View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

Journal of the American College of Cardiology Vol. 58, No. 17, 2011
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.05.060

Effects of Donor Pre-Treatment With Dopamine on Survival After Heart Transplantation

A Cohort Study of Heart Transplant Recipients Nested in a Randomized Controlled Multicenter Trial

Urs Benck, MD,* Simone Hoeger, PhD,* Paul T. Brinkkoetter, MD, PhD,† Uwe Gottmann, MD, PhD,* Duygu Doenmez, CandMed,* Detlef Boesebeck, MD,‡ Werner Lauchart, MD, PhD,§ Jan Gummert, MD, PhD,‖ Matthias Karck, MD, PhD,¶ Hans B. Lehmkuhl, MD,# Hartmuth B. Bittner, MD, PhD,** Andreas Zuckermann, MD, PhD,†† Florian Wagner, MD, PhD,‡‡ Uwe Schulz, MD,‖ Achim Koch, MD,¶ Amir K. Bigdeli, MD,§§ Christoph Bara, MD, PhD,‖‖ Stephan Hirt, MD, PhD,¶¶ Michael Berchtold-Herz, MD,## Stefan Brose, MD,*** Ulf Herold, MD,††† Johannes Boehm, MD,††† Henryk Welp, MD,‡‡‡ Thomas Strecker, MD, PhD,§§§ Andreas Doesch, MD,¶ Rainer Birck, MD, PhD,* Bernhard K. Krämer, MD, PhD,* Benito A. Yard, PhD,* Peter Schnuelle, MD, PhD*

Mannheim, Cologne, Munich, Stuttgart, Bad Oeynhausen, Heidelberg, Berlin, Leipzig, Hamburg, Hannover, Regensburg, Freiburg, Dresden, Münster, and Erlangen, Germany; and Vienna, Austria

Objectives We determined the outcome of cardiac allografts from multiorgan donors enrolled in a randomized trial of donor pre-treatment with dopamine.

Background Treatment of the brain-dead donor with low-dose dopamine improves immediate graft function after kidney transplantation.

Methods A cohort study of 93 heart transplants from 21 European centers was undertaken between March 2004 and August 2007. We assessed post-transplant left ventricular function (LVF), requirement of a left ventricular assist device (LVAD) or biventricular assist device (BVAD), need for hemofiltration, acute rejection, and survival of recipients of a dopamine-treated versus untreated graft.

Results Donor dopamine was associated with improved survival 3 years after transplantation (87.0% vs. 67.8%, $p = 0.03$). Fewer recipients of a pre-treated graft required hemofiltration after transplant (21.7% vs. 40.4%, $p = 0.05$). Impaired LVF (15.2% vs. 21.3%, $p = 0.59$), requirement of a LVAD (4.4% vs. 10.6%, $p = 0.44$), and biopsy-proven acute rejection (19.6% vs. 14.9%, $p = 0.59$) were not statistically different between groups. Post-transplant impaired LVF (hazard ratio [HR]: 4.95; 95% confidence interval [CI]: 2.08 to 11.79; $p < 0.001$), requirement of LVAD (HR: 6.65; 95% CI: 2.40 to 18.45; $p < 0.001$), and hemofiltration (HR: 2.83; 95% CI: 1.20 to 6.69; $p = 0.02$) were predictive of death. The survival benefit remained (HR: 0.33; 95% CI: 0.12 to 0.89; $p = 0.03$) after adjustment for various risks affecting mortality, including pre-transplant LVAD/BVAD, inotropic support, and impaired kidney function.

Conclusions Treatment of brain-dead donors with dopamine of 4 μg/kg/min will not harm cardiac allografts but appears to improve the clinical course of the heart allograft recipient. (Prospective Randomized Trial to Evaluate the Efficacy of Donor Preconditioning With Dopamine on Initial Graft Function After Kidney Transplantation; NCT00115115) (J Am Coll Cardiol 2011;58:1768–77) © 2011 by the American College of Cardiology Foundation

From the *University Medical Centre Mannheim, Mannheim, Germany; †Department of Medicine and Centre for Molecular Medicine, University of Cologne, Cologne, Germany; ‡Organ Procurement Organization of Bavaria, Munich, Germany; §Organ Procurement Organization of Baden-Württemberg, Stuttgart, Germany; ‖Heart and Diabetes Center North Rhine-Westphalia, Bad Oeynhausen, Germany; ¶University Hospital Heidelberg, Heidelberg, Germany; #German Heart Institute Berlin, Berlin, Germany; **Heart Center Leipzig, Leipzig, Germany; ††Medical University of Vienna, Vienna, Austria; ‡‡University Heart Center Hamburg-Eppendorf, Hamburg, Germany; §§Klinikum Grosshadern, Ludwig Maximilians University of Munich, Munich, Germany; ‖‖Hannover Medical School, Hannover, Germany; ¶¶Uni-

Optimized care for deceased heart-beating donors has the potential to improve outcome in organ transplantation (1–4). Although current guidelines advocate administration of inotropic agents for hemodynamic stabilization of the brain-dead donor, the dosage of dopamine and/or dobutamine should be limited to 10 μg/kg/min after successful volume resuscitation, when left ventricular ejection fraction

See page 1778

exceeds 45% (5). However, these recommendations remain inadequately supported in the literature, because of limited clinical data from controlled trials, on graft outcome (6,7). We recently presented a randomized, controlled clinical trial that showed that pre-treatment of brain-dead donors with low-dose dopamine of 4 μg/kg/min reduces the dialysis requirement after kidney transplantation (8). The underlying mechanism is related to antioxidant properties of the dopamine molecule (9). In the particular setting of organ preservation, dopamine increases the tolerance of the kidney graft to withstand ischemic damage during cold storage. Hence, our findings are not in contrast to the present evidence, which does no longer warrant the routine use of dopamine in the critically ill with impending or overt renal failure (10,11). Before low-dose dopamine can be implemented as a standard in the care of multiorgan donors, the outcome of nonrenal transplants included in the dopamine trial remain to be assessed. The present investigation, nested in the randomized dopamine trial, focuses on the multiorgan donor subgroup that also donated the heart for transplantation. The study evaluates cardiac transplant results based on donor assignment to pre-treatment with or without low-dose dopamine.

