Transplant International

REVIEW

Optimized donor management and organ preservation before kidney transplantation

Heiko M. Mundt, Benito A. Yard, Bernhard K. Krämer, Urs Benck& Peter Schnülle

5th Department of Medicine (Nephrology/Endocrinology/ Rheumatology), Medical Faculty Mannheim of the University of Heidelberg, University Hospital Mannheim, Mannheim, Germany

Correspondence
Heiko M. Mundt MD, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany.
Tel.: 0049 6213835172;
fax: 0049 6213833804;
e-mail: heiko.mundt@umm.de

SUMMARY

Kidney transplantation is a major medical improvement for patients with end-stage renal disease, but organ shortage limits its widespread use. As a consequence, the proportion of grafts procured from extended criteria donors (ECD) has increased considerably, but this comes along with increased rates of delayed graft function (DGF) and a higher incidence of immune-mediated rejection that limits organ and patient survival. Furthermore, most grafts are derived from brain dead organ donors, but the unphysiological state of brain death is associated with significant metabolic, hemodynamic, and pro-inflammatory changes, which further compromise patient and graft survival. Thus, donor interventions to preserve graft quality are fundamental to improve long-term transplantation outcome, but interventions must not harm other potentially transplantable grafts. Several donor pretreatment strategies have provided encouraging results in animal models, but evidence from human studies is sparse, as most clinical evidence is derived from single-center or non-randomized trials. Furthermore, ethical matters have to be considered especially concerning consent from donors, donor families, and transplant recipients to research in the field of donor treatment. This review provides an overview of clinically proven and promising preclinical strategies of donor treatment to optimize long-term results after kidney transplantation.

Transplant International 2016; 29: 974–984

Key words
brain death, donor management, kidney transplantation, organ preservation

Received: 4 June 2015; Revision requested: 2 July 2015; Accepted: 30 October 2015

Introduction

Kidney transplantation is the treatment of choice in end-stage renal disease, being superior to dialysis regarding life expectation and treatment cost [1–3]. Advances in donor management, standardized surgical techniques and improved immunosuppression have contributed to enhanced survival rates in the last decades. Due to the enormous organ shortage, an augmented use of extended criteria donors (ECD) is needed. ECDs refer to kidney donors aged >60 years or donors aged 50–59 years with two of the following three features: history of hypertension, serum creatinine >1.5 mg/dl, or death from cerebrovascular accident. The majority of organs are retrieved from donors after brain death (DBD), yet the unphysiological state of brain death (BD) with metabolic, hemodynamic, and pro-inflammatory changes is associated with impaired graft quality, increased immunogenicity, and compromised patient and graft survival [4,5]. Therefore, optimized care of DBDs is fundamental to maximize the quantity, functional quality and viability

doi:10.1111/tri.12712

of retrievable organs [6]. Improving care for the potential donor already on the intensive care unit (ICU) has the potential to attenuate irreversible harm to the graft [7]. As organs from ECDs are more prone to delayed graft function (DGF) and have a higher incidence of immune-mediated rejection, optimized donor management is of crucial importance [8]. Specific strategies solely for graft protection can only be instituted after death and only with given consent for donation. In line with the danger hypothesis, this would attenuate the vicious circle of injury and increased immunogenicity after transplantation [8]. Experimental studies highlight the benefits of this approach, but well designed clinical trials studying donor pretreatment are sparse [9]. Trials should ideally assess the results of kidney transplantation by hard outcome data such as patient and graft survival, but can also consider early parameters such as DGF, biopsy-proven acute rejection (BPAR), and evolution of graft function. Here, we discuss current evidence of specific donor management and organ preservation strategies to improve these outcome parameters after kidney transplantation.

Ethical issues of donor research

The potential of improving donor management is complicated by a myriad of logistical and ethical challenges. First, consent to donor research is unique, as intervention trials include donors, donor families, and organ recipients, but official guidelines for consent in donor-based research are missing [10]. Donor research cannot truly harm the deceased and donor's consent is not legally required, but some ethic guidelines propose the family to give informed consent [11] while others demand a surrogate informed consent for participation in clinical trials [12]. Others consider the consent from the donor family as standard to minimize the family's emotional distress and to maintain public trust in the medical profession [13]. In general, it can be assumed that donors and donor families consent to any reasonable scientific effort to improve the outcome of donated organs. Second, if donor research could pose a risk to the recipient, recipient consent depends on the intervention-related risks, ranging from absent to high particularly when investigational drugs or devices are used. If required, consent for donor research should ideally start when patients join the waiting list within the context of an institutionally approved protocol for any clinical trial. Due to the numerous potential interventions and transplant centers involved in different countries, this approach is almost unfeasible. Furthermore, transplantations are unpredictable and some recipients remain unknown even after organ procurement. The logistical obstacles are further underlined by the need to proceed quickly with the transplant procedure and the fact that donor treatment should not affect allocation [13].

Hence, the establishment of institutional review boards and ethic committees with specialist transplantation expertise is advisable to determine the consent process subject to the risk of intervention and to decide whether the recipient needs to give informed consent [9]. Additionally, a safety monitoring board is reasonable, as it can guard each study subject enrolled within the clinical trial [14].

Management strategies prior to organ retrieval

Antioxidant agents

Use of recombinant human superoxide dismutase (rh-SOD)

Throughout the transplantation course, kidneys are prone to oxidative stress by multiple pre- and post-transplant conditions, that is organ procurement, cold preservation, and ischemia reperfusion [15]. Via activation of signaling molecules, such as nuclear factor-kappa B, oxidative stress promotes inflammation through the release of reactive oxygen species [16–18]. Rh-SOD is capable of scavenging free oxygen radicals thereby minimizing oxidative stress. About 200 mg rh-SOD given at reperfusion did not affect DGF or recovery of graft function, but significantly reduced the total number of acute rejection episodes (32/33.3% of 96 controls vs. 15/18.5% of 81 rh-SOD; $P < 0.027$) and severe acute rejections resulting in graft loss (12/12.5% of controls vs. 3/3.7% of rh-SOD; $P < 0.038$). Treatment with rh-SOD also improved 4-year graft survival to 74% compared with 52% in controls. The authors hypothesized that protection of endothelial cells from early reperfusion injury would mitigate the process of "chronic obliterative rejection arteriosclerosis" translating in improved long-term graft survival [19,20].

