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Normothermic Ex Vivo Allograft Blood Perfusion in Clinical Heart Transplantation

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ABSTRACT

Background: Cold ischemia associated with cold static storage is an independent risk factor for primary allograft failure and survival of patients after orthotopic heart transplantation. The effects of normothermic ex vivo allograft blood perfusion on outcomes after orthotopic heart transplantation compared to cold static storage have been studied.

Methods: In this prospective, nonrandomized, single-institutional clinical study, normothermic ex vivo allograft blood perfusion has been performed using an organ care system (OCS) (TransMedics, Andover, MA, USA). Included were consecutive adult transplantation patients who received an orthotopic heart transplantation (oHTx) without a history of any organ transplantation, in the absence of a congenital heart disorder as an underlying disease and not being in need of a combined heart–lung transplantation. Furthermore, patients with fixed pulmonary hypertension, ventilator dependency, chronic renal failure, or panel reactive antibodies >20% and positive T-cell cross-matching were excluded. Inclusion criteria for donor hearts was age of <55 years, systolic blood pressure >85 mmHg at the time of final heart assessment under moderate inotropic support, heart rate of <120 bpm at the time of explantation, and left ventricular ejection fraction >40% assessed by an transcutaneous echo/Doppler study with the absence of gross wall motion abnormalities, absence of left ventricular hypertrophy, and absence of valve abnormalities. Donor hearts which were conventionally cold stored with histidine-tryptophan-ketoglutarate solution (Custodiol; Koehler Chemie, Ansbach, Germany) constituted the control group. The primary end point was the recipients' survival at 30 days and 1 and 2 years after their heart transplantation. Secondary end points were primary and chronic allograft failure, noncardiac complications, and length of hospital stay.

Results: Over a 2-year period (January 2006 to July 2008), 159 adult cardiac allografts were transplanted. Twenty-nine were assigned for normothermic ex vivo allograft blood perfusion and 130 for cold static storage with HTK solution. Cumulative survival rates at 30 days and 1 and 2 years were 96%, 89%, and 89%, respectively, whereas in the cold static storage group survival after oHTx was 95%, 81%, and 79%. Primary graft failure was less frequent in the recipients of an oHTx who received a donor heart which had been preserved with normothermic ex vivo allograft blood perfusion using an OCS (6.89% versus 15.3%; $P = .20$). Episodes of severe acute rejection (23% versus 17.2%; $P = .73$), as well as, cases of acute renal failure requiring haemodialysis (25.3% versus 10%; $P = .05$) were more frequent diagnosed among recipients of a donor heart which had been preserved using the cold static storage. The length of hospital stay did not differ (26 days versus 28 days; $P = .80$) in both groups.

Conclusions: Normothermic ex vivo allograft blood perfusion in adult clinical orthotopic heart transplantation contributes to better outcomes after transplantation in regard to recipient survival, incidence of primary graft dysfunction, and incidence of acute rejection.

INTRODUCTION

Orthotopic heart transplantation (oHTx) is still the gold standard for the treatment of end-stage heart failure. However, while the number of patients in need of an oHTx is rising, the number of suitable allografts is stagnating. This has already led to a shift toward extended donor criteria [Tenderich 1998] and to the establishment of an international framework for organ allocation. A crucial aspect thereby is that of ischemia. Cold ischemia is known to be an independent risk factor for survival after oHTx [Taylor 2006; Hertz 2008; Goldsmith 2009], primary allograft failure [Russo 2010], and transplant vasculopathy associated with chronic allograft failure [Derek 2007; Khan 2009]. Different from cold static storage of explanted donor hearts, normothermic ex vivo allograft

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blood perfusion (NEVABP) simulates physiologic conditions which, in contrast to cold static storage (CSS), can be continuously monitored during the entire perfusion period. Contractile, vasomotor, and metabolic functions of the allograft are preserved [Hassanein 1998], whereby the extent of myocardial edema, reperfusion injury, and apoptosis is restricted [Collins 2008]. This study should elucidate whether these effects translate into improved results in the setting of adult heart transplantation.

METHODS

This prospective, nonrandomized, single-institutional trial had the aim to compare outcomes of the allograft recipients after oHTx following NEVABP with those recipients who received donor hearts which had been preserved by conventional allograft CSS. The study was approved by the local institutional review board. Written informed consent was provided by all patients prior to the inclusion in the trial. Organ allocation was performed through the Eurotransplant Foundation, Leiden, The Netherlands. Both groups of recipients received pre-, intra-, and posttransplant standard immunosuppressive and antibiotic therapy according to the center's protocol.

