Donor Organ Management: Literature Review

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by

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Introduction

The gap between the number of patients added to national transplantation lists and those undergoing transplantation widens each year. Fundamental to this widening gap is a failure to maintain adequate support to brain-dead donors, which accounts for at least 25% of lost donor organs.\(^1,2\) Effective medical management to optimize donor organ potential may increase the number of organs retrieved for transplant.\(^3,4\) The purpose of this paper is to review the literature on the optimal management of the brain-dead (cadaveric) organ donor in preparation for a national Forum, Medical Management to Optimize Donor Organ Potential.

The purpose of this Forum is to bring together national experts in the areas of transplantation, intensive care, neurosurgery and medical administration to initiate the formulation of a national agreement on two aspects of organ donation: how to optimize the medical management of the potential solid organ donor and how to expand the eligibility of organ donors while addressing the organizational and logistical challenges from the neurological determination of death to organ procurement. It is hoped that collegial dialogue resulting from this Forum will improve the care of organ donors, expand the existing criteria for organ donation and ultimately result in improved graft and recipient survival rates as well as recipient quality of life.

The Existing Scientific Literature

Citations used in this document were selected from searches of the MEDLINE database from 1966 until present, using search terms “brain death”, “organ donation”, “organ donor”, “heart/kidney/lung/liver and transplant”, “thyroid/insulin/diabetes insipidus and brain death”. Other citations were extracted as references from the initial citations, from the personal databases of the author and members of the Forum Steering Committee and from three previous consensus conference documents from the American Society of Transplant Surgeons, the American Society of Transplantation and the Pulmonary Council of the International Society for Heart and Lung Transplantation.\(^3-6\)

Unfortunately, the existing scientific literature is largely comprised of small animal experiments, human case series and retrospective reviews. Although these studies have an important role in elucidating the pathophysiology of brain death and its effects on the inflammatory, cardiovascular, respiratory, renal, hepatic and hormonal systems, there are many limitations to the existing literature:

- Many of the therapeutic strategies investigated in animal experiments and human case series have not been evaluated in clinical trials.
- The majority of human case series that advocate specific therapeutic interventions often fail to control for the illness severity of the donor at baseline, do not adjust for the potential confounding effect of the quality of transplant services provided or may be selective in their choice of donors.
- Donor experiments involving animals utilize healthy living animals as donors, and these animals may not resemble the global pathophysiology of the brain-dead donor.
- Recipient risk factors for graft failure must be accounted for in any analysis of graft failure rate, and these factors are often not adjusted for in study results.
Collectively, these methodological problems limit the inferences obtained from these studies. Recent methodological literature has demonstrated the validity of good cohort studies compared to randomized controlled trials in determining the point estimates of treatment effect of new therapies. Some of these studies have been possible because of the development of exceptional regional and national registries capturing high-quality data on both organ donors and recipients, such as the United Network for Organ Renal Transplant Registry. These databases can provide high-quality data that can be used both for clinical studies and for monitoring safety issues related to organ procurement, infection, transplantation and the use of marginal donors.

**The Pathophysiology of Brain Death**

Literature on the pathophysiology of brain death can be categorized into three subject areas: the cardiovascular response in brain death, the systemic inflammatory response in brain death and temporal considerations.

**The Cardiovascular Response in Brain Death**

Brain death is the consequence of raised intracranial pressure (ICP) and cerebral herniation. As ICP increases, mean arterial pressure (MAP) rises in an effort to maintain cerebral perfusion pressure. As ICP rises further, cerebral herniation into the brainstem ensues and brainstem ischemia is initiated in an rostral-caudal fashion. Initial apnea, bradycardia, hypotension and a drop in cardiac output is mediated by vagal (parasympathetic) activation from midbrain ischemia. Brainstem ischemia then progresses toward the pons, where sympathetic stimulation is superimposed on the initial vagal response, resulting in bradycardia and hypertension (Cushing’s reflex). During this period, the EKG may be characterized by sinus bradycardia, junctional escape beats and even complete heart block.

Further extension into the medulla oblongata occurs, at which point the vagal cardiomotor nucleus becomes ischemic, preventing tonic vagal stimuli. This results in unopposed sympathetic stimulation and the resulting loss of baroreceptor reflexes, which may last for minutes to hours. The unopposed sympathetic stimulation manifests as hypertension with elevated cardiac output and may also manifest as a period of sinus tachycardia and multifocal ventricular tachycardia. This period of unopposed sympathetic stimulation is often termed “autonomic storm” and is hypothesized to be, in part, responsible for the end organ ischemia and pulmonary edema seen in some cadaveric donor organs. The vasoconstriction may be so severe that blood flow to organs may be significantly reduced, despite an elevated systemic perfusion pressure.

The magnitude of the rise of epinephrine after brain death and the extent of myocardial damage depend on the rate of rise in ICP. Dogs given a sudden rise in ICP demonstrated a higher epinephrine surge and poorer functioning as donor hearts. A marked rise in serum catecholamine levels has also been demonstrated in the baboon model. The autonomic storm also results in an increase in cytosolic calcium, which then activates enzymes such as lipase, protease and nitric oxide synthase and generates oxygen free radicals resulting in tissue destruction.
Following the autonomic storm, a normotensive or hypotensive phase ensues, resulting from a reduction in sympathetic flow. This stage is characterized by impaired cardiac inotropy and chronotropy, impaired vascular tone and a reduced cardiac output. Ultimately, this results in diminished blood flow and oxygen delivery to solid organs. During the later stages after brain death, the EKG may manifest ischemic changes followed by a recovery to sinus rhythm with normal ST segments and abnormal J and T waves.

In two separate series of patients suffering from severe head injury, the mean time from injury to the progression of brain death was 17.9 and 22 hours respectively. In a Polish study of 27 organ donors, only 11% of donors were hemodynamically stable according to the classification system of the United Network for Organ Sharing (UNOS), defined as requiring no catecholamines to maintain blood pressure over 100 mm Hg. In a cohort study of 63 consecutive donors who died in two Warsaw hospitals, continuous deterioration of hemodynamic stability was observed despite the administration of intravenous fluids and inotropes. Prior to organ harvesting, 26 (42%) of donors had evidence of progressive hypotension despite dopamine doses of greater than 20 mcg/kg/min. Similarly, in a study of 77 pediatric organ donors, 41 (53.2%) suffered from sustained hypotension, which was more common in patients treated with inotropic agents in the presence of a low central venous pressure (CVP) and in patients with diabetes insipidus (DI) who did not receive antidiuretic hormone replacement.

**The Systemic Inflammatory Response in Brain Death**

Brain death has been identified as triggering a cascade of inflammatory mediators which may affect graft function.

In a prospective study of 27 donors and 50 kidney transplant recipients, donor sera malondialdehyde (a measure of lipid peroxidation) levels and total antioxidant status were measured as markers of free radical mediated response. Recipients with delayed renal graft function were associated with higher levels of malondialdehyde and lower total antioxidant status in the preservation solution during the time of transplant. Patients suffering from acute rejection received kidneys from donors with significantly higher levels of malondialdehyde; both delayed renal graft function and acute rejection predicted impaired long-term graft survival.

An immunohistochemical study compared pretransplant donor biopsies from cadaveric kidney donors with those from living related kidney donors. Levels of endothelial E-selectin and proximal tubular expression of HLA-DR antigens, intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 were significantly higher in biopsies from the cadaveric donors. There was a significant association between high levels of these molecules and traumatic death, mechanical ventilation greater than three days and infectious episodes in the cadaver donors. High levels of E-selectin expression were associated with the administration of desmopressin (DDAVP) to the donor prior to organ retrieval. Transient focal cerebral ischemia has also been demonstrated to upregulate the transcriptional levels of TNF-α and IL-6. Urine IL-6 levels in recipients may predict early graft rejection.

**Temporal Considerations Following Brain Death**

The duration from brain death to organ retrieval may be associated with a differential graft survival in donors suffering from cerebral vascular accidents (CVA) compared to traumatic brain injury.
injury. A trend to poorer kidney graft survival has been observed when organs from donors suffering from CVAs were procured between 24 and 59 hours after admission; this poorer survival may result from higher inflammatory activity during this period.\textsuperscript{22}

In a large cohort study of 1,106 renal transplant recipients, Kunzendorf demonstrated a strong association between the duration of brain death (defined as the time between the neurological determination of death and the beginning of the cold ischemia time before graft explantation) and the incidence of primary renal graft dysfunction. Renal allografts retrieved from donors with a longer duration from the neurological determination of death (over 470 minutes) demonstrated significantly better primary graft function than those harvested from donors with fewer than 470 minutes from the neurological determination of death.\textsuperscript{23} This hypothesis was tested on another renal transplant recipient population of 752 in a different center, which also showed a trend to improvement of primary graft function in those receiving a kidney from donors with longer than 470 minutes duration from the neurological determination of death. Consequently, it was concluded that for renal allografts, a longer duration of donor brain death did not worsen short-term or long-term renal graft function.

In a cohort of 323 orthotopic liver transplants (OLTs), longer donor hospitalization (prior to, including and after the neurological determination of brain death) was not found to be associated with primary liver graft dysfunction using a multivariable statistical model.\textsuperscript{24}

For lung transplantation, the available literature on timing of organ procurement is limited and conflicting. Although one study utilizing the California Transplant Donor Network from 1995 to 1997 demonstrated an association between longer time to donor network referral and a reduced chance of lung procurement, an individual center in Australia has advocated delaying organ procurement until marginal donor lungs have been optimized with aggressive bronchial toilet using bronchoscopy, physiotherapy, increasing tidal volume and increasing PEEP.\textsuperscript{25,26}

In summary, the available evidence does not necessarily support the policy of immediate organ procurement after the neurological determination of death. In donors with marginal lung or kidney function, a delay in organ procurement may provide the necessary time required to optimize organ function. In circumstances where marginal lung donors are considered based on a PaO$_2$:FIO$_2$ ratio of < 300 with PEEP 5 and FIO2 100%, delaying organ procurement in order to enable sufficient time for bronchial toilet and adequate ventilation may improve oxygenation enough to consider an otherwise discarded lung or lungs for donation. Likewise the potential advantage of delaying procurement of donor hearts (to provide additional time to recover from the autonomic storm resulting from brain death, to titrate fluid and pharmacological therapy, and to permit serial investigation of myocardial function by echocardiography or other means) is appealing; however, the effect of such delay on recipient graft survival has yet to be formally tested in clinical experiments.
Hormonal Alterations in Brain Death

Endocrine Pathophysiology after Brain Death

The hormonal changes that accompany brain death include those related to the catecholamine surge during the autonomic storm, those related to posterior pituitary function (vasopressin) and those involving anterior pituitary hormones, glycemic control and adrenal function. Although there is strong evidence to suggest that dysfunction of the posterior pituitary in brain-dead donors is common, anterior pituitary function is largely preserved.27

In a study of 32 potential organ donors by Gramm et al., 78% of the organ donors developed DI; however, none of the anterior pituitary hormones demonstrated a progressive decline in their concentrations. Although free triiodothyronine (FT3) values were below normal in 62% of patients, the authors suggested that these values are similar to those found in patients with severe brain injury who survive and are compatible with low T3 and T4 syndrome (euthyroid sick syndrome) seen in severe nonthyroidal illness. Serum adrenocorticotropic hormone (ACTH) was found to be stable during the study period, and levels of thyroid stimulating hormone (TSH) and human growth hormone (hGH) were increased from baseline values after 30–40 hours.

Similar findings of preserved anterior pituitary function have been demonstrated by Powner et al., who compared thyroid, cortisol, insulin and lactate levels in 16 patients who became brain dead to 14 patients who had traumatic brain injury and a Glasgow coma score < 7 who did not progress to brain death.28 Low FT3 levels with high reverse T3 levels (rT3) and normal FT4 levels were seen in most patients in both groups and were characteristic of the euthyroid sick syndrome. The level of thyroid hormones was not correlated with either systemic lactate level or the amount of vasopressors required for the maintenance of systolic blood pressure (SBP). Anterior pituitary hormone release may be suppressed by intravenous dopamine, which has traditionally been used as the agent of choice for hemodynamic support of the organ donor.29 Intravenous dopamine infusions of 5 µg/kg/min directly inhibit TSH release and consequently, lower both T4 and T3 levels.30 Thus, an element of thyroid dysfunction described in previous studies of brain death may have been related to the use of dopamine in these patients.31

Diabetes Insipidus (DI) and Related Disorders of Antidiuretic Hormone

Arginine vasopressin (AVP) produces its physiological effects through three different receptors: V1, V2 and V3.32 V1 receptors are located within blood vessels and mediate the vasopressor effect on vascular smooth muscle. Vasopressin also acts on V1 receptors present in the kidney to increase urate clearance. The antidiuretic effect of vasopressin is mediated via the V2 receptors found on renal collecting-duct epithelia. V2 receptor stimulation increases factor VIII production from vascular endothelial cells. Stimulation of ACTH secretion is mediated by vasopressin via its effect on V3 receptors located in the anterior pituitary.

An undetectable level of vasopressin, which is responsible for the development of DI in up to 87% of brain-dead donors, has been noted in 75% of brain-dead donors before cardiac procurement.10,19,27,33 In the Warsaw database, 20% of all donors developed DI, which was associated with hemodynamic instability in up to 31.3% of these donors.18 The half-life of vasopressin is approximately 15 minutes. Below plasma vasopressin levels of 5 pg/mL, there is a
linear decrease in the body’s ability to maximally concentrate urine; with plasma levels of vasopressin of < 1 pg/mL, urine volume increases dramatically from less than 4 L/day to 20 L/day. The analog 1-desamino-8-D-arginine vasopressin (DDAVP) is highly selective for the vasopressin V2 receptor subtype found in the renal collecting duct, with no significant vasopressor activity in humans. Its duration of action ranges from 6 to 20 hours and may be given at doses of 2 µg to 6 µg IV every 6 to 8 hours. In critically ill patients, the intravenous route of administering DDAVP is preferred because bioavailability is ensured and the lack of vasopressor activity ensures its safety. In a randomized trial involving 97 brain-dead donors, DDAVP therapy had no adverse effect on early or late graft function after renal transplantation.