Donor pretreatment with N-acetylcysteine

Antioxidant molecules are proposed to limit renal ischemia-reperfusion injury, but so far clinical studies considering donor treatment with these agents are rare. Recently, an open-label monocentre trial with 160

DBDs failed to show a beneficial effect of N-acetylcysteine pretreatment. N-acetylcysteine neither affected incidence or duration of DGF nor one-year graft survival [21].

Hormonal resuscitation to antagonize unphysiological effects after BD

BD is associated with severe hormonal alterations resulting from failure of the pituitary gland [22]. Consequently, the levels of adrenocorticotropic hormone, cortisol, vasopressin, insulin, and triiodothyronine suddenly drop after the occurrence of BD. Different studies have replaced these hormonal deficits.

Blood sugar control and insulin

Today most organ donors have received insulin therapy already before BD, because monitoring of blood glucose and insulin therapy is well established in ICUs [23,24]. Current guidelines recommend target glucose levels of 180 mg/dl (9.9 mmol/l) in the critically ill [25], which were shown to be safer than lower targets [26,27]. A prospective study from the USA indicated that glucose levels above 180 mg/dl are associated with lower organ transplantation rates per donor and worsened graft outcomes. Therefore, targeting glucose levels of ≤180 mg/dl should be included as a management goal in potential organ donors [28].

Administration of thyroid hormones

Retrospective studies suggest that hormonal resuscitation including triiodothyronine/L-thyroxine could be advantageous due to improvements of cardiocirculatory function with less inotropic requirements [29–31]. Nevertheless, controlled clinical data and pooled analyses on thyroid hormone administration did not confirm a reduced requirement of vasoactive agents, a gain in cardiac output or an increase in the number of organs procured [32,33]. In addition, post-transplant kidney function was not improved [34,35]. Presumably, low triiodothyronine levels after BD reflect severe injury rather than a hypothyroid state [32].

Administration of methylprednisolone

As endogenous cortisol levels decrease early during BD, their supplementation is advocated because their anti-inflammatory properties might reduce the immunologic activation after BD [36]. In experimental transplantation, steroid use decreased immune-mediated attack and improved graft function [37,38]. However, these findings could not be confirmed in humans, as early studies failed to show an advantageous effect of donor treatment with methylprednisolone [39–43]. Few smaller studies on combined use of cyclophosphamide and methylprednisolone also suggested improved 5-year graft survival [40,41], but could not be confirmed by others [42,43].

Recently, a large randomized double-blind trial (269 DBDs) was conducted to investigate the effects of methylprednisolone pretreatment in kidney transplantation. About 1000 mg methylprednisolone 3 h before organ retrieval significantly ameliorated gene expression profiles of inflammatory and apoptotic transcripts but had no effect on incidence and duration of DGF, or decline of serum creatinine during the first week. Hence, high-dose methylprednosolone before organ retrieval is not recommended at least in kidney transplantation [36]. It was argued that the negative result of the study was due to the very short time window between study intervention and initiation of cold preservation. Nevertheless, preliminary data suggest that donor treatment with steroids might be beneficial in liver and lung transplantation [44–46]. As retrospective registry-based data indicate that hormonal resuscitation including methylprednisolone increases the yield of transplantable organs per donor, the routine use of steroids as part of a combined hormonal resuscitation has to be discussed.

Administration of low-dose dopamine

As a consequence of BD, sympathetic outflow is interrupted and vasodilatation occurs, leading to hemodynamic instability, so that 80–90% of all DBDs need vasoactive support to maintain adequate organ perfusion. Expert opinions differ, which adrenergic agent should be administered first-line, as clinical studies on use of adrenergic agents focusing on graft outcome are sparse and produced conflicting results [47].

Dopamine has traditionally been first choice for donors with hemodynamic instability [48], but one retrospective study linked the use of dopamine to an increased incidence of DGF. Yet, in-depth analysis revealed that this association was presumably confounded by severe hypotension periods in these donors [49]. Another retrospective study concluded that use of vasopressors reduced the likelihood of immediate allograft function [50]. This was confirmed by a prospective cohort study indicating that donor inotropic support is

Transplant International 2016; 29: 974–984

associated with less immediate graft function and poorer renal graft survival [51]. In contrast, a Canadian study identified no dopamine use as a determinant of initial nonfunction in a multivariate analysis and recommended low-dose therapy for all donors [52]. An intriguing finding from our center was, that donor dopamine and to a lesser extent norepinephrine were associated with less acute rejection after kidney transplantation and translated in improved graft survival [53]. A benefit was also shown in a large multicenter cohort study of 2415 kidney transplants from 1993 indicating that adrenergic agents improved 4-year graft survival in an apparently dose-dependent manner [54]. Like in the Canadian study, donor dopamine was also associated with reduced dialysis requirements after transplantation, whereas norepinephrine was not [55].

Based on these data, a multicenter randomized controlled trial was initiated in 2004, which confirmed that treatment of DBDs with low-dose dopamine (4 μg/kg/min) improves immediate graft function after kidney transplantation. The beneficial effect was enhanced for kidney grafts with prolonged cold ischemic time (CIT) exceeding 17 h and translated in improved graft survival in this subgroup. Donor dopamine only infrequently induced adverse events, namely tachycardia (10.0%) and hypertension (3.3%), that were reversible after dose reduction or premature termination of the dopamine infusion [56].

Molecular mechanism of dopamine

The advantageous effects of dopamine were not mediated through hemodynamic stabilization, because all donors were similar with respect to blood pressure and urine production. Protection is believed to result from the antioxidant properties of the dopamine molecule [57]. Cellular damage following prolonged CIT is in part ascribed to oxidative stress. Under cold storage conditions, accumulation of reactive oxygen species (ROS) leads to an increased release of calcium ions [58]. A vicious circle is activated, as intracellular calcium homeostasis depends on high energy phosphates which maintain the mitochondrial membrane potential. While synthesis of ATP is decreased under hypothermia, the influx of calcium further exhausts ATP. Abundant intracellular calcium aggravates mitochondrial damage, with the consequence that the mitochondrial membrane potential ultimately breaks down [59]. We have demonstrated that dopamine decelerates the deleterious amplification loop of intracellular calcium accumulation and subsequent ATP consumption by scavenging of ROS [60,61]. In addition, it was shown that dopamine also increases H2S-production by stimulating endogenous cystathionine-β-synthase, which protects cells from ROS-formation and apoptosis after cold storage upon rewarming [62].