Inclusion and Exclusion Criteria

Recipient Exclusion Criteria: Potential recipients were evaluated twice. In the pretransplantation setting, patients were excluded who were younger than 18 years or older than 70 years, had a congenital heart defect as an underlying disease, or needed a combined heart–lung transplantation. The listed candidates for an oHTx were reevaluated on the day of a donor referral from the organ procurement agency (Eurotransplant) and were excluded in the presence of fixed pulmonary hypertension, pulmonary vascular resistance of more than 4 Woods units, chronic renal failure as defined by a serum creatinine of more than 2.5 mg/dL with or without the need for hemodialysis, ventilator dependency, or a high level of panel-reactive antibodies (>20%) and a positive T-cell cross-matching.

Donor Inclusion Criteria: Donor inclusion criteria were age of less than 55 years and systolic blood pressure of more than 85 mmHg at the time of the final donor heart assessment (performed by the explanting heart surgeon in direct communication with the transplant cardiologist, with the prospective heart recipient under moderate inotropic support (dopamine, <10 µg/kg/min; dobutamine, <15 µg/kg/min; adrenaline, < 0.2 µg/kg/min; noradrenaline, <0.2 µg/kg/min), heart rate <120 bpm at the time of explantation, left ventricular ejection fraction >40% in the absence of gross wall motion abnormalities, absence of left ventricular hypertrophy, and absence of valve abnormalities in a transthoracic echo/Doppler study. Allografts were assigned to either NEVABP or CSS after evaluation of the organ-related data provided by Eurotransplant.

Study Logistics

All donor hearts were allocated by Eurotransplant. The explanting team of the recipient's center (consisting of a transplant surgeon, a perfusionist, and a nurse then at the donor hospital), together with a transplant cardiologist in the recipient hospital, assessed the organ which in case of eligibility was explanted and delivered to our institution either in CSS with histidine-tryptophan-ketoglutarate solution or under NEVABP. Prior to the beginning of the trial, all participants were trained in the handling of the perfusion device. Follow-up was obtained by the institution's interdisciplinary heart transplant team.

NEVABP Technique

The NEVABP technique, with an Organ Care System® (OCS) (TransMedics, Andover, MA, USA), has been described previously [Hassanein 1998]. In this trial all allografts were perfused with the OCS in the resting mode. The left ventricle of the donor heart was completely unloaded and perfused in an antegrade manner over the aortic root with a median aortic pressure of 40-80 mmHg and an antegrade coronary flow of 1.2-1.5 mL/g of cardiac weight.

Study End Points

The primary end point was the survival of heart recipients at 30 days and 1 and 2 years after they received an oHTx. Secondary end points were lactate levels during NEVABP, primary graft failure as defined by the International Society for Heart and Lung Transplantation (ISHLT), heart allograft dysfunction requiring 2 or more inotropic substances or mechanical circulatory support (intraaortic counterpulsation or ventricular assist device) within 24 hours of heart transplantation [Costanzo 2010], severe acute rejection demanding aggressive immunosuppressive therapy, noncardiac complications, length of hospital stay, and allograft vasculopathy.

Statistical Analysis

Results are expressed as median and ranges. Data were analyzed by a 2-sample *t*-test. A *P* value of <.05 was considered to indicate statistical significance. Survival after oHTx was analyzed by calculating the proportion of the survivors with a 95% confidence interval.

Table 1. Baseline Characteristics of Recipients

Recipient Characteristics	Warm Blood Perfusion (n = 29)	Cold Static Storage (n = 130)	*P* value
Age, median (range), years	50.1 (37-64)	50.7 (37-64)	.57
Female sex, %	24.1	16.9	.40
ICM, %	21	29.6	.28
DCM, %	62	36.2	.014
MCS, %	10.3	38.4	.002
IABP, %	31	20	.22

Table 2. Baseline Data of the Donors for NEVABP (n = 29) in Clinical Heart Transplantation*

Donor Characteristic	
Age, mean (range), years	36 (17-54)
Female, %	37.9
Male, %	37.9
Weight, mean (range), kg	75 (45-105)
Core temperature, mean (range), °C	34.4 (33.5-37.4)
Cross-clamping time, mean (range), min	313 (176-403)
Heart rate, mean (range), bpm	81 (62-120)
MAP, mean (range), mmHg	67 (48-110.2)
CVP, mean (range), mmHg	5 (2-12)
PAP, mean (range), mmHg	15 (9.1-22)
LAP, mean (range), mmHg	7 (3-17)
Inotropic therapy during allograft explantation, %	75.8

*MAP, mean arterial pressure; CVP, central venous pressure; PAP, pulmonary artery pressure; LAP, left atrial pressure.

