Kidney grafts from brain dead donors: Inferior quality or opportunity for improvement?

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Major improvements in immunosuppressive treatment, surgical techniques, and treatment of post-transplant complications have contributed considerably to improved outcome in renal transplantation over the past decades. Yet, these accomplishments have not led to similar improvements in transplant outcome when the results of living and deceased donors are compared. The enormous demand for donor kidneys has allowed for the increase in acceptance of suboptimal donors. The use of brain dead patients as organ donors has had a tremendous positive influence on the number of renal transplants. Unfortunately, the physiologically abnormal state of brain death has a negative effect on transplant outcome. The fact that transplanted kidneys derived from brain dead donors have a decreased viability indicates that potential grafts are already damaged before retrieval and preservation. In this review, we present an overview of the current knowledge of (patho)-physiological effects of brain death and its relevance for renal transplant outcome. In addition, several options for therapeutic intervention during brain death in the donor with the goal to improve organ viability and transplant outcome are discussed.

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INFERIOR SURVIVAL OF DECEASED DONOR KIDNEYS AFTER TRANSPLANTATION

Transplant outcome achieved with kidneys from living donors is far superior when compared to grafts obtained from deceased donors (Table 1).[1,2] The persistent donor organ shortage has caused longer waiting lists and an increasing percentage of patients that die while waiting. As a consequence, a gradual shift toward accepting suboptimal donors has taken place. The use of older and more marginal donors is now routine, and the number of non-heart beating donors has increased significantly over the past years.[1,3] Twenty years ago, the typical donor was under the age of 30 years, fairly healthy and died of traumatic cerebral injury. Today, the average donor is over 50 years old and the main cause of death is intracranial hemorrhage. The improvements that were made in treatment regimen of the recipient, organ preservation, reduction of cold ischemia time, and better allocation of donor organs have been masked by the use of lower-quality donors. In the past, much effort was directed toward post-transplantation immunosuppression and preservation of organs during transport. Now, risk factors and conditions before organ recovery in the donor need to be recognized for their impact on donor organ viability. The detrimental effects of brain death on renal transplant outcome[4,5] have been convincingly shown in the experimental setting. In clinical studies, though, it is difficult to reveal that brain death itself has an independent influence on transplant outcome, since living and deceased donors differ on more aspects than just the death of the brain. However, when survival rates are stratified for age, grafts from deceased donors have worse survival within each age-group – even in the relatively young group of 25–36-year-old donors.[2]

In 2005, 16 481 renal transplantations were performed in the United States. Of those, 9913 kidneys originated from deceased donors and 6568 were recovered from living donors.[1] Yet, at the end of 2004, 57 910 patients were on the waiting list to receive a renal transplant. For a patient enlisted in 2000, the median time to transplant was more than 3 years. Unfortunately, not every patient survived long enough to receive a transplant, which resulted in approximately 3000 deaths on the waiting list in that same year. The increased demand for donor kidneys has provoked a large shift toward living kidney donation in the United States.[1] In

Table 1 | 1- and 5-year graft survival for living and deceased donors following renal or liver transplantation.

Organ transplanted	1-year survival		5-year survival	
	2001–2002	2002–2003	1997–2002	1998–2003
Kidney				
Living donor	94.3%	94.6%	78.6%	79.2%
Deceased donor	88.7%	89.0%	65.7%	66.2%
Liver				
Living donor	79.3%	80.1%	78.1%	71.2%
Deceased donor	80.6%	81.4%	64.1%	65.4%

Source: UNOS/OPTN.

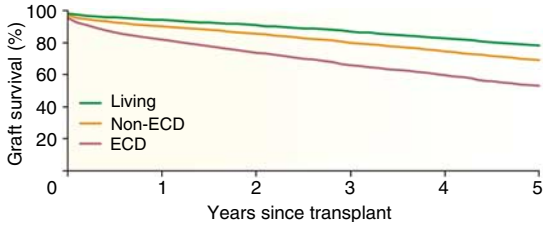

Figure 1 | Graft survival over a period of 5 years for living-, non-ECD- and ECD-derived renal grafts. Source: UNOS/OPTN

fact, the number of living kidney donors in the United States surpassed the number of deceased donors in 2000.[1,6] Still, the total number of kidneys obtained from living donors is lower since in living donation only one kidney can be donated, while in deceased donors both kidneys are recovered. In many European countries, the use of living donors has increased as well over the past decade, albeit more modestly.[3]

