Ischemia/reperfusion injury : a metabolic meltdown

Wijermars, L.G.M.

X

Donor pretreatment in clinical kidney transplantation: a critical appraisal

Clinical Transplantation

Leonie G.M. Wijermars, Dorottya K. de Vries, Marlies E.J. Reinders,
Jan H.N. Lindeman, Alexander F.M. Schaapherder

ABSTRACT

Kidney transplantation represents one of the medical achievements of the 20th century. However, its continued success is limited by the increasing shortage of donor grafts. As a result more kidney grafts from marginal donors are being considered for transplantation, with concomitantly more initial graft injury and limited organ and patient survival. This has led to an increased need for interventions aiming to optimize and preserve graft quality. Interventions within the donor may protect against ischemia/reperfusion injury and therefore donor pretreatment is a promising strategy to increase graft function and survival. During the last decade, diverse donor pretreatment interventions have been explored in animal studies. Moreover, the first human trials concerning donor pretreatment in kidney transplantation have provided encouraging results. Unfortunately, it remains difficult to determine how and where to intervene in the multifactorial and complex processes that affect the donor kidney. Moreover, ethical matters play a critical role in donor interventions, and pretreatment should principally not have any potentially unfavorable effects on other organs to be transplanted or on the living donor. This review provides an overview of promising therapeutical strategies for donor pretreatment in kidney transplantation and discusses the clinical trials that have been conducted thus far.

INTRODUCTION

Kidney transplantation is the preferred treatment of patients with end-stage renal disease.[1-3] The previous decade is characterized by a steady increase in the number of kidney transplantations. This increase largely reflects improved medical therapy for renal failure. Besides the fact that more patients are being considered eligible for kidney transplantation, improved survival after transplantation led to the emergence of patients requiring re-transplantation, due to progressive loss of graft function in the long run.[4-6] The augmented demands for kidney transplantation resulted in organ shortage and as a consequence, waiting lists for kidney transplantation are ever increasing. In June 2012 more than 99 000 American citizens were on the waiting list for a kidney transplant.[7-9]

Kidney grafts can be derived from living or deceased donors. Of deceased donors, more organs are recovered from donation after brain death than from donation after cardiac death. However, the current organ shortage necessitates expansion of the donor pool by the increased use of marginal donor kidneys. Since these marginal kidneys have worse long-term outcome, it has been proposed that they may benefit most from pre-transplantation interventions that preserve or even improve graft quality.[10]

Before and during the process of transplantation the graft is exposed to various noxious events, including donor brain death, cold preservation and ischemia/reperfusion (I/R) injury, all potentially contributing to the functional deterioration of the graft. The importance of these harmful mechanisms is illustrated by the superior results of living donor transplantation. Despite generally more accepted HLA mismatches, living donor transplantation is associated with minimal delayed graft function and improved long-term outcomes. This observation suggests that non-HLA-specific factors such as donor health and duration of the ischemic period before transplantation have substantial impact on short and long-term graft function.[11-13]

Consequently, interventions in the donor, aimed at minimizing pre-transplantation graft injury, may potentially have large effects in preventing acute and long-term graft dysfunction. This review will focus on the prevention of harmful processes that initiate graft damage in the donor. Various intervention strategies for donor pretreatment that have been tested in clinical kidney transplantation or animal experiments involving kidney transplantation will be discussed.

PROCESSES IN BRAIN DEATH

To date, the majority of deceased kidney grafts are derived from donation after brain death. Unfortunately, brain dead donor kidneys have a worse graft and patient survival as compared to living donor kidneys. Brain death leads to dysregulation of the autonomic nerve system, inducing many pathophysiological processes in the human body. Brain death is usually provoked by a period of increased intracranial pressure exceeding the mean arterial pressure and thereby blocking brain perfusion. The physiological responses to this increased pressure and brain damage can have effects on multiple organ systems. The most prevalent derangements are cardiovascular. With increasing intracranial pressure, a compensatory arterial hypertension is induced, sometimes with bradycardia. Next, the catecholamine storm sets in, with sympathetic stimulation, vasoconstriction, raised systemic vascular resistance, and tachycardia. After the catecholamine storm, there is a loss of sympathetic tone and peripheral vasodilatation. So, brain death results in severe hemodynamic instability and the resulting hypotension, if untreated, leads to hypoperfusion of all organs. This phase is well-known for the damage it can inflict in organs to be transplanted.

Other common clinical problems associated with donor brain death may include diabetes insipidus, disseminated intravascular coagulation, arrhythmias and pulmonary edema. Injury to the hypothalamus and the pituitary gland causes disturbances of hormonal homeostasis and thermoregulation.

On the microvascular level, brain death is associated with the induction of adhesion molecule expression and endothelial cell activation.[14] The hemodynamic, neurogenic, hormonal and microvascular disturbances lead to a generalized inflammatory response in the donor. This is characterized by the release of cytokines into the circulation which can trigger an inflammatory response in all organs[15,16] with tissue infiltration by granulocytes,[16] monocytes and lymphocytes.[17] All these physiological derangements should be limited as far as possible to maintain optimal graft condition before donation. Donor management is the primary approach to do so.

DONOR MANAGEMENT

After the diagnosis of brain death, there is a change from curative patient care to optimizing organ function for subsequent transplantation. This donor management is the active care of the donor from the time of diagnosis of brain death until procurement of organs, and involves correction of the widespread physiological changes that occur during brain death. If possible, early recognition of the potential organ donor and aggressive correction of the non-physiological state, even before consent to organ donation, are crucial to optimize post-transplantation graft function.

