

Kowalski et al. described an alternative approach to organ retrieval which involved the establishment of an Office of Decedent Affairs (ODA) at the Washington Hospital Center, Washington, DC, in 1994 (Kowalski, Light et al. 1996). The ODA was staffed continuously and responded to all life and death situations. It also coordinated its activities with the local organ procurement organization, allowing for the implementation of a Rapid Organ Recovery Program. In this setting, donation rates increased 300% in a one-year period.

In 2003 Brook et al. performed a detailed literature review on NHB donor kidney donation (Brook, Waller et al. 2003). They reported that centers using NHB donor kidney transplantation had witnessed an increase from 16% to 40% in transplant rate. The largest proportion of reported NHB donor transplants was from Maastricht Category II patients where WIT was generally limited to 40 minutes.

## **4. Eligibility for NHB Organ Donation**

Existing NHB transplantation protocols do not address the issue of donor eligibility criteria and reviewed articles seldom define these criteria. This is not entirely surprising since NHB donor criteria continue to evolve.

### **Maastricht criteria**

In 1995, Heineman described the criteria for NHB kidney donation at the University of Maastricht (Heineman, Daemen et al. 1995). Donors were required to be less than 65 years of age. The patient's medical history was negative for intravenous drug abuse, sepsis or serious systemic infection, a history of kidney disease, uncontrolled hypertension, or malignancy outside of primary, non-metastatic CNS tumours. Total duration of circulatory arrest was limited to 30 minutes, excluding the time of effective resuscitation and no longer than two hours maximum effective resuscitation was allowed.

### **Leicester criteria**

Brook described the eligibility criteria employed at the University of Leicester in 2003 (Brook, Waller et al. 2003). Although substantially the same, the allowable donor age ranged from 16 to 60 years and the maximum period of total circulatory arrest was limited to 40 minutes. Excluded patients included those at risk for human immunodeficiency virus, hepatitis B and hepatitis C, those with intravascular coagulation, and patients with complicated insulin dependent diabetes mellitus. Patients who died from assisted suicide or euthanasia were explicitly excluded also.

### **University of Pittsburgh criteria**

In a review of NHB organ donation at the University of Pittsburgh Medical Center (UPMC) Zawistowski et al. describe their methods for determination of eligibility for donation (Zawistowski and DeVita 2003). This article does not provide specific exclusion or inclusion criteria similar to those provided by Wood et al. Their experience dictates that the patient's primary care physician is usually the most appropriate individual to determine whether the patient is a suitable potential NHB donor. Most potential donors identified at UPMC are patients who are already being treated in the intensive care environment and would be expected to die quite suddenly following discontinuation of life-sustaining therapy. A most important factor in determining eligibility at UPMC is preservation of organ integrity by minimization of the warm ischemic period. When solid organ perfusion is allowed to become marginal, tissue oxygen supply and demand imbalance ensues and ischemic injury of the organ results. Zwiawowski and DeVita highlight the fact that patients who experience a slow progressive demise are unsuitable candidates for NHB organ donation as organs will be irreparably damaged by warm ischemic injury as the patient succumbs.

## **UNOS criteria**

The United Network for Organ Sharing (UNOS) is currently attempting to establish a set of guidelines for NHB organ donation. A proposed UNOS guideline has been published in the article by Zwiatoski and DeVita but it has limited clinical application at this time since it applies only to those cases where catastrophic neurological injury is evident in the presence of either ventilatory or circulatory support.

## **Other criteria**

In their introductory comments, Wood et al. address some of the issues related to donor eligibility (Wood, Becker et al. 2004). Patients with overwhelming sepsis are excluded from donation. However, bacteremic patients may not be completely excluded from donation as outcomes from transplantation in these cases appear to be no worse than when donors are bacteremia-free (Freeman, Giatras et al. 1999). Hepatitis B or C contaminated organs may be transplanted into recipients already infected with these same viruses. In life-saving situations, similarly infected organs may be used in patients not suffering from hepatitis B or C. Infections with HIV, human T-cell leukemia-lymphoma virus, systemic viral infection (e.g., measles, rabies, adenovirus), prion-related disease, and herpetic meningoencephalitis are absolute contraindications to organ donation. Cytomegalovirus (CMV) contamination can induce infection in organ recipients but prophylaxis against CMV infection will reduce both morbidity and mortality.

Patients with non-melanoma skin malignancies and some primary brain tumours are eligible for donation while patients with active malignancies and high-grade brain tumours are excluded.

## **Expanding the criteria**

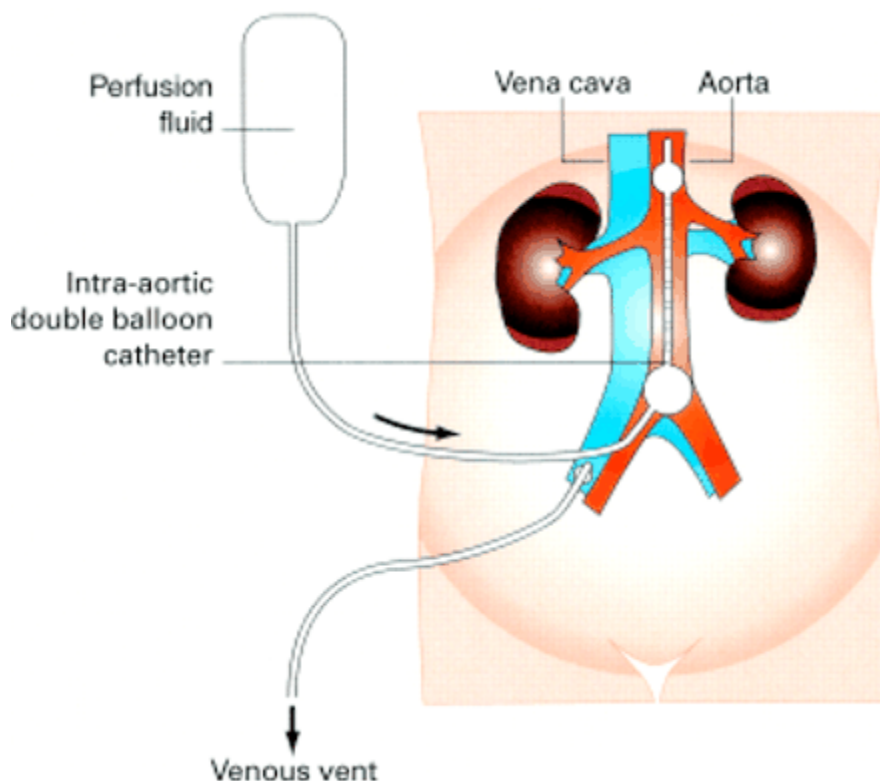
As the issue of increasing scarcity of transplantable kidneys arose, transplant surgeons began to critically re-evaluate the traditional eligibility criteria for heart-beating organ donation. Marginal donors such as patients with horseshoe kidneys and young children are now considered for donation when newer surgical techniques are employed. Elderly donors may also be considered with the advent of the double transplant which may afford the recipient sufficient glomerular mass. With new innovations in viability testing it might be expected that traditional criteria for NHB donor eligibility may also be further relaxed in the near future.