In their 1995 landmark paper, Terasaki *et al.*[2] showed that graft survival for living unrelated donation is superior compared to deceased donation, even though the average human leukocyte antigen-haplotype matching is worse in living unrelated donation. Long-term outcome after living unrelated donation is similar to that of parental or offspring donors.[7] This indicates that poor survival of grafts from deceased donors cannot be solely attributed to differences in immunogenicity. Graft performance is affected by many other factors. Donor variables such as age, gender, race, terminal serum creatinine, history of hypertension, and cause of death all affect transplantation outcome.[8–10] Deceased donors tend to be older than living donors;[1] however, within each age category, survival rates of living donor grafts are significantly higher than those of deceased donor grafts.[2] Preservation and cold ischemia time influence transplant outcome, and for logistical reasons, cold ischemia time is longer on average in deceased donor transplantation. For renal transplantation, cold ischemia time of more than 24 h is associated with worse outcome after renal transplantation.[2,11,12]

Despite the fact that grafts obtained from deceased donors have inferior outcome, these transplants have prevented death for many people on dialysis. Deceased donor kidney recipients have a 68% reduced risk of mortality compared to similar patients who stay on the waiting list receiving dialysis treatment.[13] The shortage of donor organs culminated in the use of extended criteria donation (ECD). ECD includes brain dead donors who are older than 60 years, or are aged over 50 years in combination with at least two of the following risk factors: a history of hypertension and a terminal serum creatinine >1.5 mg/dl or a cerebrovascular cause of death. The number of ECD-derived kidneys has seen marginal but steady increase over the past years,[1] even though long-term allograft survival of ECD-derived kidneys is inferior compared to non-ECD kidneys (Figure 1).[1,14] Initial doubt about the advantages of this type of donor has not been sustained. Relative mortality risk analysis has shown that the short-term risk of death in ECD kidney recipients is more than five times higher when compared to standard therapy with dialysis while waiting for a non-ECD kidney. At 226 days after transplantation, however, the risk becomes equal and is lower thereafter. In addition, the long-term cumulative mortality is significantly lower in ECD kidney recipients.[15] Kidneys discarded by transplant centers twice or more for reasons of poor organ quality showed worse initial non-function and long-term renal performance. Five-year graft and patient survival, however, were not significantly different from control kidneys that were immediately accepted.[16] Counteracting the deleterious effects that brain death has on these already compromised organs could positively affect transplant outcome and reduce the number of discarded organs, thereby increasing the number of successfully transplanted kidneys.

BRAIN DEATH, SYSTEMIC CHANGES, AND CLINICAL COURSE

The beating heart has always been considered the classic sign of life. After the report by Mollaret and Goulon[17] in 1959 which described comatose patients with vital functions sustained by mechanical ventilation, the definition of death became a major point of discussion. Owing to improved techniques, the heart was kept functioning in these patients while mechanical ventilation oxygenated the blood. Judged by their appearance, patients did not look deceased; however, it was clear that normal, self-sustained function would never be regained. In 1963, before a consensus had been reached on the implications of this irreversible coma, the first kidney was recovered from a brain dead, heart-beating donor and transplanted by the Belgian surgeon Alexandre.[18] In an effort to overcome problems that led to controversy in obtaining organs from deceased donors, but also to decrease the burden on the relatives of brain dead patients on life support, an *ad hoc* committee of the Harvard Medical School proposed to add irreversible coma to the death criterion in 1968.[19] This report generated considerable medico-legal discussion and resulted in most countries adopting a concept of death that originates from this proposition. The definition of brain death that the committee proposed concerned the following mandatory criteria: (1) unawareness of and unresponsiveness to external stimuli, (2) no spontaneous movements or