RESULTS

Baseline Characteristics of the Recipients

From January 2006 to July 2008, 159 adult patients received an oHTx at a single center. NEVABP was implemented in 29 and CCS in 130 allografts. Table 1 summarizes the baseline characteristics of the heart recipients. Recipient age and sex did not differ. The number of recipients with ischemic cardiomyopathy (ICM) (29.6% versus 21%; $P = .28$) were similar in both groups. The number of recipients with a history of mechanical circulatory support (MCS) (38.4% versus 10.3%; $P = .002$) was higher in the CSS group. Recipients with cardiogenic shock requiring intraaortic counterpulsation (IABP) were more frequent in the NEVABP group (31% versus 20%; $P = .22$), as well as recipients with a dilated cardiomyopathy (DCM) as an underlying disease (62% versus 36.2%; $P = .014$).

Allograft Characteristics

Table 2 summarizes the baseline characteristics of the allograft donors in the NEVABP group. Details of NEVABP in clinical heart transplantation (Table 3). The duration of NEVABP ranged from 176 to 343 minutes (mean 245 min). The cold ischemic time during the allograft explantation procedure (aortic cross-clamping to initiation of warm blood perfusion) ranged from 8 to 30 min (mean, 15 min) and the warm ischemic time (termination of the allograft perfusion to declamping of the aorta of the recipient) ranged from 17 to 50 min (mean 37 min). The exsanguination of the allograft at the end of the perfusion was completed at a mean of 75 s (range, 35-96 s). The quality of the allograft was assessed on the basis of the lactate levels recorded at the beginning and at the end of the NEVABP. These ranged from 1.07 mmol/L to 5.37 mmol/L (mean 1.52 mmol/L) and 1.10 mmol/L to 10.5 mmol/L (mean 1.87 mmol/L), respectively.

Table 3. Details of NEVABP in Clinical Heart Transplantation

Perfusion Details	
Warm blood perfusion, n	29
Duration of perfusion, mean (range), min	245 (176-343)
Cold ischemic time, mean (range), min	15 (8-30)
Warm ischemic time, mean (range), min	37 (17-50)
Initial lactate, mean (range), mmol/L	1.52 (1.07-5.37)
End lactate, mean (range), mmol/L	1.87 (1.10-10.5)
Exsanguination, mean (range), s	75 (35-96)

Table 4. Overall Clinical Results

Overall Clinical Results	Warm Blood Perfusion, (n = 29)	Cold Static Storage (n = 130)	*P*
Recipient survival after HTx, %			
30 Days	96	95	.39
1 Year	89	81	.24
2 Years	89	79	.19
Primary graft failure, %	6.89	15.3	.20
Severe acute rejection, %	17.2	23	.73
Hemodialysis, %	10	25.3	.05
In-hospital stay, mean (range), days	26 (20-108)	28 (19-143)	.80

Clinical Outcomes

In the NEVABP group the cumulative survival after oHTx at 30 days and 1 and 2 years was 96%, 89%, and 89%, respectively, whereas in the CSS group the survival after oHTx was 95% ($P = .65$), 81% ($P = .28$), and 79% ($P = .21$). Primary graft failure requiring hemodynamic support (2 or more inotropes, extracorporeal membrane oxygenation or IABP) was less frequent in the NEVABP recipients (6.89% versus 15,3%; $P = .20$). Episodes of severe acute rejection (23% versus 17.2%; $P = .73$), as well as cases of acute renal failure requiring hemodialysis (25.3% versus 10%; $P = .05$) were more frequent among the CSS group. The length of hospital stay did not differ (26 days versus 28 days; $P = .80$) (Table 4). Table 5 summarizes the cause of death in the 4 patients of the NEVABP group. In the first case the donor heart formally did not meet the study inclusion criteria due to high-dose norepinephrine therapy and retrospectively should have not have been transplanted at all. On ex vivo examination this allograft was bluish and edematous and the lactate levels during the NEVABP were excessively high. A weaning from the extracorporeal circulation during the oHTx procedure was not possible. The 63-year-old female recipient was then supported with extracorporeal membrane oxygenation (ECMO), underwent retransplantation 22 days later, but