Administration of desmopressin (1-deamino-8-D-arginine-vasopressin [DDAVP])

About 80–90% of all DBDs develop central diabetes insipidus with profuse polyuria and potentially severe dehydration. DDAVP promotes fluid re-absorption in the collecting duct and decreases the need for large volume infusions to hemodynamically stabilize the DBD [63]. Early studies with DDAVP did not show any favorable effect on recipients' outcome after transplantation [64,65]. However, in a more recent study, renal transplant recipients from DDAVP treated donors showed less rejections episodes and lower serum creatinine values 1 and 3 years after transplantation [66]. The retrospective analysis of the dopamine multicenter trial confirmed this observation. While DDAVP pretreatment had no effect on short-term outcome such as DGF, BPAR, or decline of serum creatinine during the first week post-transplant, it was significantly associated with improved 2-year graft survival (85.4% vs. 73.6%, log-rank $P = 0.003$). Subgroup analyses indicated that DDAVP was only beneficial if cold storage was short (below 14 h) or the donor was assigned to dopamine pretreatment. Exposure to hypoxia during cold preservation and shear stress during reperfusion induces exocytosis of Weibel-Palade bodies (WPB) releasing various pro-inflammatory cytokines. Both a shorter CIT and dopamine protect the graft's endothelium from cold storage injury. It was hypothesized that DDAVP treatment deprives WPB from the intact endothelium of the graft before its exposure to ischemia/reperfusion injury. Reduced release of pro-inflammatory cytokines during transplantation may attenuate inflammation and transplant vasculopathy.

Combined hormonal resuscitation

In a retrospective analysis of the UNOS database, combined therapy with methylprednisolone, vasopressin, and triiodothyronine/L-thyroxine as "hormonal resuscitation" raised organ yield per donor, especially kidneys by 7.3% [67] and was associated with improved kidney graft survival after 1 year [68]. As it is impossible to define the role of any single agent, optimal hormonal replacement therapy in DBDs yet remains to be estab-

Table 1. Overview of hormonal replacement and vasopressor use in organ donors.

Hormone/Treatment	Recommendation for administration
Insulin for blood sugar control	Achieve glucose levels of ≤180 mg/dl [28]
Thyroid hormones	Not recommended as a single agent Increases number of transplantable organs per donor within general "hormonal resuscitation" [67]
Methylprednisolone	General consideration Potential benefit in liver and lung transplantation [44–46] Increases number of transplantable organs per donor within general "hormonal resuscitation" [67]
DDAVP	Brain death induced diabetes insipidus (diuresis >5 ml/kg/hr with specific gravity <1005 mg/ml) Might improve kidney graft survival [69] Potentially fewer acute rejections and improved creatinine [66]
Vasopressors	Kidney donors: Low-dose dopamine (4 μg/kg/min) Reduction of DGF [56] Improved survival if CIT >17 h [56]

lished. Table 1 gives an overview of clinically proven therapies from hormonal resuscitation trials.

Fluid replacement therapy

Hypovolemia with circulatory collapse is a frequent complication in DBDs due to central diabetes insipidus, and loss of sympathetic tone [63]. Hence, adequate fluid replacement is essential to prevent acute renal failure. Crystalloid solutions such as 0.9% saline or Ringer's lactate are considered first choice because they have no specific side effects, but may rarely increase edema formation. Balanced crystalloid solutions are preferable particularly if resuscitation of larger fluid volumes is required, because administration of 0.9% saline may cause hyperchloremic metabolic acidosis [7]. Crystalloid fluid loading to a CVP of 8–10 mmHg may be deleterious to lung function and should be avoided in potential lung donors [70]. Colloid solutions could be an alternative to avoid interstitial fluid overload, but they are associated with a significant risk of anaphylactic reactions. Furthermore, HES (hydroxyl ethyl starch) should be avoided in kidney donors, because osmotic nephrosis-like lesions were detected in transplanted kidneys after HES treatment [71], which were associated with elevated creatinine levels in the recipients [72]. However, these findings were not confirmed by others [73]. Due to competing interests regarding optimal treatment of multi-organ donors, lung surgeons would perhaps prefer colloid solutions to stabilize circulation, as gas exchange might be improved by attenuation of neurogenic pulmonary edema. Nevertheless, evidence so far has linked HES to an increased risk of death and renal-replacement therapy in ICUs; therefore, use of HES is discouraged [74,75] (Table 2).

General donor management goals (DMG)

International procurement organizations have adopted critical care endpoints as management goals for donor treatment after confirmation of BD. This resulted in an increased organ yield as shown by various retrospective analyses [77,78]. Recently, a prospective evaluation by UNOS revealed that a limited number of donors only achieve target criteria, but efforts to meet DMG are associated with significantly higher rates of transplantable organs per donor [79] (Table 3). In addition, DGF after kidney transplantation was less common when DMG were met (17% vs. 30%; $P = 0.007$) [80] indicating that optimized care for DBDs will not only extend the pool of organs but also improve clinical outcome after transplantation.

Therapeutic hypothermia in deceased organ donors

Therapeutic hypothermia has been shown to be a beneficial intervention to protect neurologic function of patients with specific types of cardiac arrest or stroke [81–83]. Recently, a large prospective trial in deceased organ donors ($n = 370$) showed that mild hypothermia (34–35 °C) significantly reduced the rate of DGF among recipients (28% vs. 39%, odds ratio 0.62; $P = 0.02$) [84]. Subgroup analysis showed that high-risk donors, such as ECDs, particularly benefited from hypothermia (odds ratio 0.31; 95% CI 0.15–0.68; $P = 0.003$).

Organ storage: Static cold storage or hypothermic machine perfusion (MP)

Transplants from ECDs are more susceptible to cold storage inflicted injury, which causes higher rates of DGF and increases the risk for graft failure [85,86]. Therefore, optimizing organ preservation to maintain organ quality is a crucial factor for transplantation success. Although static cold preservation is used for the majority of organs transplanted [87,88], MP might be more appropriate to maintain graft viability, especially

Transplant International 2016; 29: 974–984

if organs are retrieved from ECDs or donors after cardiac death (DCD) [89]. Early retrospective data indicate that MP may reduce DGF and result in a mild benefit on death-censored graft survival [90,91]. Another retrospective study including 912 renal allografts revealed similar results considering DGF, albeit graft survival remained unaffected [92].

