Effects of Donor Pretreatment With Dopamine on Graft Function After Kidney Transplantation

A Randomized Controlled Trial

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Context Kidney graft function after transplantation can be improved through pharmacological donor pretreatment to limit organ injury from cold preservation.

Objective To determine whether pretreatment of brain-dead donors with low-dose dopamine improves early graft function in human renal transplant recipients.

Design, Setting, and Patients Randomized, open-label, multicenter, parallel-group trial of 264 deceased heart-beating donors and 487 subsequent renal transplants performed at 60 European centers between March 2004 and August 2007 (final follow-up, December 31, 2008). Eligible donors were stable under low-dose norepinephrine with a normal serum creatinine concentration on admission.

Interventions Donors were randomized to receive low-dose dopamine (4 µg/kg/min).

Main Outcome Measures Dialysis requirement during first week after transplantation.

Results Dopamine was infused for a median of 344 minutes (IQR, 215 minutes). Dialysis was significantly reduced in recipients of a dopamine-treated graft. Fewer recipients in the treatment group needed multiple dialyses (56/227; 24.7%; 95% CI, 19.0%-30.3%; vs 92/260; 35.4%; 95% CI, 29.5%-41.2%; $P=.01$). The need for multiple dialyses posttransplant was associated with allograft failure after 3 years (HR, 3.61; 95% CI, 2.39-5.45; $P<.001$), whereas a single dialysis was not (HR, 0.67; 95% CI, 0.21-2.18; $P=.51$). Besides donor dopamine (OR, 0.54; 95% CI, 0.35-0.83; $P=.005$), cold ischemic time (OR, 1.07; 95% CI, 1.02-1.11 per hour; $P=.001$), donor age (OR, 1.03; 95% CI, 1.01-1.05 per year; $P<.001$), and recipient body weight (OR, 1.02; 95% CI, 1.01-1.04 per kg; $P=.009$) were independent explanatory variables in a multiple logistic regression model. Dopamine resulted in significant but clinically meaningless increases in the donor's systolic blood pressure (3.8 mm Hg; 95% CI, 0.7-6.9 mm Hg; $P=.02$) and urine production before surgical recovery of the kidneys (29 mL; 95% CI, 7-51 mL; $P=.009$) but had no influence on outcome.

Conclusion Donor pretreatment with low-dose dopamine reduces the need for dialysis after kidney transplantation.

Trial Registration clinicaltrials.gov Identifier: NCT00115115

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THE MAJORITY OF KIDNEYS transplanted worldwide are retrieved from deceased heart-beating donors. As a consequence of brain death, the kidney graft is exposed to numerous injurious events prior to transplantation that predispose it to functional impairment after transplantation. Circulatory instability and a massive release of cytokines provoke a systemic inflammatory state.[1,2] Moreover, prolonged cold storage and reperfusion injury augment renal injury.[3-5] Following transplantation, allorecognition is induced when the recipient's immune system detects alloantigens

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in the context of danger signals.[6] Renal transplants with delayed graft function (DGF) and acute rejection (AR) have a greater incidence of chronic dysfunction later.[7-9] Limiting organ injury through medical donor management may therefore have a major effect on the transplantation outcome.

We have previously shown in a case-control study that the use of dopamine and norepinephrine during intensive care of the donor was associated with fewer ARs and superior long-term graft survival.[10] The latter observation was confirmed by a registry-based study disclosing a dose relationship between use of adrenergic agents in donors and kidney graft survival.[11] Donor dopamine was also associated with a reduced dialysis requirement after transplantation.[12] Apart from stimulating specific receptors, dopamine directly interacts with the cellular membrane and at clinically relevant concentrations is capable of protecting endothelial cells from oxidative stress during cold storage.[13,14] The mechanism of action is related to the dihydroxy-phenolic ring structure of the dopamine molecule. Subsequent cellular processes that govern hypothermia-mediated cell death, such as adenosine triphosphate depletion and intracellular accumulation of calcium ions, occur with considerable delay.[15]

The current recommendations on donor treatment are based on sparse evidence from observational studies only, while controlled clinical data using reasonable end points for the assessment of the outcomes after transplantation are limited.[16,17] Implementing dopamine as a standard treatment has the potential to ameliorate cold preservation injury without adverse effects for the recipients. To test the feasibility of this approach, we assessed the efficacy of donor pretreatment with dopamine by measuring the postoperative incidence of dialyses in renal transplant recipients who received a kidney graft from a brain-dead donor.

METHODS

Study Design and Patients

The study was initiated by the investigators and designed as a prospective, randomized, open-label, multicenter trial. The protocol was approved by the institutional ethics commission of the Medical Faculty of Mannheim and by the kidney advisory committee of the Eurotransplant International Foundation, Leiden, the Netherlands. The trial was performed in accordance with current Eurotransplant standards for organ sharing and was carried out in collaboration with the organ procurement organizations of Bavaria and Baden-Württemberg (BW), Germany. The regional organ procurement organizations of Bavaria and BW cover the whole area of southern Germany with a population of 23.2 million people and serve more than 300 secondary and primary care hospitals among 12 tertiary referral hospitals.