## 5. NHB Donor Organ Procurement and Preservation

Increasing numbers of articles dealing with NHB donor liver and pancreas transplantation, as well as NHB donor heart and lung retrieval, have appeared in the medical literature recently. Despite this, the bulk of medical literature dealing with NHB organ donation deals with kidney transplantation. The Leicester approach to NHB donor kidney retrieval and transplantation appears to be typical of many kidney procurement protocols. While protocols may vary between institutions, the Leicester technique may be considered a point of reference for understanding surgical techniques related to NHB donor organ retrieval (Brook, Waller et al. 2003).

### Double Balloon Triple Lumen Catheter perfusion

The Leicester technique for kidney procurement is strikingly similar to that described by Heineman et al. in 1995 and updated by Kootstra et al. in 2002 (Heineman, Daemen et al. 1995; Kootstra, Kievit et al. 2002). Its origins date back to work published in the 1970s (Kenefick, Fernando et al. 1972; Garcia-Rinaldi, Lefrak et al. 1975). In this approach, once cardiorespiratory death has been established and a 10-minute asystolic “hands-off” period has expired, mechanical ventilation and pneumatic chest compressions are re-introduced with the goal of minimizing ischemic damage of target organs. Having obtained consent for placement of vascular catheters, a common femoral arteriotomy is performed and a double balloon triple lumen (DBTL) catheter is inserted into the aorta.



*Double Balloon Triple Lumen Catheter (Kimber et al., Postgrad Med J 2001;77:681-685)*

The distal aortic balloon is first inflated with dilute radiocontrast, ensuring that it is lodged at the level of the aortic bifurcation. The proximal aortic balloon is then inflated with contrast and blood is withdrawn for appropriate laboratory evaluation. The femoral vein is secured and a urinary catheter is placed to act as a vent for the renal perfusate. The catheter is then perfused with a 4°C solution. Heparin and phentolamine are introduced in the first bag of perfusate in an effort to minimize intravascular microcirculatory thrombosis and to reverse renal arteriospasm respectively. Total volume of preservative infusion typically ranges from 10 to 15 litres. When the DBTL catheter is appropriately positioned the donor's flanks will characteristically become cold and the vented venous effluent will clear over time. Cooling of the lower limbs suggests that the distal DBTL balloon has been displaced distally and radiologic confirmation of vascular access placement should be performed. Although the Leicester technique does not include intraperitoneal cooling, some centers may choose to place intraperitoneal catheters as well.



*Radiological placement of a Double Balloon Triple Lumen Catheter (Kimber et al., Postgrad Med J 2001;77: 681-685)*

## **En bloc dissection**

Related techniques have been described for liver, lung and heart procurement. One technique for “en bloc” dissection of the liver, pancreas and kidneys has been described by D’Allesandro et al. (D’Alessandro, Hoffmann et al. 1995). Their approach involved the controlled withdrawal of therapy from Maastricht Category III patients in whom femoral arterial and venous cannulae were placed prior to discontinuation of therapy. Upon declaration of death, the femoral arterial cannula was flushed with University of Wisconsin solution. A midline abdominal incision and midline sternotomy were performed and the organs were isolated “en bloc” in a procedure taking less than 15 minutes to complete. When organ procurement for lung transplantation is undertaken, a heart-lung block technique may be employed (Steen, Sjoberg et al. 2001). This not only facilitates the explantation procedure but also allows for *ex vivo* lung assessment prior to transplantation.

## **Lung procurement**

Steen et al. have described their technique for procurement of lungs from an NHB Maastricht Category II donor with subsequent successful transplantation in detail (Steen, Sjoberg et al. 2001). Bilateral intrapleural catheters were placed and perfused with cold buffered Perfadex solution before the next of kin were allowed to spend time with the deceased. An additional infusion of Perfadex was completed following departure of the family and the deceased was subsequently taken to the surgical suite for explantation. At the conclusion of cooling, the lung temperature had diminished to 18°C. The lung is unique in its ability to withstand ischemia and to be resistant to microcirculatory thrombosis (see below). Once cooled, the heart and lungs were explanted using an “en bloc” technique.

## **Warm ischemic time (WIT)**

From a traditional viewpoint, WIT may be defined as the time from established cardiorespiratory death to the time when efforts are instituted to preserve organ viability for anticipated transplantation. Some authors have chosen to define WIT using specific physiologic parameters. For example, Olson et al. define WIT as the time at which the donor’s systolic blood pressure reaches 35 mm Hg or the donor’s oxygen saturation reaches less than 25% until the time that infusion of hypothermic cooling solution is commenced (Olson, Davi et al. 1999).

The primary goal of surgical interventions described above is to maintain organ integrity and viability by reducing target organ metabolic requirements. In the case of both renal and hepatic allografts, duration of warm ischemia is thought to be a primary determinant of organ viability. Injury from prolonged warm ischemic periods is further compounded by the effects of preservation following explantation, a period often referred to as cold ischemic time (CIT), and by reperfusion injury which occurs following transplantation. Minimization of warm ischemic time is largely related to the selection of controlled versus uncontrolled patients for organ donation.

Although there is general agreement that WIT should be minimized, various allowable time limits for WIT related to kidney transplantation have been recommended, most ranging from 30 to 45 minutes (Orloff, Reed et al. 1994; Light, Kowalski et al. 1996; Haisch, Green et al. 1997). Despite these apparently rigid recommendations, much longer WITs have resulted in satisfactory functional graft recovery in animal models for NHB kidney transplantation (Matsuno, Kozaki et al. 1999). This suggests that setting an absolute threshold for WIT is difficult if not impossible.

In clinical practice other parameters such as the age and general health of a prospective NHB donor and the progression of organ ischemia as the organ donor succumbs may also play a role in defining acceptable limits for WIT.

Not all transplant teams share the opinion that WIT is of primary importance, however (Alonso, Buitron et al. 1997). Alonso et al. argued that a still-to-be-defined allowable period of warm ischemia does not alter outcomes in NHB renal grafting. They reported transplanting organs from patients in whom allowable ischemic time included an initial asystolic time not exceeding 30 minutes plus an additional allowable period of two hours for resuscitation. While they reported significantly increased rates of delayed graft function in their NHB donor kidneys, three month recovery rates were no different when comparing NHB transplants to those from heart-beating donors. Others have countered, arguing that loss of renal cell mass can be attributed to duration of warm ischemia. It would seem inherently logical that the duration of warm ischemia might be directly related to long-term transplant viability but no evidence for this supposition could be identified during this review.

Amongst organs that may be transplanted, the lung is unique in its ability to withstand ischemia. Because of its histologic structure, consisting primarily of elastic tissue, the lung has minimal metabolic requirements. Furthermore, the alveolocapillary membrane of the lung can meet its requirements for oxygen through direct diffusion. Potential NHB lung donors would be intubated and typically ventilated with oxygen, thereby maintaining the saturation of intrapulmonary blood. Furthermore, the pulmonary endothelium is also capable of functioning for several hours following circulatory arrest. For reasons not described in the reviewed literature, this continued functioning prevents clot formation following cardiac death. Although systemic heparin was administered to the donor patient described in the report by Steen, many centers performing NHB lung transplantation no longer routinely administer heparin to the NHB lung donor (Steen, Sjoberg et al. 2001). In addition to traditional eligibility requirements for NHB organ donation, Steen's only other mandatory requirement was that cooling should be initiated within 60 minutes of witnessed arrest or failed resuscitation.