Methods

Study design and patients. Rationale, design, and execution of the randomized dopamine trial were described elsewhere (8). Briefly, the renal trial was designed to compare the dialysis frequency in renal graft recipients. After confirmation of brain death, and after consent for organ donation, heart-beating donors were randomly assigned to receive or not receive a standardized 4 μg/kg/min dopamine infusion until cross clamping. Eligible donors had to be stable while receiving norepinephrine at a dose not exceeding 0.4 μg/kg/min. Dopamine-treated and untreated donors were monitored to meet the target parameters of hemodynamic stability (5). Circulatory side effects referring to tachycardia and/or hypertension resulted in dose reduction or a premature termination of the dopamine infusion. Taking these precautions, no circulatory destabilization occurred that rendered the organs unsuitable for donation.

Abbreviations and Acronyms

AR = acute rejection
ATP = adenosine triphosphate
BVAD = biventricular assist device
GFR = glomerular filtration rate
ISHLT = International Society of Heart and Lung Transplantation
LVAD = left ventricular assist device
LVF = left ventricular function
UNOS = United Network for Organ Sharing

While planning the renal trial, a consultant statement was requested from the Eurotransplant Heart Advisory Committee to determine whether a dopamine dosage of 4 μg/kg/min could compromise the heart allograft in multiorgan donations. The Committee had no concerns since the planned pre-treatment conforms to current guidelines established for maintaining circulatory stability in brain-dead donors. All patients on the waiting list for heart transplantation consented that their depersonalized medical data can be used for scientific analyses.

The randomized dopamine study was carried out in close collaboration with the organ procurement organizations of Bavaria and Baden-Württemberg. These states have a population of >23 million people. Allocation of donor organs, including heart allografts, was centrally directed by Eurotransplant. During the recruitment period, from March 2004 to August 2007, the vast majority of hearts were allocated to critically ill patients with the classification urgent or highly urgent. In September 2005, highly urgent was redefined to further prioritize patients with the most urgent indication for heart transplantation. Only a minority of patients categorized elective received transplants based on a waiting time algorithm (12,13).

Transplant outcome in recipients was assessed in a similar way to the renal study. A questionnaire was sent to heart transplant centers after data collection for the renal trial was completed. Response rate to the questionnaire was 100%. Data on the following outcome measures were collected: post-transplant left ventricular function (LVF) assessed by echocardiography (normal/impaired), need for a left ventricular assist device (LVAD), which reflects primary graft dysfunction, and hemofiltration after transplantation, since hemofiltration is frequently used particularly for patients suffering from volume overload due to right ventricular dysfunction after heart transplantation (14). We also requested information on frequency and severity of in-hospital episodes of biopsy-proven acute rejection (AR), allograft failure, and death, including date and cause of death during a follow-up period of 3 years after transplantation. Acute rejections were graded according to the revised International Society of Heart and Lung Transplantation (ISHLT) heart biopsy grading scale (15). In addition, we gathered information on relevant medical recipient characteristics, includ-

versity Hospital Regensburg, Regensburg, Germany; ##University Medical Center Freiburg, Freiburg, Germany; ***University Heart Center Dresden, Dresden, Germany; †††German Heart Center Munich, Munich, Germany; ‡‡‡University Hospital Münster, Münster, Germany; and the §§§University Hospital Erlangen, Erlangen, Germany. This study was partially supported by a medical school grant from Novartis Pharmaceuticals, released in November 2002. Dr. Berchtold-Herz is supported by Thoratec Inc. and Novartis GmbH. All other authors have reported they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 21, 2010; revised manuscript received April 14, 2011, accepted May 10, 2011.

ing underlying heart disease, pre-transplant invasive hemodynamic assessments, pre-transplant LVAD or biventricular assist device (BVAD) therapy, pre-transplant renal function and infections, and collected data on cold ischemic time and immunosuppressive therapy administered within 24 h of transplantation, according to center practice. Data on urgency classification and time spent on the waiting list were obtained from Eurotransplant.

Donor transplant characteristics obtained from the standard Eurotransplant donor information forms included circulatory and ventilation parameters, laboratory values, concomitant medication, cold preservation, and organ quality, as assessed by the cardiac surgeon following harvesting. Anonymity of donors and recipients was ensured by the use of the Eurotransplant code numbers for data collection.

Statistical analysis. We evaluated quantitative data by using 2-sample *t* tests for means of values, and the Mann-Whitney *U* test for medians as appropriate for the data distribution. Qualitative data were compared with chi-square or 2-sided Fisher exact tests. Outcome parameters were primarily analyzed according to the intention-to-treat principle. Additional analyses were carried out as per protocol omitting subjects whose dopamine was prematurely withdrawn, or not given for organizational reasons (Fig. 1). For time-to-event data, Kaplan-Meier curves were generated. Because no patient received a second transplant during the subsequent observation period, patient death also reflects graft failure. Log-rank tests were used to test the equality of the failure/survivor function between groups. For all parameters analyzed, significance was defined as a 2-sided $p < 0.05$. We applied Cox's regression to control for putative confounding donor and recipient related variables, such as age and sex, the recipient's comorbidities, including pre-transplant mechanical support (LVAD/BVAD or intra-aortic balloon pump), pre-transplant inotropic support, pre-transplant kidney function, and donor administration of norepinephrine before organ procurement. In addition, a separate Cox regression model was used to analyze the effects of clustering by site. All results are presented as hazard ratios (HRs), with a 95% confidence interval (CI) for a 1-U change in the variable. Statistical analyses were carried out with Stata Statistical Software for MS Windows (Stata Corp., College Station, Texas).