In order to standardize management, donor goals have been developed. These aim to maintain physiology close to normal values and were based on measurements performed routinely in patients in the intensive care unit. They include objectives to maintain body temperature, ensure adequate oxygenation, circulating volume, cardiovascular stability, and adequate urine output. Indeed, in a prospective study, the application of a standardized donor management protocol increased the number of retrieved and transplanted organs per donor substantially.[18]

One part of donor management is providing cardiovascular support. This support principally includes stabilization of hemodynamics in the donor. Treatment of hypertension associated with the catecholamine storm may significantly increase available grafts for transplantation.[19] In the consecutive hypotensive period, the first priority is to maintain an adequate intravascular volume. Fluid therapy should however, be carefully titrated. Recent studies recommend restrictive fluid management, since this restriction increases the number of transplantable lungs without influencing kidney graft function or survival after transplantation.[20, 21]

In stabilizing the donor, hormone replacement can aid by correcting the loss of pituitary function after brain death. Posterior pituitary function is very commonly lost, leading to diabetes insipidus with associated fluid and electrolyte changes. Anterior pituitary function may be preserved or only partially affected. Most hormone replacement therapies use a combination of methylprednisolone, vasopressin and thyroid hormone In a retrospective study, the fraction of donors that received replacement therapy with these three hormones, had an increase in the number of procured organs by 22,5%.[22]

Aggressive donor management increases the number of organs available for transplantation and has minimized loss of potential donors due to cardiovascular collapse in the process of brain death. However, most studies deny a major effect on graft quality and survival of donor management. Therefore, grafts may benefit from additional interventions that more specifically prevent organ damage before procurement. This donor pretreatment aiming to further maximize organ quality is an evolving field that constitutes the next step in optimizing kidney graft survival.

DONOR PRETREATMENT

Donor pretreatment is the active treatment of the donor in order to improve organ quality before and after transplantation. It distinguishes itself from donor management by the fact that donor management concentrates on stabilizing the donor to normal physiological ranges, while pretreatment is aiming to inhibit potentially harmful processes. Many therapies used as donor pretreatment have been investigated for their ability to reduce or prevent renal I/R injury in

animal experiments. Few interventions have been studied in clinical trials, which are summarized in Table 1. Here we discuss the most frequently applied and promising approaches to donor pretreatment.

Table 1. Human clinical trials of donor pre-treatment and result on outcome in kidney transplantation

Intervention	*Design*	*n*	*Main result*	*References*
Dopamine	Single-blind RCT	264 brain dead donors	Dopamine pre-treatment decreased the incidence of dialysis post-transplantation. No change in acute rejection or patient or graft survival after three yr	Schnuelle et al.[42]
Steroids	Double-blind RCT	306 brain dead donors	Donor pre-treatment with corticosteroids did not reduce the incidence or duration of DGF	Kainz et al.[60]
PUVA	Non-randomized	59 deceaeddonors	PUVA pre-treated grafts had a signi˜cantly lower number of rejection episodes, other outcome parameters were not different	Oesterwitz et al.[70]
Hyperoxia	Double-blind RCT	60 living donors	Donor oxygen pre-treatment the day before transplantation improved kidney function at 10 d after transplantation	Montazeri et al.[79]

RCT, randomized controlled trial; DGF, delayed graft function; PUVA, psoralen plus ultraviolet A.

Ischemic preconditioning

Over the past decades several studies were performed, exposing an organ to brief periods of ischemia to protect against subsequent periods of ischemia and reperfusion. This phenomenon of ischemic preconditioning has been first described in 1986 in the heart.[23] Since then, many animal studies, mainly in rats, have reported beneficial effects of donor ischemic preconditioning before kidney transplantation.[24–27] Our present understanding of the molecular mechanisms causing these effects is still largely incomplete. Experimental studies have shown that the protective effects of renal ischemic preconditioning are mediated by adenosine[28], nitric oxide[29, 30] and subsequent activation of signalling networks involving protein kinases and transcription factors. Recently, more complex mechanisms have been proposed as well, including cellular actions of regulatory T cells and endothelial progenitor cells.[31, 32] It is generally acknowledged that the

mechanism of ischemic preconditioning may differ between species and organs and it still remains controversial whether ischemic preconditioning is beneficial in large animals as well. In fact, studies on kidney transplantation in dogs and renal I/R injury in pigs both failed to confirm beneficial effects of renal ischemic preconditioning and although the first description of ischemic preconditioning dates from almost thirty years ago, the technique has not yet been translated into the clinical setting.[33, 34]

In more recent studies, remote ischemic preconditioning conferred protection to I/R injury by preceding ischemia and reperfusion of another organ or tissue. In animal experiments, the donor kidney can be protected after transplantation by remote ischemic preconditioning of the hindlimb.[35] Remote ischemic preconditioning suggests the involvement of humoral mediators and consequently protection is both dialyzable, transferable, and receptor-mediated.[36] Remote ischemic preconditioning has the advantage that it is more easily applicable in clinical transplantation than ischemic preconditioning of the graft itself. At present, clinical studies in which remote ischemic preconditioning of the lower limb is explored to improve outcome of kidney transplantation have been initiated and patients are being recruited (www.clinicaltrials.gov).