## **6. Cooling Techniques**

Cooling of procured organs immediately following an appropriate asystolic period is an important step in preserving organ viability. Most commonly this includes either preservation with catheter systems such as that employed in the Leicester technique or via intra-aortic cooling at laparotomy.

No literature evidence for selecting a 4°C perfusate for cooling was identified during this search. It is quite likely that this temperature was arbitrarily selected, albeit probably based on theoretical considerations of metabolic requirements in the presence of hypothermia. It appears that 4°C perfusate has become the standard in the medical literature.

### **Via laparotomy**

Cooling via laparotomy is particularly useful where recovery of solid organs other than the kidney is anticipated. Extension of the surgical incision via median sternotomy allows placement of catheters to isolate the liver and pancreas as well as to allow for venting of cold perfusion solution. These techniques are probably most effectively executed in the controlled environment of the surgical suite in Maastricht Category III patients although these procedures may be instituted in other locations such as the intensive care unit or emergency department when necessary.

### **Intraperitoneal cooling**

While the addition of intraperitoneal cooling may enhance the rate of overall cooling achieved with intravascular techniques alone, it does not appear to confer additional advantages in terms of improved outcomes following transplantation (Matsuno, Kozaki et al. 1993).

### **Total body or core cooling**

Total body or core cooling techniques employing cardiopulmonary bypass or femoral-femoral bypass have also been described (Hoshino, Koyama et al. 1989; Hoshino, Koyama et al. 1989; Castela, Grino et al. 1993; Valero, Manyalich et al. 1993). However, these techniques are difficult to employ in cases of uncontrolled NHB donation and offer little, if any, benefit where only the kidneys are to be recovered. Hoshino's work suggests that core cooling techniques might be more applicable when multi-organ or extrarenal organ retrieval is being undertaken rather than in relation to kidney procurement alone.

## **7. Preservation Fluids**

Renal allografts may be subjected to both warm ischemic injury and the effects of cold ischemia that occur during preservation and storage. There is clinical evidence that prolonged ischemia may contribute to diminished long-term organ survival rates (Gonzalez-Segura, Castela et al. 1998). Preservation fluids are used to limit the degree of cellular ischemic damage. For the most part, currently used solutions include Euro-Collins (EC), University of Wisconsin (UW), histidine-tryptophan-ketoglutarate (HTK) and Celsior. As in the case of temperature, there was no literature evidence to support specific volumes of perfusate solution. Hence, most protocols recommend running perfusate until such time as the venous fluid return clears.

### **Euro-Collins vs. University of Wisconsin**

Results of various studies comparing EC and UW preservation have yielded varying results. Consequently, there is little uniformity in the choice of preservation fluids from center to center at this time (Bell, Dibekoglu et al. 1995). Ploeg et al. concluded that UW was superior to EC in reducing delayed graft function and extended graft survival in the transplanted kidney (Ploeg, van Bockel et al. 1992). Despite this possible benefit, the incremental increase in cost associated with the use of UW versus EC has resulted in a preferential use of EC for cold preservation in some centers (Bell, Dibekoglu et al. 1995). It has been argued, however, that this approach may be “penny wise and pound foolish” as the savings incurred through improvement in renal function and diminished post-transplant requirements for dialysis may offset the incremental cost of UW relative to EC (Rutten, Ploeg et al. 1993). Despite fairly wide use of EC solution, the literature seems to lean towards UW solution as the current gold standard for cold organ preservation.

### **Histidine-tryptophan-ketoglutarate**

Little literature on the use of HTK was identified. On the one hand, HTK may reduce the incidence of delayed graft function when compared to EC, but, on the other hand, UW was superior to HTK in preserving ischemically injured kidneys (Groenewoud and Thorogood 1993; Booster, van der Vusse et al. 1994). In light of the expense related to the use of UW solution alone and in spite of the evidence that UW solution might be superior, Kootstra described the use of HTK as their choice of preservation fluid in 1997 (Kootstra 1997). At the time of publication (1999), the use of Celsior solution, which is intended to mimic extracellular fluid, was limited to cardiac preservation (Muhlbacher, Langer et al. 1999).

### **Cold storage vs. machine perfusion**

The literature relating to organ preservation relates primarily to the kidney. There are two primary means by which the kidney may be preserved following explantation, cold static storage and pulsatile machine perfusion (MP). MP was developed prior to the 1970s and became prevalent thereafter. This technique suffers from several significant disadvantages including the cost of the device and consumables, the risk of machine failure and the requirements for an operating technician. MP was subsequently largely abandoned when the literature could find no evidence that long-term outcome was improved with MP versus cold storage alone (Opelz and Terasaki 1982).

Following a period of enthusiasm for cold storage alone, attention shifted back to the use of MP in the belief that rates of delayed graft functioning (DGF) might be diminished following MP. There was evidence to suggest that DGF contributed substantially to the cost of post-transplant care with increased requirements for dialysis and longer hospital stays. Later reports suggested that DGF might also contribute to poorer long-term outcomes (Cecka and Terasaki 1995). All of these factors contributed to a renewed interest in MP. Wight et al. undertook a meta-analysis to determine the effectiveness of MP relative to cold storage. Although they found that the literature was lacking in high quality studies, they concluded that MP results in a 20% reduction in DGF in both NHB and heart-beating kidney donation with diminished cost requirements for the care of the transplant recipient when compared to costs of patient care when cold storage was utilized (Wight, Chilcott et al. 2003; Wight, Chilcott et al. 2003).

Kootstra later reported that he had re-introduced machine preservation into his practice in 1993 (Kootstra, Kievit et al. 2002). In addition to the potential benefits mentioned above, this technology offered an additional advantage: it allowed their team to execute viability tests in which they performed intrarenal vascular resistance calculations and serial estimations of perfusate lactate dehydrogenase and glutathione S transferase concentrations. The latter, an enzyme found specifically in proximal renal tubular cells, has been shown to correlate with the degree of ischemic damage to which the procured kidney has been exposed (Daemen, Oomen et al. 1997).

Surgical recovery of the kidneys may be followed by cold storage using EC or UW solution or by machine perfusion using cryoprecipitated plasma (Matsuno, Sakurai et al. 1993; Matsuno, Sakurai et al. 1994). While the temperature and pH of the perfusate and the machine perfusion pressure were set based upon reasonable physiologic arguments, no evidence basis for these parameters could be identified. Nonetheless, Matsuno et al. concluded that their technique for machine perfusion might improve post-transplant outcomes for marginal kidneys by providing the metabolic substrates required to preserve hypothermic metabolism and that machine preservation was superior to cold storage of the kidneys alone.

## **8. End-of-Life Issues and the Potential NHB Donor**

Virtually all patients destined to become NHB donors are managed in the intensive care or emergency services/trauma room environment in the final hours of their lives. While many of these patients will have sustained catastrophic irreparable neurological injury, they may not fulfill all criteria for neurological determination of death. A small number of patients may retain their mental faculties in spite of life-sustaining intervention. An example of such an individual would be one who has sustained a cervical spinal cord injury requiring lifelong ventilation.