Heart-beating donors were randomly assigned to receive or to not receive dopamine after confirmation of brain death. Screening for eligibility was performed by the local transplant coordinators. Assessment for study inclusion and randomization occurred at the 24-hour duty desk of the regional procurement organization. For each region a computer-generated randomization list without blocking or stratification was used, which was available only to the central offices of the 2 organ procurement organizations to separate the randomization process from the transplant coordinators providing care for organ donation.

Donor eligibility required the ascertainment of brain death in accordance with the guidelines of the scientific advisory council of the German Medical Association and consent to donation given in conformity with German transplantation legislation. During consultation with the relatives of the deceased to obtain informed consent for study inclusion, another physician not involved in the transplantation procedure was present and noted the contents and outcomes of the conversation. Provided that these conditions were met, the ethical commission agreed that obtaining separate handwritten consent for the study from the relatives was not necessary.

Eligible donors had to be stable while receiving norepinephrine at a dose not exceeding 0.4 µg/kg/min. They had to have a current serum creatinine concentration less than 2 mg/dL and concentration on admission less than 1.3 mg/dL (to convert serum creatinine to µmol/L, multiply by 88.4). Donors were excluded when prior treatment with adrenergic agents other than norepinephrine occurred or when circulatory instability necessitated the administration of higher doses than specified here.

Dopamine was administered as a continuous infusion at a standard dosage of 4 µg/kg/min until cross clamping. Thorough monitoring of brain-dead donors during intensive care was ensured to prevent any circulatory destabilization rendering the organs unsuitable for donation. The dosage was halved or the infusion was terminated earlier when circulatory adverse effects occurred in association with the dopamine infusion, such as tachycardia (>120/min) or a marked increase in blood pressure (>160/90 mm Hg). The trial intervention did not influence subsequent scheduling for surgical organ recovery. Donor characteristics were collected from standard necrokidney reports.

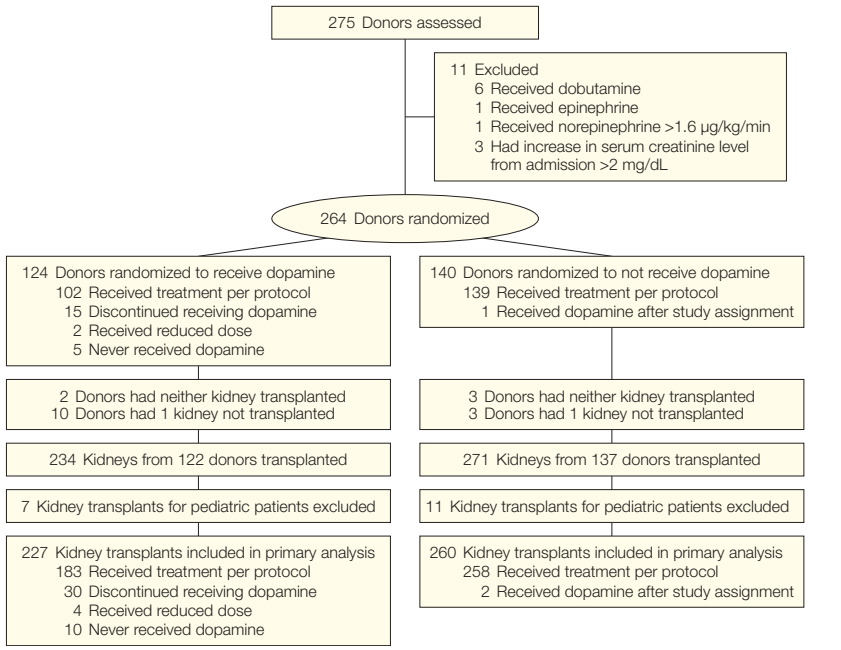
Allocation of kidneys to recipients was centrally directed by Eurotransplant. Eurotransplant delivers a computerized algorithm based on waiting time, prospective HLA antigen matching, country balance, and distance between donor and recipient centers to minimize cold ischemic time. The study was conceived to be observational in the transplant recipients. Only routine clinical parameters were used to evaluate the development of the transplant. A standardized case report form was shipped with the kidneys to the transplantation centers, which contained all relevant study information.

We assessed the following parameters: dialysis requirement (number of dialysis sessions and date of cessa-

tion posttransplant); routine serum creatinine values during the first week; occurrence and severity of biopsy-proven AR; and, in case of allograft failure, date and underlying cause of allograft failure and date and underlying cause of recipient death. We also assessed kind and dose of the immunosuppressive therapy administered within 24 hours before or after transplantation, according to the individual center's practice. Other relevant recipient baseline characteristics were obtained from the Eurotransplant database. Anonymity of all study participants was ensured by using the Eurotransplant code numbers for data collection.