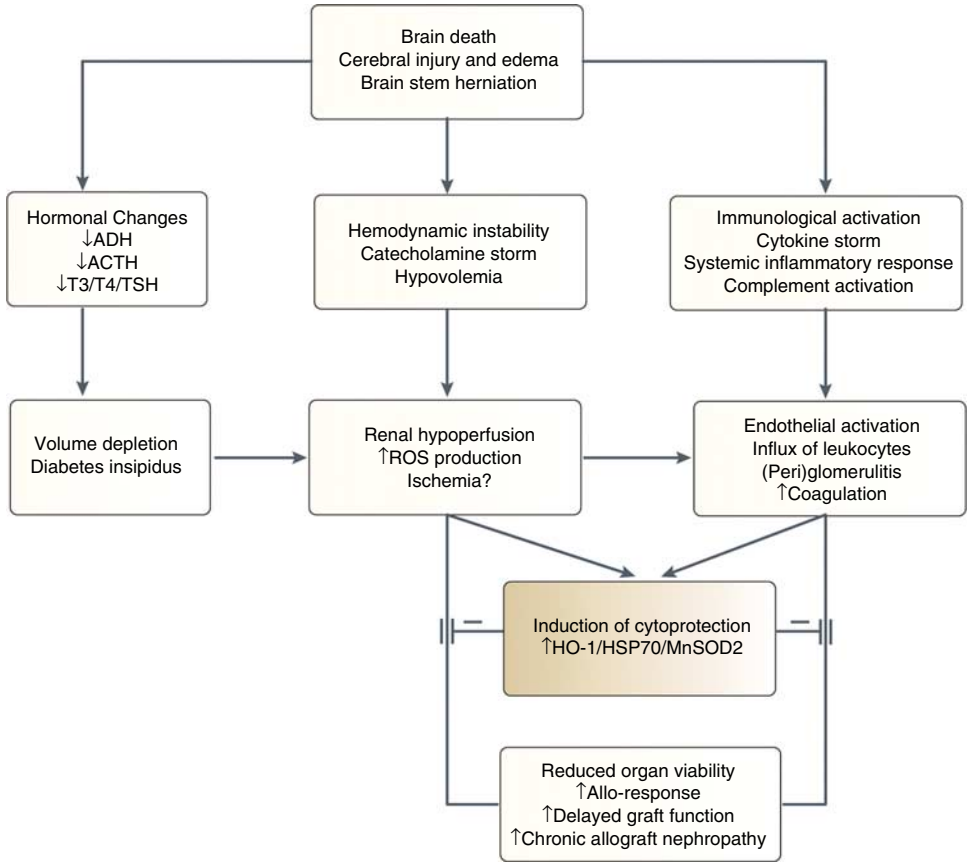

Figure 2 | Proposed model for the (patho)-physiological changes associated with brain death.

breathing, (3) absent reflexes, and (4) a flat electroencephalogram. Caution is required for conditions that can elicit similar symptoms, such as hypothermia, hypotension, or intoxication, and therefore these have to be ruled out.

Brain death as such is the terminal phase of a sequence of events frequently commencing with cerebral trauma or cerebrovascular hemorrhage. When the patient is declared brain dead, this chain of events has already affected the organs. Systemic and hormonal changes arise immediately when intracranial pressure increases. Hence, brain death is not the stationary condition as perceived from the outside, but a dynamic and rather unphysiological course of events that influences a number of (patho-)physiological processes in the human body (Figure 2).

Hemodynamic changes

Following cerebral trauma or injury, the primary rise in intracranial pressure causes additional damage to the cerebrum, which triggers parasympathetic activity and results in a decreased systemic blood pressure. The continued rise in intracranial pressure leads to herniation of the brain stem through the foramen magnum, which is accompanied by arterial compression and ultimately occlusion with progressive ischemic damage. When the pontine part of the brain stem becomes ischemic, sympathetic stimulation, together with the persisting parasympathetic activity, will cause the Cushing reflex, which was already described in 1902 by the American neurosurgeon Harvey Cushing.[20] The Cushing reflex consists of multiple disturbances in the physiology of cerebrally injured patients, including bradycardia, hypertension and an irregular breathing pattern. Ultimately, when the entire brain stem has become ischemic, the vagal cardiomotor nucleus is affected and solitary sympathetic stimulation will occur. As a result, massive catecholamine release, systemically as well as from myocardial sympathetic nerve endings, cause an increase in heart rate and leads to vasoconstriction with increased vascular resistance and blood pressure.[21–23] This process is referred to as the sympathetic or catecholamine storm, and is considered to be an attempt of the body to raise arterial blood pressure above the elevated intracranial pressure as an ultimate effort to restore perfusion of the cerebrum.