Results

In all, 275 donors were evaluated for study inclusion. Of these, 264 met the inclusion criteria, and underwent randomization; 124 donors were assigned to dopamine treatment, and 140 to controls. Of these, 101 donors were

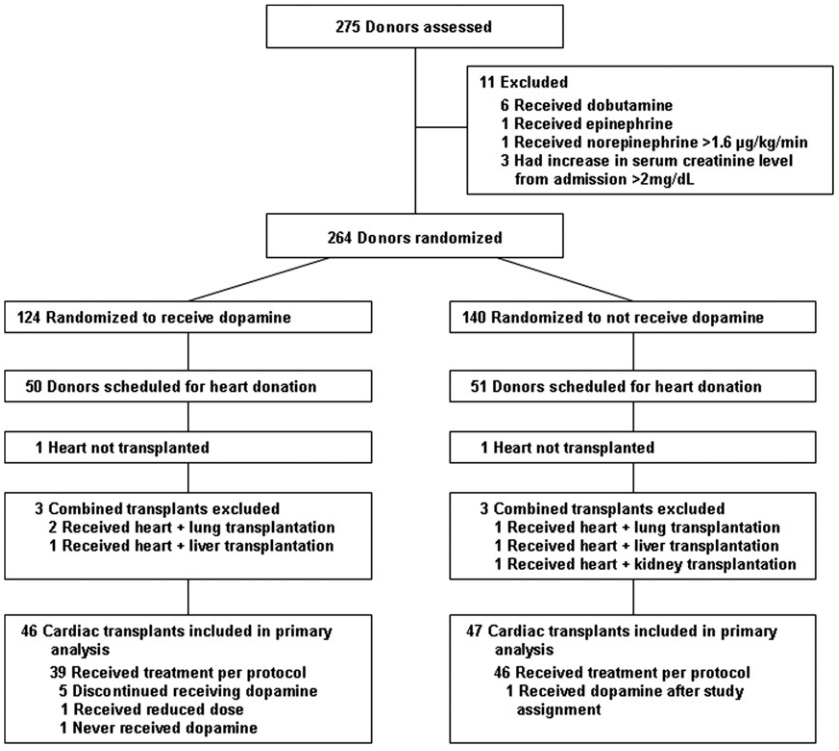

Figure 1 Flow Diagram for Study Enrollment and Outcomes

After confirmed brain death and given consent to organ donation, donors were randomly assigned to receive or not receive a standardized 4 μg/kg/min dopamine infusion until cross-clamping. Eligible donors were hemodynamically stable while receiving norepinephrine at a dose not exceeding 0.4 μg/kg/min. Allocation of the donor organs was centrally directed by Eurotransplant, prioritizing recipients with the most urgent indication for heart transplantation.

scheduled for heart donation. One heart in each group was not transplanted. To focus on heart transplants, 3 combined transplants from each study group were excluded from the primary analysis, because these patients represent a totally different patient category. Thus, 46 cardiac transplants assigned to dopamine, and 47 controls were included in the intention-to-treat analysis. From 46 cardiac transplants assigned to dopamine, 39 were treated per protocol, 5 discontinued receiving dopamine, 1 had a reduced dose, and 1 never received dopamine because of organizational reasons. Median duration of the dopamine infusion in the treatment group was 404 min (interquartile range: 222 min). One donor from the control group received dopamine after being included in the study (Fig. 1).

Fifty-two hearts (55.9%) included in the primary analysis were retrieved in Bavaria, and 41 (44.1%) came from Baden-Württemberg. Since Eurotransplant allocation rules are urgency based, most cardiac grafts went to out-of-state heart transplantation centers. In Bavaria, 33 hearts (63.5%) went to out-of-state centers, and 19 (36.5%) were locally transplanted. The respective numbers in Baden-Württemberg were 30 hearts (73.2%) to out-of-state centers, and 11 (26.8%) were locally transplanted.

The study groups had very similar demographic and clinical donor-recipient characteristics (Tables 1 and 2). In particular, recipients in both groups were comparable regarding pre-transplant invasive hemodynamic assessments, pre-transplant inotropic and mechanical support, kidney function, infections, cold ischemic time, and immunosuppressive medication after transplantation. Although statistically not significant, urgency status and female to male transplants were greater in the no-dopamine group and may have placed the controls to a higher risk after transplant. However, urgency status and female to male transplants were not explanatory variables of graft survival (highly urgent vs. urgent or elective HR: 0.85; 95% CI: 0.31 to 2.32; $p = 0.75$; female to male vs. male to female or no sex mismatch HR: 0.68; 95% CI: 0.25 to 1.85; $p = 0.45$). Notably, there were also no between-group differences in donor hemodynamics, including blood pressure, 24-h urine production, volume state, and donor ventilation parameters, including acid-base status. However, fewer donors receiving dopamine had norepinephrine during intensive care, although the used dosage was comparable between groups (33 of 46 [71.7%] vs. 42 of 47 [89.4%], $p = 0.03$). Echocardiographic findings before organ recovery were normal, except in 2 hearts from the control group and in 1 heart of the treatment group, which presented with moderately impaired LVF.

Post-transplant impaired LVF (7 of 46 [15.2%] vs. 10 of 47 [21.3%], $p = 0.59$), requirement for LVAD (2 of 46 [4.4%] vs. 5 of 47 [10.6%], $p = 0.44$), and biopsy-proven AR (9 of 46 [19.6%] vs. 7 of 47 [14.9%], $p = 0.59$) were not found to be statistically different in recipients of dopamine-treated and untreated grafts. Nevertheless, recipients of a dopamine-treated graft had more favorable in-hospital and long-term outcomes. Fewer recipients of the treatment group required hemofiltration after transplantation (10 of 46 [21.7%] vs. 19 of 47 [40.4%], $p = 0.05$) (Fig. 2, Table 3), although pre-transplant kidney function was not different among the study groups (Table 1). Impaired kidney function of the recipients pre-transplant, as defined by a serum creatinine >1.5 mg/dl, was also associated with the requirement for hemofiltration after transplant (12 of 25 [48.0%] vs. 17 of 68 [25.0%], $p = 0.03$). Multiple regression confirmed that both donor dopamine (odds ratio: 0.38, 95% CI: 0.15 to 0.97; $p = 0.04$) and impaired kidney function of the recipient (odds ratio: 3.03, 95% CI: 1.12 to 8.19; $p = 0.03$) were independent explanatory variables of hemofiltration after transplant.

When the analysis was limited to recipients with a cardiac allograft treated as per protocol, which means that the donors of the treatment group had received the dopamine infusion until cross-clamping, the statistical association of donor dopamine and a reduced requirement for hemofiltration became stronger, and the advantageous effect was enhanced (requirement for hemofiltration 7 of 39 [18.0%] vs. 19 of 46 [41.3%], $p = 0.03$) (Fig. 2, Table 3). Continuous dopamine infusion until cross-clamping was also associated with a reduced mortality 3 months after transplantation (2 of 39 [5.1%] vs. 10 of 46 [21.7%], $p = 0.03$). When data were analyzed on intention-to-treat basis, the beneficial effect on mortality at 3 months (4 of 46 [8.7%] vs. 10 of 47 [21.3%], $p = 0.10$) missed the level of statistical significance (Fig. 2).