Catecholamines

Before transplantation, the graft is exposed to harmful periods of warm and cold ischemia. Dopamine is capable of protecting endothelial cells from damage during cold preservation by inducing protective enzymes, such as heme oxygenase-1 (HO-1).[37, 38] Dopamine could therefore be a promising donor pretreatment, rendering the kidney graft more resistant to I/R injury. In a rat allogeneic kidney transplantation model it was shown that donor dopamine pretreatment diminished histological damage, monocyte infiltration and cytokine expression in the kidney graft. Moreover, both short- and long-term graft function significantly improved.[39, 40] Other catecholamines, like dobutamine and norepinefrin, did not influence post transplantation kidney function.[41]

This preclinical experimental evidence resulted in a clinical trial of donor dopamine pretreatment.[42] Almost 300 brain dead donors were randomized to receive low dose dopamine pretreatment or placebo. Donors had to be stable on low dose noradrenalin and dopamine was continuously infused at a standard rate. The main outcome measure, need for dialysis during the first week after transplantation, was significantly reduced in recipients of a dopamine pretreated graft. However, dopamine pretreatment did not affect graft or patient survival. Donors in the dopamine group showed a significant but clinically not relevant increase in systolic blood pressure. In addition, effects of dopamine pretreatment were more pronounced with increasing cold ischemia time, supporting the

hypothesis that the beneficial effects of dopamine are mediated by its protective effects on the endothelium. Moreover, dopamine pretreatment may therefore even have the largest effects in marginal donors.[42]

Heme oxygenase-1

The ischemic period before transplantation can induce oxidative stress, which on its turn induces the release of the cytoprotective enzyme HO-1. Both HO-1 and carbon monoxide (CO), a product of HO-1 metabolism, are potential candidates for donor pretreatment. Induced expression of HO-1 in rat kidney donors led to decreased cell infiltration, downregulation of inflammatory genes and diminished histological signs of chronic rejection, resulting in increased graft function and survival after transplantation.[43]

The effects of HO-1 may be mediated by its downstream CO production, since induction of CO in the donor improved graft function similarly to HO-1, and both HO-1 and CO were able to diminish donor immunogenicity.[44-47] However, cellular mechanisms may also be involved in the protective effect of HO-1. HO-1 induction in the donor decreased early post-transplant alloreactivity, donor-derived dendritic cells, and T-cell reactivity in the recipient.[48] Moreover, donor pre-treatment with HO-1 has been shown to improve microcirculation after transplantation.[49] Ultimately, both HO-1 and CO appear promising opportunities for donor pretreatment. Whether their application is feasible and beneficial in clinical practice remains to be seen.

Anti-complement therapy

The inflammatory storm in the process of brain death may induce complement activation in the donor, thereby causing damage in the kidney graft before transplantation.[50] Inhibition of complement activation in the donor could therefore be beneficial for the kidney graft. The complement system is part of the innate immune system and it can be activated through the classical, alternative and lectin pathway. Soluble complement receptor 1 (sCR1) acts as an inhibitor of the common part of all three complement pathways. Pretreatment of donor rats with sCR1 around induction of brain death prevented the increase in circulating C3d and significantly improved renal function immediately after transplantation.[51] These first encouraging results should be confirmed in further animal experiments applying other complement inhibitors, before translation to clinical application can be made.

Erythropoietin

Erythropoietin (EPO) was originally identified for its role in erythropoiesis, but is now known for its anti-apoptotic and cytoprotective effects as well. These

protective effects are mediated by different receptors and mechanisms than the ones regulating the hematopoietic effects and may defend the kidney from I/R injury, potentially even when administered to the donor. This is particularly interesting considering the conceivably unfavorable side effects of systemic EPO treatment to the recipient.
Two very recent animal studies addressed donor pretreatment with EPO.[52, 53] In a rat model, brain dead donors were pretreated with EPO or carbamylated EPO (cEPO), which lacks the hematopoietic effects of EPO. Although kidneys were not actually transplanted, short term graft function was analyzed in an isolated perfused kidney set-up. Both EPO and cEPO diminished the influx of polymorphonuclear cells into the kidney and grafts showed a normalization of creatinine clearance in this isolated perfused kidney model.[53] In a study with larger animals, involving porcine kidney transplantation, cardiac dead donors were pretreated with EPO. In as little as 4 hours after reperfusion, renal injury and inflammation decreased and renal function improved in the EPO pretreated group.[52]

Immunosuppressive and anti-inflammatory agents
The period of donor brain death is well known for causing a systemic, non-specific inflammatory reaction, and organs from brain dead donors are influenced by this inflammatory state.[17, 54-57] Moreover, the ongoing inflammatory reaction after transplantation is responsible for reperfusion induced tissue damage.[58]
When translating findings of animal experiments into human therapies, the general immunosuppressive effects of corticosteroids could be suitable to suppress the inflammatory response in brain dead donors. Methylprednisolone is frequently administered in donor management as part of hormone replacement therapy, but may also be administrated at a higher dose than normally given for replacement therapy, in order to suppress inflammatory response. Recently, limited data from a large randomized, blind, placebo-controlled trial on donor steroid pre-treatment became available. The results show that expression of pro-inflammatory genes in brain dead donors normalized after steroid pretreatment. Although the incidence and duration of delayed graft function did not change with steroid pretreatment, the follow-up period was fairly short and information on longer term graft function is not available as yet.[59, 60, 60] Nevertheless, reducing the pro-inflammatory storm after brain death remains a promising approach, as illustrated by the improved kidney graft survival in rats after donor pretreatment with JNK signal transduction inhibition.[61]
Preconditioning of rat donors with calcineurin inhibitors cyclosporine A or tacrolimus decreased structural damage and resulted in improved graft function after kidney transplantation.[62] Moreover, pretreatment with tacrolimus combined

with rapamycin even improved outcome synergistically.[63] Not all studies could confirm these results, potentially explained by gross differences in experimental set-up and dosing of immunosuppressives between studies.[64]
The basic mechanism behind immunosuppressive donor pretreatment remains unknown. The responsible mechanism appears not to be, as expected, an additional inhibition of the alloimmune response. An effect on renal I/R injury is more likely, since the protective effects have been observed in syngeneic kidney transplant models and appear related to acute renal stress.[65]