### **Ethical principles**

Van Norman describes many of the important issues that arise in the management of NHB donors from ethical, legal, and policy perspectives in a comprehensive review of these issues (Van Norman 2003). The principles that apply to all patient care must be applied to the care of all critically ill patients and, hence, to all potential NHB donors. All patient related decisions must respect patient autonomy and beneficence while ensuring nonmaleficence.

#### ***Patient autonomy***

Respect for patient autonomy is based on the tenet that the competent patient has the fundamental right to make all decisions regarding their body, their medical care, and their lives. Furthermore, patients have the inherent right to forgo life-sustaining procedures as they see fit. These principles apply in most, if not all, Western nations. A problem that may arise more commonly in the care of uncontrolled NHB donors is that the wishes of the patient may remain unknown. This may be further complicated by the absence of an appropriate surrogate decision maker, preferably one who has some knowledge of the patient's wishes prior to the critical event. Most potential NHB donors will not have the opportunity or the ability to participate in decision-making in regards to their medical treatment or the decisions regarding potential organ donation. Durable power of attorneys and living wills must be accommodated by medical caregivers whenever identified. Using these tools, patients can make their wishes known and can participate in decision-making in regards to their terminal medical care to the greatest extent possible.

#### ***Beneficence***

Beneficence refers to the principle of doing "good" for the patient foremost and taking into account the welfare of society secondly. Provision of life-sustaining therapy places significant psychosocial burdens on both the patient and the patient's family. Physicians often describe a sense of discomfort with the idea of withdrawing therapy from a patient, yet withdrawal of therapy is consistent with the principle of beneficence and nonmaleficence provided that patient dignity and suffering are preserved and avoided respectively. The decision to donate organs at the end of life may provide both the patient and the family with some degree of fulfillment that they are contributing positively to the life of another human being and this may help ease the grieving process.

### ***Nonmaleficence***

Nonmaleficence refers to the principle of “doing no harm.” This must not be interpreted to suggest that physicians have the right to do anything in their power to sustain life. The withdrawal of therapy is entirely consistent with the principle of nonmaleficence where it is executed while preserving the patient’s dignity and respect for the patient’s rights to self-determination. Nonetheless the principle of nonmaleficence may be undermined if, in the process of proceeding with organ donation, the patient’s imminent death is manipulated for the purpose of organ procurement, or if the patient’s death is somehow precipitated by the administration of medical therapy. Medical treatments to attenuate pain and suffering may be administered to patients and may, in some cases, accelerate the process of death, but they are administered to comfort the patient and to relieve suffering rather than to purposefully modify the process of death.

### **End-of-life care and addressing conflicts of interest**

Because the above principles are inherently fundamental to the patient’s medical care, the treatments and processes related to end-of-life care must be totally separated from any discussions regarding organ donation. By definition, this is always the case when dealing with uncontrolled NHB donors. With Maastricht Category III patients, treatment is usually withdrawn in a sequential fashion in anticipation that the patient will die, usually within the first hour following withdrawal of treatment. Discussions regarding organ donation should proceed only following a decision to withdraw treatment, unless specific questions arise from the patient and the family beforehand. In the latter instance, it may be more appropriate to involve individuals from an organ procurement program in addressing concerns regarding organ donation so as not to create a conflict of interest for physicians involved in the medical management of the patient’s care.

Although not always possible, in most instances the more detailed discussions regarding organ donation and procurement are best separated from the medical care. These concerns are raised by a letter from Guest in response to an article published by Campbell and Sutherland (Campbell and Sutherland 1999; Guest 2000). Physicians would be clearly in conflict of interest were they to provide medical care for a critically ill patient and advocate for organ donation at the same time. In response Sutherland is in agreement that the imminent death of a loved one must be accompanied by sufficient time to “digest” the circumstances. Sutherland goes on to cite two papers which illustrate that separation of these two processes yields a better rate of consent for organ donation in the long run (Cutler, David et al. 1993; Gortmaker, Beasley et al. 1998).

In these instances, it is often most appropriate for medical caregivers to divorce themselves from discussions regarding organ donation to the greatest extent possible. It is also most appropriate to delegate these discussions to representatives from an organ procurement organization and/or a program representative from the health care organization itself. Individuals from programs such as these are trained professionals who are capable of determining suitability for organ donation and who are familiar with the intricacies of the donation process. Moreover, these individuals usually have access to other professionals capable of providing appropriate support for the patient, surrogate, and the grieving family. Decisions can be made regarding the involvement of surrogates and family during the patient’s death and arrangements for timely transfer to the operating room can be made.

The Pittsburgh (University of Pittsburgh Medical Center or UPMC) Protocol (Appendix I) for the management of the non-heart-beating organ donor is typical of many developed worldwide. While clearly formulated on the principles of American jurisprudence and legal precedent and rooted in the morals, values, and ethics of American society, it can serve as a useful model for NHB donor protocols elsewhere.

This protocol unambiguously enunciates the basic principle that patient care issues must be totally differentiated from those related to organ procurement. Patient care must be optimized while preserving the rights of the patient to autonomy and comfort. Any interventions intended to prospectively address preservation of a procured organ are expressly forbidden if they are likely to hasten the death of the patient or impose pain or suffering on the patient. Detailed discussions regarding organ donation and procurement are not to be held until the decision to withdraw medical therapy has been made. Documentation of the nature and details of the discussions with the patient and/or the medical surrogate must be provided in the patient's medical record.

### ***Role of the physician***

It is equally important that physicians involved in the initial patient care and in the withdrawal of therapy as the patient dies must not be involved in the procurement and transplantation processes. The Pittsburgh Protocol requires physicians and caregivers who may be in conflict to voluntarily withdraw from such cases.

The job of the physician withdrawing life-sustaining therapy may also include the declaration of death in the surgical suite. To avoid conflict of interest, this individual should not be a member of either the procurement or the recipient transplant team.

### ***Role of the anesthesiologist***

Anesthesiologists involved in managing organ recipient cases should not be involved in the management of the donor. Van Norman analyzes issues regarding the involvement of third party anesthesiologists during withdrawal of life-sustaining measures (Van Norman 2003). This question may arise as access to a surgical suite is typically required for organ procurement. Many anesthesiologists only learn of their potential role in these cases when they are "assigned" to deal with these cases.

Van Norman provides a cogent argument, stating that the withdrawal of therapy for a patient requires specific knowledge about the complex interventions that have been introduced and that physicians providing such care require detailed knowledge and have significant experience in the management of end-of-life issues. While anesthesiologists often have sufficient understanding of pharmacology and interventions offered to these patients, they are seldom trained in other matters pertaining to end-of-life. Van Norman concludes that individuals involved in withdrawal of therapy should also have been involved in the earlier care of the NHB donor. Her arguments were reinforced by Truog who agreed that withdrawal of supportive therapies should not be diverted to anesthesiologists with limited experience in end-of-life care (Truog 2003).

