

Hemodynamics during Humoral Rejection Events with Total Versus Standard Orthotopic Heart Transplantation

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Purpose: We hypothesized that total orthotopic heart transplantation (TOHT) improves humoral rejection hemodynamics compared with biatrial transplantation or standard orthotopic heart transplantation (SOHT).

Methods: We reviewed 1942 biopsies from 134 patients (pts) and right heart catheterization data obtained at endomyocardial biopsy. Biopsies that displayed humoral rejection by histological findings and positive immunofluorescence for immunoglobulins and complement were analyzed. Patients with pacemakers, atrial fibrillation or β -blocker therapy at the time of biopsy were excluded. Thirty-two pts after TOHT and 22 after SOHT matching these criteria were identified.

Results: Demographic data, underlying disease, pretransplant hemodynamics, and donor demographics were similar. Cardiac output and index were higher in the total orthotopic group (5.9 ± 1.1 vs 5.1 ± 1.4 L/min, $p=0.027$; 3.3 ± 0.5 vs 2.8 ± 0.6 L/min/m², $p=0.016$). Right atrial and pulmonary capillary wedge pressure were lower after TOHT (7 ± 3 vs 11 ± 5 mmHg, $p<0.001$; 13 ± 4 vs 16 ± 5 mmHg, $p=0.035$). Pulmonary pressures, pulmonary vascular resistance and heart rate were similar.

Conclusion: TOHT offers improved hemodynamics during humoral rejection as evidenced by higher cardiac output and index with lower right atrial and pulmonary capillary wedge pressures. Future studies must examine the potential benefits of TOHT during combined cellular and humoral rejection events. (*Ann Thorac Cardiovasc Surg* 2004; 10: 285–9)

Key words: heart transplantation, rejection, hemodynamics

Introduction

Rejection is one of the most important reasons for allograft dysfunction after cardiac transplantation. Several studies have suggested a role for humoral mechanisms in significant and often irreversible, heart transplant rejection.^{1,2} Hammond et al.³ defined humoral rejection in endomyocardial biopsy specimens by demonstrating capillary deposition of immunoglobulin and complement by

immunofluorescence and capillary endothelial cell swelling in hematoxylin-eosin-stained paraffin-embedded tissue. The clinical course is more aggressive and hemodynamic compromise more frequent.² Patients with humoral rejection face increased risks of fatal rejection and accelerated transplant vasculopathy.²

The original technique of standard orthotopic heart transplantation (SOHT technique), as described by Lower and Shumway,⁴ anastomoses the donor's atria to those of the recipient, leaving a large cuff of the recipient's right and left atria.

Another technique, termed "total orthotopic heart transplantation" (TOHT), employs separate anastomoses of the right and left pulmonary veins and of the superior and inferior venae cavae.⁵ The potential advantage of this technique is better preservation of the anatomy and function of the atria of the transplanted heart as demonstrated

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by echocardiographic findings of improved left-atrial transport and ejection force.⁶⁾

After previously demonstrating hemodynamic benefits of TOHT in patients without any rejection⁷⁾ and during cellular rejection events⁸⁾ we wanted to examine if TOHT could improve hemodynamics during humoral rejection when compared with the SOHT technique of heart transplantation.

Methods

Patients and biopsies

Medical records and biopsies with concomitant right heart catheterization from 64 patients transplanted with the SOHT technique and 70 transplanted with the TOHT technique were evaluated for possible inclusion in this study. These patients were transplanted consecutively with the SOHT technique being the first technique applied. Among 1942 biopsies reviewed, 229 were censored because of incomplete data or lack of screening for humoral rejection.

Patients were considered eligible for further study if they had humoral rejection by histological findings and positive immunofluorescence for immunoglobulins and complement⁴⁾ but no significant cellular rejection (> grade 1A) according to the International Society for Heart and Lung Transplantation criteria. Endomyocardial biopsy and right heart catheterization were performed according to the following schedule in all patients: first three biopsies weekly, two biopsies every other week, two biopsies each month, and the last two biopsies every other month; later, in the absence of significant rejection, biopsies were scheduled once every 6 months.

Pathologic evaluation

Starting in May 1990, one tissue sample was wrapped in saline-soaked gauze and fresh frozen in chilled isopentane at -70°C in OCT compound (Tissue-Tek O.C.T. compound, Miles Inc, Elkhart, Ind.) for later hematoxylin-eosin staining, immunofluorescence, or research studies. Direct immunofluorescence was performed on $4\mu\text{m}$ thick cryostat sections fixed briefly in acetone, washed, and incubated for 30 minutes with antibodies directed against IgG, IgM, IgA, C'3, C1Q, Fibrinogen and HLA-DR.