Other pretreatment therapies
Photosensitizer + UVA (PUVA) treatment was applied in a series of studies nearly 30 years ago. Donor rats were pretreated with a photosensitizer and during hypothermic storage the kidney was irradiated with UVA. PUVA pretreatment improved graft survival in rats, with a dose-response relationship of the irradiation period.[66] The positive effect is ascribed to decreased graft immunogenicity.[67-69] To validate these results, a clinical study was performed in 1986 showing that PUVA pretreated grafts had a significantly lower number of rejection episodes, although all other outcome parameters were not different.[70] Altogether, PUVA pretreatment showed some successes but since then results have never been validated or reproduced by others.
Diverse rodent studies report on donor pretreatment with various substances with antioxidant capacities. Amongst others N-acetylcysteine (NAC), melatonin, danshen, and taurine were applied in animal kidney donors. Most studies showed improvement in biochemical parameters or secondary endpoints only, although some also demonstrated increased survival.[71-74] Nevertheless, unconfirmed results of these single studies on various antioxidants will probably not have a great impact on clinical donor pretreatment in the next few years, unless confirmed or applied in clinical studies.

Within the last few years, miscellaneous studies using diverse donor pretreatment strategies have been published with varying results. Vagus nerve stimulation was applied as donor pretreatment in brain dead donors for its potential anti-inflammatory effects. Vagus nerve stimulation decreased the expression of pro-inflammatory genes, decreased TNF-α production, diminished monocyte infiltration and more importantly, improved post-transplantation graft function.[75] Another study showed that donor statin pretreatment increased graft function and reduced renal inflammation in a rat kidney transplantation model.[76] Others showed that ICAM-1 inhibition in rat kidney donors improved graft survival, although effects were even larger when ICAM-1 was inhibited in the recipient or during preservation.[77] Disappointing results in animal studies have also been

reported; glutamine donor pretreatment did not affect the post-transplantation renal function in rats.[78] Finally, in humans a remarkable randomised clinical trial showed that hyperoxic donor pretreatment resulted in improved urine production and creatinine clearance after transplantation.[79] Previous animal experiments involving renal I/R without transplantation showed identical results.[80, 81] It may be speculated that hyperoxia induces oxidative stress in the donor, which enhances endogenous antioxidant mechanisms of the kidney. Another explanation is that hyperoxia leads to an improved oxygen reserve capacity of the kidney that protects the energy metabolism during the ischemic period. Finally, there have been reports on successes of hyperthermic donor preconditioning in rodent experiments. Two studies of the same group described beneficial effects of donor hyperthermia on kidney function and graft survival after transplantation. Hyperthermia induced renal expression of heat shock proteins was held responsible for the beneficial effects.[82, 83]

FUTURE PERSPECTIVES

Although the principle of donor pretreatment is not new, the clinical trend to use more marginal donors for transplantation only recently necessitated the search for new ways to optimize donor organ quality. Much preclinical research on donor pretreatment has been done, with promising results. The first human trials have recently shown protective effects of donor pretreatment with dopamine and corticosteroids, and these are likely to be of great influence in the coming years. Despite all the promising results from preclinical studies, the amount of clinical trials studying donor pretreatment is regretful. Moreover, studies specifically aimed at effects in marginal donor grafts are scarce. It has been suggested that the great amount of groups of interests involved in transplantation, the difficult ethical debate concerning informed consent of deceased donors and the effect of pretreatment on other organs considered for transplantation hampers the translation into the clinical setting.[9, 84] In the near future we expect results from some ongoing clinical trials, studying the effects of glucose, ischemic preconditioning, HO-1 induction and dopamine. Donor pretreatment targeting the immune system or oxidative stress responses remain interesting topics, but still have to prove themselves in the clinical setting.

In this review we focused on kidney transplantation. Research on transplantation of other organs will also provide new targets for pretreatment of kidney donors. For example, animal experiments with 17β-Estradiol as donor pretreatment showed improved outcome after transplantation of different organs.[85] Donor pretreatment with metformin improved acute and chronic rejection in cardiac transplantation in mice.[86] Ultimately, it is to be expected that a combination of agents will be used as tailored donor pretreatment, and timing may turn out to be

crucial in the success of donor pretreatment.

ETHICAL CONSIDERATIONS

In trying to translate donor pretreatment strategies to the clinical setting, ethical issues may be raised, particularly involving deceased donors. Most issues are related to the fact that manipulations will not benefit the donor directly in any way. Living donors provide the simplest situation, where the donor and recipient are fully aware of the donation procedure and are able to provide detailed consent, with prolonged time for consideration and reflection. It is obvious that donor pretreatment may never harm the living donor. The situation is more difficult for deceased donors. The act of participating in an organ donor register or carrying a donor card is considered as consent to organ donation, but it is not clear whether such consent would extend to invasive pretreatment strategies, and when they could be started. There is a need to establish whether pretreatment could be seen as no different from other medical interventions, such as the administration of heparin to donors. One can argue that consent to organ donation suggests consent to all techniques required to allow optimal quality of grafts. However, as long as donor pretreatment is applied in the experimental setting, trials will need informed consent of all parties involved.