Eligible recipients had to fulfill the usual criteria as a renal transplant candidate. We excluded recipients younger than 18 years. All transplant candidates who are placed on the waiting list sign their consent for the transmission of depersonalized medical data to the Eurotransplant database for scientific analyses. Because the study was strictly observational for the recipients, and the intervention was limited to the deceased donor with a fully approved drug before organ recovery, the ethical commission agreed that separate written informed consent for the study was not required from the recipients.

Figure 1. Flow Diagram for Study Enrollment and Outcomes



Effects of Dopamine Therapy on Transplant Development

Dialysis during the first week after transplantation was the primary outcome parameter. Because no existing standard criteria mandate its necessity posttransplant, dialysis was categorized as single and multiple application to address possible confounding by indication. Multiple dialyses was defined as the need for more than 1 dialysis session during the first week after transplantation. Multiple rather than single dialysis is considered a superior indirect parameter for more deteriorated kidney graft function. A single dialysis session is more likely to be required because of the recipient's overall state of health and the physician's clinical judgment. Secondary efficacy end points included incidence and severity of biopsy-proven AR within 30 days and patient and allograft survival.

We investigated dopamine-mediated effects on hemodynamics and urine production in relation to the primary end point and evaluated the particular influence of cold ischemia in treated and untreated grafts. We also performed post hoc analyses of dialysis use and renal function after 1 week on study medication, stratified by the duration of the dopamine infusion. For assessment of renal function, we generated a dichotomous threshold derived from the median split of the estimated glomerular filtration rate, which was calculated according to the Cockcroft-Gault formula[18] in patients who no longer needed dialysis by day 7.

Statistical Analysis

Based on our retrospective data,[12] the original protocol sought to include enough donors for 302 renal transplant recipients in the expectation that a 15% reduction would be detected in the number requiring multiple dialysis sessions. Mean cold ischemic time was 22 hours at that time. Considerable effort was made in recent years to reduce the duration of cold ischemia. Mean cold ischemic time was decreased to 15 hours in the Eurotransplant area during the present study because of organizational improvements.[19] It was assumed that this decrease would not only diminish the number of posttransplant dialyses needed, but also diminish the net effect of dopamine pretreatment. The data from our retrospective study[12] indicated that a 12.8% reduction in the number of required dialysis sessions could be achieved if mean cold ischemic time was limited to 15 hours. However, the net effect from dopamine pretreatment was about 20% when cold ischemia exceeded 22 hours. On the basis of these data, it seemed reasonable to target the risk reduction of posttransplant dialysis at 12% to estimate the required sample size. Hence, the number of renal transplant recipients was increased to 480 to provide a power of 80% for detection of a 12% decrease in the use of multiple dialyses posttransplant at a 2-sided significance level of .05, given a 35% expected dialysis frequency in the control group.

We compared qualitative data using χ^2 or 2-sided Fisher exact tests, when appropriate. Quantitative data were evaluated with 2-sample *t* tests. Nonzero correlation between ordinal variables was tested with the Cochran-Mantel-Haenszel test. To compare 2 groups with ordinal scaled variables, the Cochran-Armitage test for trend was used. The study outcome was analyzed according to the intention-to-treat principle. The primary outcome was reanalyzed in a multiple logistic regression model to find out if differences remained after adjustment for possible confounding influences. These influences included donor age, concomitant treatment of the donor with norepinephrine, donor systolic blood pressure and urine production during the last hour before organ recovery, cold ischemic time, and recipient body weight. To elaborate on the presumed underlying molecular mechanisms of protection, we carried out subgroup analyses within quartiles of cold ischemic time. We also carried out subgroup analyses within quartiles of the temporal dopamine application. These subgroup analyses were not preplanned.

Cumulative survival was calculated according to the Kaplan-Meier method and group differences were assessed by the log-rank test. Significance was defined according to a 2-sided $P < .05$. Statistical analyses were performed with SAS release 9.1 (SAS Institute Inc, Cary, North Carolina).