Intravenous vasopressin has also been demonstrated to be effective in case series of adults and children with DI. Other authors and committees have advocated the use of vasopressin for the treatment of DI. Vasopressin may be administered intravenously, subcutaneously or intranasally; however, if used, the intravenous route is recommended because for predictable absorption. Doses between 0.5 and 15 U/hr (8–250 mU/kg/hr) of vasopressin have been advocated; however, high doses may cause coronary, renal and splanchnic vasoconstriction, potentially jeopardizing cardiac, renal, pancreatic and hepatic function.

An early study of vasopressin use in brain-dead donors suggested that its use resulted in poor function of transplanted kidneys. Despite these early concerns, other authors have demonstrated that vasopressin can be used successfully in organ donors with no significant adverse effect on renal graft function. Its use in combination with epinephrine has been shown to allow prolonged hemodynamic maintenance of brain-dead patients without apparent organ damage. A rational approach to therapy would be to use vasopressin alone or a combination of DDAVP (for its antidiuretic effect) in conjunction with vasopressin as a vasopressor. The safety and efficacy of this combination on cardiovascular and laboratory endpoints has been described previously.

Although clinical trials of the optimal dosage of vasopressin in brain-dead donors are lacking, based on a rigorous review of the use of vasopressin in sepsis and with traumatic brain-injured and brain-dead patients, a safe approach would be to limit the dose of vasopressin to 0.04 U/min (40 mU/kg/hr). This upper limit is within the recommendations of the Transplantation Committee of the American College of Cardiology, which advocates the use of vasopressin infusion at 0.8–1.0 U/hr (13–17 mU/kg/hr) to treat DI.

**Thyroid Dysfunction**

The use of thyroid hormone therapy in brain-dead donors appears to be largely based on experimental animal models and small human case series. In a study involving 22 brain-dead donors, TSH, T4 and T3 were decreased to below normal levels in 85%, 55% and 90% of patients. In a brain-dead baboon model, T3 levels became depleted and were associated with a transition from aerobic to anaerobic metabolism, which could be reversed with the administration of 2 µg of T3 at hourly intervals. A regimen of T3 2 µg, cortisol 100 mg and insulin 20 units administered intravenously at hourly intervals in brain-dead patients was found to reduce the serum lactate to pyruvate ratio, decrease bicarbonate requirements and inotropic support, and improve the rate of cardiac graft procurement compared to a group not receiving this hormonal regimen. However, other investigators using a similar
regiment of T_3, cortisol and insulin did not demonstrate an improvement in either echocardiographic function or organ retrieval rates with the use of this hormonal regimen.\textsuperscript{49}

In another study of 31 consecutive brain-dead donors, all had normal or high serum reverse T_3. Free T_4 index was low in 29\%, and TSH was low in 23\%. However, in no donors were the levels of T_4 and TSH both subnormal, indicating that these patients were suffering from euthyroid sick syndrome rather than TSH deficiency.\textsuperscript{27}

In a small case-control study of the effect of vasopressin on transplant organ recovery in children, vasopressin was demonstrated to have a significantly beneficial effect on weaning these children off other vasopressor medications; however, the infusion of thyroxine (10 \(\mu\)g/hr or 0.16 \(\mu\)g/kg/hr) did not demonstrate a similar effect.\textsuperscript{50}

The strongest evidence supporting the use of T_3 in organ donors comes from a recent analysis of the UNOS database.\textsuperscript{51} Hearts harvested from donors receiving triple hormonal therapy demonstrated a significantly improved one-month survival rate (96.2\%) compared to hearts from donors not receiving triple hormonal therapy. A multivariable model demonstrated a 46\% reduced odds of death within 30 days and a 48\% reduced odds of early cardiac graft dysfunction. Benefit was also found in those donors receiving corticosteroids alone or in combination with T_3/T_4.

Results of studies using T_3 in patients undergoing coronary artery bypass grafting (CABG) have been conflicting. It has previously been hypothesized that T_3 may attenuate ischemia-reperfusion injury in the heart through effects on high-energy phosphate metabolism and membrane stability.\textsuperscript{52–55} In a small randomized trial of 20 patients undergoing CABG, the infusion of T_3 did not significantly improve the post-CABG levels of T_3, any hemodynamic parameters or the density and affinity of lymphocyte \(\beta\)-adrenoceptors compared to controls.\textsuperscript{56} In a subsequent randomized trial of 211 patients undergoing CABG and at high risk for requiring inotropic drug support, patients in the treatment arm were given a 0.8 \(\mu\)g/kg load followed by 0.12 \(\mu\)g/kg/hour of T_3 for 6 hours. Control patients were administered either dopamine (5 \(\mu\)g/kg/min for 6 hours) or normal saline. Although T_3 administration prevented a decrease in serum thyroid hormone concentration associated with CABG, it did not have any effect on any hemodynamic variables within the 24 hours after surgery.\textsuperscript{57}

In contrast, two small randomized trials of T_3 after CABG demonstrated improvement in cardiac function with T_3 compared to placebo in patients with a preoperative left ventricular ejection fraction of < 30\% or > 40\%.\textsuperscript{58} A randomized trial of 142 patients undergoing CABG with an ejection fraction < 40\% demonstrated a lower incidence of atrial fibrillation, cardioversion, antiocoagulation and antiarrhythmic use in the group randomized to receive T_3 as a 0.8 \(\mu\)g/kg intravenous bolus at the time of aortic cross-clamp followed by an infusion of 0.113 \(\mu\)g/kg/min for 6 hours. In a randomized trial of 170 patients undergoing elective CABG, treated patients were administered 0.4 \(\mu\)g/kg bolus of T_3 followed by a 0.1 \(\mu\)g/kg infusion administered over a 6-hour period after cross-clamp removal. Patients randomized to T_3 had a higher cardiac index, lower inotropic requirements, a lower incidence of postoperative myocardial ischemia, lower pacemaker dependence and a lower requirement for postoperative mechanical assistance (ballon pump or left ventricular assist device) after CABG.\textsuperscript{59}
Collectively, the evidence to support the routine use of T₃ in the brain-dead organ donor is conflicting. Although data from the UNOS database support the use of T₃ in combination with corticosteroids or as triple hormonal therapy (including AVP), the lack of adjustment for the potential confounding effect of the transplant center in this analysis limits inference from its conclusions.⁵¹

**Disorders of Glucose Homeostasis**

Hyperglycemia is common in brain-dead donors and is thought to be secondary to insulin resistance, as pancreatic function appears to be preserved in donors.⁶⁰ The hyperglycemia may be aggravated by the use of hypotonic dextrose solutions for the treatment of hypernatremia resulting from DI. Although the hypothesis that tight glycemic control with insulin improves graft survival has not been tested in brain-dead patients, it has been demonstrated in a population of critically ill patients to improve survival primarily by reducing septic deaths. The use of insulin infusions to maintain glucose levels within physiological ranges is now commonplace in the ICU.

**Adrenal Dysfunction**

Severe traumatic brain injury results in a stress-associated rise in serum cortisol. In one study of 36 traumatic brain injury survivors, mean admission serum cortisol was 807 nmol/L.²⁷ Compared to this physiological response to stress, Howlett et al. noted that 50% of brain-dead donors were relatively ACTH deficient as defined by a serum cortisol < 400 nmol/L.²⁷ In adopting therapeutic strategies with intravenous corticosteroids in organ donors, one must differentiate the use of the steroids to treat relative adrenal insufficiency as opposed to their use as immunosuppressive agents to suppress the inflammatory response noted in brain-dead patients.

The evidence for the use of immunosuppressive doses of corticosteroids is largely based on a single retrospective analysis of 118 consecutive donors administered a non-uniform protocol of methylprednisolone (mean 14.5 mg/kg) compared with 38 donors not receiving methylprednisolone; there was significant improvement in donor oxygenation (in terms of arterial oxygen pressure/forced inspired oxygen) and lung procurement rate in the methylprednisolone group.⁶¹ In critically ill patients suffering from septic shock, serum cortisol levels in response to ACTH have been demonstrated to predict survival, and the use of hydrocortisone at a dose of 50 mg q6hrs with fludrocortisone 100 µg once daily has been demonstrated to improve survival in patients deemed to be relatively adrenal insufficient.⁶²,⁶³

**Combination Hormonal Therapy**

The Heart Work Group of the Crystal City Consensus Conference recommended that donors with a left ventricular ejection fraction of less than 45% after standard donor management be treated with combination hormonal therapy.³,⁴ The recommended hormonal therapy consisted of methylprednisolone 15 mg/kg bolus, T₃ bolus administration of 4 µg and then continuous infusion of 3 µg/hr and arginine vasopressin bolus administration of 1 unit and then continuous infusion of 0.5 to 4 units/hr (8–67 mU/kg/hr).

In a study using UNOS data and involving 10,292 consecutive brain-dead organ donors, 701 of whom received triple hormonal therapy and 9,591 of whom received none, one or double hormonal therapy, significantly more organs were transplanted from donors who received triple
hormonal therapy compared to those who did not. Also, triple hormonal therapy was associated with a 28% increase in the odds of a donor becoming a heart donor.\textsuperscript{41} In a subsequent study, UNOS data was analysed on 4,543 cardiac transplant recipients.\textsuperscript{51} Hearts harvested from donors receiving triple hormonal therapy demonstrated a significantly improved one-month survival rate (96.2%) compared to those from donors not receiving triple hormonal therapy.

A multi-variable model demonstrated a 46% reduced odds of death within 30 days and a 48% reduced odds of early cardiac graft dysfunction. Benefit was also found in those donors receiving corticosteroids alone or in combination with T\textsubscript{3}/T\textsubscript{4}. Although these results are grounded on reliable UNOS data, no adjustment was made for the potential contribution of the quality of transplant care or services by the individual center.

In a recent publication describing the merits of implementing a standardized critical pathway for the management of the potential organ donor, it was noted that there were wide variations between the 10 U.S. organ procurement organizations in their rates of organ donors, organ procurement, and delayed cadaveric renal graft function and survival.\textsuperscript{64} Moreover, only 394 (9%) of recipients in this database received triple hormonal therapy.

Although triple hormonal therapy has been suggested to improve both cardiac graft procurement and recipient cardiac graft survival in retrospective analyses of UNOS data, the heterogeneity of hormonal dosing schedules and other aspects of donor and recipient care between centers limits the conclusions that can be obtained from this data.
Organ-Specific Considerations

Each donor organ—heart, lung, kidney, liver—has specific considerations for effective medical management to optimize organ potential. In addition, the literature reports investigations into donor infection, hematology and malignancy.

Cardiovascular Considerations

Cardiovascular pathophysiology following brain death

Management of the cardiovascular compromise that results from brain death is central to the maintenance of solid organ perfusion. The complete sympathectomy associated with brain death results in a low systemic vascular resistance that often requires the use of vasopressor agents.

Canine models of brain death have demonstrated microscopic evidence of ischemic myocardium and subsequent myocardial dysfunction when intracranial pressure is raised rapidly compared to when it is raised slowly. In addition, hypotension may be caused by the intravascular volume depletion resulting from the use of osmotic diuretics in the treatment of raised intracranial pressures associated with cerebral edema as well as from DI.

Most authors recommend maintaining systolic blood pressure greater than 90 mm Hg, MAPs greater than 60 mm Hg and heart rates less than 100 beats per minute when maintaining an organ donor. They also recommend a CVP in the range of 10 to 12 mm Hg to volume replete those patients in whom only abdominal organs are to be harvested, a CVP of less than 8 for potential lung donors and a CVP of between 8 and 10 mm Hg if both thoracic and abdominal organs are to be harvested. Traditionally, dopamine has been used as the initial inotrope of choice in the brain-dead patient. However, no randomized clinical trials exist comparing the hemodynamic effects of dopamine to other vasopressors. Moreover, a recent review of the literature has called into question the role of dopamine in modern critical care practice. The basis for this argument is that there is no evidence that renal-dose dopamine improves renal function, alters the outcome of acute renal failure or improves hepatosplanchnic circulation. Furthermore, dopamine has been demonstrated to suppress the secretion and function of anterior pituitary hormones, including growth hormone and TSH.

The concern over the use of alpha agonists such as norepinephrine has arisen because of the fear of inducing central and peripheral vasoconstriction and subsequent ischemia in vascular beds supplying potentially transplantable organs. However, in studies of septic patients, whose low systemic vascular resistance is similar to that seen in the sympathectomized brain-dead donor, norepinephrine, compared to dopamine, was demonstrated to increase mean perfusion pressures without adverse effects to renal and splanchnic blood flow.
Sympathetic baroreceptor dysfunction and arginine vasopressin

Yoshioka has demonstrated that hemodynamic stability could be maintained after brain death for an average of 23 days with a combination of low-dose vasopressin (1–2 units/hour or 17–34 mU/kg/hr) and epinephrine (0.5 mg/hr or 8 µg/kg/hr). These authors also demonstrated that the use of low-dose vasopressin decreased the amount of epinephrine required to maintain hemodynamic stability with a preservation of renal function for a mean of 14 days after brain death. The catecholamine-sparing effects of vasopressin have also been noted by other authors.