## **9. Defining, Declaring and Predicting Death**

### **Defining death**

In the United States, the Universal Determination of Death Act (UDDA) forms the foundation upon which death is declared. It specifies that death may be ascertained by the irreversible loss of all brain function (often referred to as determination of death by neurological criteria) *or* by the irreversible cessation of cardiorespiratory function. A key point of note is that the UDDA has never provided rigid criteria for determination of death regardless of applied approach to declaration of death. It is held that the death should be declared based upon current standards established by the medical community. This approach allows for a gradual evolution of the criteria as new scientific developments emerge.

### **Cardiorespiratory declaration of death**

A very important aspect related to NHB organ donation is the appropriate and prompt diagnosis of death by cardiorespiratory criteria. The “dead donor rule” clearly requires assurances that the patient has expired prior to procurement-related endeavors outside of possibly moving the patient from the intensive care setting into the surgical suite.

The diagnosis of cardiorespiratory death is dependent upon documentation of irreversible cessation of cardiac functioning over a satisfactory period of time. Outside of review articles on the management of NHB donor patients, the cardiorespiratory criteria for death are rarely mentioned in the literature. This literature review did not identify any studies examining the various methods of monitoring for cardiac function at or near the time of death. Furthermore, some of the published protocols do not clarify the criteria to be used, e.g., Guidelines and Procedures of the New England Organ Bank (Institute of Medicine 2000). These guidelines usually specify the required duration of asystolic circulatory arrest but may not specify the methods by which arrest of cardiac function is to be confirmed.

### **The asystolic “hands-off” period**

While there has been substantial work published on neurological determination of death, literature pertaining to death by cardiopulmonary criteria is largely lacking. The 1997 report of the Institute of Medicine recommended that a five-minute interval be allowed to elapse following cardiopulmonary arrest and declaration of death before proceeding with controlled NHB organ procurement (Institute of Medicine 1997). This position was based upon expert judgment and knowledge of the physiology of the central nervous and cardiovascular systems. Nonetheless, the IOM also recommended that further study to validate this five-minute interval was in order, citing a lack of scientific evidence to support their position.

### **Irreversibility of death**

In a work commissioned for the IOM, the concept of irreversibility related to cardiopulmonary arrest was raised by Younger, DeVita, and Arnold. Although little is written about it, there has been speculation that a phenomenon known as autoresuscitation may exist. This refers to a spontaneous resumption of cardiac function following cardiopulmonary arrest. However, irreversibility of cardiorespiratory arrest may be conceptualized differently by different readers. For example, one view might perceive irreversibility as an absence of spontaneous return of

cardiopulmonary activity while a second view might describe irreversibility as a failure to return spontaneous cardiac activity following maximal efforts to resuscitate the patient (e.g., defibrillation or advanced cardiac pharmacotherapy).

The IOM argues that, in the context of end-of-life care for intended NHB donation, the patient or the patient's designate has made a conscious decision to terminate supportive measures. The IOM goes on to argue that it would seem appropriate, therefore, that irreversibility would be defined by the absence of spontaneous recovery of cardiorespiratory function in this instance (Institute of Medicine 2000).

## **Neuromuscular blocking agents**

Neuromuscular blocking agents are frequently administered in the intensive care environment. To meet the requirements cited above, either spontaneous resolution or reversal of pre-existing neuromuscular blockade would be required prior to declaration of death. Truog, however, has concluded that "when death is expected to be both rapid and certain after removal of the ventilator," reversal of neuromuscular blockade is not necessary (Truog, Burns et al. 2000). This opinion is also supported in a publication by Henig et al. (Henig, Faul et al. 2001).

## **Protocols in declaring death**

### ***Leicester protocol***

In the Leicester protocol, efforts to diminish the effects of ischemia are introduced following a 10-minute asystolic period. This "hands-off" time period was felt to be most appropriate to ensure NHB donor brain death. It is also consistent with the recommendations of the President's Commission in 1981 which applied a 10-minute period of cardiorespiratory arrest as the threshold for declaration of death (The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research 1981).

### ***University of Maastricht protocol***

In contrast, in 1995 Heineman supported the use of a five-minute asystolic period following declaration of death by cardiorespiratory criteria at the University of Maastricht (Heineman, Daemen et al. 1995). In the subsequent discussion, Hené described a 10 to 15 minute "hands-off" period in Category III patients that he managed in Utrecht, Netherlands, arguing that patients were not necessarily brain dead unless that amount of time was allowed to expire. In response Kootstra commented that, because these patients are in a highly controlled environment and efficient placement of vascular cannulae should keep WIT under 30 minutes duration, there is often little concern in extending the waiting period to 15 minutes. However, he also suggested that because cooling catheter placement may take up to 20 minutes, the procedure of placing such catheters could proceed prior to the completion of elapsed asystolic period. While longer warm ischemic periods may be tolerated by the kidneys, there is evidence that this may not be the case when procuring livers for transplantation

### ***Pittsburgh protocol***

At the University of Pittsburgh, policy requires documentation of appropriate placement of electrocardiographic leads and absent femoral pulsation (a non-detectable pulse pressure) as documented by a femoral arterial catheter (Institute of Medicine 2000). The patient must remain apneic and non-responsive to verbal stimuli. Two minutes of ventricular fibrillation, electrical asystole, or pulseless electrical activity (formerly referred to as electromechanical dissociation) are considered adequate to meet cardiorespiratory criteria for death, providing the aforementioned conditions are met. These exact criteria for death are also used by SHANDS at the University of Florida, Gainesville (Institute of Medicine 2000). The Pittsburgh Protocol is perhaps the most controversial, using only a two-minute period of circulatory arrest prior to surgical intervention. This criterion was adopted based upon the belief that spontaneous resumption of respiration and circulation will not return following this length of time. Resuscitative measures are not introduced by the team; hence, it remains unclear if the patient could be resuscitated at this point were attempts initiated. The rationale for this timing is based upon a report by DeVita et al. with data from 108 patients. Nonetheless, as successful resuscitation has been documented as late as 15 minutes following cardiorespiratory arrest, it would appear that even a 10 to 15 minute asystolic period is at least somewhat arbitrary in duration (DeVita, Snyder et al. 2000). In light of these reports, some clinicians have called for a prospective study of dying patients to ensure that autoresuscitation does not occur beyond the two-minute time interval described in the Pittsburgh Protocol.

### **Controversies in declaring death**

Not everyone is in agreement with the position taken by the IOM, however. Menikoff has probably been one of the most vocal critics of the IOM's current position (Menikoff 2002). He notes that until recently there was little need for the medical community to concern itself with the timing of a patient's death. Whether the patient was declared dead 5, 10, or 30 minutes following cardiopulmonary arrest was irrelevant. However, when contemplating NHB organ procurement, the duration of circulatory arrest becomes an important issue as the organs will deteriorate rapidly following cessation of perfusion and oxygenation. Menikoff's arguments are two-fold: 1) that irreversibility of cardiopulmonary functioning may not be guaranteed following a five-minute period of arrest and 2) that portions of the dying person's brain may not have ceased functioning totally at this point. This literature review could not identify any evidence base for either Menikoff's arguments or the IOM position. The absence of supportive scientific evidence lends credence to the IOM recommendation that further study be undertaken to clarify these issues.