Impaired LVF on echocardiography (HR: 4.95; 95% CI: 2.08 to 11.79; $p < 0.001$), requirement for LVAD (HR: 6.65; 95% CI: 2.40 to 18.45; $p < 0.001$), and hemofiltration after transplantation (HR: 2.83; 95% CI: 1.20 to 6.69; $p = 0.02$) were predictive of a recipient's death, but occurrence of a biopsy-proven AR episode during the in-hospital stay was not (HR: 1.50; 95% CI: 0.55 to 4.10; $p = 0.43$). In fact, the majority of deaths occurred in patients who required hemofiltration after transplantation (11 of 29 [37.9%] vs. 10 of 64 [15.6%], hemofiltration vs. no hemofiltration, $p = 0.02$). Post-transplant patient and allograft survival of the entire study cohort was 90.3%, 81.7%, and 77.3% after 1, 12, and 36 months, respectively. Donor pre-treatment with dopamine resulted in a significant effect on allograft survival 3 years after transplantation (87.0% vs. 67.8%, $p = 0.03$) (Fig. 3). This survival benefit remained when combined transplants, which had been excluded from the primary analysis, were added to the survival data (85.7% vs. 65.7%, $p = 0.02$).

Causes of mortality at 3 months were the following: in the dopamine group, 3 patients died of primary graft failure and 1 of myocardial infarction. In the no-dopamine group, 7 died of multiorgan failure, 2 of primary graft failure, and 1 of pneumonia. During follow-up, 7 additional deaths occurred: 2 in the dopamine group (1 multiorgan failure, 1 rejection) and 5 in the no-dopamine group (1 each of cardiovascular event, lung cancer, rejection, infectious complication, and unknown cause).

Table 1 Baseline Characteristics of Recipients

	Dopamine (n = 46)	No Dopamine (n = 47)	p Value
Demographics			
Age, yrs	56 (48–62)	56 (50–62)	0.96
Female	10 (21.7%)	10 (21.3%)	0.96
Underlying heart disease			0.19
Ischemic heart disease	25 (54.4%)	17 (36.2%)	
Dilated cardiomyopathy	18 (39.1%)	27 (57.4%)	
Other*	3 (6.5%)	3 (6.4%)	
Time on waiting list, days	146 (51–354)	141 (62–511)	0.62
Pre-transplant hemodynamics, most recent assessment†			
Systemic blood pressure			
Systolic, mm Hg	99 ± 14	102 ± 15	0.34
Diastolic, mm Hg	62 ± 11	61 ± 11	0.65
Cardiac index, l/min/m^2	1.9 ± 0.3	1.8 ± 0.4	0.35
Mixed venous oxygen saturation, %	53 ± 10	51 ± 8	0.26
Pulmonary artery pressure			
Systolic, mm Hg	45 ± 13	43 ± 15	0.47
Diastolic, mm Hg	22 ± 7	21 ± 8	0.84
Mean, mm Hg	31 ± 9	30 ± 10	0.48
Mean PCWP, mm Hg	23 ± 7	21 ± 9	0.25
PVRI, Wood units/m^2	3.9 (2.6–5.6)	4.7 (2.9–6.3)	0.39
Pre-transplant inotropic support			
Dopamine	13 (28.3%)	9 (19.2%)	0.34
Dobutamine	16 (34.8%)	18 (38.3%)	0.73
Adrenaline	5 (10.9%)	4 (8.5%)	0.74
Milrinone	12 (26.1%)	10 (21.3%)	0.63
Pre-transplant mechanical support			
LVAD/BVAD	10 (21.7%)	12 (25.5%)	0.67
IABP	3 (6.5%)	2 (4.3%)	0.68
Pre-transplant kidney function, most recent assessment			
Serum creatinine, mg/dl	1.31 ± 0.50	1.28 ± 0.45	0.75
Serum creatinine >1.5 mg/dl	13 (28.3%)	12 (25.5%)	0.77
Renal replacement therapy	0 (0%)	1 (2.1%)	>0.99
Pre-transplant infections			>0.99
LVAD/BVAD	2 (4.4%)	3 (6.4%)	
Invasive lines/drains	1 (2.2%)	0 (0%)	
Transplant characteristics			
Donor/recipient sex mismatch	14 (30.4%)	17 (36.2%)	0.56
Female to male	12 (26.1%)	17 (36.2%)	0.37
Male to female	2 (4.4%)	0 (0%)	0.24
Donor/recipient weight ratio	1.05 ± 0.17	1.02 ± 0.16	0.46
Urgency code			0.22
Highly urgent	33 (71.7%)	40 (85.1%)	
Urgent	4 (8.7%)	1 (2.1%)	
Elective	9 (19.6%)	6 (12.8%)	
Panel reactive antibody >5%	2 (4.4%)	1 (2.1%)	0.62
Cold ischemic time, min‡	206 ± 52	207 ± 58	0.91
Immunosuppressive medication§			
CNI	45 (97.8%)	44 (93.6%)	0.62
MMF/MPA	29 (63.0%)	30 (63.8%)	0.94
mTOR inhibitors	2 (4.4%)	5 (10.6%)	0.44
Corticosteroids	46 (100.0%)	46 (97.8%)	>0.99

Values are median (interquartile range), n (%), or mean ± SD. *Other includes hypertrophic cardiomyopathy (n = 2), valvular heart disease (n = 1), amyloidosis (n = 1), congenital heart disease (n = 1), ventricular arrhythmia (n = 1). †Excluding patients on pre-transplant LVAD/BVAD. ‡Data on cold ischemic time was not documented in 1 patient of the dopamine-treated group. One heart of either group was warm preserved on Organ Care System. §Administered according to the center's practice within 24 h before or after transplantation.

BVAD = biventricular assist device; CNI = calcineurin inhibitors; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; MMF = mycophenolate mofetil; MPA = mycophenolic acid; mTOR = mammalian target of rapamycin; PCWP = pulmonary capillary wedge pressure; PVRI = pulmonary vascular resistance index.