The rise in serum epinephrine levels has been reported to be as high as 100–1000-fold higher compared to normal values in animal models of brain death.[23–26] The magnitude of catecholamine release is related to the severity of brain damage. The faster the rise in intracranial pressure, the higher the peak in catecholamine levels.[23] Also, serum norepinephrine and dopamine concentrations are vastly increased after onset of brain death. The values of

catecholamine release in animal experiments appear to be similar to those described in the clinical situation.[27] In addition, a parallel cardiac response to brain injury is seen, as demonstrated by even higher levels of myocardial catecholamines compared to the serum[28] leading to injury of myocytes.[21,29] The catecholamine-induced increase in vascular resistance can be severe, reaching four times higher levels than basal values in the rat kidney.[26] This causes renal blood flow to decrease by a factor of 2.4 and supports the hypothesis that the rigorous decline in organ perfusion leads to ischemic damage of potential grafts.

Over time, sympathetic pathways are deactivated due to ischemia of the spinal cord. This leads to a gradual decrease of the hyperdynamic state with a subsequent decline in blood pressure, heart rate, and cardiac output to normal or subnormal values. Ultimately, a state of hypoperfusion is reached, which is harmful to the potential donor kidneys. Prolonged brain death results in high rates of tubular necrosis.[30] Many brain dead patients need hemodynamic support during this phase, and receive vasopressors and/or anti-diuretic hormone.

Hormonal changes

In addition to the catecholamines, other hormonal alterations take place. There is evidence that some residual cerebral blood flow and hypothalamic function can persist after brain death.[31–33] In most brain dead patients, however, a gradual decrease in the release of adrenocorticotropic hormone and anti-diuretic hormone is seen,[24,25,34] which is associated with cardiovascular failure that eventually causes the requirement of hemodynamic support. The failure to keep anti-diuretic hormone levels in the range needed for a normal osmolarity[24,25,31] has been suggested as the cause of diabetes insipidus in up to 78% of patients.[34,35] A more recent explanation is the downregulation of aquaporin-2 channels,[36] which could affect water re-uptake in the renal collecting ducts. Free-circulating triiodothyronine (T3) gradually decreases after brain death,[34,35,37–40] but not every study has found comparable results concerning the serum concentrations of T3 and T3-related hormones, such as T4 and TSH.[32,39–41]

Any acute stress will enhance the condition known as 'diabetes of injury,' consisting mainly of hyperglycemia caused by increased gluconeogenesis and insulin resistance. Intensive insulin therapy is now applied in many intensive care units, and as a result mortality in intensive care units has been greatly reduced when strict glycemic control is achieved.[42,43] A lower incidence of newly acquired renal injury, earlier weaning from mechanical ventilation, and a faster discharge from the intensive care unit and from the hospital were observed.[43] The rise in serum creatinine was attenuated by the maintenance of normoglycemia. Also, insulin therapy reduces the inflammatory response: ICAM-1 and C-reactive protein are both decreased in the serum of intensive care unit patients receiving intensive insulin treatment.[44,45] Thus, the use of intensive insulin therapy in brain dead patients could attenuate renal damage, reduce inflammation, and enhance donor organ viability resulting in a better transplantation outcome.

EXPERIMENTAL BRAIN DEATH MODELS

To obtain a better insight in the (patho-)physiological processes that occur during brain death, standardized models have been developed to investigate the discrepancies in outcome between deceased and living donor transplantation. In these models, the detrimental effects of brain death can be studied and possible interventions evaluated.[46–49] Various research groups have studied brain death in the rat model. Epidural hematoma is simulated using an inflatable catheter inserted through a trepanation in the skull. Inflation of the catheter causes cerebral damage followed by edema, a rise in intracranial pressure and eventually herniation of the brain stem. The models vary in details such as the speed of balloon catheter inflation and the use of hemodynamic support. Brain death can be confirmed – as in the human situation – by the absence of the apnea reflex, cornea reflex, and observation of the typical course of blood pressure changes. The effects of brain death induction in the current animal models of brain death closely mirror observations from the clinical situation.