Table 1. Baseline Characteristics of Recipients and Donors

Variable	Dopamine (n = 227)	No Dopamine (n = 260)	*P* Value
Recipient characteristics			
Age, mean (SD), y	52.8 (12.7)	52.0 (12.4)	.50
Female sex, No. (%)	94 (41.4)	96 (36.9)	.31
Weight, mean (SD), kg	75.0 (15.1)	73.0 (12.9)	.12
Time spent on waiting list, mean (SD), y	3.9 (2.7)	3.9 (2.7)	.97
Previous transplant, No. (%)	27 (11.9)	47 (18.1)	.06
Combined transplantation, No. (%)	27 (11.9)	33 (12.7)	.79
Kidney + pancreas	23 (10.1)	24 (9.2)	
Kidney + liver	4 (1.8)	7 (2.7)	
Kidney + heart	0	1 (0.4)	
Kidney + lung	0	1 (0.4)	
Immunosuppressive medication[a]			
Cyclosporine, No. (%)	109 (48.0)	122 (46.9)	.81
Dose, mean (SD), mg/kg/d	7.5 (4.2)	7.3 (3.4)	.63
Tacrolimus, No. (%)	102 (44.9)	109 (41.9)	.50
Dose, mean (SD), mg/kg/d	0.14 (0.06)	0.14 (0.07)	.58
Mycophenolate mofetil, No. (%)	189 (83.3)	210 (80.8)	.48
Dose, mean (SD), mg/d	1940 (700)	1930 (690)	.86
Mycophenolic acid, No. (%)	28 (12.3)	29 (11.2)	.69
Dose, mean (SD), mg/d	1480 (950)	1590 (820)	.64
Corticosteroids, No. (%)	227 (100)	258 (99.2)	>.99
Prednisolone equivalent, mean (SD), mg/d	400 (270)	400 (270)	.93
Induction therapy, No. (%)[a]			
Anti-CD25	70 (30.8)	95 (36.5)	.12
Anti-CD3	0	2 (0.8)	
ATG/ALG	49 (21.6)	63 (24.2)	
Transplant characteristics			
Antigen mismatches A, B, and DR, mean (SD), No.	2.8 (1.6)	2.8 (1.6)	.81
Panel reactive antibody >5%, most recent assessment, No. (%)	22 (9.7)	29 (11.2)	.60
Cold ischemic time, mean (SD), h	13.7 (5.5)	14.2 (5.2)	.25
Second warm ischemic period, mean (SD), min[b]	38 (15)	38 (15)	.98
Donor characteristics[c]			
Donor age, mean (SD), y	50.6 (14.5)	50.8 (14.5)	.89
Cause of brain death			
Trauma, No. (%)	56 (24.7)	55 (21.2)	.36
Intracranial bleeding, No. (%)	131 (57.7)	150 (57.7)	.99
Donor systolic blood pressure, mean (SD), mm Hg	132 (18)	129 (16)	.02
Donor diastolic blood pressure, mean (SD), mm Hg	72 (11)	71 (11)	.55
Urine production during last 24 h, mean (SD), mL	4919 (2484)	4838 (2599)	.72
Urine production during last h, mean (SD), mL	208 (140)	178 (106)	.009
Concomitant donor treatment			
Norepinephrine, No. (%)	178 (78.4)	223 (85.8)	.03
Dose, mean (SD), µg/kg/min	0.10 (0.09)	0.12 (0.10)	.07
Desmopressin, No. (%)	166 (73.1)	196 (75.4)	.57
Prednisolone, No. (%)	70 (30.8)	101 (38.8)	.07

(continued)

RESULTS

Study Population

From March 2004 to August 2007, 275 brain-dead donors were assessed for study inclusion. Of these, 264 underwent randomization (FIGURE 1). Fifteen donors assigned to treatment were prematurely withdrawn from dopamine because of circulatory adverse effects, and another 2 donors received a reduced dose of 2 µg/kg/min. In 5 donors, no dopamine was administered for organizational reasons. Median duration of the dopamine administration in donors assigned to treatment was 344 minutes (interquartile range, 215 minutes). One donor received dopamine after being assigned to the control group. All donors underwent subsequent nephrectomy. Fourteen kidneys in the treatment group and 9 controls were not transplanted because of an inciden-

tal tumor or because the kidneys were judged unsuitable for transplantation. Thus, 234 kidneys selected for treatment and 271 controls retained the initial randomization status (Figure 1). According to the protocol, 7 and 11 pediatric recipients were excluded from the treatment and control groups, respectively. Consequently, 487 renal transplant recipients from 60 European centers were included in the primary analysis: 227 in the treatment group and 260 controls. Of the 227 kidneys assigned to dopamine, 183 had received treatment per protocol (4 µg/kg/min), 30 were prematurely withdrawn from dopamine, 4 had received a reduced dose (2 µg/kg/min), and 10 had never received dopamine due to organizational reasons. In the control group, 2 kidneys had been treated with dopamine after study assignment (Figure 1).