Perhaps the most rigorous evidence with respect to the hemodynamic support of the brain-dead patient through the use of vasopressin has come from Pennefather et al. In this study, brain-dead organ donors supported with dopamine were volume loaded with Ringer’s lactate to a CVP of 8 mm Hg and were given DDAVP, 2 mg IV in repeated boluses, if their urine output exceeded 3 ml/kg/hr for 2 hours. The brain-dead donors were then randomly assigned to receive either a 300 µU/kg/min infusion of vasopressin or a saline infusion, targeting a MAP of between 65 and 85 mm Hg. Those randomized to therapy with vasopressin demonstrated a significant decrease in urine output (related to the mild effect on free water retention), a decrease in plasma osmolality, an increase in MAP and systemic vascular resistance (SVR) and a decrease in dopamine dose. Similar catecholamine-sparing effects of vasopressin have been demonstrated in several case series of critically ill patients with low systemic vascular resistance secondary to septic shock. Doses of vasopressin exceeding 0.04 U/min (650 µU/kg/min or 39 mU/kg/hr) resulting in plasma levels > 100 pg/mL are associated with potentially harmful excessive vasoconstriction of the renal, mesenteric, pulmonary and coronary vasculature. The Transplantation Committee of the American College of Cardiology advocates the use of vasopressin infusion at 0.8 to 1.0 U/hr (13 to 17 mU/kg/hr) to treat DI.

In a study of 10 brain-dead organ donors who required catecholamine vasopressors to maintain a MAP of ≥ 70 mm Hg, all patients were found to have plasma vasopressin levels < 8 pg/mL (normal serum levels of vasopressin in hypotensive patients with a serum osmolality > 290 mOsm/L are > 20 pg/mL). These low vasopressin levels in the setting of shock were suggestive of a defect in the baroreceptor-mediated secretion of vasopressin. Furthermore, the use of low-dose vasopressin at a dose of 0.04 to 0.1 U/min (40 to 100 mU/kg/hr) IV resulted in an increase in MAP by an average of 17 mm Hg and was of sufficient magnitude to allow complete discontinuation of catecholamine vasopressors in 40% and a reduction in vasopressor dose in an additional 40% of patients.

These findings in adult populations of brain-dead patients have been confirmed in a case control study of 34 vasopressin treated brain-dead children and 29 age-matched controls. In this study, a mean dose of 41 ± 69 mU/kg/hr of vasopressin had been administered to the brain-dead cases prior to organ recovery. Average MAP after initiation of vasopressin was approximately 10 mm Hg higher in the children treated with vasopressin than in their age-matched controls. Alpha agonists (norepinephrine, epinephrine or phenylephrine) were discontinued from 78% of vasopressin-treated children versus 0% of non-vasopressin-treated children (odds ratio [OR] of 7.3), and there was no significant difference in the quality of kidneys, livers and hearts recovered from vasopressin-treated children versus controls.
Based on the available evidence, the use of vasopressin at doses up to 0.04 U/min (40 mU/kg/hr) can be used to support the MAP and spare the use of catecholamines in both adult and pediatric brain-dead organ donors. It appears that doses of this magnitude are also effective in treating the DI seen after brain death. Further clinical investigations should be performed to determine the optimal dosage of vasopressin and its effects on organ procurement and allograft survival.

**Invasive hemodynamic monitoring**

Experts agree that, at the very least, brain-dead patients should undergo invasive hemodynamic monitoring of their CVP. There is some evidence to suggest that the use of the pulmonary artery catheter improves the rate of organ procurement. In a case series of 52 donors considered “unsuitable”, Wheeldon et al. demonstrated that 44 of these donors (92%) yielded transplantable organs after aggressive management, including invasive monitoring with a pulmonary artery catheter, inotropes and hormonal therapy with glucocorticoids, insulin, vasopressin and T3. The overall survival in the group of 89 recipients was 76% and 84% over a follow-up period of 13 to 48 months.

The Transplantation Committee of the American College of Cardiology has recommended titrating volume infusion to maintain a CVP at 8–12 mm Hg or PCWP 12–14 mm Hg using a pulmonary artery catheter, systolic blood pressure 90 to 140 mm Hg. In the setting of normal or elevated cardiac output and a low systemic vascular resistance, it is logical to use a vasopressor to increase MAP rather than an inotrope, which increases myocardial work. This philosophy has been espoused by Potter et al., who described the use of nomograms using physiological parameters recorded from a pulmonary artery catheter (right atrial pressure) and arterial line (MAP) to optimize both left and right ventricular static power and thus to maintain hemodynamic equilibrium.

**Echocardiography and angiography**

Investigators have searched for hemodynamic parameters to predict successful cardiac graft function.

Echocardiographic parameters have been demonstrated to be beneficial in predicting successful cardiac transplant outcomes. The fractional area changes measured by transesophageal echocardiography in the left ventricular short axis view is an independent predictor of successful cardiac allograft procurement. However, echocardiography performed on the brain-dead donor does have limitations. In a study of 66 consecutive patients with brain death, echocardiographic systolic myocardial dysfunction was present in 42% in this study, myocardial dysfunction tended to be more often segmental in patients who had spontaneous subarachnoid or intracerebral hemorrhage and more often global in patients suffering from head trauma. In 11 of the 66 hearts biopsied, there was a poor correlation between pathological findings of contraction band necrosis (characteristic of neurogenic myocardial injury) and echocardiographic dysfunction.

In another case series describing serial echocardiography in 12 patients with subarachnoid hemorrhage, myocardial wall motion defects seen on echocardiography within 12 hours of the initial event improved on repeat echocardiographic studies within two to three weeks. This suggests that one isolated echocardiogram is a valuable tool but also that it has limitations in predicting the presence of reversible myocardial dysfunction in the brain-dead patient.
To further the hypothesis of reversible myocardial dysfunction in a “neurogenically stunned myocardium”, Kono et al. studied a group of 30 brain-dead patients from the neurological determination of death until cardiac standstill (more than 7 days after the neurological determination of death). Patients were divided into two groups; group 1 had left ventricular fractional shortening of ≥ 30% and group 2 had left ventricular fractional shortening of < 30% on initial echocardiography. Group 2 subsequently underwent dobutamine stress echocardiography using 3-minute interval increments of dobutamine at doses of 5, 10, 15 and 20 µg/kg/min. With dobutamine infusion, the left ventricular fractional shortening improved in three patients and remained unchanged in four patients. In the subgroup of three patients with dobutamine-responsive wall motion studies, left ventricular function became normal prior to cardiac standstill (mean 15.0 ± 5.6 days), whereas left ventricular function remained decreased in the four patients without dobutamine-induced wall motion improvement prior to cardiac standstill (mean 3.5 ± 0.6 days).

Coronary angiography is often performed on donors if they are over 40 years of age, require high inotropic support or have other risk factors for coronary artery disease such as diabetes mellitus. The recent recommendations from the cardiac working group at the 2001 Crystal City Consensus Conference recommended that coronary angiography should be performed in male donors > 45 years of age and in women donors > 50 years of age at younger ages if there is a history of cocaine abuse or ≥ 3 risk factors for coronary artery disease (e.g., hypertension, diabetes, smoking). The committee also recommended that contrast left ventriculography be avoided in donors with technically adequate echocardiograms to avoid the risk of contrast nephropathy in the donor kidneys. If coronary angiography is performed, the use of acetylcysteine with hydration both prior to and after the angiographic procedure has been demonstrated to reduce the risk of developing contrast nephropathy in patients with chronic renal insufficiency. The administration of acetylcysteine and hydration was found to reduce the relative risk of contrast nephropathy by 56%. Although the populations of patients in these studies were not organ donors, the use of acetylcysteine may have its most beneficial effect in preserving the renal function of marginal kidney donors such as those with age > 60, with a terminal creatinine clearance < 90 ml/L or with a history of diabetes or hypertension.

**Donor cardiac troponin**

Changes in catecholamine levels resulting in an increase in peripheral resistance may result in a sudden increase in myocardial work and oxygen consumption leading to myocardial ischemia or infarction and subsequent elevation of cardiac troponin I and T. This sudden increase is well documented in massive subarachnoid hemorrhage. In a case series, brain-dead cardiac donors with cardiac troponin I values > 3.1 ng/mL were found to have diffuse subendocardial myocytolysis and coagulative necrosis, and five of eight of these hearts were diagnosed as having graft failure after transplantation. Interestingly, echocardiographic function and CK-MB values were not associated with cardiac troponin I levels in this study. In a larger study of 126 consecutive brain-dead donors, the OR for the development of acute graft failure after heart transplantation was 42.7 for donors with cardiac troponin I > 1.6 µg/L and 56.9 for donors with cardiac troponin T > 0.1 µg/L. In another study assessing the predictive value of donor troponin T levels, donors with subarachnoid hemorrhage
had slightly higher troponin T levels than those suffering from traumatic brain injury, and higher donor troponin T levels were associated with more frequent requirement of epinephrine in the corresponding heart transplant recipients within 24 hours of transplantation. Higher cardiac allograft rejection rates have also been associated with high donor troponin levels.

**Expanding the donor cardiac pool**

The major factors contributing to the expansion of the cardiac donor pool include donor age and coronary artery disease, structural abnormalities such as left ventricular hypertrophy, donor-recipient size mismatch, donor hepatitis B status and cold ischemia time.

**Donor age and cardiac structural abnormalities**

Sweeney et al. have demonstrated 12-month survival rates of 75.9% in cardiac transplant recipients who received hearts from high-risk donors. Donors at high risk included those with age greater than 40, systemic non-cardiac infection, ischemic time longer than 5 hours and the requirement for high doses of inotropes (> 10 µg/kg/min dopamine or > 5 µg/kg/min epinephrine).

In a study comparing 296 recipients of hearts from donors less than or equal to 63 years of age to 13 recipients of hearts from donors older than 63 years of age, a significantly higher incidence of cardiac morbidity (myocardial infarction, malignant arrhythmias, coronary stenosis, transplant vasculopathy) and cytomegalovirus (CMV) infection was observed in the recipients of older donor hearts. However, no significant difference was seen between groups in mean left and right ventricle ejection fraction after one year, in early postoperative mortality or in cumulative survival.

In another series of 859 heart transplant recipients, 19 of whose hearts were from donors between 60 and 65 years of age, early and late (94-month) mortality in the older donor group was significantly higher than that in the younger donor group (16% vs. 11.5% and 53% vs. 38.2% respectively).

A solution to the problem of donor coronary artery disease is the use of “bench” CABG after organ procurement. In a small series of 10 cardiac recipients of donor hearts for which bench CABG was performed, eight recipients had long-term survival with a two-year graft patency of 65%. The 2001 Crystal City Consensus Conference cardiac committee has recommended the use of hearts with mild left ventricular hypertrophy (≤ 13 mm by echocardiography), particularly if cold ischemia time is short. However, the use of donor hearts with left ventricular hypertrophy of > 13 mm and EKG criteria for left ventricular hypertrophy (LVH) was not recommended. These and other recommendations for expanding the existing cardiac donor pool from the Crystal City Consensus Conference are outlined in table 1.
Table 1. Crystal City modifications of existing heart donor criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Modifications</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>Donors &gt; 55 may be used selectively, though co-existing LVH and longer ischemic times may increase recipient mortality risks.</td>
</tr>
<tr>
<td>Size</td>
<td>Despite an increased risk associated with small donors, a normal sized adult male (&gt; 70 kg) donor is suitable for most recipients.</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (LVH)</td>
<td>Mild LVH (wall thickness (\leq 13) mm by echocardiography and no LVH by ECG criteria) does not preclude recovery, particularly with shorter ischemic times.</td>
</tr>
<tr>
<td>Valvular lesions</td>
<td>Certain lesions, such as mild or moderate mitral or tricuspid regurgitation, or a normally functioning bicuspid aortic valve, may be amenable to bench repair prior to transplantation.</td>
</tr>
<tr>
<td>Congenital lesions</td>
<td>Certain lesions, such as secundum type ASD, may be amenable to bench repair.</td>
</tr>
</tbody>
</table>
| Coronary angiography                          | a. Male donor age 35–45 years or female donor age 35–50 years: Perform angiography if there is a history of cocaine use or \(\geq 3\) risk factors for CAD.  
 c. Age > 55 years: Angiography strongly recommended. |
| CAD                                          | Donor hearts with mild coronary artery disease should be considered for recipients with relatively urgent need. |


Donor bacteremia and hepatitis B

Successful cardiac transplants have been performed from bacteremic donors. Consequently, the hearts from certain bacteremic donors without evidence of cardiac infection may be safely considered for transplantation.

The effectiveness of transplanting hearts from donors serologically positive for hepatitis B virus (HBV) has been studied in endemic regions by Ko et al. In this series, hepatitis B surface-antigen-positive (HBsAg+) donor hearts were safely transplanted into anti-HBsAg+ recipients, HBV-naïve recipients and recipients with HBsAg-, anti-HbsAg-, anti-HBc+ and negative HBV DNA. HBV recurrences and new infections were successfully treated with lamivudine. (One recipient who was HbsAg-, anti-HbsAg-, anti-HBc+ and positive HBV DNA developed HBV hepatitis after transplantation.) Therefore, expanding the donor pool by utilizing hearts from HBsAg+ donors is a reasonable option for recipients with or without previous HBV infection.
In an analysis of heart transplantations from 1994 to 1997 using the UNOS database, 12% of cardiac allograft recipients initially anti-HBc- converted to anti-HBc+ one year after being transplanted with a heart from an anti-HBc+ donor. In an analysis of the same data from the UNOS database, the one-year risk of an initially HCV-negative heart transplant recipient seroconverting to HCV positive when transplanted from an HCV-positive donor is 30%, with an associated increase in one- and three-year mortality of 126% and 214% respectively. Consequently, the use of HCV-positive donor cardiac allograft is advocated in HCV-negative recipients only in grave circumstances when there is little alternative to death.

Pulmonary Considerations

Pulmonary pathophysiology following brain death

The maintenance of adequate respiratory function to permit the successful procurement of the lungs appears to be the most challenging of all aspects of donor maintenance. Unfortunately, lungs are retrieved in less than 20% of brain-dead donors. Brain death is associated with both the syndrome of neurogenic pulmonary edema and the induction of the inflammatory response. Neurogenic pulmonary edema is thought to be produced through two potential mechanisms: hemodynamic stress failure or the direct sympathetic stimulation of increased pulmonary capillary permeability. Brain death has also been identified as inducing the inflammatory and immunological responses, including the upregulation of MHC I and II antigens and the induction of various cytokines such as interleukin 6 (IL-6), which may damage the lung parenchyma. Evidence that neurogenic pulmonary edema may be alleviated with glucocorticoids also suggests that an inflammatory component exists in this process.