In recent years, the use of animal models with brain death has made it clear that organ quality is significantly affected and frequently diminished in brain dead animals. In contrast to the clinical circumstances, in the animal model, heterogeneity is reduced and the pathophysiology of cerebral injury leading to brain death in donors can be studied in far greater detail.

PATHOPHYSIOLOGICAL EFFECTS OF BRAIN DEATH ON RENAL FUNCTION AND STRUCTURES

Before 1997, the concept of brain death did not exist in Japan. Patients who would be considered brain dead and eligible for organ donation in the United States or Europe were kept in a coma until cardiac arrest. This presented Nagareda *et al.*[30] with the unique opportunity to investigate the time course of the effects of brain death on the kidney up to 48 days. Their study revealed that the mean urinary sodium output increased during the first 14 days, mean urine osmolarity was above normal on the first day but decreased gradually, and urine volume during the first 14 days was high as a consequence of the cerebral injury-related diabetes insipidus. On histological examination, degenerative changes of renal structures were found, including vacuolization, atrophy, and necrosis of renal proximal and distal tubules. Advancing glomerulitis and progressing periglomerulitis expressed inflammatory changes. Periglomerular fibrosis and proliferation of the arterial intima and glomerular endothelium reflected the structural changes in the kidney.

In experimental conditions in rats, renal function is already negatively affected during 4 h of brain death followed by inferior results after reperfusion in an isolated perfused kidney set up. During isolated perfused kidney, urine volume, and glomerular filtration rate were significantly higher than

controls.[50] Interestingly, potassium excretion was increased in these kidneys, possibly explained by the depletion of ATP in these kidneys, which can trigger the opening of ATP-sensitive potassium channels (K_{ATP} channels). An impaired sodium/potassium homeostasis was observed after brain death in a renal slice model as well.[51] Organs can also become more prone to ischemia/reperfusion injury: livers derived from brain dead rats are more susceptible to cold storage-induced injury. This was demonstrated by a decreased survival after 20 h of cold storage when compared to living donor livers stored equally long.[52]

Renal tubular damage as a consequence of brain death can be observed in urine as well. Brush-border enzymes, such as alkaline phosphatase and alanine amino peptidase, as well as the lysosomal enzyme *N*-acetyl-β-D-glucosaminidase,[50] are released into the urine. Kidney injury molecule-1, is a recently discovered brush-border enzyme which is considered a marker of tubular damage, for example, in ischemia/reperfusion injury.[53] As a result of brain death, we found that kidney injury molecule-1 is massively upregulated. Interestingly enough, it can be detected on the luminal side of the renal cortical tubule, but is also shed into the urine,[54] which may simplify viability assessment of potential donor organs.

Immunological activation

In ischemia/reperfusion injury, a clear-cut correlation was found between endothelial injury and acute rejection. This association between the innate immune response and subsequent alloreactivity could be explained by Matzinger's danger hypothesis.[55] It is of importance that an increased immunogenicity is also observed in the brain dead donor organ as well. Endothelial activation is present with the upregulation of adhesion molecules (E-selectin, P-selectin, intracellular adhesion molecule-1, and vascular cellular adhesion molecule-1) that promote the rolling, adhesion, diapedesis, and subsequent leukocyte migration into the interstitium of the kidney.[46,56–59] Multiple cytokines and chemokines do play a role in the immunological response to cerebral injury. Upregulation of interleukin (IL)-1, IL-2, IL-6, tumor necrosis factor-α, transforming growth factor-β, interferon-γ, vascular endothelial growth factor, macrophage inflammatory protien-1α, macrophage inflammatory protien-1β, membrane cofactor protein-1, and osteopontin have been reported.[36,56,58,60] The expression of the major histocompatibility complex class II is increased as well.[56] Amplification of cytokines, chemokines, and adhesion molecules causes a chemotactic gradient that promotes the influx of leukocytes to the kidney. T cells, macrophages, and polymorphonuclear leukocytes are all found in higher quantities in donor kidneys during brain death.[46,56,57,61]

After reperfusion, a large difference in neutrophil infiltration and P-selectin expression can be observed between living and deceased donor grafts. Koo *et al.*[62] showed that 53% of deceased donor renal allografts had increased neutrophil infiltration, against 0% of living related grafts. P-selectin expression was increased in 44% of deceased donor grafts, and 9% of living related grafts.