Table 1. Baseline Characteristics of Recipients and Donors (continued)

Variable	Dopamine (n = 227)	No Dopamine (n = 260)	*P* Value
Laboratory values, most recent assessment, mean (SD)			
Hemoglobin, g/dL	10.9 (1.9)	10.9 (1.9)	.78
Leukocytes, $\times 10^9$/L	13.2 (4.9)	13.5 (6.1)	.56
Sodium, mEq/L	146 (7)	147 (8)	.09
Potassium, mEq/L	4.1 (0.5)	4.1 (0.5)	.84
Creatinine, mg/dL	0.82 (0.29)	0.84 (0.27)	.53
Glucose, mg/dL	137 (43)	143 (46)	.16
Cold perfusion, No. (%)			
UW solution	139 (61.2)	148 (56.9)	.34
HTK solution	88 (38.8)	112 (43.1)	
Organ quality assessment, No. (%)[d]			
Good	185 (86.0)	231 (93.5)	.01
Acceptable	29 (13.5)	15 (6.1)	
Poor	1 (0.5)	1 (0.4)	

Abbreviations: ATG/ALG, antithymocyte globuline/antilymphcyte globuline; HTK, histidine-tryptophan-ketoglutarate; UW, University of Wisconsin.
SI conversion factors: To convert serum creatinine to µmol/L, multiply by 88.4; glucose to mmol/L, multiply by 0.0555.
[a] Administered according to the center's practice within 24 hours before or after transplantation.
[b] Data on second warm ischemia were not documented in 32 and 34 patients of the dopamine and control groups, respectively.
[c] Data correspond to kidney transplants included in primary analysis.
[d] Rated by the surgeon on organ procurement. Twelve and 13 kidneys were not rated in the dopamine and control groups, respectively.

Of the kidneys included in the trial, 296 (60.8%) came from the procurement region of Bavaria and 191 (39.2%) from BW. The difference in the numbers was due to the populations of the regions. The percentages of kidneys allocated from each procurement site to the same region or to an outside region were similar because allocation of the kidneys to individual recipients proceeded in accordance with Eurotransplant standards. In Bavaria, 181 kidneys (61.2%) went to the same region, 83 (28.0%) to another region of the same country, and 32 (10.8%) to another country. In BW, 114 kidneys (59.7%) went to same region, 54 (28.3%) to another region of the same country, and 23 (12.0%) to another country (χ^2=0.20, *P*=.91).

The study groups were similar with respect to demographic and clinical donor-recipient characteristics and immunosuppressive therapy. However, there was a significant between-group difference in the concomitant administration of norepinephrine (178/227 [78.4%] vs 223/260 [85.8%]; *P*=.03) (TABLE 1). Dopamine-treated donors presented with clinically meaningless but statistically significant increases of systolic blood pressure (3.8 mm Hg; 95% CI, 0.7-6.9 mm Hg; *P*=.02) and urine production before organ recovery (29 mL; 95% CI, 7-51 mL; *P*=.009). Also, a larger number of the kidneys from the dopamine-treated donors were rated suboptimal by the surgeons (30/215 [13.9%] vs 16/247 [6.5%], *P*=.01) because of advanced vascular atherosclerosis or inadvertent infringement of the renal vessels in single cases (Table 1).

Effects of Dopamine Therapy on Transplant Development

Donor dopamine treatment resulted in a significantly reduced use of dialysis after transplantation (TABLE 2). Fewer recipients in the treatment group needed multiple dialyses before renal function recovered than did recipients in the nondopamine group (56/227 [24.7%; 95% CI, 19.0%-30.3%] vs 92/260 [35.4%; 95% CI, 29.5%-41.2%]; *P*=.01). This is equivalent to a relative risk of 0.86 (95% CI, 0.76-0.96) and a risk difference of 10.7% (95% CI, 2.7%-18.8%). Accordingly, when both kidneys of each donor were transplanted, pretreatment of 10 donors prevented the need for multiple dialyses in 2 renal transplant recipients.

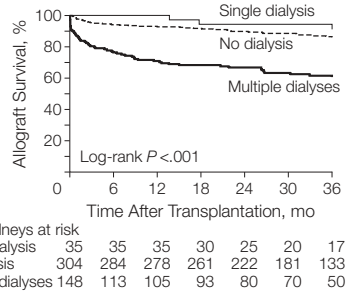
Since significant differences were found among the study groups on some of the baseline measurements (Table 1), multiple logistic regression of the binary outcome (multiple dialyses, yes/no) was applied to control for possible confounding factors. This binary outcome was selected because multiple dialyses (hazard ratio, 3.61; 95% CI, 2.39-5.45; *P*<.001; reference, no dialysis) increased the chances of graft failure in the long-term, whereas a single dialysis posttransplant (hazard ratio, 0.67; 95% CI, 0.21-2.18; *P*=.51) did not (FIGURE 2). Disparities in the concomitant treatment of the donors, eg, the administration of norepinephrine (odds ratio [OR], 0.82; 95% CI, 0.47-1.41; *P*=.47; reference, no norepinephrine), or dopamine-mediated effects on systolic blood pressure (OR, 1.00; 95% CI, 0.98-1.01 per mm Hg; *P*=.58) and urine production before organ recovery (OR, 1.00; 95% CI, 0.99-1.00 per mL; *P*=.18) had no measurable effect. Donor age (OR, 1.03; 95% CI, 1.01-1.05 per year; *P*<.001), cold ischemic time (OR, 1.07; 95% CI, 1.02-1.11 per hour; *P*=.001), and recipient body weight (OR, 1.02; 95% CI, 1.01-1.04 per kg; *P*=.009) were significant