Acute pulmonary allograft failure is usually associated with inadequate lung preservation, ischemia-reperfusion injury and cellular rejection. Pathological studies of lungs deemed unsuitable for donation have indicated that bronchopneumonia, diffuse alveolar damage and diffuse lung consolidation are the three most common reasons for refusal of the organs. One-year survival for patients with primary lung allograft failure is 40%, compared with a 69% one-year survival for patients without graft failure. The syndrome of primary pulmonary graft failure has pathological features of acute lung injury and occurs in 12% to 50% of transplanted patients.

Pulmonary infection and aspiration

Bronchial colonization or infection with bacteria is common in the ventilated organ donor. In a series of 40 heart-lung transplants performed at Stanford, tracheal aspirate cultures demonstrated gram-positive bacteria in 80% of donors, gram-negative bacteria in 35% and yeast in 25%. In a retrospective study of 115 cadaveric lung transplants, recipients with donor bronchoalveolar lavage (BAL) culture that was positive for either gram-positive or gram-negative bacteria had longer mean mechanical ventilation times and inferior six-month to four-year survival rates than recipients with a negative bacterial BAL culture. Recipients with BAL positive for fungi alone had similar mechanical ventilation and survival outcomes as those with a negative BAL.

Bacterial pneumonia, usually caused by gram-negative organisms originating from the donor, is the most common cause of recipient lung transplant infection. Lungs transplanted from CMV-
seropositive donors into CMV-seronegative recipients result in up to a 90% rate of development of CMV infection in the recipient. This rate contrasts to an approximately 10% rate of CMV infection in a CMV-seronegative recipient who receives an organ from a CMV-seronegative donor.

The mechanism of organ donor death appears to influence the types of organisms found on BAL of the procured lungs just prior to implantation. In a retrospective series of 123 lung donors, 57 of whom died from major trauma and 66 of whom died of nontraumatic causes (typically intracerebral hemorrhage), significantly more of the traumatic donor group had undergone more than 48 hours of ventilation prior to organ procurement; however, no significant difference was noted in the mean PaO$_2$/FIO$_2$ ratio just prior to donation or in the mean ischemic time of the donor lungs. Although no difference was observed in the incidence of pathogenic bacteria isolated by BAL, gram-negative enteric bacilli were isolated more often in the traumatic group (30%) than in the nontraumatic group (7%). Staphylococcus aureus (36%), followed by gram-negative enteric bacilli (30%), were the most commonly isolated organisms in the traumatic group compared to Hemophilus influenzae (34%) and Staphylococcus aureus (30%) in the nontraumatic group. Of importance is the fact that, for organs from traumatized donors who died within 30 days of the trauma, five of the 16 recipients died as a result of gram-negative bacterial pneumonia in which the causative organisms were also identified in the corresponding donor’s BAL. The higher incidence of enteric gram-negative bacilli in the traumatized group was hypothesized to be a result of possible gastric aspiration, the potentially less sterile site of intubation in the field or the administration of broad-spectrum antibiotics and the resulting antibiotic pressure on the donor.

Given these findings, it is recommended that every potential lung organ donor undergo bronchoscopy to isolate potential pathogens and better guide therapy in both the donor and the recipient. At present, no guidelines exist for the empiric use of antibiotics in donors with no evidence of bronchopneumonia. In a canine model of brain death and lung transplant, the use of aerosolized and intravenous antibiotics combined (but not either alone) prevented pneumonia in lung recipients. General principles dictate that antibiotic use be limited and that the narrowest spectrum antibiotic necessary to treat isolated pathogens be used.

**Chest x-ray**

The limited role of the chest radiograph in the lung donor selection process has recently been demonstrated in a study involving 84 potential lung donor radiographs reviewed by three thoracic surgeons and three respirologists. Observer agreement among the surgeons was slight and among the respirologists was only fair, indicating the significant variability present in radiograph interpretation even among transplant specialists.

**Therapeutic strategies**

Therapeutic strategies to preserve pulmonary function include the judicious use of intravenous fluids and the careful consideration of cardiopulmonary interactions, including inhaled β-2 agonists, dopamine, corticosteroids, mechanical ventilation strategies, surfactant and intravenous prostacyclin.

**Fluid management.** Fluid loading has been recommended to improve blood pressure in brain-dead donors. However, given the complexity of cardiopulmonary interactions, the strict
reliance on CVP measurements to guide donor maintenance may be deleterious to the lungs. In a study of 26 brain-dead donors, Ringer’s solution was infused to achieve a CVP of 8–10 mm Hg in 13 donors and CVP was maintained at 4–6 mm Hg in a second group of 13 donors. A significant increase in the alveolar arterial oxygen gradient occurred in those patients who were fluid loaded to achieve a CVP of 8–10 mm Hg. This increase may be a result of increased pulmonary capillary permeability that accompanies raised ICP.

Pennefather demonstrated that there is a poor correlation between left-sided and right-sided filling pressures after brain death, with right ventricular pressures underestimating left ventricular pressures and putting patients at risk for elevated left-sided filling pressures and pulmonary edema. A similar disparity between right and left ventricular heart function has been observed in experimental canine models of brain death. After brain death in a canine model, a significant increase in right and left ventricular end-diastolic pressures and a decrease in systemic and pulmonary resistance and pulmonary impedance occurred. Right ventricular function decreased by 35%, which was significantly more than the 19% decrease in left ventricular function. It was postulated that the increase in blood flow to the pulmonary vasculature as a result of decreased resistance and impedance causes significant pulmonary overflow injury and increases the extravascular lung water.

Current expert consensus recommends the use of the pulmonary artery catheter to optimize both right- and left-sided filling pressures in the potential heart and lung donor. Pulmonary artery catheterization and echocardiography may provide complementary information to assist in the appropriate management of the pulmonary and cardiac allograft donor.

**Inhaled β-2 agonists and dopamine.** In *ex vivo* human donor lungs, terbutaline has been shown to stimulate alveolar fluid clearance. A similar improvement in oxygenation has been demonstrated with the use of salmeterol in patients at risk for high altitude pulmonary edema. Moreover, a linear association has been noted between the rate of alveolar fluid clearance and doses of dopamine ≤ 6 µg/kg/min. Although inhaled β-2 agonists show promise in the treatment of certain forms of pulmonary edema, the lack of clinical studies in brain-dead organ donors precludes the recommendation of inhaled β-2 agonists as routine therapy in this circumstance.

**Corticosteroids.** Several publications have advocated the use of high-dose methylprednisolone to diminish the inflammatory response thought to be present in brain-dead donor lungs. This recommendation is largely based on a single retrospective comparison of 118 consecutive lung donors administered a non-uniform protocol of methylprednisolone (mean 14.5 mg/kg) versus 38 donors not receiving methylprednisolone and demonstrating a significant improvement in donor oxygenation (in terms of arterial oxygen pressure or forced inspired oxygen) and lung procurement rate in the methylprednisolone group. A recent analysis of the California Donor Network database comparing donor factors predicting the procurement of lungs with or without hearts (88 donors) versus the procurement of hearts but no lungs (163 donors) demonstrated an independent effect of using methylprednisolone (OR 3.0) in the donor.

Corticosteroids have also been successfully utilized in treating non-infected patients with acute respiratory distress syndrome (ARDS) during the later phase of the disease.
**Mechanical ventilation.** Contemporary methods of mechanical ventilation have been generally driven by its use in ARDS.\(^{106,122}\) No randomized trials have been conducted to test the hypothesis about whether one mode of ventilation is better than another in improving lung graft survival in organ donors.

Recent reviews have advocated the use of pressure-controlled ventilation rather than volume-controlled modes of mechanical ventilation; however, these statements have not been substantiated with randomized controlled trials or well-designed cohort studies with brain-dead organ donors.\(^{10,123}\) The use of pressure-controlled ventilation has, however, been compared to the use of volume-controlled ventilation in a randomized trial of patients suffering from ARDS.\(^{124}\) In this study, the mode of mechanical ventilation was not independently associated with patient mortality. Hypothesized protective mechanisms of maintaining alveolar expansion include the continued stimulation of surfactant in addition to reduced hypoxic vasoconstriction, reduced endothelial edema, reduced microvascular plugging by blood elements and reduced mediator-induced lung injury and vasospasm.

Shearing forces that produce stress on alveoli, epithelial and endothelial damage, augmentation of the cytokine response, and capillary stress fractures resulting in hemorrhagic edema are all proposed mechanisms for the alveolar injury seen with mechanical-ventilator-induced lung injury.\(^{125}\) Recruitment maneuvers in the form of high sustained PEEP or pressure-controlled ventilation for short durations have been proposed as useful adjuncts to the lung protective ventilatory strategies used to prevent alveolar stress and collapse in ARDS or acute lung injury.\(^{126}\) Such strategies involve either the use of PEEP delivered up to 30 cm H\(_2\)O and limiting maximal plateau pressures at 45 cm H\(_2\)O or, alternatively, the use of pressure-controlled ventilation to a plateau pressure of 45 cm H\(_2\)O (including up to 20 cm H\(_2\)O of PEEP) for 15-minute intervals. A correlation between end-inspiratory and end-expiratory alveolar collapse was demonstrated in this study, indicating the advantage of alveolar expansion in both the inspiratory and expiratory phase.\(^{127}\)

Ventilating donors to achieve PaO\(_2\) of at least 60 mm Hg, using adequate doses of PEEP of \(\geq 5\) cmH\(_2\)O to minimize donor pulmonary atelectasis, and minimizing delivered tidal volumes (irrespective of the mode of ventilation) aiming for a plateau pressure of \(\leq 30\) cm H\(_2\)O to minimize donor lung injury appear to be reasonable targets given the available limited data in organ donors.\(^{122}\)

**Surfactant.** Animal models of surfactant have demonstrated the anti-inflammatory, antibacterial, and antiviral effects of surfactant.\(^{128}\) In the acutely injured lung, hyperoxia and plasma proteins leaking into the alveoli have been shown to inhibit alveolar surfactant. In a rat model of lung transplantation, a significant reduction in pulmonary compliance, functional residual capacity and decrease in surfactant composition were demonstrated immediately after pulmonary artery flushing with modified Euro-Collins solution and persisted over six hours. These observations have prompted other investigators to demonstrate the benefit of exogenous surfactant to improve the pulmonary dysfunction resulting from the ischemia-reperfusion injury of donor lungs in a porcine lung transplant model.\(^{129}\) The use of surfactant in human lung donors has not been rigorously investigated.
**Prostacyclin and inhaled nitric oxide.** In a rat model of double lung transplantation, the vasodilatory effects of prostacyclin (35 µg/kg PGI₂), given both intravenously and into the pulmonary flush solution, were compared with the effects of inhaled nitric oxide (targeting an expiratory NO concentration of 20 ppm) for donor treatment. During 120 minutes of reperfusion, serial measurements of graft pulmonary vascular resistance (PVR) and alveolar arterial oxygen difference (AaDO₂) were obtained. During reperfusion, the compliance was significantly reduced in NO in comparison with controls and PGI₂. The PVR was significantly elevated and the AaDO₂ was significantly reduced in the NO group compared with controls and PGI₂. Histological analysis demonstrated significantly more interstitial edema in the NO group. The deterioration of graft function with NO, even in comparison to untreated grafts, was attributed to the preferential vasodilation of the ventilated alveoli, with no effect on those alveoli that were collapsed.

Due to prolonged ventilation and a supine position, microatelectasis is a common finding in the lungs of potential donors. In an experimental rat model, donor lungs developed microatelectasis despite PEEP and a relatively short ventilatory period before organ procurement. Nitric oxide inhalation before and during organ perfusion then resulted in regional malperfusion in those areas where atelectasis was present.

Due to malperfusion, blood cells may not be cleared from the capillary bed, resulting in activation of the inflammatory cascades during ischemia and reperfusion. In contrast, prostacyclin given intravenously reaches the entire vascular bed, independent of regional ventilation, thus allowing homogeneous distribution of the preservation solution. Some transplant centers, such as the Barnes-Washington University Lung Transplant Group, administer 500 µg of prostaglandin E-1 directly into the pulmonary artery prior to flushing with modified Euro-Collins solution and procuring the lung.

**Predictors of lung allograft dysfunction**

In a recent cohort study of 225 consecutive lung transplants, independent predictors for the development of primary graft failure (incidence 11.8%) included recipient diagnosis of primary pulmonary hypertension (OR 4.52), donor African-American race (OR 5.56), donor female gender (OR 4.11) and donor age < 21 years (OR 4.06) or > 45 years (OR 6.79). Of note was that neither smoking history nor the mode of donor death was associated with an increased risk of primary graft failure.

An analysis of the database from the California Transplant Donor Network demonstrated that the presence of clear breath sounds in the donor (OR 2.1) and donor treatment with methylprednisolone (OR 3.0) independently predicted successful lung procurement as opposed to heart but no lung procurement.

Most studies evaluating the total lung graft ischemic time and its influence on acute and chronic rejection and recipient survival after lung transplantation have been small, single-center studies and have failed to find an association between total lung graft ischemia time and recipient survival. However, one Australian study demonstrated a significant association with prolonged total lung ischemic time and recipient mortality.
An analysis of 5,052 lung transplants performed between 1987 and 1997 using the combined UNOS and International Society for Heart and Lung Transplantation (ISHLT) Registry showed that donor age < 11 years or > 50 years but not total lung graft ischemia time had a significant worsening effect on recipient survival. However, when a multivariable model was fit to the data, a significant interaction was present between donor age and total cold ischemia time, and the interaction between older donor age and longer ischemia time was a significant predictor of one-year recipient mortality. This interaction was particularly true with donor ages of 45 and total lung ischemic time of more than 8 hours or with donor ages of 55 and total lung ischemic times of more than 6 hours. However, recipients of lungs from 284 donors over 50 years old had an encouraging one-year survival of 65.6%, which was 5–7% less than the 1997 cohort of recipients of lung transplants in the ISHLT registry. Similar results were demonstrated in a multivariable analysis of a cohort of 1,800 lung transplant recipients using the UNOS database between 1993 and 1996, where age and cold ischemia time (within cold ischemic time limits permitted for transplantation at the local centers) were not independently predictive of mortality at a two-year follow-up.