In the declaration of Helsinki is stated that all participants of scientific research should know the aims, methods, anticipated benefits and potential risk of a study, before giving their informed consent.[87] How this should be implemented in deceased donors would naturally be by consent of the family. Although posing this extra question to the familiy may cause reluctance in doctors, it is important to respect and protect the deceased and to maintain public trust in organ donation program. Field experts discussed the lack of uniform standards when it comes to consent in donor pretreatment. They conclude that uniform standards are needed to overcome institutional pluralism.[88]
Indeed, several guidelines to deal with consent issues in performing research on donor management and donor pretreatment have been published recently. The Consensus Panel on Research with the Recently Dead (CPRRD) stated that research in organ transplantation donors is only allowed when it does not interfere with organ procurement and the donor must have given informed consent. In the absence of a statement from the donor, the family is allowed to give informed consent.[89]

However, donor pretreatment does not only influence the donor and all its organs suited for transplantation; it also involves all the recipients of the transplanted organs. It can be argued that recipients are no research subjects in studying

donor pretreatment, because this could only affect them indirectly. But conform the declaration of Helskinki, all research subjects have to give consent before performing an experiment. Indeed, ideally recipients would be asked for informed consent while being placed on the waiting list. However, recipients that do not consent to a pretreated kidney should not be disadvantaged when pretreated organs are being allocated. Consent would not be voluntary anymore then. Moreover, in the allocation process, some of the recipients remain unknown until the donor management period or even after organ procurement. It is suggested that an exception of recipients consent could fall under 'emergency research consent waiver'; because there is only a very small time window for asking permission. Off course this exception of consent is more easily accepted when the risk of the experiment is minimal.[88] It is clear that recipient consent to donor pretreatment poses many ethical and logistical questions. For now, it seems that institutional review boards have to determine what interventions are allowed and how donors and recipients provide informed consent.

The timing of pretreatment may be crucial, particularly with regard to agents that require a significant length of time prior to donation, to provide the beneficial effect. Thus, there may be requirements to commence administration of the agent before lack of objection is obtained. Although this might be an unusual principle, this type of approach has already been approved by ethical committees and has been used in clinical trials on organ donors.[90]

Deceased donors are often multiple organ donors. Intervention on behalf of one organ may be harmful to other potentially transplantable organs or at least affect them differentially. Donor pretreatment should be carefully tested for the effects on all potential grafts. If multiple organs from one donor are being sent to different transplant centers, the institutional board of the recipient centers should have been consulted before acceptance of the organ. Whether all recipients should provide informed consent when the intervention is targeted at another organ, and no adverse effects on the particular organ are demonstrated, is a matter of debate. Since matching of donor and recipients may sometimes be complete during or after the organ retrieval, it seems unreasonable that individual recipients or review boards can veto against donor pretreatment.

In conclusion, the great potential benefits of donor pretreatment are clear and preclinical results are promising. Clinical trials however are hampered by the intriguing and extensive ethical issues that are raised by experimental treatment of deceased donors and how we should handle issues on informed consent of donor and recipients. At present, one of the biggest challenges for donor pretreatment

trials is how they could be implemented in the current donation and organ allocation systems. It is stated that multi-disciplinary organisation with all those involved in the logistics of deceased donor procedures is fundamental to perform studies in donor intervention and that these studies are essential to raise graft quality to the next level.[91]

CONCLUSION

In these times of scarcity of donor organs, it is absolutely necessary to search for therapeutical options to render more marginal donor organs suitable for transplantation and to improve graft quality. During and before the process of transplantation the graft is exposed to various noxious events, which will lead to functional deterioration. Prevention of injury already in the donor could facilitate transplantation of more marginal donor grafts and provide better outcomes. Donor management is the first step to prevent derangements in the donor and has been much improved by standardization. Further, more specific improvement of graft condition is the aim of donor pretreatment. Donor pretreatment by various strategies, including ischemic preconditioning, HO-1 induction, anti-inflammatory and anti-complement interventions, erythropoietin and catecholamines have all been proven successful in animal experiments. Although many of these promising results in animals have yet to be confirmed in human kidney transplantation, the first pretreatment strategies have already shown encouraging beneficial effects in clinical studies. Current clinical studies are however limited by the large amount of ethical considerations on both the donor and recipient side. The lack of international guidelines makes institutional review boards and research groups repeat the same ethical questions and discussions on this topic worldwide.