In a syngeneic animal model of renal transplantation, short-term inflammatory changes to the kidneys were investigated by Kusaka *et al.*[58] The extent of leukocyte infiltration reaches its peak at 24 h after transplantation in this syngeneic transplant model and corresponds with the levels of E- and P-selectin. After this period, the extent of immunological activation gradually decreases, but histological changes to the kidney can still be observed. Allotransplant experiments have shown that after experimental brain death, recipients of brain dead donor kidneys suffered from a greatly increased acute rejection rate.[4] Similar effects have been observed in other organs, such as lung[63] and heart.[64] When kidney allografts are treated with cyclosporine to prevent acute rejection, long-term renal function is adversely affected by brain death compared to syngeneic transplants. Thus, the state of brain death can also enhance the development of chronic renal transplant dysfunction.[5]

Protection and repair

Interestingly, not only detrimental or degenerative changes take place during brain death. Protective or recuperative mechanisms are induced as well. This is reflected by increased expression of the cytoprotective genes heme oxygenase-1 (HO-1), heat-shock protein 70, and manganese superoxide dismutase.[36,61,65] Kunzendorf *et al.*[66] showed that a prolonged duration of brain death positively influences long-term graft survival. The mechanism behind this observation could well be the delayed induction of protection or initiation of repair. In another study, increased HO-1 expression at organ recovery was correlated with outcome after renal transplantation in the living donor setting.[61] Expression of HO-1 was not related to graft survival in deceased donor kidneys. Donor HO-1 gene polymorphisms have been associated with transplantation outcome.[67] Surprisingly, in a liver transplant study, livers with an initial low HO-1 expression before transplantation, but a high HO-1 expression after reperfusion, had superior outcome when compared to livers with high HO-1 expression at organ recovery.[68] These observations indicate that the ability to induce HO-1 is important, and not a high expression of HO-1 *per se*. Two different mechanisms should be considered here: while the increase in expression of HO-1 in living donors may initiate protection against the hits to the kidney during transplantation and thereafter, in deceased donors, on the other hand, HO-1 may well be a reflection of the level of stress to the kidney due to brain death.

EXPERIMENTAL AND CLINICAL INTERVENTIONS

Different concepts and approaches have been considered to counteract the detrimental effects caused by brain death (Table 2). Some research groups focus on the induction of protective proteins, while others aim at reducing the immune response.

Table 2 | Overview of studies that investigated the effects of specific interventions on brain death related damage

Study	Treatment	Main renal outcome
Human studies		
Kuecuek (2005)[79]	Steroids	Reduced expression of proinflammatory cytokines
Schnuelle (1999)[69]	Dopamine	Improved graft survival, less acute rejection
	Norepinephine	Improved graft survival, less acute rejection
Schnuelle (2001)[70]	Catecholamines[§]	Improved graft survival
Schnuelle (2004)[71]	Dospamine	Improved graft survival, improved short-term renal function
Animal studies		
Coleman (2006)[83]	CEPO	Reduced expression of proinflammatory factors
Gasser (2002)[80]	rPSGL-Ig	Improved graft survival, reduced chronic rejection
Kotsch (2006)[77]	CoPP (HO-1induction)	Improved graft survival, reduced leukocyte infiltration
Pratschke (2001)[78]	rPSGL-Ig	Improved graft survival, reduced acute rejection
	Steroids	Improved graft survival, reduced acute rejection
Schaub (2004)[48]	Dospamine	Reduced monocyte infiltration, reduced expression proinflammatory factors

CEPO, carbamylated erythropoietin; rPSGL-Ig, recombinant P-selectin glycoprotein ligand; CoPP, cobalt protoporphyrin; HO-1, heme oxygenase-1.
[§]Catecholamine treatment was defined as administration of any of the following adrenergic substances: dopamine, norepinephrine, epinephrine, dobutamine.