Table 2 Baseline Characteristics of Donors

	Dopamine (n = 46)	No Dopamine (n = 47)	p Value
Demographics			
Age, yrs	45 (33–51)	43 (31–50)	0.90
Female	20 (43.5%)	27 (57.5%)	0.18
Cause of brain death			
Trauma	12 (26.1%)	14 (29.8%)	0.69
Intracranial bleeding	26 (56.5%)	25 (53.2%)	0.75
Laboratory values, most recent assessment			
Hemoglobin, g/l	107 ± 17	106 ± 17	0.66
Leukocytes, $\times 10^9$/l	14.4 ± 4.5	12.8 ± 5.9	0.13
Sodium, mmol/l	147 ± 8	147 ± 9	0.85
Potassium, mmol/l	4.1 ± 0.5	4.2 ± 0.5	0.27
Serum creatinine, mg/dl	0.84 ± 0.29	0.82 ± 0.22	0.72
Glucose, mg/dl	127 ± 35	139 ± 39	0.14
Hemodynamic parameters			
Systolic blood pressure, mm Hg	128 ± 16	128 ± 17	0.95
Diastolic blood pressure, mm Hg	70 ± 11	70 ± 12	0.87
Urine production during last 24 h, l	4.4 (3.4–6.1)	4.5 (3.0–5.7)	0.50
Urine production during last h, ml	178 (110–260)	140 (100–200)	0.06
CVP, mm Hg	7 ± 3	6 ± 3	0.11
Ventilation parameters			
PEEP, cm H_20	7 ± 3	7 ± 3	0.94
PaO_2/FiO_2, mm Hg	294 ± 97	312 ± 118	0.44
$PaCO_2$, mm Hg	40 ± 9	38 ± 6	0.27
Base excess, mmol/l	1.0 ± 3.4	0.4 ± 3.3	0.35
pH	7.42 ± 0.06	7.43 ± 0.06	0.78
Concomitant donor treatment			
Norepinephrine	33 (71.7%)	42 (89.4%)	0.03
Dose (μg/kg/min)	0.05 (0.03–0.11)	0.07 (0.04–0.12)	0.63
Desmopressin	37(80.4%)	32 (68.1%)	0.17
Prednisolone	17 (37.0%)	22 (46.8%)	0.34
Cold perfusion*			0.61
UW Solution	8 (17.4%)	11 (23.4%)	
HTK Solution	35 (76.1%)	30 (63.8%)	
Other	1 (2.2%)	2 (4.3%)	
Organ quality assessment†			0.79
Good	37 (80.4%)	37 (78.7%)	
Acceptable	5 (10.9%)	7 (14.9%)	

Values are median (interquartile range), n (%), or mean ± SD. *Kind of perfusion solution was not documented in 2 and 4 donors of the dopamine-treated and untreated group, respectively. †Rated by the cardiac surgeon upon organ procurement. Four and 3 hearts were not rated in the dopamine-treated and untreated group, respectively.

CVP = central venous pressure; HTK = histidine-tryptophane-ketoglutarate; $paCO_2$ = partial pressure of arterial carbon dioxide; paO_2/FiO_2 = partial pressure of arterial oxygen to the fraction of oxygen inspired; PEEP = positive end-expiratory pressure; UW = University of Wisconsin.

A separate analysis of graft recipients from the dopamine group, but not pre-treated as per protocol, showed that patient survival was 71.4% at both 12 and 36 months. This result was very similar to the observed survival rate in the no-dopamine group (Table 3). Median infusion time in those donors, who were prematurely withdrawn from dopamine due to circulatory side effects, was 60 min only. All side effects referring to tachycardia and hypertension were transient and fully reversible after termination of the dopamine infusion (8).

Clustering by site had no effect on mortality. Site of procurement (Bavaria HR: 1.11; 95% CI: 0.47 to 2.64; p = 0.81) and of transplantation (out-of-state centers HR: 0.73; 95% CI: 0.30 to 1.76; p = 0.49) did not alter the HRs. The advantageous effects of dopamine treatment persisted in the multiple Cox regression analysis (HR: 0.33; 95% CI: 0.12 to 0.91; p = 0.03). Although norepinephrine was more frequently applied to the no-dopamine group, its use (HR: 0.67; 95% CI: 0.20 to 2.30; p = 0.53) did not affect the principal finding of the study (Table 4).

Discussion

This study indicates that pre-treatment of brain-dead donors with low-dose dopamine may considerably improve the clinical course of the cardiac allograft recipient after trans-