Other inclusion criteria

We selected hemodynamic measurements from patients who met the following additional criteria: (1) no pacemaker insertion, (2) no treatment with inotropic or nega-

tively chronotropic drugs (e.g. beta-blockers), and (3) absence of atrial fibrillation or other arrhythmias at the time of biopsy and right heart catheterization. By these criteria, 54 patients had biopsies with humoral rejection. During right heart catheterization, mean right atrial, pulmonary arterial, pulmonary capillary wedge pressures and cardiac output were measured by means of a standard balloon-guided pulmonary artery catheter. Cardiac output was determined by injection of 10 ml of cold 5% dextrose solution and the index was calculated.

Immunosuppression

All patients received murine monoclonal antibody muromonab-CD3 (Orthoclone-OKT3; Ortho Biotech, Raritan, NJ) for 7 to 14 days. Triple-drug immunosuppression consisted of cyclosporine, azathioprine, and prednisone. The only difference in the immunosuppressive protocols consisted of shorter periods of induction therapy with OKT3. In the standard orthotopic group, all patients received 14 days of OKT3 treatment but in the total orthotopic group 19 patients received 10 days of OKT3 therapy and 25 patients received 7 days of OKT3, respectively. For humoral rejection, 1 gm of intravenous cyclophosphamide was given monthly, with or without plasmapheresis, until resolution.

Statistical analysis

Baseline and postoperative parameters were compared using the Mann-Whitney U test for continuous variables and Fisher's exact test for binary variables. All tests are two-sided with an alpha level of 0.05. The Kaplan-Meier method was applied for time-related events, i.e. any kind of rejection and humoral rejection. The first-event probability of any kind of rejection and of humoral rejection was compared using the Mantel-Cox test. The statistical software package SAS was used. Values are expressed as mean \pm standard deviation (SD) or percent where appropriate.

Results

Among 54 patients included in this study based on the defined criteria, 32 suffered from humoral rejection after TOHT and 22 after SOHT. Humoral rejection was analyzed in 119 biopsies.

Recipient age, gender, race, and underlying disease were similar between both groups. Donor age, gender, ethnic distribution and donor/recipient weight ratio were similar (0.94 ± 0.16 for TOHT recipients and 1.02 ± 0.26

Table 1. Pretransplant hemodynamics of patients after SOHT and TOHT experiencing humoral rejection

	Total orthotopic group (n=32)	Standard orthotopic group (n=22)	P value
RAMP (mmHg)	15±10	14±7	NS
PASP (mmHg)	56±18	50±18	NS
PADP (mmHg)	29±10	28±10	NS
PAMP (mmHg)	39±12	37±11	NS
PCWP (mmHg)	27±10	26±10	NS
CO (L/min)	3.6±1.1	4.3±1.3	0.086
CI (L/min/m ²)	1.9±0.5	2.4±0.9	0.027
PVR (WU)	3.6±2.4	2.6±1.7	NS

RAMP, right atrial mean pressure; PASP, pulmonary arterial systolic pressure; PADP, pulmonary arterial diastolic pressure; PAMP, pulmonary arterial mean pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; WU, Wood units.

Table 2. Hemodynamics during humoral rejection

	Total orthotopic group (n=32)	Standard orthotopic group (n=22)	P value
CO (L/min)	5.9±1.1	5.1±1.4	0.027
CI (L/min/m ²)	3.3±0.5	2.8±0.6	0.016
RAMP (mmHg)	7±3	11±5	<0.001
PASP (mmHg)	34±7	37±7	NS
PADP (mmHg)	16±5	17±5	NS
PAMP (mmHg)	23±5	24±5	NS
PCWP (mmHg)	13±4	16±5	0.035
PVR (WU)	1.7±0.6	1.8±0.7	NS
Heart rate (bpm)	84±12	79±22	NS

Abbreviations see Fig. 1; bpm, beats per minute

for SOHT recipients, P=NS).

Preoperative right atrial mean, pulmonary arterial, pulmonary capillary wedge pressure, cardiac output and pulmonary vascular resistance were similar. Pretransplant cardiac index was higher in the SOHT group (2.4±0.9 vs 1.9±0.5 l/min/m² in the TOHT group, Table 1).

Intraoperative ischemic time was longer for the TOHT group (165±44 vs 141±36 minutes in the SOHT group, P=0.027).

The analysis of hemodynamic parameters demonstrated higher cardiac output and index in patients with TOHT experiencing humoral rejection than in patients with SOHT. Right atrial mean and pulmonary capillary wedge pressure were lower after the total orthotopic technique. There were no differences in pulmonary arterial systolic, diastolic, mean pressures, pulmonary vascular resistance and heart rate (Table 2).

In order to exclude any confounding effects of different time intervals from transplantation until any detected rejection and from transplantation to humoral rejection a Kaplan-Meier analysis was performed. Such analysis of

all rejection events did not show any difference between the TOHT and the SOHT group (P=NS, Mantel-Cox test, Fig. 1). Neither did additional Kaplan-Meier analysis of all humoral rejection events (P=NS, Mantel-Cox test, Fig. 2).