In a case–control study performed by Schnuelle *et al.*,[69] treatment of the donor with the vasopressors dopamine or noradrenalin was identified as an independent beneficial factor in renal transplant outcome. They confirmed these results in a study using the Eurotransplant database,[70] and also in a recent study, where donor dopamine was found to be associated with a more rapid decrease in serum creatinine and better long-term survival.[71] Experimentally, dopamine treatment has shown beneficial effects in a model of brain death induced renal damage. Dopamine treatment resulted in HO-1 induction as well as an inhibition of P-selectin expression and decreased mononuclear infiltration.[48] In other experiments, the effects of ischemia/reperfusion and cold preservation were attenuated by low-dose dopamine treatment.[72,73] *In vitro*, decreased production of chemokines, chemokine (C-X-C motif) ligand 1 (CXCL-1), epithelial neutrophil activating peptide-78 (ENA78), and IL-8 in proximal tubular epithelial cells, has been observed after dopamine treatment.[74] In endothelial cells, production of CXCL-1 and ENA78 was reduced, but IL-8 increased. In addition, dopamine pretreatment delayed expression of intracellular adhesion molecule-1, and vascular cellular adhesion molecule-1 after tumor necrosis factor-α stimulation in these cells. These immunological effects seen in experimental conditions could be part of the explanation for the improved renal transplantation outcome after catecholamine treatment of the brain dead donor.

Selective upregulation of HO-1 has proven to be beneficial in different models of stress or damage, including ischemia/reperfusion[75] and experimental renal transplantation.[76] Owing to its antioxidative, antiapoptotic, and immune regulatory effects, HO-1 has become an extensively investigated protein in the search for protection against insults during and before the transplant process. Experimental transplantation after upregulation of HO-1 by cobalt protoporphyrin treatment in the brain dead donor resulted in improved renal allograft survival.[77] Also, a reduction was seen in the infiltration of $ED1^+$ monocytes/macrophages, $CD4^+$ T cells and $CD8^+$ T cells in the cobalt protoporphyrin-treated group. The application of novel and existing approaches in the field of HO-1 induction can therefore be regarded as a promising possibility to improve clinical renal transplant outcome.

Inhibition of the immunological activation due to brain death is one of the strategies to improve transplant outcome in experimental models. Glucocorticosteroid treatment of brain dead rats improved graft survival after transplantation to a level comparable with living donor transplants.[78] Steroids suppress cellular infiltration and expression of cytokines and the intensity of morphological changes are noticeably different in the recipients of a graft from an untreated brain dead donor. The only prospectively designed human study known to us has reported some promising results in reducing the expression of proinflammatory cytokines using steroid therapy.[79] Long-term results after kidney transplantation, however, have yet to be reported.

Treatment of the donor with the recombinant soluble P-selectin glycoprotein ligand, an inhibitor of P- and E- and L-selectin, has also been shown as advantageous in experimental models.[78,80] Three days after transplantation, untreated brain dead donor kidneys showed severe tubular necrosis and mononuclear infiltration, whereas recipients where the donor was treated with recombinant soluble P-selectin glycoprotein ligand showed similar serum

creatinine levels to living donor iso- and allograft recipients. In addition, recombinant soluble P-selectin glycoprotein ligand treatment was able to affect chronic transplant dysfunction in animals that received brain dead donor kidneys, reducing long-term graft injury to a level seen in the living donor situation.

Carbamylated recombinant human erythropoietin is an EPO derivative that does not have hematopoietic effects, but has tissue-protective capacities in different models of neural damage such as stroke.[81] Recently, we found that carbamylated recombinant human erythropoietin can reduce the renal inflammatory response and attenuate the increase in serum creatinine levels due to brain death[82,83] Also, an improved glomerular filtration rate was observed in kidneys derived from carbamylated recombinant human erythropoietin-treated brain dead rats compared to untreated controls. The combination of immunomodulation and tissue protection could be effective in reducing brain death-related damage.