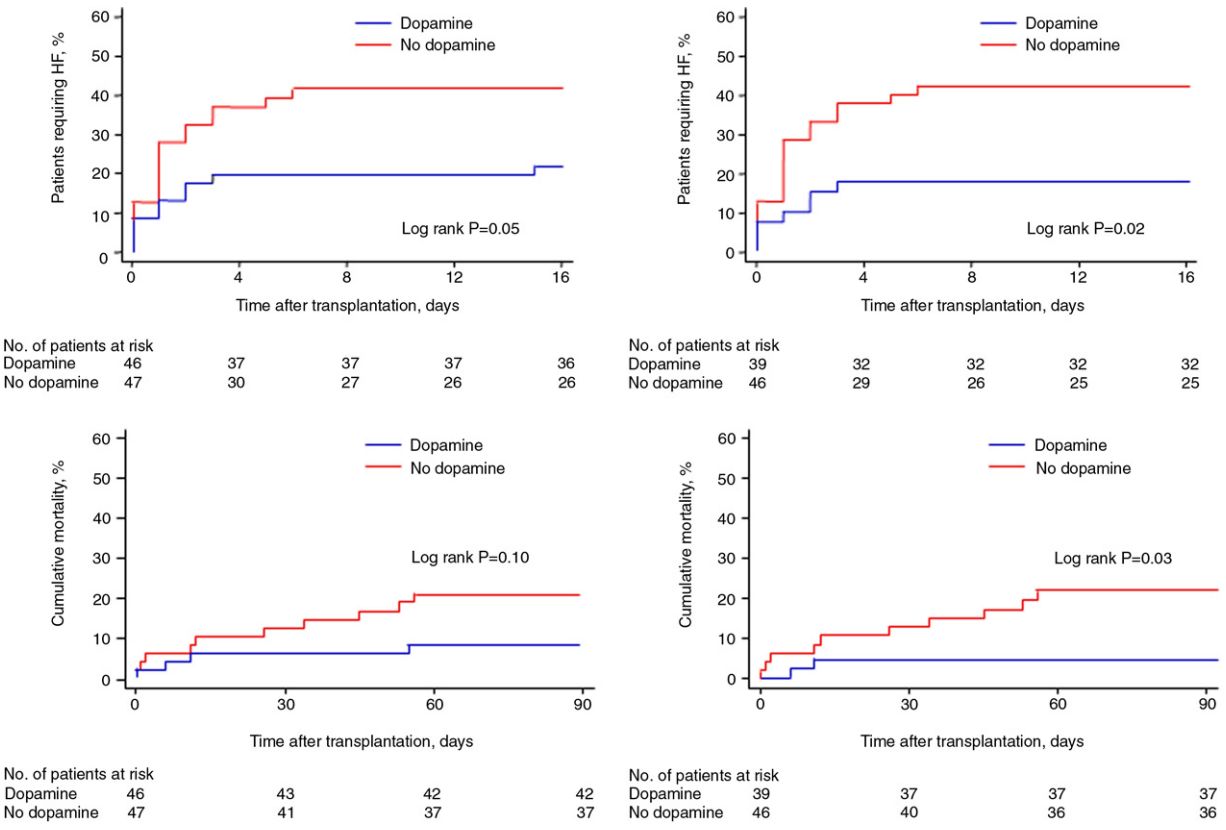

Figure 2 **Requirement of Hemofiltration and Mortality at 3 Months, According to Donor Pre-Treatment With Dopamine**

Data are displayed **(left)** on intention-to-treat, and **(right)** on per-protocol analyses. **Blue lines** = dopamine; **red lines** = no dopamine. HF = hemofiltration.

plantation. The most striking finding was that fewer recipients of a dopamine-treated graft died during a follow-up of 3 years, although pre-transplant donor cardiac function and the recipients' physical disability on the waiting list were very similar in the dopamine group and control group. The overall survival rates of the cohort analyzed in the present study are in line with recent continent-specific data from the ISHLT registry at 1 and 3 years, and hence, reflect current standards of care for adult heart transplantation in Europe (16). In our study, 78.5% of the recipients were listed as highly urgent and 5.4% as urgent at time of transplantation (Table 1). The proportion of patients who were trans-

Table 3 **Clinical Outcomes**

	Intention-to-Treat Analysis			Per-Protocol Analysis		
Variable	Dopamine (n = 46)	No Dopamine (n = 47)	p Value	Dopamine (n = 39)	No Dopamine (n = 46)	p Value
Events occurring after transplantation						
Impaired LVF on echocardiography	7 (15.2%)	10 (21.3%)	0.59	5 (12.8%)	10 (21.7%)	0.39
Requirement of LVAD	2 (4.4%)	5 (10.6%)	0.44	1 (2.6%)	5 (10.9%)	0.21
Requirement of hemofiltration	10 (21.7%)	19 (40.4%)	0.05	7 (18.0%)	19 (41.3%)	0.03
Acute biopsy-proven rejection episode*	9 (19.6%)	7 (14.9%)	0.59	8 (20.5%)	6 (13.0%)	0.39
Grade 0–1	6 (13.0%)	7 (14.9%)		6 (15.4%)	6 (13.0%)	
Grade 2–3	3 (6.5%)	0 (0%)		2 (5.1%)	0 (0%)	
Mortality at 3 months	4 (8.7%)	10 (21.3%)	0.15	2 (5.1%)	10 (21.7%)	0.03
Long-term allograft/patient survival†						
At 12 months	91.3%	72.3%	0.02	94.9%	71.7%	0.007
At 24 months	87.0%	70.2%	0.05	89.7%	69.6%	0.02
At 36 months	87.0%	67.8%	0.03	89.7%	69.6%	0.02

Values are n (%) or %. *According to the revised International Society of Heart and Lung Transplantation heart biopsy grading scale (15). †Values are Kaplan-Meier estimates over time.
LVAD = left ventricular assist device; LVF = left ventricular function.

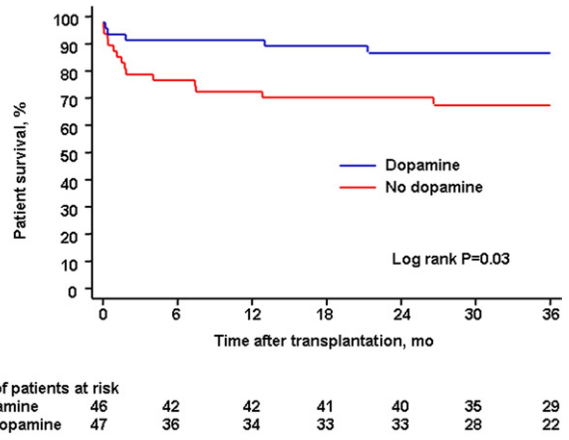

Figure 3 **Kaplan-Meier Estimates of Patient Survival After Heart Transplantation, According to Donor Pre-Treatment With Dopamine**

Data are displayed as intention to treat. **Blue line** = dopamine; **red line** = no dopamine. Mo = months.

planted in the U.S. between 2004 and 2007 with adult candidate status 1A and 1B was 43.1% and 35.4%, respectively (17). Although the Organ Procurement and Transplantation Network and the United Network of Organ Sharing (OPTN/UNOS) adult candidate status for heart transplantation differs from the Eurotransplant urgency classification to some extent, the higher proportion of critically ill patients in our study may partly explain the inferior outcome results as compared to the OPTN and the Scientific Registry of Transplant Recipients (OPTN/SRTR) database (17).

Regarding early clinical events, fewer recipients of a pre-treated graft required hemofiltration after transplant, although there were no between-group differences in pre-transplant kidney function. Furthermore, post-transplant LVF impairment, requirement of a LVAD, and mortality at 3 months were consistently reduced in recipients of a pre-treated graft but failed to reach the level of significance, presumably because of lack in statistical power. The incidence of acute renal failure after heart transplantation as defined by the requirement of renal replacement therapy before discharge from the hospital ranges from 6% to 40% (14,18,19). The rather frequent use of hemofiltration in our study was driven by 2 independent factors, which were donor dopamine and the recipients' impaired kidney function. In fact, 48% of recipients with an elevated serum-creatinine pre-transplant required hemofiltration after transplant.