### **Predicting death**

Lewis et al. recently reported the development of the University of Wisconsin Donation After Cardiac Death Evaluation Tool (Lewis, Peltier et al. 2003). The objective of this paper was to develop a predictive instrument by which patients expected to die within a 120-minute period upon discontinuation of life-sustaining medical therapy could be identified. Since 1974, the University of Wisconsin has gained extensive experience with donation after cardiac death and it currently derives 10% to 15% of its donors from its NHB organ donation program. Lewis's team sought to develop a tool that accurately identified potential NHB donors. The testing protocol collected information which included patient age, airway status, vasopressor and inotrope

therapy, and the respiratory status following 10 minutes of disconnect from the ventilator including respiratory rate, tidal volume and negative inspiratory force, as well as vital signs including blood pressure, pulse, and oxygenation saturation. An assigned scoring system yielded a final total score which correlated well with the time it took for a patient to die following extubation. The authors cautioned that this paper was an early iteration of a process that required additional work including analyses of other variables that might further improve the sensitivity and specificity of the tool.

## **10. Ethical Implications of Donor-Based Interventions**

For controlled donation, the ethical implications are related to interventions after consent but prior to death. For uncontrolled donation, the ethical implications are related to interventions after death but prior to consent.

### **Pharmacotherapeutic agents**

Questions of timing may be asked in relation to the administration of pharmacotherapeutic agents around the time of death. The administration of these agents does not offer any benefit to the prospective donor. There is potential for harm in situations where these drugs may be contraindicated. The Institute of Medicine recommends full disclosure for administration of pharmacotherapeutic agents to prospective donors when seeking consent for NHB organ donation.

#### ***Heparin***

Excluding supportive pharmacotherapy, heparin is the most commonly administered drug around the time of death of NHB donors. Some institutions administer heparin routinely while others decide on a case-by-case basis. Evidenced-based literature supporting a specific dosage or timing protocol for heparin administration could not be identified. The Institute of Medicine recommends that heparin administration be considered on a case-by-case basis and that it is contraindicated in the presence of active bleeding. Where required, end-of-life protocols call for the administration of heparin once perfusion pressure begins to diminish.

#### ***Phentolamine***

Phentolamine, a non-specific  $\alpha$ -receptor antagonist, may also be administered resulting in vasodilatation which is intended to enhance target organ blood flow. It, too, provides no benefit to the prospective donor and may result in a decrease in perfusion pressure in some instances. As with heparin, the Institute of Medicine advises that decisions regarding the administration of phentolamine should be made on a case-by-case basis. Review of published protocols would suggest that phentolamine is seldom given routinely. Although the literature suggests that phentolamine is commonly administered, an evidence-base for this practice could not be identified during this review.

### **Organ perfusion following death**

Following declaration of death some centers may also choose to re-introduce cardiopulmonary resuscitation in an effort to provide some degree of perfusion of targeted organs and oxygenation of the lungs. These measures may include manual cardiopulmonary resuscitation with re-intubation (if necessary) and manual cardiac compressions, machine controlled ventilation and pneumatic cardiac compression, or extracorporeal membrane oxygenation where applicable. This review could not find any evidence-base for any of these interventions although efforts to sustain organ perfusion would appear to be inherently logical.

## **11. Consent of in situ preservation**

### **Uncontrolled donors**

Management of uncontrolled NHB donors is complicated by the fact that medical teams are unprepared for commencement of in situ preservation. Ideally, in North America, informed consent prior to the introduction of preservation catheters should be sought, but the patient's wishes may be unknown and next of kin may be absent at the time of presentation. Because of these issues, some jurisdictions, including some American states, have adopted laws which allow for in situ preservation without consent (District of Columbia DC ST 2002; Florida Statutes 2002; Virginia State Code 2002). Despite legalization of these interventions, serious ethical questions regarding the appropriate conduct of physicians at the time of the patient's death remain an issue. There are two schools of thought on the issue of in situ preservation without prior consent. Minimization of WIT preserves organ post-transplant function and provides the family with an opportunity to consider the merits of organ donation in a less hurried and somewhat less stressful environment. Nonetheless, ethical questions may arise when medical interventions are performed in the absence of prior informed consent from the patient and/or the family. Many authors do not support these interventions, arguing that dignity for the dead is undermined by the unilateral decision of medical caregivers to proceed with these interventions. Some of these authors go on to argue that the decision to allow in situ interventions without consent mandates the approval of society at large. It has been suggested that these discussions would best be held in the public domain and support from "an overwhelming majority" should be assured before proceeding with non-consented practices. Without broad community support for such practices, public confidence in the medical community and transplant processes could be severely undermined. Potentially, this could serve to further reduce the numbers of future potential organ donors.

### **Presumed consent for cannulation**

In his historical account of organ donation after cardiorespiratory death, DeVita describes a series of events involving physicians at the Regional Organ Bank in Illinois (DeVita, Snyder et al. 1993). They unsuccessfully attempted to secure permission to procure organs from 35 eligible NHB donor candidates by approaching the families for consent to insert intravascular preservation cannulae. In a total reversal of strategies they then undertook to approach families for consent having already placed catheters, thereby employing the notion of presumed consent. Given the opportunity to consider the option of organ donation in a less stressful and hurried environment, six of seven families opted to proceed with organ donation. Despite this dramatic reversal in support for NHB donor after presumed consent, this approach is not without risk. Seltzer et al. reported results from a public survey in which 74% of respondents opposed allowing physicians to proceed with intravascular cannulation without prior consent (Seltzer, Arnold et al. 2000).

## **12. Transplantation Outcomes from NHB Donors**

Numerous published articles attest to the long-term efficacy of NHB kidney transplantation in the management of dialysis-dependent chronic renal failure patients (Daemen, Heineman et al. 1995; Cho, Terasaki et al. 1998; Hoshinaga, Shiroki et al. 1998). Despite these encouraging results a significant number of medical management issues may still arise, particularly delayed and primary graft non-function. Some U.S. medical centers have also reported success in transplanting extrarenal organs derived from NHB donors (Casavilla, Ramirez et al. 1995; D'Alessandro, Hoffmann et al. 1995).

### **Early kidney graft function**

Cho et al. examined early graft function and transplant survival rates of 229 NHB kidney grafts obtained in patients in whom treatment was withdrawn (Maastricht Category III – controlled) when compared to transplants from 8,718 cadaveric donors with heartbeats (Cho, Terasaki et al. 1998). Transplants were performed in 64 American centers from 1994 to 1996. At the end of one year, graft survival rate was 83% in the NHB donors while 86% of grafts from heart-beating donors had survived ( $P=0.26$ ). This modest difference in survival rate was evident within the first month of transplantation, suggesting that ischemic injury during the procurement and transplantation process might have contributed to the poorer early phase outcome. NHB donor kidney grafting was characterized by increased rates of delayed graft function with an early dialysis rate of 48% in the first week post-transplantation as compared with a 22% dialysis rate in patients who had undergone transplantation with heart-beating renal grafts. Cho further analyzed the data and documented an 89% survival rate for renal grafts from NHB trauma victims which exceeded the 78% survival rate from kidney grafts from NHB donors who had succumbed to other causes ( $P=0.04$ ). It was thought that this increased rate of survival might be related to the age of the trauma victim, but age stratification of the data did not bear out this hypothesis. The authors also concluded that improved techniques for determination of kidney viability after procurement might contribute to better selection of transplanted grafts and, hence, better graft survival.