REFERENCES

1. McDonald SP, Russ GR. Survival of recipients of cadaveric kidney transplants compared with those receiving dialysis treatment in Australia and New Zealand, 1991-2001. Nephrol Dial Transplant 2002: 17: 2212.
2. Schnuelle P, Lorenz D, Trede M, van der Woude FJ. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. J Am Soc Nephrol 1998: 9: 2135.
3. Port FK, Wolfe RA, Mauger EA, Berling DP, Jiang K. Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. JAMA 1993: 270: 1339.
4. Marcen R, Teruel JL. Patient outcomes after kidney allograft loss. Transplant Rev (Orlando) 2008: 22: 62.
5. Marcen R, Pascual J, Teruel JL et al. Outcome of cadaveric renal transplant patients treated for 10 years with cyclosporine: is chronic allograft nephropathy the major cause of late graft loss? Transplantation 2001: 72: 57.
6. Meier-Kriesche HU, Schold JD, Kaplan B. Long-term renal allograft survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? Am J Transplant 2004: 4: 1289.
7. Ravanan R, Udayaraj U, Steenkamp R, Ansell D. UK Renal Registry 11th Annual Report (December 2008): Chapter 5 Demographics and biochemistry profile of kidney transplant recipients in the UK in 2007: national and centre-specific analyses. Nephron Clin Pract 2009: 111 Suppl 1: c69-c96.
8. Harper AM, Rosendale JD. The UNOS OPTN Waiting List and Donor Registry: 1988-1996. Clin Transpl 1996: 69.
9. Smith JM, Biggins SW, Haselby DG et al. Kidney, pancreas and liver allocation and distribution in the United States. Am J Transplant 2012: 12: 3191.
10. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. N Engl J Med 1995: 333: 333.
11. Pratschke J, Wilhelm MJ, Kusaka M, Hancock WW, Tilney NL. Acute rejection of rat renal allografts is accelerated by donor brain death. Transplant Proc 1999: 31: 874.
12. Goes N, Urmson J, Ramassar V, Halloran PF. Ischemic acute tubular necrosis induces an extensive local cytokine response. Evidence for induction of interferon-gamma, transforming growth factor-beta 1, granulocyte-macrophage colony-stimulating factor, interleukin-2, and interleukin-10. Transplantation 1995: 59: 565.
13. van der Woude FJ, Schnuelle P, Yard BA. Preconditioning strategies to limit graft immunogenicity and cold ischemic organ injury. J Investig Med 2004: 52: 323.
14. van der Hoeven JA, Molema G, Ter Horst GJ et al. Relationship between duration of brain death and hemodynamic (in)stability on progressive dysfunction and increased immunologic activation of donor kidneys. Kidney Int 2003: 64: 1874.
15. Weiss S, Kotsch K, Francuski M et al. Brain death activates donor organs and is associated with a worse I/R injury after liver transplantation. Am J Transplant 2007: 7: 1584.
16. Schuurs TA, Morariu AM, Ottens PJ et al. Time-dependent changes in donor brain death related processes. Am J Transplant 2006: 6: 2903.
17. de Vries DK, Lindeman JH, Ringers J et al. Donor brain death predisposes human kidney grafts to a proinflammatory reaction after transplantation. Am J Transplant 2011: 11: 1064.
18. Rosendale JD, Chabalewski FL, McBride MA et al. Increased transplanted organs from the use of a standardized donor management protocol. Am J Transplant 2002: 2: 761.
19. Audibert G, Charpentier C, Seguin-Devaux C et al. Improvement of donor myocardial function after treatment of autonomic storm during brain death. Transplantation 2006: 82: 1031.

20. Pennefather SH, Bullock RE, Dark JH. The effect of fluid therapy on alveolar arterial oxygen gradient in brain-dead organ donors. Transplantation 1993: 56: 1418.
21. Minambres E, Rodrigo E, Ballesteros MA et al. Impact of restrictive fluid balance focused to increase lung procurement on renal function after kidney transplantation. Nephrol Dial Transplant 2010: 25: 2352.
22. Rosendale JD, Kauffman HM, McBride MA et al. Aggressive pharmacologic donor management results in more transplanted organs. Transplantation 2003: 75: 482.
23. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986: 74: 1124.
24. Fuller TF, Freise CE, Feng S, Niemann CU. Ischemic preconditioning improves rat kidney graft function after severe ischemia/reperfusion injury. Transplant Proc 2005: 37: 377.
25. Jia RP, Xie JJ, Luo FY, Zhu JG. Ischemic preconditioning improves rat kidney allograft function after ischemia/reperfusion injury: the role of tumor necrosis factor-alpha. Transplant Proc 2008: 40: 3316.
26. Jia RP, Zhu JG, Wu JP, Xie JJ, Xu LW. Experimental study on early protective effect of ischemic preconditioning on rat kidney graft. Transplant Proc 2009: 41: 69.
27. Reutzel-Selke A, Pratschke J, Martins PN et al. Ischemic preconditioning produces systemic protective and adoptively transferable effects. Kidney Int 2008: 74: 622.
28. Grenz A, Osswald H, Eckle T et al. The reno-vascular A2B adenosine receptor protects the kidney from ischemia. PLoS Med 2008: 5: e137.
29. Ogawa T, Nussler AK, Tuzuner E et al. Contribution of nitric oxide to the protective effects of ischemic preconditioning in ischemia-reperfused rat kidneys. J Lab Clin Med 2001: 138: 50.
30. Yamasowa H, Shimizu S, Inoue T, Takaoka M, Matsumura Y. Endothelial nitric oxide contributes to the renal protective effects of ischemic preconditioning. J Pharmacol Exp Ther 2005: 312: 153.
31. Kinsey GR, Huang L, Vergis AL, Li L, Okusa MD. Regulatory T cells contribute to the protective effect of ischemic preconditioning in the kidney. Kidney Int 2010: 77: 771.
32. Patschan D, Krupincza K, Patschan S et al. Dynamics of mobilization and homing of endothelial progenitor cells after acute renal ischemia: modulation by ischemic preconditioning. Am J Physiol Renal Physiol 2006: 291: F176-F185.
33. Behrends M, Walz MK, Kribben A et al. No protection of the porcine kidney by ischaemic preconditioning. Exp Physiol 2000: 85: 819.
34. Kosieradzki M, Ametani M, Southard JH, Mangino MJ. Is ischemic preconditioning of the kidney clinically relevant? Surgery 2003: 133: 81.
35. Wever KE, Warle MC, Wagener FA et al. Remote ischaemic preconditioning by brief hind limb ischaemia protects against renal ischaemia-reperfusion injury: the role of adenosine. Nephrol Dial Transplant 2011: 26: 3108.
36. Kharbanda RK, Nielsen TT, Redington AN. Translation of remote ischaemic preconditioning into clinical practice. Lancet 2009: 374: 1557.
37. Salahudeen AK, Yang M, Huang H, Dore S, Stec DE. Fenoldopam preconditioning: role of heme oxygenase-1 in protecting human tubular cells and rodent kidneys against cold-hypoxic injury. Transplantation 2011: 91: 176.
38. Yard B, Beck G, Schnuelle P et al. Prevention of cold-preservation injury of cultured endothelial cells by catecholamines and related compounds. Am J Transplant 2004: 4: 22.
39. Gottmann U, Notheisen A, Brinkkoetter PT et al. Influence of donor pretreatment with dopamine on allogeneic kidney transplantation after prolonged cold storage in rats. Transplantation 2005: 79: 1344.
40. Liu Z, Hoeger S, Schnuelle P et al. Donor dopamine pretreatment inhibits tubulitis in renal allografts subjected to prolonged cold preservation. Transplantation 2007: 83: 297.