**Expanding the lung donor pool**

A detailed and recent review of lung transplant donor acceptability criteria has been published by Orens et al. The criteria for an ideal lung donor are outlined in table 2.

**Table 2. Currently accepted “ideal” donor for lung transplantation**

<table>
<thead>
<tr>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>Age &lt; 55</td>
</tr>
<tr>
<td>ABO compatibility</td>
</tr>
<tr>
<td>Clear chest radiograph</td>
</tr>
<tr>
<td>PaO₂ &gt; 300 on FIO₂ = 1.0, PEEP 5 cm H₂O</td>
</tr>
<tr>
<td>Tobacco history &lt; 20 pack-years</td>
</tr>
<tr>
<td>Absence of chest trauma</td>
</tr>
<tr>
<td>No evidence of aspiration/sepsis</td>
</tr>
<tr>
<td>No prior cardiopulmonary surgery</td>
</tr>
<tr>
<td>Sputum gram stain shows absence of organisms</td>
</tr>
<tr>
<td>Absence of purulent secretions at bronchoscopy</td>
</tr>
</tbody>
</table>

Adapted from Orens JB et al. J Heart Lung Transplant 2003;22:1183-200

In an effort to improve donor lung selection, Ware et al. used physiological, microbiological and histological methods to examine 29 pairs of rejected lungs from the California transplant registry. Twelve of 29 (41%) pairs of rejected lungs would have been potentially suitable for transplantation based on the level of pulmonary edema, intact alveolar fluid clearance and histology. Based on these findings, the authors suggested that there is probably room for improving the current criteria for donor selection.
In a case series of 15 brain-dead patients, lung grafts that did not meet the usual criteria for transplantation were found to have higher dynamic and static elastance measurements than donor lungs that met standard transplantation criteria.\textsuperscript{141}

**Donor oxygenation**

Traditional oxygenation criteria used as a threshold in the acceptance of donor lungs include a donor PaO\textsubscript{2} of more than 300 mm Hg on inspired oxygen fraction (FIO\textsubscript{2}) of 100% and PEEP of 5 cm H\textsubscript{2}O.\textsuperscript{98,116} Aziz et al. have challenged donor PaO\textsubscript{2} criteria by arguing that many pathophysiological factors in the organ donor influence the level of PaO\textsubscript{2} independent of individual lung function.\textsuperscript{104} In this study, no difference in median duration of mechanical ventilation and one-year mortality was shown between recipients of lungs procured from donors with a PaO\textsubscript{2} of greater than 300 mm Hg and a pulmonary vein oxygen level (PvO\textsubscript{2}) of greater than 300 mm Hg and recipients of lungs harvested from donors with a PaO\textsubscript{2} less than 300 mm Hg and a PvO\textsubscript{2} greater than 300 mm Hg.

In an occasional patient, parenchymal abnormalities may be isolated to one lung; despite poor global oxygenation, the contralateral lung has been successfully procured.\textsuperscript{142} Sundaresan et al. studied the outcomes of 133 consecutive lung transplants performed between 1991 and 1994.\textsuperscript{98} Eighty-nine donors were considered ideal according to the following criteria:

- age younger than 55 years
- smoking less than 20 pack-years
- arterial oxygen tension greater than 300 mm Hg using an inspired oxygen fraction of 100% and a PEEP of 5 cm H\textsubscript{2}O
- chest radiograph negative for infiltrate or trauma including contusion or pneumothorax

Forty-four donors were considered to be marginal because of the failure to meet one or more of the above criteria. Recipients from the ideal versus the marginal group showed no significant difference in median duration of postoperative mechanical ventilation and no significant difference in alveolar-arterial oxygen gradient immediately after transplantation or at 24 hours.

Encouraging results have also been demonstrated in Australia.\textsuperscript{26} In a series of 219 potential lung donors, 59 donors had a PaO\textsubscript{2}:FIO\textsubscript{2} ratio of < 300 mm Hg on an FIO\textsubscript{2} of 100% and PEEP 5, and 18 of these 59 were clearly unsuitable donors. The remaining 41 potential lung donors were treated with aggressive bronchial toilet using bronchoscopy, physiotherapy, increasing tidal volume and increasing PEEP. After such therapy, 20 (34%) of the remaining 59 potential lung donors improved their PaO\textsubscript{2}:FIO\textsubscript{2} ratio to > 300 mm Hg on FIO\textsubscript{2} 100% and PEEP 5, and these lungs were subsequently transplanted. No difference in ICU length of stay or 30-day mortality was noted between recipients from ideal donors and from donors whose gas exchange was initially suboptimal. A subsequent multivariable model demonstrated that only cold ischemic time of the graft (and not donor PaO\textsubscript{2}/FIO\textsubscript{2} ratio before explantation) was predictive of recipient PaO\textsubscript{2}:FIO\textsubscript{2} ratio.
Renal Considerations

Renal pathophysiology following brain death

A recent review of the effects of nonimmune tissue injury in renal transplantation outlined two principal mechanisms through which nonimmune organ damage occurs after renal transplantation; first by inciting the immune response and second by direct tissue injury.\[163\]

Nonimmune tissue damage is involved in part in the development of delayed graft function, in which brain death, prolonged ischemic time and immunologic factors play a role. Delayed graft function also predicts the development of adverse morbid events such as decreased graft survival, decreased recipient survival, increased rejection and increased allograft nephropathy.\[143\]

The 1997 Banff working classification of renal allograft pathology characterizes the histopathologic features of renal allograft nephropathy as tubular atrophy, interstitial fibrosis and fibrous intimal thickening leading to a reduced glomerular filtration rate (GFR).\[144\] Glomerular hyperemia and inflammation are characteristic histopathologic features of kidneys in brain-dead donors.\[145\] Donor brain death causes upregulation of the inflammatory response in an antigen-independent manner. Early immune-mediated injury has been thought to result in primary nonfunction and failure of the renal allograft. However, the effects of nonimmunologic, antigen-independent damage to the kidney and other organs may be a trigger for subsequent renal alloresponsiveness.

In a rat model of brain death, animals bearing kidneys from brain-dead donors compared to those from living donors and those from living controls anesthetized for six hours had significantly increased neutrophil, macrophage and T-cell infiltration on histological exam. The mRNA of proinflammatory mediators detected in kidneys from brain-dead donor animals also increased compared to both control groups. An acceleration and amplification of the host immune response, manifested by the augmented expression of chemokines (MCP-1, MIP-1, IL-8), cytokines (TNF-α, interferon-γ, IL-1β), adhesion molecules (E-selectin, ICAM-1) and major histocompatibility complex class II antigens, were also noted in the brain-dead donors.\[146\] This expression of P-selectin and the rapid infiltration of the cadaveric donor kidneys by neutrophils may trigger subsequent inflammatory changes that increase the incidence of delayed graft function and prime the kidneys for subsequent host immune mediated damage.

Cytokines are also thought to play a role in donor organ injury and subsequent worsening graft survival. Increased serum and urine interleukin 8 (IL-8) concentrations and increased urine interleukin 6 (IL-6) concentrations in recipients 24 hours after kidney transplantation can predict the severity of graft rejection.\[147\]

Serum IL-1β and macrophage inhibitory protein-1 in the kidneys of brain-dead rats compared to living anesthetized controls were elevated within six hours of induction of brain death and one hour of revascularization. Moreover, by immunohistology, there was an increased number of neutrophils and induction of P- and E-selectins, complement and cytokines up to five days after recipient engraftment.\[148\] This supports the hypothesis that an initial nonimmune response in brain-dead donor organs leads to later immune reactivity in the recipient and subsequent graft failure.
Another rat model of brain death induction demonstrated an increase in immunological activation of endothelial cells in the liver and kidney as evidenced by ICAM-1 expression, enabling leukocyte recruitment to the underlying organs. This may explain some of the disparity in outcome between living and cadaveric donors. A biochemical and pathological study of 20 brain-dead patients who were maintained on life support for 0 to 48 days after brain death by administration of vasopressin and epinephrine demonstrated a diuretic phase of prerenal failure on day 0 (day of brain death), which recovered by day 1 and remained almost normal over a 14-day period. This phase was accompanied by mild hyponatremia and hypo-osmolarity with high urinary sodium output and osmolarity for days 0 to 14. Of note was that the mean value for creatinine clearance was below the normal range on day 0 but improved to within the normal range on days 1 to 14. Initial pathological changes included glomerular hyperemia on day 0 with improvement thereafter and later development of tubulointerstitial nephritis, arterial intimal proliferation and glomerular endothelial proliferation after a week. Mechanisms hypothesized for the protracted excess sodium excretion included (1) the diuretic phase of acute renal failure, (2) neurogenic impairment of renal function through renal sympathetic nerve denervation resulting in an increase in urine flow and sodium excretion, (3) the direct effects of high serum levels of vasopressin and (4) the predominantly distal tubular pathology and interstitial fibrosis seen on pathological examination representative of tubulointerstitial nephritis. Most of the brain-dead patients received vasopressin at an infusion rate of 1–2 units per hour (285 ± 45 µU/kg/min) with epinephrine to sustain a systolic blood pressure of more than 90 mm Hg. The serum antidiuretic hormone level in the patients receiving vasopressin was 10–40 pg/ml (normal range = 0.3–4.2 pg/ml). This delay of over one day to recover renal function may be responsible for the epidemiological observation that renal allografts procured from donors after 470 minutes from the neurological determination of death demonstrate significantly better primary graft function than those harvested from donors fewer than 470 minutes from the neurological determination of death.

**Predictors of kidney allograft dysfunction**

Post-transplantation renal function is associated with hemodynamic instability during and after brain death. Donor hemodynamic instability is correlated with post-transplant acute tubular necrosis (ATN). Other factors that affect long-term kidney function are long duration of cold ischemia times, donor age, recipient age, gender, extent of HLA match, duration of time on dialysis prior to transplantation and immunosuppression protocol toxicity. Renal graft failure and ATN increase if donor systolic blood pressure is consistently less than 80–90 mm Hg. Kidneys from hemodynamically stable donors have a lower rate of early graft nonfunction compared with those from hemodynamically unstable donors. Reduced graft survival may occur in organs retrieved from donors receiving high-dose dopamine, but this effect may be limited to donors who are hypotensive at the time of organ retrieval. Mean donor arterial blood pressure below 80 mm Hg and high doses of dopamine (> 10 µg/kg/min) for donor maintenance are known risk factors of ATN after transplantation, as autoregulation of renal blood flow and glomerular filtration are declining below these levels. In a study of 77 pediatric organ donors, 27 (35%) suffered at least one cardiac arrest, and 36 kidneys from 31 donors suffered either ATN or primary nonfunction. The donors of these organs spent longer in the ICU.
(60.6 vs 42 hours) and had a higher mean maximum serum sodium concentration (163.4 vs 158.5 mmol/L) than those without these complications.\textsuperscript{19}

As with other organs, prolonged cold ischemia time is associated with poor renal allograft function. In an analysis of the Collaborative Transplant Study database of kidney transplants, a cold ischemic preservation time over 12 hours resulted in progressively worsening recipient graft survival, particularly if the cold ischemic time was greater than 48 hours.\textsuperscript{151} Interestingly, kidneys procured with a cold ischemic time of 0 to 6 hours had a worse graft survival time than kidneys procured between 25 and 36 hours because of a disregard for HLA matching in the kidneys with short ischemic times. The policy of certain centers was not to perform HLA matching in organs with a cold ischemia time of 0–6 hours, as it was not thought to be important for long-term outcome in these otherwise healthy organs. Within the group of transplants with cold ischemic times of 0–6 hours, increasing HLA A, B, DR mismatching was associated with a progressively worsening recipient graft survival.

\textbf{Expanding the kidney donor pool}

The pool of potential kidney donors may be expanded by considering potential donors over 60 years of age, those with cerebrovascular accidents as an etiology of death, those with a serum creatinine greater than 133 $\mu$mol/L (> 1.5 mg/dL) or a reduced creatinine clearance and those with a history of hypertension or type 1 or 2 diabetes mellitus.\textsuperscript{158–162} No uniformly accepted definition of the marginal donor exists in the literature; however, a proposal by Tullius et al. includes donor age > 65 years, creatinine clearance < 90 ml/min, serum creatinine > 133 $\mu$mol/L (1.5 mg/dl) during a stable phase of the donor, degree of glomerulosclerosis > 15%, certain anatomic abnormalities such as more than one renal artery, etiology of donor death and cold ischemic time to define marginal renal allografts.\textsuperscript{163}

\textbf{Technical and logistical considerations}

Data from the National Transplant Database of the United Kingdom indicate that 9,014 kidneys were procured in the United Kingdom and Ireland between 1992 and 1996. Of these, 1,726 (19%) were identified by either the retrieval or recipient centers as having renovascular or parenchymal damage.\textsuperscript{164} Older donors had a significantly higher incidence of being damaged. Of the damaged kidneys, 1,630 (94%) were transplanted. Although there was significantly worse one- and three-year graft survival in recipients of kidneys from donors ≥ 40 years old, the presence of kidney damage did not significantly affect graft survival.
Donor age, creatinine clearance, hypertension and etiology of death

Using a cohort of 29,068 kidney transplant recipients from the Organ Procurement and Transplantation Network, Port et al. used a Cox statistical model to define “expanded donor kidneys” as those with a relative risk of graft loss greater than 1.70, meaning a greater than 70% risk of graft failure. Donor characteristics that were independently associated with significantly increased risk for graft failure were older age (40 years or older), age younger than 10 years, impaired renal function by creatinine > 133 µmol/L (> 1.5 mg/dL), history of hypertension and cerebrovascular accident (CVA) as the cause of donor death. Cold ischemia time was found to be predictive of poor graft survival only if it was greater than 24 hours. Interestingly, a history of diabetes mellitus was present in 2.9% of these donors but was not significantly associated with graft failure in the multivariable model, nor was the duration of hypertension significant. Consistent with findings in populations undergoing lung transplantation, black race (versus all other donor races) and female gender of the donor were both associated with an increased graft loss. Serum creatinine greater than 133 µmol/L (> 1.5 mg/dL) was associated with a 10% higher risk of graft failure, as was a creatinine clearance < 60 ml/min. Using a decision probability matrix based on this large database, all donors older than 60 years and those aged 50–59 years with two or more additional risk factors (donor etiology of death CVA, creatinine > 133 µmol/L, hypertension) produced a relative risk of graft failure of greater than 1.70 (table 3, next page). Forty-six percent of kidneys with a relative risk greater than 1.70 were discarded compared to a 4.5% discard rate for donors with a 1.00 relative risk. Ultimately, the one-year (three-year) kidney graft survival using a kidney from a donor with a risk status of < 1.70 was 90.6% (79.4%), from a donor with a risk status of 1.70–2.0 was 86.5% (71.1%) and from a donor with a risk status of > 2.5 was 84.5% (68.0%).