Table 2. Primary and Secondary Outcome Measures[a]

End Point	Dopamine (n = 227)	No Dopamine (n = 260)	*P* Value
Dialysis during first week posttransplant, No. (%)			
Multiple use	56 (24.7)	92 (35.4)	.04[b]
Single use	21 (9.2)	14 (5.4)	
No dialysis	150 (66.1)	154 (59.2)	
Repeated dialysis during first week posttransplant, No. (%)			
Multiple use	56 (24.7)	92 (35.4)	.01
No dialysis/single use only	171 (75.3)	168 (64.6)	
Biopsy-proven acute rejection during 30 d posttransplant, No. (%)[c]			
Borderline	7 (3.1)	4 (1.5)	.21[b]
Banff grade 1	20 (8.8)	17 (6.5)	
Banff grade 2	17 (7.5)	18 (6.9)	
Banff grade 3	3 (1.3)	6 (2.3)	
Allograft survival, %[d]			
At 12 mo	85.4	87.7	.26
At 24 mo	83.4	81.5	
At 36 mo	81.4	75.7	
Patient survival, %[d]			
At 12 mo	95.3	96.7	.33
At 24 mo	93.6	92.0	
At 36 mo	92.9	89.5	

[a] Analyses performed on intention-to-treat principle.
[b] *P* values are derived from Cochran-Armitage test for trend.
[c] Graded according to Banff 97 diagnostic categories for renal allograft biopsies–Banff 07 update.[20]
[d] Values are Kaplan-Meier estimates over time. *P* values are derived from log-rank test.

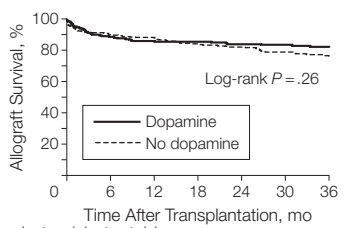
Figure 2. Relative Risk of Graft Failure According to Dialysis Requirement After Transplantation



No. of kidneys at risk

Single dialysis	35	35	35	30	25	20	17
No dialysis	304	284	278	261	222	181	133
Multiple dialyses	148	113	105	93	80	70	50

Figure 3. Cumulative Probability of Allograft Survival According to Study Group



No. of transplant recipients at risk

Dopamine	227	200	193	183	155	130	97
No dopamine	260	232	225	200	171	140	103

determinants in the multiple analysis, but the beneficial effect of dopamine remained (OR, 0.54; 95% CI, 0.35-0.83; *P* = .005).

Clustering by site did not disclose any significant differences in the principal findings. Neither the procurement region nor the transplantation site resulted in significant ORs when multiple logistic regression of the principal outcome measure (multiple dialyses) was applied with adjustment for donor age, cold ischemic time, and the recipient's body weight (Bavaria: OR, 1.19; 95% CI, 0.78-1.81; *P* = .43; transplantation site in outside region in same country: OR, 0.96; 95% CI, 0.58-1.60; *P* = .89; transplantation site in another country: OR, 0.75; 95% CI, 0.36-1.57; *P* = .49; reference, transplantation site in same region).

There were no significant differences between the study groups in incidence (47/227 vs 45/260; $\chi^2 = 0.91$, *P* = .34) and severity of biopsy-proven AR until 30 days and in patient survival (92.9% vs 89.5%, log-rank *P* = .33) and graft survival (81.4% vs 75.7%, log-rank *P* = .26) after 3 years (Table 2 and FIGURE 3).

Post Hoc Subgroup Analyses

Stratifying the analysis by quartiles of cold ischemic time (TABLE 3) suggested that the effect of dopamine was particularly enhanced in the subgroup of kidneys that were transplanted after a mean cold ischemic time of 21.2 hours (range, 17.1-34.4 hours). Applying multiple logistic regression, the influence of dopamine pretreatment and the interaction term were not statistically significant (*P* = .52 and *P* = .72, respectively), whereas dialysis requirement was associated with quartile (*P* = .009). Donor dopamine also translated in improved long-term graft survival in this particular subgroup, which was 90.5% (95% CI, 78.6%-95.9%) in the treatment group and 73.5% (95% CI, 59.6%-83.3%) in the control group after 3 years (log-rank *P* = .04). Reanalyzing the data on study medication within strata of dopamine infusion time suggested positive correlations between treatment duration, dialysis independency, and recovery of kidney function by day 7 (TABLE 4).