These initial studies were followed by a large prospective multicenter trial assessing the influence of MP on DGF [93]. In this study, one kidney of each donor was randomly assigned to MP or to static cold preservation. MP significantly reduced the rate of DGF (20.8% vs. 26.5%; $P = 0.05$) and numerically halved primary nonfunction (PNF) (2.1% vs. 4.8%; $P = 0.08$). Duration of hospital stay and BPAR were unaffected, but MP significantly improved 1-year graft survival (94% vs. 90%, $P = 0.04$). The beneficial effect of MP was similar for standard criteria and for ECDs. Recently, 3-year follow-up data indicated superior long-term graft survival (91% vs. 87%; $P = 0.04$) with MP. Interestingly, the benefit of MP could be detected in the subgroup of DBDs only (91% vs. 86%; $P = 0.02$), being pronounced in the subgroup of ECDs (86% vs. 76%; $P = 0.01$) but not in DCDs [94]. The suggested beneficial effect for ECDs could also be shown in 85 ECD kidneys allocated in the Eurotransplant Senior Program. MP reduced the rate of PNF and improved 1-year graft survival of kidneys suffering from DGF, however, no benefit on the incidence of DGF was found, possibly due to the short CIT of 11 h [95]. However, the above study [93,94] has been criticized, as MP reduced DGF only slightly from 89/336 to 70/336, that is, a prevention of 19 episodes in 336 transplantations (= 5.7%) and may thus not explain a 4% difference in graft survival. Furthermore, in 25 donors assigned to MP in whom vascular anatomy was considered unsuitable the contralateral kidneys was used instead. These kidney pairs were not excluded but analyzed according to the actual preservation technique and not "intention to treat". This ambiguous assignment resulted in a higher number of kidneys with vascular abnormalities in controls. Also, MP failed in seven instances. These kidney pairs were excluded from analysis, although they were transplanted. Failure of the pump could have increased DGF risk and exclusion of these kidneys might bias results in favor of MP. Therefore, the value of MP in kidney transplantation is still a matter of debate, also because other studies could not confirm these findings.

The UK multicenter trial which randomly assigned DCD kidneys either to MP or static cold storage failed to show any effect on DGF (58% vs. 56%; $P = 0.99$). Surprisingly, MP was associated with an increased rate of BPAR in the first 3 months (22% vs. 7%; $P = 0.06$), but this did not influence graft or patient survival after 12 months [96]. Also, MP was associated with lower graft survival in a large registry-based study ($n = 2202$), even when the analyses were stratified for duration of CIT [87].

Finally, several meta-analyses have been performed to summarize the available evidence on MP in different donor types. A meta-analysis including all donor types revealed that MP reduced DGF rates, but had no influence on PNF, acute rejections, and graft or patient survival [97]. Subsequent meta-analyses were restricted to DCDs and found that MP reduced DGF, but the incidence of PNF and 1-year graft or patient survival was unaffected [98,99]. Another meta-analysis considering ECDs only (2374 MP vs. 8716 CS) concluded that MP was superior in preventing DGF, and increased 1-year graft survival, however did not affect PNF or patient survival [100]. Meta-analysis is limited due to study heterogeneity in terms of

Table 2. Overview of reported risks and disadvantages of crystalloid and colloid solutions in potential multi-organ donors.

Crystalloid solutions	Colloid solutions
Increase of neurogenic pulmonary edema in potential lung donors [70,76]	Risk of anaphylactic reactions
Edema formation	Induction of osmotic nephrosis-like lesions [71] Increased risk of death and renal-replacement therapy in ICUs [74,75]

Table 3. Recommended donor management goals to raise organ yield per donor, adapted from [79].

United Network for Organ Sharing (UNOS) region 5 donor management goals	
Central venous pressure	4–10 mmHg
Ejection fraction	>50%
Vasopressors	≤1 and low dose*
Arterial blood gas pH	7.3–7.45
PaO_2:FiO_2	>300
Serum sodium	135–155 mmol/l
Blood glucose	<150 mg/dl
Urine output	0.5–3 ml/kg/h over 4 h
Mean arterial pressure	60–100 mmHg

*Dopamine ≤10 μg/kg/min, phenylephrine ≤60 μg/kg/min, and norepinephrine ≤10 μg/kg/min.

the pump systems, perfusion pressures, and cold storage solutions examined [100]. In summary, the available evidence about the use of MP is controversial [101]. The use of MP may prove to be beneficial in high-risk grafts from ECDs or after prolonged CIT [85].

Preclinical and experimental donor treatment strategies

Ischemic preconditioning (IPC)

Remote IPC is one potential approach to protect kidneys from ischemia-reperfusion injury. Although the underlying mechanism needs to be fully defined [102], the concept of IPC was shown to be beneficial in rodent models of kidney transplantation [103–106], but large animal models failed to confirm these results [107,108]. Furthermore, remote IPC by occluding the thigh (three times for 5 min, either in donors or recipients) failed to improve renal function within 72 h after human living donor transplantation [109]. Nonetheless, patients are currently recruited into an interventional randomized trial to investigate the effect of remote IPC on immediate and 1-year graft function (NCT01395719) [9].

Vagus nerve stimulation

Electric stimulation of the vagal nerve in a BD rodent decreased transcription of pro-inflammatory genes, reduced monocyte infiltration of the graft, and improved its function after transplantation [110]. The mechanism of action is presumably related to restoring vagus nerve activity, resulting in recovery of the anti-inflammatory reflex. Recently, also a long-term benefit with less chronic allograft nephropathy (CAN) was shown [111].

Atorvastatin

In an isogeneic transplantation model, atorvastatin prevented ischemia-reperfusion injury and improved renal function [112]. Atorvastatin may be beneficial by inhibiting aldose reductase, which plays a major role in oxidative stress [113–115], but the benefit of statin treatment could not be shown in animal transplantation models after BD induction [116].