### **Delayed kidney graft function**

Early work focused on the importance of minimizing ischemic injury to the NHB donor organ. While it is widely accepted that delayed graft function (DGF) in kidney transplant recipients is a consequence of warm ischemic injury to the donor organ, it has also been recognized that other factors may also play a role in DGF. Premorbid donor status is thought to play a significant role in the development of DGF, hence the exclusion criteria for NHB donors (Cacciarelli, Sumrani et al. 1992; Cecka, Cho et al. 1992; Thorogood, van Houwelingen et al. 1992). Perhaps, more surprisingly, there is some evidence that recipient factors may also play a role in graft survival. Yokoyama et al. documented that longer duration of dependency on hemodialysis and increased recipient body weight may contribute to graft dysfunction (Yokoyama, Uchida et al. 1996). Cold ischemic time associated with organ preservation following procurement and the type of preservation methodology has also been correlated with DGF and may compound the impact of WIT (Cacciarelli, Sumrani et al. 1992).

## **Other kidney outcome studies**

Hoshinaga et al. reported the results from a single Japanese center's experience with NHB kidney grafting (Hoshinaga, Shiroki et al. 1998). They reported on 359 grafts obtained from 181 NHB donors acquired from April 1979 until December 1997. Donor deaths were related to cerebrovascular disease in 114 cases and due to other causes in 67 donors. Informed consent for placement of intravascular catheters prior to or immediately following death was reported, implying that procured kidneys were derived from controlled donors. Age range of NHB donors was from 7 months to 70 years. In situ preservation techniques were used in procuring transplanted organs. Of the acquired kidneys, 9.7% were discarded because of bacterial contamination or due to poor arterial perfusion of the organ. Post-transplant immunotherapy varied amongst the recipients of these grafts, presumably due to evolution of therapy over this long time frame. Azathioprine treated patients suffered a higher rate of primary non-function, consistent with reports from other centers, when compared to patients treated with cyclosporine and tacrolimus. Hoshinaga also noted that increased serum creatinine levels were associated with prolonged post-transplant dialysis and that increased donor age was directly associated with an increase in serum creatinine levels. Donors with cerebrovascular disease were also noted to have elevated levels of serum creatinine. It is not surprising, therefore, that NHB grafts from cerebrovascular disease patients and more elderly patients ( $\geq 56$  years) were associated with impaired post-transplant function. Rates of NHB donor graft survival followed for 10 years were substantially similar to those documented by the UNOS Transplant Registry up to 10 years following transplantation.

Balupuri et al. reported their experience with renal transplantation as their program transitioned from using Maastricht Category III controlled donors to Category II uncontrolled donor patients (Balupuri, Buckley et al. 2000). Using Category III NHB donors, Balupuri had documented a 90.5% graft success rate, the same as that for heart-beating kidney transplantation. His results were similar to those reported above. Early efforts using kidney grafts from Category II patients, however, resulted in poor rates of graft survival (45.5% success) and the program was temporarily halted. The problems encountered by Balupuri were consistent with those described by surgeons in Maastricht (Daemen, Heineman et al. 1995; Daemen, de Vries et al. 1997). Although earlier efforts of kidney preservation using machine perfusion did not seem to afford any benefit in terms of graft survival, the introduction of UC preservation solution resulted in significant decreases in rates of delayed graft function. By using improved machine perfusion techniques and by introducing NHB donor glutathione S transferase analysis to assess viability, Balupuri was able to achieve a graft success rate of 92.3% excluding two patients who apparently died from unrelated causes.

## **Liver transplant outcomes**

D'Allesandro subsequently described the results of NHB donor liver transplantation in 19 patients when compared to 364 recipients of heart-beating donor livers (D'Alessandro, Hoffmann et al. 2000). He reported that primary non-function was more likely to occur when NHB donor livers were used and that allograft survival was diminished with NHB donor transplantation (53.8% vs. 80.9%,  $P=0.007$ ). Nonetheless, D'Allesandro considered these early results to be encouraging and recommended that further efforts to use NHB donor livers should be pursued with caution.

A more recent article by Abt et al. casts some doubts upon the practice of NHB liver transplantation (Abt, Desai et al. 2004). Using the UNOS database they retrospectively examined and compared the outcomes of 144 NHB transplantations with that of 26,856 heart-beating liver grafts. The NHB livers were reported to come from a mixed group of patients: 117 from controlled patients; 16 from uncontrolled patients; and the status of the remaining 11 patients could not be identified. While controlled and uncontrolled allografts had similar survival rates, patients with unrecorded status had poorer survival for inexplicable reasons. When controlled NHB graft recipients alone were compared to heart-beating recipients, the difference in one-year survival bordered on statistically significant ( $P=0.056$ ). This trend did not persist at three years however. Overall, NHB graft survival was significantly diminished relative to that of heart-beating graft recipients ( $P=0.003$  and  $P=0.012$  at one and three years respectively). Prolonged cold ischemic time and recipient life support were correlated with poorer outcomes among recipients of NHB liver grafts. Despite the poorer overall outcomes with NHB liver grafting, the authors cautiously support the continued practice of NHB liver transplantation. They concluded that by minimizing cold ischemic time to less than eight hours and by selecting non-intubated recipients who did not require vasopressor support, outcomes might be improved.

## **Multi-organ**

D'Alessandro et al. described their experience with “en bloc” retrieval of the liver, pancreas, and kidneys (D'Alessandro, Hoffmann et al. 1995). The authors related their experience with 16 controlled NHB donors presenting from January 1993 through May 1994. Extrarenal organ procurement was achieved in 10 of 16 NHB donors with a mean warm ischemic period of 15.4 minutes. Isolated renal transplantation was performed in 21 patients, three of whom required hemodialysis during recovery. At the time of publication 19 of 21 kidney transplants remained functional. Five livers were transplanted. One case of primary non-function due to technical problems was described and required re-transplantation. Of the remaining four liver transplants, three patients were still alive after a mean follow-up of 12.7 months. Six patients underwent combined kidney-pancreas transplantation. All of these patients remained free of insulin dependency at the time of publication. Only one of six patients required hemodialysis during recovery. A single lung transplant was also attempted during this time period. The lung allograft was lost 81 days following transplantation but the patient survived subsequent re-transplantation. The authors concluded that, using controlled NHB organ donors, salvage of extrarenal organs can be successful. At their institution, the total number of organs transplanted increased by 8.6% with the introduction of renal and extrarenal organ transplantation from NHB donors.

## **13.A Canadian Perspective on NHB Donation**

### **Addressing the gap between supply and demand**

In 2003, Knoll and Mahoney reported that the number of Canadians awaiting transplant had increased by 84% in the last decade while cadaveric organ donation rates remained steady (Knoll and Mahoney 2003).