Table 5. Causes of Death in NEVABP*

Age, years	Sex	Underlying Heart Disease	MCS	Cause of Death	Postoperative Day
63	Female	ICM	No	Multiorgan failure	55
63	Male	ICM	Yes	Multiorgan failure	153
54	Female	ICM	Yes (TAH)	Graft failure	302
46	Male	DCM	No	Severe graft vasculopathy	372

*ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; TAH, total artificial heart.

unfortunately died at the 33rd day due to severe multiorgan failure. The second patient (male, 63 years old) initially had a complex postoperative course with a critical illness, polyneuropathy, and prolonged ventilation. The recipient recovered and was discharged but had to be readmitted in the follow-up due to an episode of severe rejection. He died on postoperative day 153 due to irreversible multiorgan failure. The third patient (female, 54 years old) received a donor heart from a carbon-monoxide-intoxicated donor and experienced a primary graft failure necessitating ECMO therapy. Following a prolonged postoperative course with secondary respiratory failure due to recurrent pneumonia and acute renal failure with the need for hemodialysis the patient was initially discharged but died on postoperative day 302 due to graft failure. Finally, the fourth patient (male, 46 years old) repeatedly experienced severe rejection episodes during the early postoperative course. Following discharge, angiography revealed severe graft vasculopathy. The patient died on postoperative day 372 after oHTx due to refractory ventricular fibrillation.

DISCUSSION

It is well known that the duration of cold ischemia is directly associated with the extent of ischemic and reperfusion injury [Yellon 2007] and therefore has a profound effect on the early [Fyfe 1996] and the 1-, 5-, and 10-year survival after oHTx [Hosenpud 1998; Hosenpud 2000] of cardiac allograft recipients. As the ISHLT suggests, a decrease of the duration of cold ischemia down <1 hour would contribute to a decrease of 1 year mortality risk of up to 50% [Hertz 2008]. Tenderich and colleagues reported first about successful clinical use of an OCS [Tenderich 2007] in oHTx. Ghodsizad and colleagues reported first about the long-distance transfer of cardiac allografts using normothermic allograft blood perfusion. They also used the system for coronary angiography to evaluate the allograft before transplantation [Ghodsizad 2012]. In the NEVABP cases, continuous perfusion of the allograft throughout the assessment and transport procedure (176-343 min) resulted in clear reduction of the duration of cold ischemia, which ranged from 8 to 30 min. This seems to contribute to the observed lower incidence of primary graft failure and therefore improved survival after oHTx in adults. This is in accordance with the results of Hassanein et al, which demonstrated that perfusion with warm donor blood preserves the allograft at a physiologic state, avoiding myocardial edema, intracellular acidosis, and endothelial damage [Hassanein 1998]. Two of the 4 patients with a fatal course had unfavorable allografts implanted, the first due to high-dose norepinephrine therapy and the second due to carbon monoxide intoxication of the donor; their death seems therefore not related to the implementation of NEVABP. Apart from the beneficial effect on preservation, the NEVABP setting allows the assessment of the function and the metabolism of the allograft. Lactate levels were measured throughout the assessment. In the one case in which lactate was already excessively high at the beginning of the perfusion and continuously increased during the transport it came to a fatal primary allograft failure. The high incidence of acute renal failure in the CSS group can be explained by the higher incidence of severe acute rejection episodes requiring aggressive immunosuppressive therapy. A limitation of this trial is that it is a nonrandomized study, a single-institutional design, and a small number of cases.

In conclusion, the present study which to our knowledge is the first one prospectively done in a systematic fashion shows that NEVABP contributes to better outcomes after oHTx in adult heart recipients. Considering the fact that the results in regard to survival after oHTx following CSS are still relatively poor [AQUA Institut 2010], NEVABP can be considered to be the first step in the right direction towards better outcomes by minimizing the extent of ischemic and reperfusion injury, assessing the quality of the allograft prior to the transplantation and by expanding the donor pool [Tenderich 2007].

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