In another study comparing 63 kidney grafts from donors over 60 years of age transplanted into recipients younger than 60 years of age compared to a control group where both donor and recipients were less than 60 years of age, one- and five-year graft survival rates were 95% and 83% in the control group compared to 94% and 81% favouring the older donor group, although there was a significant difference in composite death-graft survival rates (favoring younger donors) when the increased death rates in the older donor group were included as a “competing risk” in the analysis of graft failure.

Donor diabetes mellitus

Using the University of Wisconsin transplant database, Becker et al. compared 42 recipients (30 of these being nondiabetic) of kidneys from diabetic donors to 1,971 recipients of kidneys from nondiabetic donors. Ironically, a significantly increased five-year patient and graft survival was noted in nondiabetic patients who received a kidney from a donor with type 2 diabetes mellitus compared to recipients of kidneys from nondiabetic donors. There was no significant difference in the rates of graft rejection between groups. However, recipients of grafts from diabetic donors had a higher discharge creatinine level, an increased risk of proteinuria and more post-transplant glucose intolerance compared to recipients of kidneys from nondiabetic donors. As expected, both patient and graft survival were decreased in recipients with pre-existing diabetes.
Table 3. Relative risk of graft loss by four kidney donor characteristics

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Relative Risk</th>
<th>Normal Creatinine</th>
<th>High Creatinine</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>No HTN</td>
<td>HTN</td>
</tr>
<tr>
<td>Cause of death not CVA</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0–9</td>
<td>1.40&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.59&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.52&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>10–39</td>
<td>1.00 (ref)</td>
<td>1.14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.09&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>40–49</td>
<td>1.17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.33&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.28&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>50–59</td>
<td>1.41&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.60&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>2.16&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.07&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
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<td>1.30&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.24&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>1.83&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.75&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>60+</td>
<td>2.17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.47</td>
<td>2.37&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Modified from Port FK et al. Transplantation 2002;74:1281-6*

Risk of graft loss relative to donors aged 10–39 years with a terminal serum creatinine < 133 µmol/L (< 1.5 mg/dL) but without HTN and CVA (reference population); other factors held constant. Adjusted for donor gender and race and recipient age, gender, race, BMI, primary cause of end-stage renal disease, years on dialysis, HLA mismatches, year of transplantation and cold ischemic time. Bold numbers highlight RR > 1.70.

Terminal creatinine > 133 µmol/L (> 1.5 mg/dL)

<sup>a</sup><i>p < 0.0005</i>

<sup>b</sup><i>p < 0.05</i>

**Donor hepatitis B and C status**

In an analysis of kidney transplantations from 1994 to 1997 using the UNOS database, 15% of recipients initially anti-HBc- converted to anti-HBc+ one year after being transplanted with a kidney from an anti-HBc+ donor.<sup>97</sup> Moreover, recipients transplanted from donors positive to both anti-HBc- and antibody to HCV had a 170% increase in the odds of one-year mortality.

If a donor is HBsAg- and anti-HBc+, it is recommended that IgM and IgG serology be obtained from the donor and that kidneys from IgM+ donors not be used for transplantation because of their high potential for infecting the recipient.<sup>97</sup> Organs from anti-HBc+ IgG+ donors are
recommended for anti-HBsAg- recipients in life-threatening situations or for anti-HBsAg+ recipients with extenuating need such as vascular access failure for dialysis. Management of the recipients of these kidney allografts should include therapy with lamivudine and HBIG.

Using the data from the same UNOS database, the one-year risk of an initially HCV- kidney transplant recipient developing HCV positivity when transplanted with an HCV+ donor is 39%. Consequently, the use of HCV+ kidney donors is not recommended in HCV- recipients.

**Simultaneous double kidney transplant into a single recipient**

A Spanish study of 181 kidney transplant recipients (21 simultaneous double kidney transplants) implemented a protocol whereby a kidney biopsy was always performed in donors who were 60 years of age or older in order to analyse for the presence of glomerulosclerosis. Simultaneous double kidney transplant was performed for a single recipient when the donor age was 75 years or older or when a donor between 60 and 74 years of age had a glomerulosclerosis rate of more than 15% (group I). A single kidney transplantation was performed for recipients when donors were between 60 and 74 years of age with a glomerulosclerosis rate of less than 15% (group II) or when donors were younger than 60 years of age (group III). Kidneys with glomerulosclerosis rates greater than 50% were not used for transplantation. The primary nonfunction rate was low in all three groups (5%, 5% and 4% respectively) and there was no significant difference in one-year recipient or graft survival rates (95%, 90% and 93% respectively).165

In a study from Germany, the authors developed a scoring system for the donor kidneys that incorporated points for older donor age, worsening degree of glomerulosclerosis, donor stable-state serum creatinine and kidney weights (weight > 300 gram being optimal). Donors with 0–1 points had two kidneys used for two separate transplants, donors with 2 points had both kidneys used for one simultaneous kidney transplant, and donors scoring more than 2 points were not used. Twenty-six recipients were studied, 22 of whom survived after an average of 18 months of follow-up. Two-year patient and graft survival was 92%, primary nonfunction occurred in 31% and acute rejection occurred in 14%.166

A comparison of dual kidney donors looked at 84 recipients of dual kidneys from donors ≥ 54 years of age from the Dual Kidney Registry between 1993 and 1999 against 4,803 recipients of single kidney transplants from the UNOS database transplanted between 1994 and 1997.167 Mean terminal creatinine clearance in the dual transplant donors was 70 ± 26 ml/min, and dual recipients were more poorly HLA matched than single kidney recipients. Recipients of dual kidneys from donors ≥ 54 years of age versus single donor transplants from donors ≥ 54 years of age had a significantly lower incidence of delayed graft function (19% versus 37%), significantly lower serum creatinines after two years (151 µmol/L versus 204 µmol/L) and improved one-year graft survival (90.8% versus 79.9%).

**Survival and economic benefits of accepting marginal kidney donors**

Ojo et al. reviewed the UNOS Scientific Renal Transplant Registry in conjunction with the United States Renal Data System.162 The survival of patients on the kidney transplant waiting list and receiving dialysis was compared to the survival of patients transplanted with a marginal donor kidney and those transplanted with an ideal donor kidney. Marginal donor kidneys were defined as those procured from donors > 55 years of age, donors with a > 10 year history of hypertension, donors with a history of diabetes mellitus longer than 10 years duration, non-heart-
beating donors and donor organs with a cold preservation time > 36 hours. Five-year graft and patient survival rates were 53% and 74% for recipients of marginal donor kidneys compared with 67% and 80% for recipients of ideal donor kidneys. The adjusted annual death rate was 6.3% in those waiting on dialysis compared to 4.7% and 3.3% for those receiving marginal and ideal kidneys respectively. The average increase in life expectancy for recipients of marginal donor kidneys compared to those waiting for a kidney transplant was five years.

The economic cost of performing renal transplants using expanded donor criteria have been assessed in an analysis using the UNOS Renal Transplant Registry linked with Medicare claims (Medicare was the primary payer data on 34,534 kidney transplants from 1991 to 1996). Expanded donors were defined as donors aged 5 or ≥ 55 years, non-heart-beating donors and donors with a history of hypertension or diabetes. High-risk recipients were defined as those aged > 60 years or receiving a repeat transplant. The five-year present value of payments ranged from $121,698 for non-expanded donor/non-high-risk recipient to $165,716 for expanded donor/high-risk recipient pairings. The break-even point with hemodialysis ranged from 4.4 years for non-expanded donor/ non-high-risk recipient to 13 years for the expanded donor/high-risk recipient pairs.

Thus, the available literature supports both the survival and the economic benefits of accepting marginal kidney donors for transplantation.
Hepatic Considerations

Hepatic pathophysiology following brain death

As with other solid organs, the major factors compromising liver graft survival include factors related to brain death as well as preservation-reperfusion injury. More specifically, the extent of the preservation-reperfusion injury depends directly on the duration of cold ischemia and not upon reperfusion. Cold preservation causes the sinusoidal lining cells (SLC) of the liver to become edematous, and with extended periods of cold ischemia the sinusoidal cells detach and the hepatocyte microvilli become exposed to the sinusoidal lumen, resulting in cell death.

Leukocyte and lymphocyte aggregation and adherence to ischemic SLC also play major roles in donor liver injury. It is hypothesized that overexpression or conformational changes in adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) on the surface of SLC or endothelial cells respectively may mediate the attachment and subsequent injury caused by leukocytes. Platelet adherence to the abnormal sinusoids as well as Kupffer cell activation and procoagulant activity are also thought to mediate hepatocellular damage to the donor liver. Intermediate molecules in this process include reactive oxygen intermediates and cytokines and possibly proteases, calcium, eicosanoids and platelet activating factor. Collectively, it is postulated that these pathophysiological changes are directly related to the development of primary dysfunction of the liver graft described below.

Risk factors for liver allograft dysfunction

Primary dysfunction (PDF) of the liver in the transplant recipient is the standard outcome measure for the success of a hepatic graft.

PDF is subdivided into primary nonfunction (PNF) and initial poor function (IPF). PNF is defined as non-life-sustaining function of the liver after orthotopic liver transplant (OLT) leading to death or retransplantation within seven days, and IPF is often defined as AST > 2000 IU/L and prothrombin time of more than 16 (or equivalent INR units) on postoperative days 2 to 7. In general, liver dysfunction beginning after the first week following liver transplantation is not attributable to pre-operative or intra-operative variables.

Historically, PNF occurs in 2-23% of liver transplant series. In a series of 323 consecutive OLTs from Madison Wisconsin, the incidence of PDF was 22%, including a 16% incidence of IPF and the balance of 6% as PNF. IPF was associated with significant mortality (21%), liver graft failure rate (34%) and retransplantation rate (15%) within the first three months of transplantation. In a comparable long-term cohort study of 288 patients after the introduction of the University of Wisconsin (UW) preservation solution in Europe, PDF was identified in 21% of recipients with PNF and IPF rates of 7% and 14% respectively. In this European cohort, three-month and six-year liver graft failure rate in patients with IPF was 42% and 61% compared with 9% and 28% in those with immediate function.

Within the University of Wisconsin study, reduced-size livers, older donor age (> 49 years), moderate to severe fatty changes in the donor liver biopsy and prolonged preservation times (> 18 hrs) were associated with a higher risk of PDF in multivariable analysis. Based on these
findings, routine donor liver biopsies have been recommended in all liver donors in an effort to decrease the rate of IPF and PNF.

In an analysis of 649 OLTs performed in 11 centers in Spain from 1992 to 1993, extended cold ischemia time > 12 hr (OR = 2.2) and arterial complications (OR = 5) were independently associated with biliary complications. ABO incompatibility (relative risk [RR] = 3.2) and donor plasma sodium > 155 mmol/L (RR = 1.4) were independently associated with an increased rate of retransplantation before 30 days, and donor plasma sodium > 155 mmol/L (RR = 2.0) and ABO incompatible grafts (RR = 3.3) were independently associated with death or retransplantation within 30 days.172 Other authors have demonstrated a similar detrimental effect of high sodium levels on liver graft outcomes.173 In a series of 168 liver transplants, a high donor serum sodium concentration, longer total ischemia time, large platelet transfusion during surgery and prolonged recipient prothrombin time were independently associated with more severe hepatic dysfunction after transplantation.174 High serum sodium levels in the donor may promote the accumulation of idiogenic osmoles such as amino acids and methylamines within liver cells as is seen with neurons and renal tubular cells. The subsequent transplantation of these livers in recipients with relatively normal sodium levels may promote intracellular water accumulation through osmosis, possibly leading to cell lysis and death manifested as PNF or IPF. The benefit of correcting donor serum sodium to levels below 155 mmol/L has been described by Totsuka et al. in a prospective study of 181 consecutive OLTs.175 The frequency of liver graft loss was found to be significantly higher in the patients with uncorrected sodium (33%) compared to the frequency of graft loss in a normal sodium (12.7 %) or corrected sodium (11.1%).