Erythropoietin

High-dose erythropoietin provides anti-apoptotic and cytoprotective effects and might enhance the graft's resistance to ischemic injury after BD. In a rat model, erythropoietin diminished the expression of pro-inflammatory genes, decreased the infiltration of polymorphonuclear cells and restored kidney function after BD [117]. In a large animal model of donor pigs erythropoietin decreased renal injury, inflammation and improved kidney function after transplantation [118]. Nevertheless, clinical studies using erythropoietin before surgery and/or following transplantation had no beneficial effect on graft outcome [119,120]. In one trial, administration of erythropoietin even increased the risk of thrombotic events 1 year after transplantation [121].

Carbon monoxide (CO)

Upcoming evidence suggests that application of carbon monoxide in DBDs is another promising approach for prevention of ischemia-reperfusion injury [122]. Additionally, it was demonstrated in rat transplant models that CO is capable of diminishing the graft's immunogenicity, that is donor-derived dendritic cells already before transplantation [122–124]. Furthermore, CO was shown to inhibit CAN and to improve survival even when the treatment is started after diagnosis of CAN [125]. The promising role of CO in transplantation is reviewed in detail elsewhere [126,127].

Conclusion

As a consequence of organ shortage, grafts from ECDs need to be used to supply the demand of transplantable organs. Grafts from ECDs are more susceptible to vari-

Table 4. Human randomized controlled trials of donor management showing a beneficial effect after kidney transplantation.

Specific donor treatment	Effect on outcome after kidney transplantation
Glucose levels of <180 mg/dl	Higher organ transplantation rate per donor [28]
Meeting donor management goals	Higher rate of transplantable organs per donor [79] Reduction of DGF [80]
Low-dose dopamine (4 μg/kg/min)	Reduction of DGF [56]
Human superoxide dismutase (rh-SOD)	Reduced number of acute rejections, improved 4-year graft survival [19]
Hypothermic machine perfusion	Reduced rate of DGF, Improved 1- and 3-year graft survival, especially for ECDs [93,94]
Therapeutic hypothermia	Reduction of DGF, especially for ECDs [84]

ous deleterious events occurring during the course of transplantation. To preserve graft viability, optimized donor management is increasingly important. Several (pre) clinical donor treatment strategies have revealed promising results, demonstrating the great potential of specific interventions in the DBD.

According to the available evidence, donor management goals have been elaborated to increase organ yield per donor. Regarding specific interventions, randomized controlled trials indicate that donor pretreatment with low-dose dopamine or the administration of human superoxide dismutase at time of reperfusion improve the outcome after kidney transplantation by scavenging of ROS. Additionally, as recently shown, mild hypothermia lowers the rate of DGF among recipients, especially in high-risk donors like ECDs. While optimal organ storage is still a matter of debate, current data suggest a beneficial effect by hypothermic machine perfusion, especially for ECDs (Table 4).

In general, overall clinical evidence of donor interventions on graft outcome is sparse and mostly lacks long-term results. Important additional issues comprise competing interests of some organ-specific interventions [on quality and procurement of other organs from the same donor] and ethical considerations, that is informed consent from donors and recipients with regard to trials in donor management. Current donation and allocation systems should incorporate donor management protocols to optimize results for transplant recipients and be better designed to facilitate further research that can improve the utility of this most precious resource.

Funding

The authors have declared no funding.

Conflicts of interest

All authors declare that they do not have any conflict of interest with this publication.

REFERENCES

1. Jassal SV, Krahn MD, Naglie G, *et al.* Kidney transplantation in the elderly: a decision analysis. *J Am Soc Nephrol* 2003; **14**: 187.
2. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, *et al.* Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725.
3. 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.
4. Barklin A. Systemic inflammation in the brain-dead organ donor. *Acta Anaesthesiol Scand* 2009; **53**: 425.
5. Floerchinger B, Oberhuber R, Tullius SG. Effects of brain death on organ quality and transplant outcome. *Transplant Rev* 2012; **26**: 54.
6. Mascia L, Mastromauro I, Viberti S, Vincenzi M, Zanello M. Management to optimize organ procurement in brain dead donors. *Minerva Anestesiol* 2009; **75**: 125.
7. Schnuelle P, Johannes van der Woude F. Perioperative fluid management in renal transplantation: a narrative review of the literature. *Transpl Int* 2006; **19**: 947.
8. Martins PN, Chandraker A, Tullius SG. Modifying graft immunogenicity and immune response prior to transplantation: potential clinical applications of donor and graft treatment. *Transpl Int* 2006; **19**: 351.
9. de Vries DK, Wijermars LG, Reinders ME, Lindeman JH, Schaapherder AF. Donor pre-treatment in clinical kidney transplantation: a critical appraisal. *Clin Transplant* 2013; **27**: 799.
10. 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.
11. Pentz RD, Cohen CB, Wicclair M, *et al.* Ethics guidelines for research with the recently dead. *Nat Med* 2005; **11**: 1145.
12. 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.
13. Feng S. Donor intervention and organ preservation: where is the science and what are the obstacles? *Am J Transplant* 2010; **10**: 1155.
14. Mone T, Heldens J, Niemann CU. Deceased organ donor research: the last research frontier? *Liver Transplant* 2013; **19**: 118.
15. Nafar M, Sahraei Z, Salamzadeh J, Samavat S, Vaziri ND. Oxidative stress in kidney transplantation: causes, consequences, and potential treatment. *Iran J Kidney Dis* 2011; **5**: 357.
16. McCord JM. Oxygen-derived free radicals in postischemic tissue injury. *N Engl J Med* 1985; **312**: 159.
17. Parks DA, Granger DN. Ischemia-reperfusion injury: a radical view. *Hepatology* 1988; **8**: 680.
18. Ambros JT, Herrero-Fresneda I, Borau OG, Boira JM. Ischemic preconditioning in solid organ transplantation: from experimental to clinics. *Transpl Int* 2007; **20**: 219.
19. Land W, Schneeberger H, Schleibner S, *et al.* The beneficial effect of human recombinant superoxide dismutase on acute and chronic rejection events in recipients of cadaveric renal transplants. *Transplantation* 1994; **57**: 211.
20. Land W. Innate alloimmunity: history and current knowledge. *Exp Clin Transplant* 2007; **5**: 575.
21. Orban JC, Quintard H, Cassuto E, Jambou P, Samat-Long C, Ichai C. Effect of N-acetylcysteine pretreatment of deceased organ donors on renal allograft function: a randomized