PERSPECTIVES ON DONOR MANAGEMENT AND PRETREATMENT

The deleterious effects of brain death on the donor kidney provoke pathophysiological changes that have a negative impact on the outcome after transplantation. Ischemia of the brain results in non-function of the central nervous system, and is associated with pertinent hemodynamic instability, hormonal changes, and diminished perfusion. This abnormal physiological state induces proinflammatory changes in the potential donor organs that negatively affect function and cause an increased chance of acute rejection. These compromising changes in the donor urge us to develop treatment regimens for application during brain death.

The use of pharmacological interventions to provide optimal conditions for the donor organ and prevent the decline of renal function will become an important part of the entire donation and transplantation process. Reducing hemodynamic instability is crucial to maintain normal perfusion of organs. The use of catecholamines for this purpose would benefit renal transplant outcome. Caution is needed, however, since interventions that can be of benefit to one organ may be detrimental to another. This was demonstrated by Schnuelle *et al.*[70] in their analysis of catecholamine use in the donor. Although renal transplant survival was increased, liver transplant outcome was not improved and cardiac results appeared to be adversely influenced by catecholamine administration in the donor. A randomized prospective clinical trial is currently underway to assess the effects of donor pretreatment with dopamine (Table 3).

The application of intensive insulin therapy for strict glycemic control could be beneficial to prevent damage to the organs during brain death. It is not clear yet if the effect will be large enough, however, to have consequences for graft viability and transplant outcome.

The use of immunomodulators, such as steroids or recombinant soluble P-selectin glycoprotein ligand, has shown some promising results in experimental models.

Table 3 | Interventions that counteract the negative effects of brain death on the kidney, or could be used for this purpose in the future

Potential interventions for in the brain dead donor
Hemodynamic
Catecholamines (Dopamine, Epinephrine, Norepinephrine)
Antidiuretic hormone (ADH)
Anti-inflammatory
Immunosuppressants (Glucocorticods, Calcineurin inhibitors)
Monoclonal antibodies against cytokines (TNF-α, IFN-γ, IL-2, IL-6
Inhibitors of chemokines (MCP-1, MIP-1α, MIP-1β)
Carbamylated recombinant human Erythropoietin (CEPO)
Recombinant P-Selection Glycoprotein Ligand–Ig (rPSGL-Ig)
Induction of cytoprotection
HO-1 induction (Cobalt Protoporphyrin (CoPP)), HSP induction (Pyrrolidine Dithicarbamate (PDTC), Geranylgeranylacetone (GGA))
Signal transduction
Selective inhibitors of kinases (JNK, p38, ERK, RhoA)
Gaseous substances
Carbon Monoxide (CO)
Nitrous Oxide (NO)
Hormonal
Intensive insulin therapy

ERK, extracellular signal-regulated kinase; IL, interleukin, IFN-γ, interferon-γ; JNK, Jun N-terminal kinase; MCP-1, membrane cofactor protein-1; MIP-1α, macrophage inflammatory protein-1α, MIP-1β, macrophage inflammatory protein-1β; TNF-α, tumor necrosis factor-α.

Counteracting inflammatory changes in the deceased donor kidney improved function and survival after transplantation. In fact, steroid treatment is effective in modulating the immune response in human organ donors.[79] Since all organs exhibit inflammatory changes as a result of brain death, immunomodulating treatment has a high probability to be of benefit for all transplanted organs.

The induction of protective mechanisms, such as HO-1 upregulation, is an important development in donor pretreatment. Initiation of protective pathways can diminish brain death-related damage and ischemia/reperfusion injury. The products created during heme degradation by HO-1 are involved in cytoprotective processes. In addition, immunomodulating effects of HO-1 could be of use in the improvement of deceased donor transplantation. Another option is the addition of gaseous substances to the breathing air of brain dead donors. Carbon monoxide has demonstrated a beneficial effect in modulating ischemia/reperfusion injury,[84] and low-dose inhalation of carbon monoxide after experimental renal transplantation prevents the development of chronic allograft nephropathy.[85]

To date, many challenging opportunities do exist to counteract the deleterious effects of brain death on the donor kidney. A better characterization and understanding of the mechanisms of injury and repair that play a role during massive cerebral injury and its effect on potential donor organs will lead to novel treatment options. As a result, the

outcome after deceased donor organ transplantation may improve, and approach that of living donors.

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