The influence of donor nutrition on graft survival has been studied in several small animal models but not in human studies. In a rabbit and porcine model, Boudjema et al. demonstrated that animals receiving livers from donors that received enteral nutrition prior to transplantation had better survival than animals receiving livers from fasting donors.176 Similarly, a significant improvement in SLC viability has been demonstrated in rats receiving liver grafts from donor rats receiving enteral feeding plus intraperitoneal glucose prior to liver procurement. Uchida et al. demonstrated an improvement in liver graft survival with livers procured from rats who were given only water or water containing glucose for four days compared to fed rats.177 In a porcine model of liver transplantation, donor pigs provided with parenteral nutrition in the form of 20% glucose had reduced preservation-reperfusion injury compared to donor pigs that were provided with an enteral diet. The only human series of liver transplants that included donor nutritional status failed to identify an independent effect of donor nutrition on postoperative liver graft function.174

In summary, the sinusoidal lining cells of the liver appear to be particularly vulnerable to injury resulting from both donor brain death and preservation-reperfusion. Older donor age in adult transplantation and very young age in pediatric transplantation, moderate to severe steatosis on liver biopsy, prolonged cold ischemia time (in excess of 12–18 hours), ABO incompatibility, and donor hypernatremia (sodium > 155 mmol/L) appear to be the most robust predictors of PNF and IPF related to the donor (table 4). Other factors that may be associated with liver allograft dysfunction include (1) donor gender, race, etiology of brain death and ICU length of stay, (2) perioperative warm ischemia time, extent of platelet transfusions and technical complications and (3) recipient age, medical status, renal insufficiency, retransplantation and vasopressor use. It is reasonable to consider preventing or treating causes of hypernatremia in the organ donor,
targeting a serum sodium of < 155 mmol/L. The latter would include the limitation of excessive doses of osmotic diuretic agents, adequate fluid resuscitation, and the rapid diagnosis and management of DI.

Table 4. Potential risk factors associated with liver graft dysfunction

<table>
<thead>
<tr>
<th>Donor</th>
<th>Perioperative</th>
<th>Recipient</th>
</tr>
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<tbody>
<tr>
<td>Age &gt; 50</td>
<td>Warm ischemia time</td>
<td>Age</td>
</tr>
<tr>
<td>Gender (female donor in male recipient)</td>
<td>Technial complications</td>
<td>Medical status</td>
</tr>
<tr>
<td>Race (black donor in white recipient)</td>
<td>Blood product use including platelets</td>
<td>Renal insufficiency</td>
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<tr>
<td>Weight</td>
<td>Retransplantation</td>
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<tr>
<td>Cause of brain death</td>
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<tr>
<td>ICU length of stay &gt; 5 days</td>
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<td></td>
</tr>
<tr>
<td>Use of vasopressors</td>
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<td></td>
</tr>
<tr>
<td>Cold preservation time &gt; 12 hours</td>
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<td></td>
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<tr>
<td>High serum sodium &gt; 155 mmol/L</td>
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<td></td>
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<tr>
<td>Steatosis &gt; 30%</td>
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<td></td>
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<tr>
<td>Partial liver grafts</td>
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Expanding the liver donor pool

The American Society of Transplant Surgeons and the American Society of Transplantation have reviewed the issues related to optimizing the use of cadaveric donors, and their recommendations about liver transplantation have recently been published.3,5

A liver may be transected to the right of the middle hepatic vein, resulting in the creation of two equally sized adult grafts, or it may be prepared for an extended right lobe graft for an adult recipient and a left lateral segment graft for a pediatric recipient by transection along the plane of the falciform ligament.178,179 Splitting of the liver graft may be performed ex vivo or in situ before aortic cross-clamping.180 In general, results obtained from splitting for adult/child pairs have been more favourable than results from splitting for two adults.5

In the largest adult/child pair series of in vivo liver grafts, Ghobrial et al. did not demonstrate a significant difference in patient survival at a median of 14.5 months between recipients who received a split-liver graft (76%) and those who received a whole organ OLT.181 Similar results have been reported using ex vivo splitting for adult/child pairs of recipients by the King’s College Hospital Liver Transplant Programme.183 In this series, 22 donor livers were transplanted into 41 patients. After a median follow-up of 12 months, patient and graft survival
rates were 90% and 88% respectively. In a review of the European Split Liver Registry between 1988 and 1993, comparable patient and graft survival rates were demonstrated between split liver grafts and whole liver grafts.\textsuperscript{183}

Based on these and other studies (table 5), the Crystal City committee overseeing liver transplantation recommends the use of split-liver transplantation for adult/child recipient pairs in suitable liver donors, defined as follows:\textsuperscript{180,181,184–192}

- age > 10 yrs, < 45 yrs
- hemodynamically stable enough to be a heart donor
- intensive care unit duration < 5 days
- liver function tests < 5 times upper limit of normal
- serum sodium < 170 mmol/L
Table 5. Split-liver transplantation

<table>
<thead>
<tr>
<th>Center</th>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Recipient Survival</th>
<th>Graft Survival</th>
<th>Complication Rate</th>
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<td>Broerin</td>
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<tr>
<td>London</td>
<td>Rela</td>
<td>1998</td>
<td>41</td>
<td>90%</td>
<td>88%</td>
<td>39%</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>Ghobrial</td>
<td>2000</td>
<td>102</td>
<td>80%</td>
<td>78%</td>
<td>N/A</td>
</tr>
<tr>
<td>Hamburg</td>
<td>Broering</td>
<td>2001</td>
<td>49</td>
<td>82%</td>
<td>76%</td>
<td>28%</td>
</tr>
<tr>
<td>Hannover</td>
<td>Nashan</td>
<td>2001</td>
<td>78</td>
<td>80%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Milano</td>
<td>Maggi</td>
<td>2001</td>
<td>29</td>
<td>88%</td>
<td>66%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Adapted from Emond JC et al. Liver Transpl 2002;8:863-72

Donor liver age

An early review of the UNOS data from 1987 to 1990 suggested that there was a significantly worse one-year recipient survival with liver allografts from donors aged 45–55 years compared to those from donors aged 15–45 years. However, this survival difference was less than 10%. Several studies have demonstrated that recipients of liver allografts from donors who are older than 50 years of age have similar outcomes to those who receive their liver from younger donors as long as no additional risk factors are present.

Donor hepatitis B and C

The incidence of anti-HBc+ in the donor population varies by geography and has been demonstrated to be as high as 15% at an urban transplant center in the United States and 27% in Spanish donors over 60 years of age. Antibody against hepatitis B core antigen (anti-HBc+)
in the donor predicts risk of transmission of hepatitis B virus (HBV) and hepatitis B reactivation in the recipient after transplantation. A decrease in the risk of HBV reactivation is evident in recipients who are anti-HBc+ and have antibodies against hepatitis B surface antigen (anti-HBsAg+). Conversely, an increase in the risk of HBV reactivation is evident in recipients who are anti-HBc- and anti-HBsAg-. The detection of HBsAg+ in the donor implies that the donor is at risk for transmitting hepatitis B virus; this organ may be considered for recipients who are anti-HBsAg+ or critically ill. Donors with isolated anti-HBsAg+ (with HBsAg- and anti-HBc-), usually obtained from immunization or previous HBV infection, have no active viral replication and are unlikely to transmit hepatitis B to the recipient. Alternatively, donors who are HBsAg- (with anti-HBsAg+ and anti-HBc+) demonstrate immunity to the hepatitis B virus; however, after transplantation into an immunosuppressed host, transmission of the infection to the liver transplant recipient has been demonstrated, with rates between 8% and 100%. In this circumstance, liver biopsy of the donor organ may be necessary to assess for evidence of active hepatitis; some authors recommend routine biopsies in anti-HBc+ donors.

The liver donor of perhaps most concern is the donor who is anti-HBc+ (with HBsAg- and anti-HBsAg-), reflecting an insufficient period for the development of anti-HBsAg+ and an actively infectious state. Prieto et al. have demonstrated that such donors infect recipient livers at a rate of 50% compared to a rate of 2% in recipient livers from donors who are anti-HBc-. Other investigators have demonstrated good one-year graft survival of 85–88.6% in recipients of anti-HBc+ liver grafts if these recipients received HBIG and lamivudine therapy. Yu et al. reviewed 15 recipients of liver allografts from anti-HBc+ donors, six of whom were HBsAg+ and nine of whom were HBsAg- before transplantation. All the recipients were administered lamivudine 100 or 150 mg/day after transplantation, and recipients who were HBsAg+ also received HBIG prophylaxis. One of two recipients who was HBsAg+ and received a liver biopsy had detectable hepatic HBV DNA. None of the recipients who were HBsAg- acquired anti-HBc or HBsAg+, and none of the seven patients who underwent a liver biopsy had hepatic HBV DNA isolated.

Recipient anti-HBc status is important in predicting the development of HBV after transplantation, as small series of patients have demonstrated a 0–13% frequency of reactivation in recipients of anti-HBc+ livers who were also anti-HBc+ compared to 33–100% frequency of reactivation in recipients who were anti-HBc- prior to transplantation. The frequency of HBV reactivation from anti-HBc+ donors to anti-HBsAg+ recipients is uncertain because of limited clinical series addressing this topic, but ranges from 0–33%. Most authors have suggested that routine prophylaxis with lamivudine and HBIG is not necessary for recipients who are anti-HBc+ and or anti-AbsAg+; however, one author recommends routine prophylaxis for all recipients of anti-HBc+ livers. A summary of the management of recipients of anti-HBc+ liver donors is outlined in table 6.

Anti-HBc+ livers should initially be offered to HBsAg+ recipients, as limited data suggest that transplantation of these livers in patients with HBV cirrhosis or fulminant HBV infection does not affect mortality. Failing this match, anti-HBc+ livers should then be offered to anti-HBC+ and anti-HBsAg+ recipients, with close serological and virological monitoring of HBV DNA, HBsAg, anti-HBc and anti-HBsAg. If neither of these recipient types are available, then the anti-HBc+ organ should be offered to an anti-HBsAg- recipient with the understanding that there
is a high probability of HBV reactivation and that recipients should be placed on prophylactic therapy with lamivudine and HBIG.

Table 6. Risk of HBV and management of anti-HBc+ liver recipients

<table>
<thead>
<tr>
<th>Anti-HBc / anti-HBsAg Status</th>
<th>Risk of HBV Reactivation</th>
<th>Proposed Management Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor</td>
<td>Recipient</td>
<td></td>
</tr>
<tr>
<td>+/+ or +/-</td>
<td>+/-</td>
<td>high</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0% - 13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>low</td>
</tr>
<tr>
<td></td>
<td>any type</td>
<td>very low</td>
</tr>
<tr>
<td>HBV DNA+</td>
<td>any type</td>
<td>high</td>
</tr>
<tr>
<td>IgM anti-HBc+</td>
<td>any type</td>
<td>high</td>
</tr>
<tr>
<td>HBsAg+</td>
<td>any type</td>
<td>high</td>
</tr>
</tbody>
</table>

Abbreviations: lam = lamivudine; IgM = immunoglobulin M

Antibodies to hepatitis C virus are isolated in approximately 5% of all organ donors. The presence of the antibody indicates infection, and all organ donors with a positive HCV PCR will transmit HCV to the recipient. Transplantation of HCV+ donors to HCV- recipients should be performed only in exceptional circumstances. Transplantation of a liver from an HBC- donor to an HBV+ recipient does not significantly increase the recipient’s mortality. According to the UNOS database for 1994 to 1997, 2,923 HCV+ patients underwent OLT; 96 (3%) of these received an HCV+ allograft, and 2,827 (97%) received an HCV- allograft.

In summary, adult/child split-liver donation, older donors without significant steatosis or prolonged cold ischemic time, and anti-HBsAg+ or anti-HBc+ donor livers in combination with lamivudine and HBIG therapy should be considered for transplantation in an effort to expand the liver donor organ pool. Liver allografts from donors who are HCV+ should be used only in recipients who are HCV+. 

Munoz SJ. Liver Transplantation 2002;8:S82-7
Infection Considerations

Donor bacteremia

Isolated cases of solid organ infection in the donor being transmitted to the recipient have been documented, with potentially devastating consequences including graft infection, sepsis and poor initial graft function in a liver recipient. However, with careful attention to the use of prophylactic antibiotics such as vancomycin, ceftazidime and cefotaxime in the recipient immediately after transplantation and until donor blood culture results were obtained, two authors have demonstrated no transmission of bacterial infection in 124 recipients of solid organs.

In a study of 569 liver and heart donors, 29 (5%) of donors were subsequently found to be bacteremic at the time of organ procurement. The recipients of all of the organs from these donors were routinely treated with vancomycin and either ceftazidime or cefotaxime until the third day after transplantation, followed by norfloxacin until discharge as well as standard co-trimoxazole prophylaxis. Gram-positive bacteria were isolated in 76% of the bacteremic patients and gram-negative bacteria were isolated in 24%. None of the recipients became bacteremic with organisms that had been isolated from their respective donors, and there was no difference in 60-day patient or graft survival.

In an analysis of all organ donors cared for by the New England Organ Bank between 1990 and 1996, 95 (5.1%) of 1,775 organ donors were identified as bacteremic. No evidence of bacterial transmission could be identified in 212 recipients. There was no difference in 30-day graft and patient survival for recipients of organs from bacteremic compared to non-bacteremic donors.

Other authors have described the successful transplantation of organs from donors declared brain dead from meningitis caused by Neisseria meningitidis, Streptococcus pneumoniae and Escherichia coli without transmission to the recipient.

Prophylactic antibiotics and screening

Little or no literature exists on the use of prophylactic antibiotic therapy in the organ donor. General principles of antibiotic use in other critically ill patients suggest that minimizing the use of empiric antibiotics and narrowing the spectrum of coverage to target specifically isolated bacteria or fungi would be reasonable.

Recently, standards for the handling of donor organs have been published by the Canadian Standards Association. These standards state that the degree to which risk of infectious complications should be accepted in the recipient is to some extent governed by the urgency of the transplant as well as the availability of the donor organ.
Hematological Considerations

There are no rigorous studies that assess the role of red blood cell transfusions in the brain-dead donor. Both the Crystal City Consensus Conference Report and Van Bakel et al. have recommended maintaining a hemoglobin level $\geq 10$ g/L or a hematocrit greater than 30\%. In contrast, current critical care practice advocates the use of red blood cell transfusions in non-bleeding patients only at a hemoglobin level $< 70$ g/L.