41. Gottmann U, Brinkkoetter PT, Bechtler M et al. Effect of pre-treatment with catecholamines on cold preservation and ischemia/reperfusion-injury in rats. Kidney Int 2006: 70: 321.
42. Schnuelle P, Gottmann U, Hoeger S et al. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. JAMA 2009: 302: 1067.
43. Tullius SG, Nieminen-Kelha M, Buelow R et al. Inhibition of ischemia/reperfusion injury and chronic graft deterioration by a single-donor treatment with cobalt-protoporphyrin for the induction of heme oxygenase-1. Transplantation 2002: 74: 591.
44. Martins PN, Reutzel-Selke A, Jurisch A et al. Induction of carbon monoxide in donor animals prior to organ procurement reduces graft immunogenicity and inhibits chronic allograft dysfunction. Transplantation 2006: 82: 938.
45. Martins PN, Reuzel-Selke A, Jurisch A et al. Induction of carbon monoxide in the donor reduces graft immunogenicity and chronic graft deterioration. Transplant Proc 2005: 37: 379.
46. Kotsch K, Martins PN, Klemz R et al. Heme oxygenase-1 ameliorates ischemia/reperfusion injury by targeting dendritic cell maturation and migration. Antioxid Redox Signal 2007: 9: 2049.
47. Caumartin Y, Stephen J, Deng JP et al. Carbon monoxide-releasing molecules protect against ischemia-reperfusion injury during kidney transplantation. Kidney Int 2011: 79: 1080.
48. Martins PN, Kessler H, Jurisch A et al. Induction of heme oxygenase-1 in the donor reduces graft immunogenicity. Transplant Proc 2005: 37: 384.
49. Holzen JP, August C, Bahde R et al. Influence of heme oxygenase-1 on microcirculation after kidney transplantation. J Surg Res 2008: 148: 126.
50. Damman J, Nijboer WN, Schuurs TA et al. Local renal complement C3 induction by donor brain death is associated with reduced renal allograft function after transplantation. Nephrol Dial Transplant 2011: 26: 2345.
51. Damman J, Hoeger S, Boneschansker L et al. Targeting complement activation in brain-dead donors improves renal function after transplantation. Transpl Immunol 2011: 24: 233.
52. Maio R, Sepodes B, Patel NS et al. Erythropoietin preserves the integrity and quality of organs for transplantation after cardiac death. Shock 2011: 35: 126.
53. Nijboer WN, Ottens PJ, van DA et al. Donor pretreatment with carbamylated erythropoietin in a brain death model reduces inflammation more effectively than erythropoietin while preserving renal function. Crit Care Med 2010: 38: 1155.
54. Nijboer WN, Schuurs TA, van der Hoeven JA et al. Effects of brain death on stress and inflammatory response in the human donor kidney. Transplant Proc 2005: 37: 367.
55. Nijboer WN, Schuurs TA, van der Hoeven JA et al. Effect of brain death on gene expression and tissue activation in human donor kidneys. Transplantation 2004: 78: 978.
56. Schuurs TA, Gerbens F, van der Hoeven JA et al. Distinct transcriptional changes in donor kidneys upon brain death induction in rats: insights in the processes of brain death. Am J Transplant 2004: 4: 1972.
57. Stangl M, Zerkaulen T, Theodorakis J et al. Influence of brain death on cytokine release in organ donors and renal transplants. Transplant Proc 2001: 33: 1284.
58. Eltzschig HK, Eckle T. Ischemia and reperfusion--from mechanism to translation. Nat Med 2011: 17: 1391.
59. Kuecuek O, Mantouvalou L, Klemz R et al. Significant reduction of proinflammatory cytokines by treatment of the brain-dead donor. Transplant Proc 2005: 37: 387.