controlled trial. *Transplantation* 2015; **99**: 746.
22. Ranasinghe AM, Bonser RS. Endocrine changes in brain death and transplantation. *Best Pract Res Clin Endocrinol Metab* 2011; **25**: 799.
23. Van den Berghe G. Insulin therapy in the intensive care unit should be targeted to maintain blood glucose between 4.4 mmol/l and 6.1 mmol/l. *Diabetologia* 2008; **51**: 911.
24. Derde S, Vanhorebeek I, Van den Berghe G. Insulin treatment in intensive care patients. *Horm Res* 2009; **71**: 2.
25. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004; **79**: 992.
26. Chase JG, Pretty CG, Pfeifer L, *et al.* Organ failure and tight glycemic control in the SPRINT study. *Crit Care* 2010; **14**: R154.
27. Finfer S, Chittock DR, Su SY, *et al.* Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360**: 1283.
28. Sally MB, Ewing T, Crutchfield M, *et al.* Determining optimal threshold for glucose control in organ donors after neurologic determination of death: a United Network for Organ Sharing Region 5 Donor Management Goals Workgroup prospective analysis. *J Trauma Acute Care Surg* 2014; **76**: 62.
29. Salim A, Vassiliu P, Velmahos GC, *et al.* The role of thyroid hormone administration in potential organ donors. *Arch Surg* 2001; **136**: 1377.
30. Jeevanandam V, Todd B, Regillo T, Hellman S, Eldridge C, McClurken J. Reversal of donor myocardial dysfunction by triiodothyronine replacement therapy. *J Heart Lung Transplant* 1994; **13**: 681; discussion 5-7.
31. Zuppa AF, Nadkarni V, Davis L, *et al.* The effect of a thyroid hormone infusion on vasopressor support in critically ill children with cessation of neurologic function. *Crit Care Med* 2004; **32**: 2318.
32. Macdonald PS, Aneman A, Bhonagiri D, *et al.* A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors. *Crit Care Med* 2012; **40**: 1635.
33. Powner DJ, Hernandez M. A review of thyroid hormone administration during adult donor care. *Prog Transplant* 2005; **15**: 202.
34. Gifford RR, Weaver AS, Burg JE, Romano PJ, Demers LM, Pennock JL. Thyroid hormone levels in heart and kidney cadaver donors. *J Heart Transplant* 1986; **5**: 249.
35. Koller J, Wieser C, Gottardis M, *et al.* Thyroid hormones and their impact on the hemodynamic and metabolic stability of organ donors and on kidney graft function after transplantation. *Transpl Proc* 1990; **22**: 355.
36. 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.
37. Reutzel-Selke A, Zschockelt T, Denecke C, *et al.* Short-term immunosuppressive treatment of the donor ameliorates consequences of ischemia/reperfusion injury and long-term graft function in renal allografts from older donors. *Transplantation* 2003; **75**: 1786.
38. Pratschke J, Kofla G, Wilhelm MJ, *et al.* Improvements in early behavior of rat kidney allografts after treatment of the brain-dead donor. *Ann Surg* 2001; **234**: 732.
39. Chatterjee SN, Terasaki PI, Fine S, Schulman B, Smith R, Fine RN. Pretreatment of cadaver donors with methylprednisolone in human renal allografts. *Surg Gynecol Obstet* 1977; **145**: 729.
40. Guttmann RD, Morehouse DD, Meakins JL, Klassen J, Knaack J, Beaudoin JG. Donor pretreatment in an unselected series of cadaver renal allografts. *Kidney Int Suppl* 1978; **8**: S99.
41. Zincke H, Woods JE. Donor pretreatment in cadaver renal transplantation. *Surg Gynecol Obstet* 1977; **145**: 183.
42. Jeffery JR, Downs A, Grahame JW, Lye C, Ramsey E, Thomson AE. A randomized prospective study of cadaver donor pretreatment in renal transplantation. *Transplantation* 1978; **25**: 287.
43. Soulillou JP, Baron D, Rouxel A, Guenel J. Steroid-cyclophosphamide pretreatment of kidney allograft donors. A control study. *Nephron* 1979; **24**: 193.
44. Venkateswaran RV, Patchell VB, Wilson IC, *et al.* Early donor management increases the retrieval rate of lungs for transplantation. *Ann Thorac Surg* 2008; **85**: 278; discussion 86.
45. Kotsch K, Ulrich F, Reutzel-Selke A, *et al.* Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial. *Ann Surg* 2008; **248**: 1042.
46. Follette DM, Rudich SM, Babcock WD. Improved oxygenation and increased lung donor recovery with high-dose steroid administration after brain death. *J Heart Lung Transplant* 1998; **17**: 423.
47. Bugge JF. Brain death and its implications for management of the potential organ donor. *Acta Anaesthesiol Scand* 2009; **53**: 1239.
48. Wood KE, Becker BN, McCartney JG, D'Alessandro AM, Coursin DB. Care of the potential organ donor. *N Engl J Med* 2004; **351**: 2730.
49. Ferguson CJ, Hillis AN, Williams JD, Griffin PJ, Salaman JR. Calcium-channel blockers and other factors influencing delayed function in renal allografts. *Nephrol Dial Transplant* 1990; **5**: 816.
50. O'Brien EA, Bour SA, Marshall RL, Ahsan N, Yang HC. Effect of use of vasopressors in organ donors on immediate function of renal allografts. *J Transpl Coord* 1996; **6**: 215.
51. Marshall R, Ahsan N, Dhillon S, Holman M, Yang HC. Adverse effect of donor vasopressor support on immediate and one-year kidney allograft function. *Surgery* 1996; **120**: 663; discussion 6.
52. Sutherland FR, Bloembergen W, Mohamed M, Ostbye T, Klar N, Lazarovits AI. Initial nonfunction in cadaveric renal transplantation. *Can J Surg* 1993; **36**: 141.
53. Schnuelle P, Lorenz D, Mueller A, Trede M, Van Der Woude FJ. Donor catecholamine use reduces acute allograft rejection and improves graft survival after cadaveric renal transplantation. *Kidney Int* 1999; **56**: 738.
54. Schnuelle P, Berger S, de Boer J, Persijn G, van der Woude FJ. Effects of catecholamine application to brain-dead donors on graft survival in solid organ transplantation. *Transplantation* 2001; **72**: 455.
55. Schnuelle P, Yard BA, Braun C, *et al.* Impact of donor dopamine on immediate graft function after kidney transplantation. *Am J Transplant* 2004; **4**: 419.
56. 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.
57. Beck G, Brinkkoetter P, Hanusch C, *et al.* Clinical review: immunomodulatory effects of dopamine in general inflammation. *Crit Care* 2004; **8**: 485.