In a randomized trial of allogeneic red blood cell transfusions in critically ill patients, treatment protocols included a restrictive strategy of transfusing at a hemoglobin threshold of 70 g/L (and maintaining hemoglobin between 70 and 90 g/L) versus a liberal strategy of receiving red blood cells at 100 g/L (and maintaining hemoglobin between 100 and 120 g/L). Overall mortality rates were not different between groups but there was a trend toward worsening survival in those with acute coronary syndromes not transfused liberally. However, the endpoints of transfusion studies in the ICU are patient survival, not organ preservation.

Donor Malignancy

Brain-dead patients with certain types of skin and central nervous system (CNS) cancers should be considered for potential organ donation.

In a cohort study of 14,705 cadaveric donors within the UNOS registry, 257 donors from whom 650 organs were procured. Three-hundred ninety-five of the 650 organs were obtained from donors suffering from non-melanoma skin and CNS cancers. During a mean follow-up of 45 months, no recipients of these organs developed a donor-associated tumour (by histology), and 71.5% of all the non-skin and non-CNS cancer donors had a cancer-free interval of greater than five years.

In another analysis of 42,340 cadaveric donors within the UNOS registry from 1992 to 1999, 397 had a past history of CNS tumour. No significant difference in recipient survival was identified between patients receiving organs from CNS tumour donors and patients receiving organs from donors without CNS tumors. Moreover, of the 39 patients reporting malignancies in the post-transplant period, none had tumours that were associated with the donor tumour.

Nonetheless, previous authors have described isolated cases of the transmission of medulloblastoma, glioblastoma and high grade glial neoplasms from donors to transplant recipients, particularly if the donors had undergone previous intracranial surgery or ventriculoperitoneal shunting. With this in mind, Detry et al. estimated the risk of CNS tumour transmission to be between 0% and 3% based on retrospective studies.

Based on these findings, it has been recommended that donors with CNS tumors are acceptable as long as the recipient’s risk of dying on the waiting list is much higher than 3%. However, both Detry and Kauffman have cautioned against the use of organs from donors with previous intracranial manipulation.

An outline of acceptable and marginal organs from donors with previous malignancy is provided in table 7 (next page). This outline is adapted from the 2001 Crystal City Report and the consensus report of the Pulmonary Council of the International Society for Heart and Lung Transplantation.
Logistics and Organization of Transplant Programs

UNOS demonstrated that implementing a critical pathway of structured organ donor management (compared to a similar period one year prior to the critical pathway) resulted in an overall increase of 10.3% in the number of organs recovered per 100 donors, an 11.3% increase in the number of organs transplanted per 100 donors and an overall increase of 19.4% for transplanted hearts. This critical pathway is the current protocol recommended by the UNOS. However, the benefit of this strategy appears to have more of an impact on the procurement of heart, lung and pancreas; there was no significant increase in the number of kidneys or livers transplanted per 100 donors when comparing the critical pathway group to the historical control group.

Table 7. Summary of literature for donors with a history of malignancy

<table>
<thead>
<tr>
<th>Acceptable</th>
<th>Not acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade skin cancer (basal cell and squamous cell)</td>
<td>If previous treatment with presumed cure, consider organs as marginal, including:</td>
</tr>
<tr>
<td>Carcinoma in situ of organs such as the uterine cervix</td>
<td>• renal cell cancer</td>
</tr>
<tr>
<td>Primary tumours of central nervous system</td>
<td>• lung cancer</td>
</tr>
<tr>
<td>• lowest risk</td>
<td>• melanoma</td>
</tr>
<tr>
<td>• benign meningiomas</td>
<td>• choriocarcinoma</td>
</tr>
<tr>
<td>• pituitary adenomas</td>
<td>• breast cancer</td>
</tr>
<tr>
<td>• acoustic schwannomas</td>
<td>• colon cancer</td>
</tr>
<tr>
<td>• cranioopharyngiomas</td>
<td></td>
</tr>
<tr>
<td>• astrocytoma grade I</td>
<td></td>
</tr>
<tr>
<td>• epidermoid cysts, colloid cysts</td>
<td></td>
</tr>
<tr>
<td>• low-grade oligodendrogliomas</td>
<td></td>
</tr>
<tr>
<td>• gangliogliomas, gangliocytomas</td>
<td></td>
</tr>
<tr>
<td>• pineocytomas, ependymomas</td>
<td></td>
</tr>
<tr>
<td>• well-differentiated teratomas</td>
<td></td>
</tr>
<tr>
<td>• papillomas</td>
<td></td>
</tr>
<tr>
<td>• hemangioblastomas</td>
<td></td>
</tr>
</tbody>
</table>
If there are risk factors for metastases, consider organs as marginal, including:

- **moderate risk**
  - astrocytoma grade II
  - gliomatosis ceribri
- **highest risk**
  - anaplastic astrocytoma grade III
  - glioblastoma multiforme
  - medulloblastoma
  - anaplastic oligodendroglioma
  - pineoblastomas
  - chordomas
  - malignant ependymomas
  - primary cerebral lymphoma
- **high grade histology**
- glioblastoma and medulloblastoma
- previous craniotomy
- ventricular shunts
- tumor radiation
- recurrence in the brain, or a long interval from primary therapy

*Adapted from Orens JB et al. J Heart Lung Transplant 2003;22:1183-200,*

*and Rosengard BR et al. Am J Transplant 2002;2:701-11*
Conclusion

There has been significant progress in the understanding of the pathophysiology of brain death and its effects on donor and recipient organ function over the last 20 years. Much of this information has come from animal experimentation and case series of brain-dead donors. Several cohort studies have provided valuable information about donor characteristics that decrease recipient graft survival and increase recipient mortality. The databases used in these studies have also been very helpful in modelling the statistical risk of allograft failure when predefined marginal donors have been used for transplantation.

Both evolving clinical experience and the analysis of institutional and national donor-recipient databases has demonstrated that previously “untransplantable” organs can be safely and effectively transplanted with good graft survival. Analysis of the datasets indicates that older donor age and longer cold ischemic time are consistent predictors of poor graft survival irrespective of the organ (heart, lung, kidney or liver). Despite these challenges with marginal donors, it is hoped that further scientific research into better donor management, better organ preservation techniques and improved predictive models for matching marginal donors with recipients will permit the expansion of the Canadian donor pool in the future.

A summary of routine investigations and management strategies for the multi-organ donor is provided in table 8. Although many of these recommendations have a sound physiological foundation, very few therapeutic recommendations have been tested within the context of randomized clinical trials. Rather, specific recommendations for therapies to improve the maintenance of donor function and graft survival have generally come from expert panels of transplant physicians and surgeons. As the demand for donor organs increases and the number of donors remains stable, future emphasis should be placed on testing various therapeutic hypotheses within the context of well-designed randomized trials and cohort studies.
Table 8. Summary of donor investigation and management

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Investigation</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EKG • troponin • echocardiogram: consider if male donor age &gt; 45 years or female donor age &gt; 50 years • dobutamine stress echocardiography: 5, 10, 15, 20 µg/kg/min at 3-minute intervals • angiography</td>
<td>For autonomic storm: esmolol (Brevibloc) loading dose of 1.5 mg/kg over 30 seconds followed by an infusion of 50–300 µg/kg/min. Titrate to achieve SBP ≤ 160 mm Hg and HR ≤ 80 /min</td>
</tr>
<tr>
<td></td>
<td>Monitoring</td>
<td>Maintain SBP ≥ 90 mm Hg or MAP ≥ 60 mm Hg</td>
</tr>
<tr>
<td></td>
<td>central venous line • arterial line • pulse oximetry • pulmonary artery catheter if hemodynamically unstable or evidence of cardiac dysfunction or pulmonary edema</td>
<td>Maintain CVP 6–8 mm Hg and PCWP 8–12 mm Hg for potential lung donors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintain CVP 8–10 mm Hg and PCWP 8–12 mm Hg if both thoracic and abdominal organs are considered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintain CVP 10–12 and PCWP 8–12 mm Hg if only abdominal organs are to be considered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac index ≥ 2.4 L/min/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SVRI 800–1,200 dyn/sec/cm²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Optimize stroke work index using</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• vasopressin up to 40 mU/kg/hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• norepinephrine 0–20 µg/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• dopamine or dobutamine ≤ 10 µg/kg/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• acetylcysteine 0.6–1.0 gram IV within 24 hours of coronary angiography and repeat within 24 hours after angiography</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Chest x-ray • Bronchoscopy to evaluate airway for anatomical abnormalities • Bronchoscopy and bronchoalveolar lavage for microbiological tests</td>
<td>Frequent endotracheal suctioning</td>
</tr>
<tr>
<td></td>
<td>Monitoring • Arterial blood gasses • Plateau pressure monitoring</td>
<td>Chest physiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchoscopy for bronchial toilet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PaO2 &gt; 100 mm Hg, FIO2 ≤ 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• maintain arterial pH 7.35–7.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• volume-controlled or pressure-controlled ventilation varying tidal volumes to maintain plateau pressures ≤ 30 cm H2O</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PEEP ≥ 5 cm H20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• recruitment maneuvers of PEEP 10–20 cm H2O and pressure-controlled ventilation of 35–45 cm H2O for duration of 15 minutes every 4 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salbutimol 2.5 mg nebulized q4h for bronchodilatation and pulmonary edema</td>
</tr>
</tbody>
</table>
### Table 8. Summary of donor investigation and management (cont’d)

<table>
<thead>
<tr>
<th>Renal/Metabolic</th>
<th>Investigations:</th>
<th>Monitoring:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• electrolytes, urea, creatinine, Ca++, Mg++, PO4=</td>
<td>Vasopressin, norepinephrine to maintain a MAP ≥ 80 mm Hg if donor only considered for kidneys</td>
</tr>
<tr>
<td></td>
<td>• terminal creatinine clearance measurement (Cockcroft-Gault equation)</td>
<td>Crystalloids or colloids to maintain urine output ≥ 1 mL/kg/hr</td>
</tr>
<tr>
<td></td>
<td>Monitoring:</td>
<td>Maintain K+ &gt; 4.0 mmol/L</td>
</tr>
<tr>
<td></td>
<td>• urine output hourly</td>
<td>Maintain Na+ &lt; 150 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintain physiological levels of Ca++, Mg++, PO4=</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintain pH 7.35 to 7.45 with bicarbonate if necessary</td>
</tr>
<tr>
<td>Liver</td>
<td>Bilirubin, AST, ALT, alkaline phosphatase, INR, PTT, glucose</td>
<td>Maintain MAP ≥ 90 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Liver biopsy when hepatic steatosis suspected or with marginal donors</td>
<td>Maintain serum Na+ &lt; 155 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glucose as D5W, D5/0.9% saline or D5/0.45% saline</td>
</tr>
<tr>
<td>Hematological</td>
<td>CBC, INR, PTT</td>
<td>Red blood cells to maintain Hb &gt; 70 g/dL for uncomplicated patients and Hb &gt; 100 g/dL for marginal cardiac donors</td>
</tr>
<tr>
<td></td>
<td>ABO screening</td>
<td>Fresh frozen plasma to correct coagulopathy</td>
</tr>
<tr>
<td></td>
<td>Cytotoxic screen</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Blood cultures</td>
<td>Vasopressin 0–40 mU/kg/hr IV or DDAVP 2 units IV q 6–8 hrs for DI</td>
</tr>
<tr>
<td></td>
<td>Bronchoscopy and bronchoalveolar lavage for culture and sensitivity</td>
<td>Insulin Toronto 0–20 U/hr to maintain physiological glucose levels</td>
</tr>
<tr>
<td></td>
<td>CMV</td>
<td>Methylprednisolone 15 mg/kg IV q24h</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B, anti-HBc, anti-HBsAg, HbsAg, hepatitis C</td>
<td>T3 bolus 4 µg followed by a continuous infusion of 3 µg/hr</td>
</tr>
<tr>
<td></td>
<td>HIV, human T-cell lymphotropic virus type 1 (HTLV-1)</td>
<td>Vancomycin 1 gm IV q12h + ceftazidime 1 gram IV q8h</td>
</tr>
<tr>
<td></td>
<td>Toxoplasma gondii, Epstein-Barr virus (EBV), syphilis, mycobacterium tuberculosis</td>
<td></td>
</tr>
</tbody>
</table>
Abbreviations

ADH  antidiuretic hormone (vasopressin)
ARDS  acute respiratory distress syndrome
ATN  acute tubular necrosis
AVP  arginine vasopressin (vasopressin)
CABG  coronary artery bypass grafting
CMV  cytomegalovirus
CNS  central nervous system
CVA  cerebrovascular accident
CVP  central venous pressure
DDAVP  1-desamino-8-D-arginine vasopressin
DI  diabetes insipidus
GFR  glomerular filtration rate
HBV  hepatitis B virus
HBC  hepatitis C virus
ICP  intracranial pressure
ICU  intensive care unit
IPF  initial poor function (liver)
ISHLT  International Society for Heart and Lung Transplantation
MAP  mean arterial pressure
OLT  orthotopic liver transplant
PDF  primary dysfunction (liver)
PGI₂  prostacyclin
PNF  primary nonfunction (liver)
SBP  systolic blood pressure
SLC  sinusoidal lining cells
SVR  systemic vascular resistance
T₃  triiodothyronine
T₄  levothyroxine
TSH  thyroid stimulating hormone
UNOS  United Network for Organ Sharing

Note: Drugs converted to units/kg/hr utilize a reference weight of 60 kg unless otherwise specified.
References


133. Winton TL, Miller JD, deHoyos A, Snell G, Maurer J. Graft function, airway healing, rejection, and survival in pulmonary transplantation are not affected by graft ischemia in excess of 5 hours. Transplantation Proceedings 1993;25:1649–50.


207. Van Thiel DH, De Maria N, Colanonti A, Friedlander L. Can hepatitis B core antibody positive livers be used safely for transplantation: Hepatitis B virus detection in the liver of individuals who are hepatitis B core antibody positive. Transplantation 1999;68:519–22.