60. Kainz A, Wilflingseder J, Mitterbauer C et al. Steroid pretreatment of organ donors to prevent postischemic renal allograft failure: a randomized, controlled trial. Ann Intern Med 2010: 153: 222.
61. Chen L, Xu D, Gao Y et al. Effect of Donor JNK Signal Transduction Inhibition on Transplant Outcome in Brain Dead Rat Model. Inflammation 2012: 35: 122.
62. Shihab FS, Bennett WM, Andoh TF. Donor preconditioning with a calcineurin inhibitor improves outcome in rat syngeneic kidney transplantation. Transplantation 2009: 87: 326.
63. Cicora F, Roberti J, Vasquez D et al. Preconditioning donor with a combination of tacrolimus and rapamacyn to decrease ischaemia-reperfusion injury in a rat syngenic kidney transplantation model. Clin Exp Immunol 2012: 167: 169.
64. Martinez-Palli G, Hirose R, Liu T et al. Donor pre-treatment with everolimus or cyclosporine does not reduce ischaemia-reperfusion injury in a rat kidney transplant model. Nephrol Dial Transplant 2011: 26: 1813.
65. Shihab FS, Bennett WM, Andoh TF. Role of cellular cholesterol in pharmacologic preconditioning with cyclosporine in experimental kidney transplantation. Am J Nephrol 2010: 31: 134.
66. Oesterwitz H, Scholz D, Kaden J, Mebel M. Prolongation of rat renal allograft survival time by donor pretreatment with 8-methoxypsoralen and longwave ultraviolet irradiation of the graft (PUVA therapy). Urol Res 1985: 13: 95.
67. Oesterwitz H, Kaden J, Scholz D, Mrochen H, Mebel M. Synergistic effect of donor pretreatment with 8-methoxypsoralen and ultraviolet irradiation of the graft plus azathioprine and prednisolone therapy in prolonging rat renal allograft survival. Urol Res 1986: 14: 21.
68. Oesterwitz H, Kaden J, Schneider W, Schirrow R, Scholz D. Synergistic effect of photochemical donor pretreatment and cyclosporin therapy of the recipient on rat renal allograft survival. Nephrol Dial Transplant 1987: 2: 42.
69. Kaden J, Oesterwitz H, Schirrow R. Effects of photochemical donor pretreatment on the pattern of dog renal allograft infiltrating cells. Urol Res 1989: 17: 131.
70. Oesterwitz H, Scholz D, Kaden J et al. Photochemical donor pretreatment in clinical kidney transplantation--preliminary report. Urol Res 1987: 15: 211.
71. Fuller TF, Serkova N, Niemann CU, Freise CE. Influence of donor pretreatment with N-acetylcysteine on ischemia/reperfusion injury in rat kidney grafts. J Urol 2004: 171: 1296.
72. Li Z, Nickkholgh A, Yi X et al. Melatonin protects kidney grafts from ischemia/reperfusion injury through inhibition of NF-kB and apoptosis after experimental kidney transplantation. J Pineal Res 2009: 46: 365.
73. Guan X, Dei-Anane G, Liang R et al. Donor preconditioning with taurine protects kidney grafts from injury after experimental transplantation. J Surg Res 2008: 146: 127.
74. Guan X, Dei-Anane G, Bruns H et al. Danshen protects kidney grafts from ischemia/reperfusion injury after experimental transplantation. Transpl Int 2009: 22: 232.
75. Hoeger S, Bergstraesser C, Selhorst J et al. Modulation of brain dead induced inflammation by vagus nerve stimulation. Am J Transplant 2010: 10: 477.
76. Gottmann U, Brinkkoetter PT, Hoeger S et al. Atorvastatin donor pretreatment prevents ischemia/reperfusion injury in renal transplantation in rats: possible role for aldose-reductase inhibition. Transplantation 2007: 84: 755.
77. Stepkowski SM, Wang ME, Condon TP et al. Protection against allograft rejection with intercellular adhesion molecule-1 antisense oligodeoxynucleotides. Transplantation 1998: 66: 699.
78. Fuller TF, Rose F, Singleton KD et al. Glutamine donor pretreatment in rat kidney transplants with severe preservation reperfusion injury. J Surg Res 2007: 140: 77.

79. Montazeri K, Vakily M, Honarmand A et al. Short-time intermittent preexposure of living human donors to hyperoxia improves renal function in early posttransplant period: a double-blind randomized clinical trial. J Transplant 2011: 2011: 204843.
80. Wahhabaghai H, Rasoulian B, Esmaili M et al. Hyperoxia-induced protection against rat's renal ischemic damage: relation to oxygen exposure time. Ren Fail 2009: 31: 514.
81. Rasoulian B, Mohammadhosseniakbari H, Kadkhodaee M et al. Preconditioning with oxygen attenuates rat renal ischemia-reperfusion injury. J Surg Res 2008: 146: 282.
82. Redaelli CA, Tien YH, Kubulus D et al. Hyperthermia preconditioning induces renal heat shock protein expression, improves cold ischemia tolerance, kidney graft function and survival in rats. Nephron 2002: 90: 489.
83. Redaelli CA, Wagner M, Kulli C et al. Hyperthermia-induced HSP expression correlates with improved rat renal isograft viability and survival in kidneys harvested from non-heart-beating donors. Transpl Int 2001: 14: 351.
84. Feng S. Donor intervention and organ preservation: where is the science and what are the obstacles? Am J Transplant 2010: 10: 1155.
85. Yang X, Qin L, Liu J, Tian L, Qian H. 17beta-Estradiol protects the liver against cold ischemia/reperfusion injury through the Akt kinase pathway. J Surg Res 2012: 178: 996.
86. Chin JT, Troke JJ, Kimura N et al. A novel cardioprotective agent in cardiac transplantation: metformin activation of AMP-activated protein kinase decreases acute ischemia-reperfusion injury and chronic rejection. Yale J Biol Med 2011: 84: 423.
87. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects: Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the: 9th WMA General Assembly, Seoul, Korea, October 2008.
88. Rey MM, Ware LB, Matthay MA et al. Informed consent in research to improve the number and quality of deceased donor organs. Crit Care Med 2011: 39: 280.
89. Pentz RD, Cohen CB, Wicclair M et al. Ethics guidelines for research with the recently dead. Nat Med 2005: 11: 1145.
90. Guesde R, Barrou B, Leblanc I et al. Administration of desmopressin in brain-dead donors and renal function in kidney recipients. Lancet 1998: 352: 1178.
91. Abt PL, Marsh CL, Dunn TB et al. Challenges to research and innovation to optimize deceased donor organ quality and quantity. Am J Transplant 2013: 13: 1400.