Because the administration of dopamine to the donors precludes any interference with kidney function in the recipient, it was an intriguing finding that dopamine affected the need for hemofiltration independently from pre-existing renal failure. Acute renal failure after heart transplantation is caused by various pre-disposing factors, including graft dysfunction (19,20). In particular, right ventricular dysfunction is a frequent complication after heart transplantation (21), which presumably remained underdiagnosed in our study to some extent. Serial Swan-Ganz catheter measurements after transplant were unavailable, since invasive lines were removed in the majority of cases immediately after transplantation to minimize the risk of invasive line related infections in the immunosuppressed cardiac transplant recipient. Echocardiography, which enables a reasonable estimate of LVF, is rather insensitive to evaluate right ventricular function. Given its greater dependency on loading conditions right ventricular ejection fraction is a poor measure of true right ventricular function (22), which may have prevented the diagnosis of right ventricular failure in less severe cases. Hemofiltration is frequently used to correct an underlying refractory volume overload in instances of deteriorating glomerular filtration rate (14). Cardiac dysfunction accompanied by acute renal failure is known to increase post-operative mortality after cardiac surgery and after heart transplantation (23,24). In accordance with these data, need for hemofiltration significantly predicted allograft failure and mortality in our study. Nonetheless, the post-operative use of hemofiltration and post-operative graft failure rates were relatively high compared to non-European transplant centers, so the generalizability of the results regarding the magnitude of benefit from donor pre-treatment may be less in situations where graft failure is less likely.

Since donor hemodynamic stability under low-dose norepinephrine was a prerequisite of eligibility for study inclusion (8), the beneficial effects of dopamine should not be seen as a consequence of an additional circulatory stabilization of the deceased donor. Even though the individual dosage of norepinephrine did not differ between groups, it was more frequently used in the control group. However, including norepinephrine as an explanatory variable into the multiple Cox regression model failed to influence the principal finding of this study.

Cardiac allografts are highly susceptible to prolonged cold ischemia. There is evidence that ischemic time negatively affects allograft survival in adult heart transplantation (25).

Table 4 **Multiple Cox Regression of Recipient Mortality**

	Hazard Ratio	95% CI	p Value
Donor dopamine pre-treatment	0.33	0.12–0.89	0.03
Donor age, yrs	1.01	0.97–1.06	0.53
Donor on norepinephrine	0.67	0.20–2.30	0.53
Recipient age, yrs	1.01	0.96–1.05	0.79
Recipient female	1.48	0.50–4.37	0.48
Recipient on mechanical support pre-transplant	1.69	0.60–4.76	0.32
Recipient on inotropic support pre-transplant	0.71	0.27–1.89	0.49
Recipient with elevated serum creatinine pre-transplant	1.05	0.41–2.69	0.92

CI = confidence interval.

Cellular cardiac damage after prolonged cold ischemia is in part ascribed to oxidative stress (26,27). Under cold storage conditions, the accumulation of reactive oxygen species leads to an increased release of calcium ions from intracellular stores, and from the extracellular environment through store-operated channels (28). A vicious circle is activated, because intracellular calcium homeostasis depends on high-energy phosphates that 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 (29). Strategies that reduce intracellular calcium with novel hyperpolarizing preservation solutions have been shown to ameliorate ischemic damage during cold preservation in experimental heart transplantation (27). We were able to demonstrate that dopamine decelerates the deleterious amplification loop of intracellular calcium accumulation, and subsequent ATP consumption by scavenging of reactive oxygen species (9,30). These findings have been recently expanded and confirmed by in vitro studies with cardiomyocytes in culture (31). Serial biopsies from human donor hearts, taken at pre-defined time points during the pre-operative and post-operative transplantation procedure, indicated an increased risk of graft failure if the heart failed to replenish its ATP stores within 10 min after reperfusion (21). Obviously, the cardiac allograft is highly dependent on a sufficient supply of high energy phosphates to meet the circulatory demands after transplantation.

The net effects of donor pre-treatment, and the statistical associations in our study became stronger when the analyses were done as per protocol. This observation suggests that it is crucial to continue the dopamine infusion until cross-clamping. Dopamine is inactivated by oxidative deamination by mitochondrial monoamine oxidase and by O-methylation by catechol-O-methyltransferase. This rapid enzymatic degradation accounts for a half-life of a few minutes when dopamine is circulating in the blood (32,33). Dopamine's ability to protect against cold preservation injury depends on its diffusion into cells (34). Hence, to facilitate dopamine accumulation within the intracellular compartment, it is of utmost importance that a pharmacokinetic steady state is achieved before cold preservation. This view is supported by our observation that recipients of a pre-treated graft that was prematurely withdrawn from dopamine due to transient side effects had very similar survival rates as the no-dopamine group.

Study limitations. The randomized dopamine trial was designed to assess the incidence of dialysis after transplantation in renal transplant patients. Neither study endpoints nor a quantitative hypothesis that included sample size calculations was pre-specified during the planning phase for heart allograft recipients. Albeit reaching statistical significance, the beneficial effect mediated through donor dopamine treatment derives from a relatively small study cohort of cardiac transplant recipients, limiting the external validity of our findings. Under formal considerations, our study is a post-hoc analysis that was nested in a randomized controlled clinical trial. As in the renal trial, we evaluated the frequency of biopsy proven AR during the in-hospital period after transplantation, and assessed long-term patient and graft survival. In addition, we selected early clinical events, such as a required LVAD and need for hemofiltration, which are well known to predict mortality after transplantation (16). The principal limitation of the open-label study design, where endpoints are based on therapeutic interventions, is well recognized. Theoretically, it can not be excluded that knowledge of study interventions in the donor influenced the indication for therapy in the recipient. However, it was deemed unlikely that the indication for treatment with a LVAD or hemofiltration was initiated by other factors than organ dysfunction in the cardiac transplant recipient. Nonetheless, both outcome measures were highly predictive of mortality in our study, which is definitely a hard endpoint devoid of classification bias.

A major strength of the present investigation is its high internal validity. No recipient was lost, and follow-up data are complete for a minimum of 2 years after transplantation. The study evaluates a multicenter transplant activity under real-life conditions, where transplant recipients were not exposed to protocol-mandated interventions. Clustering by site failed to reveal an effect on the principal outcome of long-term patient and graft survival. Most importantly, although the study was strictly observational in the recipients, the donor's treatment was carried out according to a prospective, randomized study design, which enhanced the reliability of the study findings beyond the potential of selection bias.