Early efforts to address the organ supply-demand imbalance focused on public education regarding the benefits to be derived from organ donation programs. At the outset, it was thought that this alone would address the issue of dwindling organ donation in both the United States and Canada. It has now become apparent that supply and demand disparity is a far more complex issue and that other factors are at play in determining a donation rate such as that found in Spain (Baxter 2001). For example, population demographics play a significant role in organ donation with an increase in organ availability in regions where patient populations are younger and are engaging in potentially riskier activities (Baxter 2000). It is widely recognized that younger populations are more susceptible to death through blunt traumatic injury.

Despite this and a youthful age demographic, Canada has still been experiencing a diminution in the numbers of catastrophic brain injured organ donors. This may be a result of active preventative public health initiatives and legislative changes, both of which have raised public awareness of safety in regards to traumatic brain injury. A reduction in the severity of head injury in conjunction with improved neurological resuscitative measures in the presence of severe head injury has contributed to improved clinical outcomes for closed head injured patients. In this regard, Canada's experience is similar with that of much of the Western world.

### **Potential of NHB donation in Canada**

Canadian transplant surgeons have performed retrospective analyses of medical records in an effort to define the potential number of unidentified NHB donors. Taylor et al. completed a health records audit to determine the number of potential NHB donors in their practice in a 12-month period (Taylor, Field et al. 1996). They identified 28 patients who had treatment electively withdrawn, all of whom met solid organ donation criteria. Of these 28 patients there were no organ donors. Lacroix et al. performed a similar audit at the Ottawa Hospital to determine whether renal transplantation rates could be improved with the introduction of an NHB donor program (Lacroix, Mahoney et al. 2004). They concluded that recruitment of NHB donors would add 12 to 34 kidneys per year to the pool of donors from their hospital alone. In both cases, the authors concluded that rates of cadaveric organ transplantation would be significantly increased were Canadian hospitals to introduce NHB donor protocols and procedures. Campbell and Sutherland performed a chart review of 209 patients who died in the intensive care units and emergency department of the Foothills Hospital in Calgary in 1995 (Campbell and Sutherland 1999). A potential total of 17 controlled NHB donors, with a mean age of 62 +/- 19 years, were identified in this review. Seventy-one percent of patients had suffered a cerebrovascular accident and 59% did not meet criteria for neurological determination of death as they had at least one persistent brain stem reflex. Thirteen of the seventeen patients died within one hour of having ventilatory support withdrawn. During the same time period 33

“conventional” heart-beating donors were identified and, of these, 21 (64%) became organ donors. Projecting similar percentages for refusal and non-viability of procured organs, Campbell and Sutherland concluded that an additional 10 donors per year could be identified if a program for controlled NHB donor organ retrieval were instituted at their facility.

## **Barriers to NHB donation in Canada**

Organ donation from patients declared dead by neurological criteria is well established throughout Canada and the Western world. Consideration for NHB organ donation is far less well established. This literature review could not identify any existing protocols for NHB organ donation in Canada. There are a number of issues that must be carefully considered in developing protocols for NHB organ donation. Knoll and Mahoney identified three primary impediments to adopting a policy for NHB organ donation in Canada: education, ethics, and availability of resources (Knoll and Mahoney 2003).

### ***Education***

The current generation of Canadian clinicians is generally more familiar with organ transplantation from brain-dead donor organs compared with that derived from NHB donors. Older physicians, who may recall NHB cadaveric transplantation from days gone by, may be equally unfamiliar with recent medical literature which documents that outcomes of transplantation using NHB kidney donors are comparable to those following renal transplantation using brain-dead donors (Weber, Dindo et al. 2002). Furthermore, many physicians remain unaware that NHB donors may also provide organs for liver, pancreas, and lung transplantation. These educational shortcomings underscore the need for extensive education programs in transplantation issues for all medical caregivers working in emergency departments, intensive care units, and surgical suites across Canada.

### ***Ethics***

It is also evident that many Canadian physicians may be reluctant to engage in the care of NHB donors, citing ethical concerns regarding this practice. This, too, may be related to an incomplete understanding of medical issues pertaining to NHB organ donation within the Canadian medical community.

### ***Availability of resources***

Finally, Knoll goes on to argue that emergency departments and intensive care units may be incapable of dealing with NHB donors as resources required to deal with these patients might divert care away from other seriously ill patients. He recommends the creation of coordinating teams which would provide comprehensive facilitation of organ and tissue procurement, a suggestion which is consistent with the evolution of OPOs in the U.S.

These obstacles to change are substantially similar to those described by the Institute of Medicine (IOM) in their report on NHB organ transplantation published in 2000 (Institute of Medicine 2000). The IOM surveyed participating organizations seeking to define factors that limited acceptance of NHB organ donation. These were broadly categorized as being related to:

1. internal hospital issues
2. OPO related factors
3. concerns regarding negative publicity
4. concerns regarding ethics
5. organ quality.

The IOM report concluded that to introduce change and to foster clinical innovation in NHB organ transplantation there will be a need for extensive education, training, research, and financial investment—a challenge similar to that found in Canada today.

## **Conclusion**

Scarcity of organs for transplantation is a common thread in much of the medical literature written in the Western world about NHB organ donation. As far back as 1996, Taylor examined data from a Canadian hospital and concluded that NHB organ donation could provide significant numbers of organs for transplantation (Taylor, Field et al. 1996). While probably not meeting requirements to address this disparity between supply and demand, these additional organs would go a long way to dealing with the current shortfall. Approximately eight years have passed and this literature review did not find any published evidence that Canadian hospitals have moved forward on the issue of procuring organs from NHB donors. Given the complex logistics in administering any program for NHB organ donation and the strained financial resources that Canadian health institutions have faced in the last decade, this is not particularly surprising.

As governments have begun to reign in the significant debt load at all levels and as there appears to be a greater interest in investing in health programs, this may be a most opportune time to scrutinize the issue of NHB organ donation more closely. It would appear that a reasonable starting point might be the introduction of controlled NHB organ donation in selected centers across the country.

To proceed with such a program, several major hurdles must be overcome. This review could not identify any protocols for non-heart-beating organ donation in Canada. All policies and procedures for such a program must be carefully planned and elucidated. These policies and procedures must be guided by current legal and ethical standards and, to the greatest extent possible, must be supported by public opinion. The experiences of other nations teach us that alienation of the community may have significant long-term negative impacts on organ transplantation proceedings that may be difficult to overcome.

Introduction of NHB organ donation into Canadian medical institutions will require significant financial investment from all levels of government. While some transplant support programs do currently exist in Canada, few seem to have the in-depth experience and access to resources that organ procurement organizations elsewhere have. Certainly, the presence of currently existing transplant support organizations and their activities remain largely unknown in the community today.

If there is interest in extending efforts into securing uncontrolled Maastricht Category II and Category IV NHB organ donation, then the pressures of timely intervention will place an even greater burden on support organizations and the medical community. Some authors have already expressed doubts that a typical Canadian emergency department will be able to meet the needs of its normal patient population while providing for a non-heart-beating organ donation patient.

At the conclusion of this literature review, it is abundantly clear that NHB organ procurement is an opportunity that the Canadian medical community has largely failed to address. There are numerous challenges and obstacles to be met in considering this opportunity. The task of moving forward will not be easy and will face many impediments. The Canadian Forum on Donation after Cardiocirculatory Determination of Death is a commendable first step in moving forward in this direction.

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