Circulatory Adverse Effects in the Deceased Donors

Adverse effects following the study intervention were reported in 15 cases of 120 brain-dead donors who were exposed to dopamine at any time during the trial (12.5%). All adverse effects referring to tachycardia (10.0%) and hypertension (3.3%), or a combination, were transient and fully reversible after either dose reduction or premature termination of the dopamine infusion.

COMMENT

Our study confirms that donor pretreatment with low-dose dopamine improves the performance of the renal graft after transplantation. It is unlikely that the salutary effect was achieved by stabilization of circulatory disturbances in the brain-dead donor, because, first, according to the inclusion criteria, eligible donors were

stable under low-dose norepinephrine. Second, donors in both study arms were similar in serum creatinine concentration, blood pressure, and 24-hour urine production. Third, dopamine-mediated effects on blood pressure and urine production ultimately failed to have an effect on allograft function. Evidence from our own experimental studies indicates that dopamine is able to mitigate injurious processes caused by the accumulation of reactive oxygen species under cold storage conditions.[13] Consequently, endothelial barrier function and vascular integrity are restored on rewarming.[14] In experimental transplantation, donor pretreatment inhibited tubulitis and improved outcome after prolonged cold ischemia independently from circulatory effects in the donor.[21,22] Rather than stabilize the renal hemodynamics, dopamine improved the kidney's tolerance to withstand ischemic damage during cold preservation.[23]

The definition of the primary study end point is in line with the commonly used definition for DGF. Nevertheless, need for dialysis posttransplant is an arbitrary surrogate parameter of impaired graft function. To date there is no agreement among nephrologists on specific criteria to be met for initiation of dialysis after transplantation. Some indications, such as fluid overload or hyperkalemia, are derived from the recipient's overall state of health rather than reflecting severe functional impairment of the graft. Furthermore, the use of dialysis may depend on the clinical assessment of the treating physician, particularly when a single dialysis session was applied. In fact, a single dialysis posttransplant was not associated with the long-term prognosis of the graft in our study, whereas the requirement of multiple dialyses ultimately was. Categorizing the main outcome measure according to the number of posttransplant dialysis sessions was therefore used to reduce confounding by indication.

A limitation of our study was the fact that the transplant physicians at the numerous centers were not blinded regarding dopamine pretreatment, since this information was documented in the standard necrokidney reports. Despite the shortcomings of the open-label study design, it was deemed unlikely that lack of blinding caused major treatment bias. The indication for dialysis after transplantation is based on assessed graft function in the recipient rather than on any pretreatment in the donor. It is medically not justifiable to prolong dialysis after transplantation for reasons other than delayed graft function. Therefore, the possible knowledge of pretransplant intervention in the donor was unlikely to trigger multiple dialyses after transplantation. Nevertheless, to reappraise the principal shortcoming of the open-label design, we also assessed kidney graft function from routine serum creatinine values. Reanalyzing the data based on the time stratification of the dopamine infusion (analysis on study medication) indicated a significant dose relationship with respect to both dialysis requirement and recovery of kidney function by day 7. This finding

Table 3. Donor Pretreatment and Dialysis Requirement by Quartile of Cold Ischemic Time

		No. (%)				
		Dopamine		No Dopamine		
Quartile	Cold Ischemic Time, Mean (Range), h	0-1 Dialysis Session	≥2 Dialysis Sessions	0-1 Dialysis Session	≥2 Dialysis Sessions	*P* Value[a]
First	7.8 (2.0-10.0)	52 (81.3)	12 (18.7)	44 (73.3)	16 (26.7)	.29
Second	11.8 (10.1-13.3)	40 (76.9)	12 (23.1)	43 (66.2)	22 (33.8)	.20
Third	15.2 (13.4-17.0)	42 (77.8)	12 (22.2)	49 (71.0)	20 (29.0)	.40
Fourth	21.2 (17.1-34.4)	36 (65.5)	19 (34.5)	30 (47.6)	33 (52.4)	.05

[a] *P* values are derived from χ^2 tests comparing dialyses requirement according to donor pretreatment in each quartile of cold ischemic time. Applying multiple logistic regression, dialysis requirement was associated with the quartile (*P*=.009), whereas the influence of dopamine pretreatment and the interaction term were not statistically significant (*P*=.52 and *P*=.72, respectively).