Conclusions

This study shows that donor pre-treatment with low-dose dopamine does not harm the cardiac allograft but appears to improve the clinical course of the heart allograft recipient after transplantation. It is suggested that low-dose dopamine for heart-beating multiorgan donors with confirmed brain death should receive further evaluation by a prospective randomized controlled trial as no adverse side-effects have been recognized in the recipients, whereas it has the potential to considerably improve the outcome after both kidney and heart transplantation.

Reprint requests and correspondence: Dr. Peter Schnuelle, University Medical Centre Mannheim, 5th Department of Medicine, Theodor Kutzer Ufer 1-3, Mannheim 68167, Germany. E-mail: peter.schnuelle@umm.de.

REFERENCES

1. Rosendale JD, Kauffman HM, McBride MA, et al. Aggressive pharmacologic donor management results in more transplanted organs. Transplantation 2003;75:482–7.

2. Rosendale JD, Kauffman HM, McBride MA, et al. Hormonal resuscitation yields more transplanted hearts, with improved early function. Transplantation 2003;75:1336–41.
3. Novitzky D, Cooper DK, Rosendale JD, Kauffman HM. Hormonal therapy of the brain-dead organ donor: experimental and clinical studies. Transplantation 2006;82:1396–401.
4. 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;72:455–63.
5. Wood KE, Becker BN, McCartney JG, D'Alessandro AM, Coursin DB. Care of the potential organ donor. N Engl J Med 2004;351: 2730–9.
6. Rosengard BR, Feng S, Alfrey EJ, et al. Report of the Crystal City meeting to maximize the use of organs recovered from the cadaver donor. Am J Transplant 2002;2:701–11.
7. Zaroff JG, Rosengard BR, Armstrong WF, et al. Consensus conference report: maximizing use of organs recovered from the cadaver donor: cardiac recommendations, March 28–29, 2001, Crystal City, Virginia. Circulation 2002;106:836–41.
8. 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;302:1067–75.
9. Brinkkoetter PT, Song H, Lösel R, et al. Hypothermic injury: the mitochondrial calcium, ATP and ROS love-hate triangle out of balance. Cell Physiol Biochem 2008;22:195–204.
10. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet 2000;356:2139–43.
11. Galley HF. Renal-dose dopamine: will the message now get through? Lancet 2000;356:2112–3.
12. van den Hout WB, Smits JM, Deng MC, et al. The heart-allocation simulation model: a tool for comparison of transplantation allocation policies. Transplantation 2003;76:1492–7.
13. Komoda T, Hetzer R, Lehmkuhl HB. Influence of new Eurotransplant heart allocation policy on outcome of heart transplant candidates in Germany. J Heart Lung Transplant 2008;27:1108–14.
14. Hoskote A, Carter C, Rees P, Elliott M, Burch M, Brown K. Acute right ventricular failure after pediatric cardiac transplant: predictors and long-term outcome in current era of transplantation medicine. J Thorac Cardiovasc Surg 2010;139:146–53.
15. Billingham M, Kobashigawa JA. The revised ISHLT heart biopsy grading scale. J Heart Lung Transplant 2005;24:1709.
16. Taylor DO, Stehlik J, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth official adult heart transplant report–2009. J Heart Lung Transplant 2009;28: 1007–22.
17. The 2009 OPTN/SRTR Annual Report: Tables 11.4 and 11.11. Available at: http://optn.transplant.hrsa.gov/ar2009/. Accessed on April 8, 2011.
18. Boyle JM, Moualla S, Arrigain S, et al. Risks and outcomes of acute kidney injury requiring dialysis after cardiac transplantation. Am J Kidney Dis 2006;48:787–96.
19. Jokinen JJ, Tikkanen J, Kukkonen S, et al. Natural course and risk factors for impaired renal function during the first year after heart transplantation. J Heart Lung Transplant 2010;29:633–40.
20. Garrido IP, Crespo-Leiro MG, Paniagua MJ, et al. Independent predictors of renal dysfunction after heart transplantation in patients with normal pre-transplant renal function. J Heart Lung Transplantation 2005;24:1226–30.
21. Stoica SC, Satchithananda DK, Atkinson C, et al. The energy metabolism in the right and left ventricles of human donor hearts across transplantation. Eur J Cardiothorac Surg 2003;23:503–12.
22. Poston RS, Griffith BP. Heart transplantation. J Intensive Care Med 2004;19:3–12.
23. Gummert JF, Bucerius J, Walther T, et al. Requirement for renal replacement therapy in patients undergoing cardiac surgery. Thorac Cardiovasc Surg 2004;52:70–6.
24. Ouseph R, Brier ME, Jacobs AA, Erbeck KM. Continuous venovenous hemofiltration and hemodialysis after orthotopic heart transplantation. Am J Kidney Dis 1998;32:290–4.
25. Banner NR, Thomas HL, Curnow E, Hussey JC, Rogers CA, Bonser RS. The importance of cold and warm cardiac ischemia for survival after heart transplantation. Transplantation 2008;86:542–7.
26. Southard JH, Belzer FO. Organ preservation. Annu Rev Med 1995; 46:235–47.
27. Hoenicke EM, Sun X, Strange RG Jr., Damiano RJ Jr. Donor heart preservation with a novel hyperpolarizing solution: superior protection compared with University of Wisconsin solution. J Thorac Cardiovasc Surg 2000;120:746–54.
28. 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;63:554–63.
29. 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: 69–79.
30. Brinkkoetter PT, Beck GC, Gottmann U, et al. Hypothermia-induced loss of endothelial barrier function is restored after dopamine pretreatment: role of p42/p44 activation. Transplantation 2006;82:534–42.
31. Hepp C, Vettel C, Benck U, et al. Both dopamine and its derivative N-octanoyl-dopamine protect cardiomyocytes against cold preservation injury (abstr). Am J Transplant 2010;10:194.
32. Homcy CJ, Graham RM. Molecular characterization of adrenergic receptors. Circ Res 1985;56:635–50.
33. Yan M, Webster LT Jr., Blumer JL. Kinetic interactions of dopamine and dobutamine with human catechol-O-methyltransferase and monoamine oxidase in vitro. J Pharmacol Exp Ther 2002;301:315–21.
34. 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;4:22–30.

Key Words: antioxidants ■ cardiac transplantation ■ dopamine ■ ischemia ■ survival.

APPENDIX

For a list of investigators who made invaluable contributions to this study, please see the online version of this article.