58. Ahlenstiel T, Burkhardt G, Kohler H, Kuhlmann MK. Bioflavonoids attenuate renal proximal tubular cell injury during cold preservation in Euro-Collins and University of Wisconsin solutions. *Kidney Int* 2003; **63**: 554.
59. Haddad P, Cabrillac JC, Piche D, Musallam L, Huet PM. Changes in intracellular calcium induced by acute hypothermia in parenchymal, endothelial, and Kupffer cells of the rat liver. *Cryobiology* 1999; **39**: 69.
60. 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.
61. Brinkkoetter PT, Song H, Losel R, *et al.* Hypothermic injury: the mitochondrial calcium, ATP and ROS love-hate triangle out of balance. *Cell Physiol Biochem* 2008; **22**: 195.
62. Talaei F, Bouma HR, Van der Graaf AC, Strijkstra AM, Schmidt M, Henning RH. Serotonin and dopamine protect from hypothermia/rewarming damage through the CBS/H2S pathway. *PLoS ONE* 2011; **6**: e22568.
63. Dictus C, Vienenkoetter B, Esmaeilzadeh M, Unterberg A, Ahmadi R. Critical care management of potential organ donors: our current standard. *Clin Transplant* 2009; **23** (Suppl 21): 2.
64. Hirschl MM, Matzner MP, Huber WO, *et al.* Effect of desmopressin substitution during organ procurement on early renal allograft function. *Nephrol Dial Transplant* 1996; **11**: 173.
65. 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.
66. 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.
67. Rosendale JD, Kauffman HM, McBride MA, *et al.* Aggressive pharmacologic donor management results in more transplanted organs. *Transplantation* 2003; **75**: 482.
68. Novitzky D, Cooper DK, Rosendale JD, Kauffman HM. Hormonal therapy of the brain-dead organ donor: experimental and clinical studies. *Transplantation* 2006; **82**: 1396.
69. Benck U, Gottmann U, Hoeger S, *et al.* Donor desmopressin is associated with superior graft survival after kidney transplantation. *Transplantation* 2011; **92**: 1252.
70. 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.
71. Legendre C, Thervet E, Page B, Percheron A, Noel LH, Kreis H. Hydroxyethylstarch and osmotic-nephrosis-like lesions in kidney transplantation. *Lancet* 1993; **342**: 248.
72. Cittanova ML, Leblanc I, Legendre C, Mouquet C, Riou B, Coriat P. Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. *Lancet* 1996; **348**: 1620.
73. Deman A, Peeters P, Sennesael J. Hydroxyethyl starch does not impair immediate renal function in kidney transplant recipients: a retrospective, multicentre analysis. *Nephrol Dial Transplant* 1999; **14**: 1517.
74. Myburgh JA, Finfer S, Bellomo R, *et al.* Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; **367**: 1901.
75. Perner A, Haase N, Guttormsen AB, *et al.* Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; **367**: 124.
76. Busl KM, Bleck TP. Neurogenic pulmonary Edema. *Crit Care Med* 2015; **43**: 1710.
77. Franklin GA, Santos AP, Smith JW, Galbraith S, Harbrecht BG, Garrison RN. Optimization of donor management goals yields increased organ use. *Am Surg* 2010; **76**: 587.
78. Hagan ME, McClean D, Falcone CA, Arrington J, Matthews D, Summe C. Attaining specific donor management goals increases number of organs transplanted per donor: a quality improvement project. *Prog Transplant* 2009; **19**: 227.
79. Malinoski DJ, Patel MS, Daly MC, Oley-Graybill C, Salim A. The impact of meeting donor management goals on the number of organs transplanted per donor: results from the United Network for Organ Sharing Region 5 prospective donor management goals study. *Crit Care Med* 2012; **40**: 2773.
80. Malinoski DJ, Patel MS, Ahmed O, *et al.* The impact of meeting donor management goals on the development of delayed graft function in kidney transplant recipients. *Am J Transplant* 2013; **13**: 993.
81. Debaty G, Maignan M, Savary D, *et al.* Impact of intra-arrest therapeutic hypothermia in outcomes of prehospital cardiac arrest: a randomized controlled trial. *Intensive Care Med* 2014; **40**: 1832.
82. van der Worp HB, Macleod MR, Bath PM, *et al.* EuroHYP-1: European multicenter, randomized, phase III clinical trial of therapeutic hypothermia plus best medical treatment vs. best medical treatment alone for acute ischemic stroke. *Int J Stroke* 2014; **9**: 642.
83. Nielsen N, Wetterslev J, Cronberg T, *et al.* Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med* 2013; **369**: 2197.
84. Niemann CU, Feiner J, Swain S, *et al.* Therapeutic hypothermia in deceased organ donors and kidney-graft function. *N Engl J Med* 2015; **373**: 405.
85. Yuan X, Theruvath AJ, Ge X, *et al.* Machine perfusion or cold storage in organ transplantation: indication, mechanisms, and future perspectives. *Transpl Int* 2010; **23**: 561.
86. Port FK, Bragg-Gresham JL, Metzger RA, *et al.* Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation* 2002; **74**: 1281.
87. Opelz G, Dohler B. Multicenter analysis of kidney preservation. *Transplantation* 2007; **83**: 247.
88. Maathuis MH, Leuvenink HG, Ploeg RJ. Perspectives in organ preservation. *Transplantation* 2007; **83**: 1289.
89. Minor T, Paul A. Hypothermic reconditioning in organ transplantation. *Curr Opin Org Transplant* 2013; **18**: 161.
90. Schold JD, Kaplan B, Howard RJ, Reed AI, Foley DP, Meier-Kriesche HU. Are we frozen in time? Analysis of the utilization and efficacy of pulsatile perfusion in renal transplantation. *Am J Transplant* 2005; **5**: 1681.
91. Wight J, Chilcott J, Holmes M, Brewer N. The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors. *Health Technol Assess* 2003; **7**: 1.
92. Matsuoka L, Shah T, Aswad S, *et al.* Pulsatile perfusion reduces the incidence of delayed graft function in expanded criteria donor kidney transplantation. *Am J Transplant* 2006; **6**: 1473.
93. Moers C, Smits JM, Maathuis MH, *et al.* Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med* 2009; **360**: 7.
94. Moers C, Pirenne J, Paul A, Ploeg RJ. Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med* 2012; **366**: 770.