Table 4. Dialysis Requirement and Recovery of Kidney Graft Function During the First Week by Time Duration of Donor Pretreatment[a]

Dopamine Infusion Time by Quartile, Mean (Range), min	Recipients Requiring Dialysis by No. of Sessions, No. (%)			*P* Value[b]	Kidney Graft Function by Day 7, No. (%)			*P* Value[b]
	0	1	≥2		GFR >25 mL/min	GFR ≤25 mL/min	On Dialysis	
First and second quartiles[c]	158 (59.0)	14 (5.2)	96 (35.8)		125 (46.6)	66 (24.6)	77 (28.7)	
Third quartile 208 (4-328)	61 (62.2)	10 (10.2)	27 (27.6)	.008	42 (42.9)	33 (33.6)	23 (23.5)	.01
Fourth quartile 531 (330-1929)	85 (70.2)	11 (9.1)	25 (20.7)		72 (59.5)	27 (22.3)	22 (18.2)	

Abbreviation: GFR, glomerular filtration rate.
[a] Analyses were performed on study medication by quartile of dopamine infusion time.
[b] *P* values are derived from Cochran-Mantel-Haenszel tests for nonzero correlations between ordinal variables.
[c] The first and second quartiles refer to kidneys that were not treated. Kidney function was categorized according to the median split of the estimated GFR by day 7.

largely excluded treatment bias, since the transplantation centers were unaware of the timing of the dopamine infusion in the donors. In addition, clustering the analyses by transplantation site (same region, outside region of same country, another country) did not reveal significant differences.

A main strength of the study is that it was carried out under real-life conditions in a multicenter setting. No intervention in the recipients was mandated by the protocol. On the other hand, the strictly observational design of the study also has another limitation. Despite considerable improvements of initial graft function, the incidence of AR was not affected by dopamine. The complex interrelationship of DGF, alloimmune-mediated attack, and the long-term prognosis of the renal graft is well recognized.[24] Because protocol biopsies were not obtained, subclinical rejection cannot be ruled out.[25] It is therefore possible that we missed an existing difference between the study groups. Growing evidence suggests that subclinical rejection is hazardous specifically if accompanied by interstitial fibrosis and tubular atrophy.[26-28] In a prospective study from Australia, chronic histological damage in the tubulointerstitial compartment at 3 months correlated with cold ischemia, DGF, and vascular rejection and profoundly influenced the ultimate prognosis of the graft.[29] Ameliorating injury from cold storage through donor pretreatment is a logical consequence of these findings. A registry-based study found that cold ischemia up to 18 hours was not detrimental for the outcome of the renal graft.[30] Mean cold ischemic time was 14 hours in our study, and the trial intervention did not confer a significant survival benefit after 3 years. Hence, apart from the limitation that our trial was presumably underpowered for detecting survival benefit, it is also possible that the duration of the cold ischemia, to which the majority of all renal grafts were exposed, was not particularly injurious. Our observation of an improved graft survival in the highest quartile of cold ischemic time—albeit derived from a post hoc subgroup analysis—supports the notion that donor pretreatment was probably more efficacious when the kidneys were exposed to prolonged cold storage.

Our findings do not contradict studies that found the routine use of dopamine in the critically ill with impending or overt renal failure is no longer warranted.[31] Previously, a comprehensive meta-analysis that involved 3361 patients from 61 parallel-group, randomized and quasi-randomized trials of low-dose dopamine had shown that dopamine does not protect renal function despite transient improvements in renal medullary perfusion. That review was unable to detect increasing adverse events at the level of statistical significance, presumably because of underreporting.[32] Nevertheless, low-dose dopamine can be harmful because of large individual variations in dopamine clearance, particularly in the critically ill.[33] Variations in plasma concentrations predispose to unpredictable β- and α-adrenergic action. Tachycardia accompanied by hypertension accounted for considerable drug-related adverse effects occurring in 12.5% of the treated donors, which promptly reversed after dose reduction or termination of the dopamine infusion. Because these precautions were taken, donors were not compromised by circulatory destabilization that would have rendered their organs unsuitable for donation.

In conclusion, this study shows that pretreatment of the deceased heartbeating donor with low-dose dopamine reduces the need for dialysis in the recipient after kidney transplantation.

Author Contributions: Dr Schnuelle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Schnuelle, Gottmann, Hoeger, Boesebeck, Lauchart, Weiss, Yard.
Acquisition of data: Schnuelle, Boesebeck, Lauchart, Fischereder, Jauch, Heemann, Zeier, Hugo, Pisarski, Krämer, Lopau, Rahmel.
Analysis and interpretation of data: Schnuelle, Gottmann, Benck, Birck, Yard.
Drafting of the manuscript: Schnuelle.
Critical revision of the manuscript for important intellectual content: Schnuelle, Gottmann, Hoeger, Boesebeck, Lauchart, Weiss, Fischereder, Jauch, Heemann, Zeier, Hugo, Pisarski, Krämer, Lopau, Rahmel, Benck, Birck, Yard.
Statistical analysis: Schnuelle, Weiss.
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I hope I shall always possess firmness and virtue enough to maintain (what I consider the most enviable of all titles) the character of *an honest man*.
—George Washington (1732-1799)