95. Gallinat A, Moers C, Treckmann J, *et al.* Machine perfusion versus cold storage for the preservation of kidneys from donors >/= 65 years allocated in the Eurotransplant Senior Programme. *Nephrol Dial Transplant* 2012; **27**: 4458.
96. Watson CJ, Wells AC, Roberts RJ, *et al.* Cold machine perfusion versus static cold storage of kidneys donated after cardiac death: a UK multicenter randomized controlled trial. *Am J Transplant* 2010; **10**: 1991.
97. O'Callaghan JM, Morgan RD, Knight SR, Morris PJ. Systematic review and meta-analysis of hypothermic machine perfusion versus static cold storage of kidney allografts on transplant outcomes. *Br J Surg* 2013; **100**: 991.
98. Deng R, Gu G, Wang D, *et al.* Machine perfusion versus cold storage of kidneys derived from donation after cardiac death: a meta-analysis. *PLoS ONE* 2013; **8**: e56368.
99. Bathini V, McGregor T, McAlister VC, Luke PP, Sener A. Renal perfusion pump vs cold storage for donation after cardiac death kidneys: a systematic review. *J Urol* 2013; **189**: 2214.
100. Jiao B, Liu S, Liu H, Cheng D, Cheng Y, Liu Y. Hypothermic machine perfusion reduces delayed graft function and improves one-year graft survival of kidneys from expanded criteria donors: a meta-analysis. *PLoS ONE* 2013; **8**: e81826.
101. Irish WD, Katz E. Cold machine perfusion or static cold storage of kidneys: why the debate continues. *Am J Transplant* 2010; **10**: 1955.
102. Gassanov N, Nia AM, Caglayan E, Er F. Remote ischemic preconditioning and renoprotection: from myth to a novel therapeutic option? *J Am Soc Nephrol* 2014; **25**: 216.
103. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; **74**: 1124.
104. Fuller TF, Freise CE, Feng S, Niemann CU. Ischemic preconditioning improves rat kidney graft function after severe ischemia/reperfusion injury. *Transpl Proc* 2005; **37**: 377.
105. 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. *Transpl Proc* 2008; **40**: 3316.
106. Jia RP, Zhu JG, Wu JP, Xie JJ, Xu LW. Experimental study on early protective effect of ischemic preconditioning on rat kidney graft. *Transpl Proc* 2009; **41**: 69.
107. Behrends M, Walz MK, Kribben A, *et al.* No protection of the porcine kidney by ischaemic preconditioning. *Exp Physiol* 2000; **85**: 819.
108. Kosieradzki M, Ametani M, Southard JH, Mangino MJ. Is ischemic preconditioning of the kidney clinically relevant? *Surgery* 2003; **133**: 81.
109. Chen Y, Zheng H, Wang X, Zhou Z, Luo A, Tian Y. Remote ischemic preconditioning fails to improve early renal function of patients undergoing living-donor renal transplantation: a randomized controlled trial. *Transplantation* 2013; **95**: e4.
110. Hoeger S, Bergstraesser C, Selhorst J, *et al.* Modulation of brain dead induced inflammation by vagus nerve stimulation. *Am J Transplant* 2010; **10**: 477.
111. Hoeger S, Fontana J, Jarczyk J, *et al.* Vagal stimulation in brain dead donor rats decreases chronic allograft nephropathy in recipients. *Nephrol Dial Transplant* 2014; **29**: 544.
112. 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.
113. Amano S, Yamagishi S, Kato N, *et al.* Sorbitol dehydrogenase overexpression potentiates glucose toxicity to cultured retinal pericytes. *Biochem Biophys Res Commun* 2002; **299**: 183.
114. Chung SS, Ho EC, Lam KS, Chung SK. Contribution of polyol pathway to diabetes-induced oxidative stress. *J Am Soc Nephrol* 2003; **14**(8 Suppl 3): S233.
115. Obrosova IG, Van Huysen C, Fathallah L, Cao XC, Greene DA, Stevens MJ. An aldose reductase inhibitor reverses early diabetes-induced changes in peripheral nerve function, metabolism, and antioxidative defense. *FASEB J* 2002; **16**: 123.
116. Hoeger S, Benck U, Petrov K, *et al.* Atorvastatin donor pre-treatment in a model of brain death and allogeneic kidney transplantation in rat. *Ann Transplant* 2012; **17**: 79.
117. Nijboer WN, Ottens PJ, van Dijk A, van Goor H, Ploeg RJ, Leuvenink HG. 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.
118. Maio R, Sepodes B, Patel NS, Thiemermann C, Mota-Filipe H, Costa P. Erythropoietin preserves the integrity and quality of organs for transplantation after cardiac death. *Shock* 2011; **35**: 126.
119. Martinez F, Kamar N, Pallet N, *et al.* High dose epoetin beta in the first weeks following renal transplantation and delayed graft function: results of the Neo-PDGF Study. *Am J Transplant* 2010; **10**: 1695.
120. Sureshkumar KK, Hussain SM, Ko TY, Thai NL, Marcus RJ. Effect of high-dose erythropoietin on graft function after kidney transplantation: a randomized, double-blind clinical trial. *Clin J Am Soc Nephrol* 2012; **7**: 1498.
121. Aydin Z, Mallat MJ, Schaapherder AF, *et al.* Randomized trial of short-course high-dose erythropoietin in donation after cardiac death kidney transplant recipients. *Am J Transplant* 2012; **12**: 1793.
122. 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.
123. 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.
124. 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.
125. Nakao A, Faleo G, Nalesnik MA, Seda-Neto J, Kohmoto J, Murase N. Low-dose carbon monoxide inhibits progressive chronic allograft nephropathy and restores renal allograft function. *Am J Physiol Renal Physiol* 2009; **297**: F19.
126. Nakao A, Choi AM, Murase N. Protective effect of carbon monoxide in transplantation. *J Cell Mol Med* 2006; **10**: 650.
127. Nakao A, Toyoda Y. Application of carbon monoxide for transplantation. *Curr Pharm Biotechnol* 2012; **13**: 827.