Discussion

Despite ongoing rejection, heart rate, blood pressure, and even cardiac output may frequently remain unchanged up to 24 hours before cardiac arrest.⁹⁾ Even with myocyte necrosis present systolic function of the transplanted heart does not reliably reflect the results of endomyocardial biopsy.¹⁰⁾ In contrast, signs of left ventricular diastolic dysfunction, such as elevated resting filling pressures,¹¹⁾ prolonged relaxation time,¹²⁾ and an abnormal response to volume challenge¹³⁾ have been observed clinically during acute rejection episodes. Despite these changes in diastolic function, systolic function remains normal in most cases.

In this study, two markers of diastolic dysfunction,

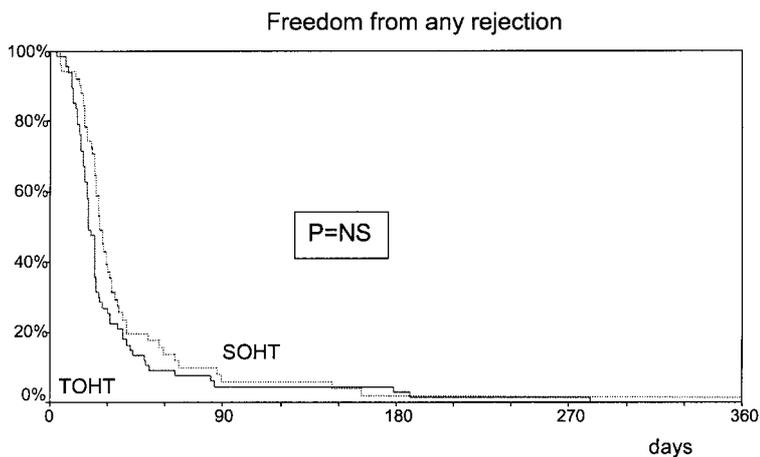


Fig. 1. Kaplan-Meier analysis of freedom from any kind of rejection for patients after TOHT and SOHT, respectively.

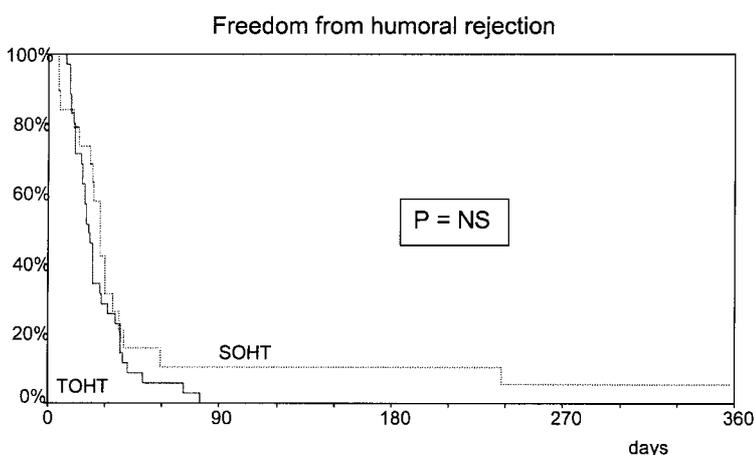


Fig. 2. Kaplan-Meier analysis of freedom from humoral rejection for patients after TOHT and SOHT, respectively.

namely right-sided filling pressure and pulmonary capillary wedge pressure, were lower with the total orthotopic technique. Since ventricular filling is significantly dependent on active atrial contraction in the setting of any kind of restrictive physiology like rejection, the more physiologic performance of the allograft atria as seen with the total orthotopic technique should allow for ventricular filling with less preload.

Michaels et al.¹⁴⁾ reviewed hemodynamic parameters and the incidence of transplant coronary artery disease in 44 patients with humoral rejection. They described hemodynamic compromise defined as shock, hypotension, decreased cardiac output/index and/or a rise in capillary wedge or pulmonary artery pressure in 47% of patients at the time of diagnosis of humoral rejection. The incidence of transplant coronary artery disease was 10% greater at 1 year and 36% greater at 5 years compared with patients without humoral rejection events.

Milano and coworkers¹⁵⁾ did not identify consistent late hemodynamic benefits after bicaval or total orthotopic versus standard biatrial transplantation. The differences

in cardiac output observed in their own study group were not attributed to simple differences in preload because mean central venous pressure measurements were similar after bicaval and standard heart transplantation. Consistent with Milano and coworkers' conclusion a higher index was achieved despite less preload in the TOHT group in our study.

In view of these two studies our findings of higher cardiac index with lower right atrial and pulmonary capillary wedge pressures after total orthotopic heart transplantation must be caused by preservation of atrial function and proper timing of atrial contraction. This indicates a benefit of the total orthotopic technique during humoral rejection events. Considering the frequent occurrence of humoral rejection in the early post-transplant period²⁾ as displayed in Fig. 2, hemodynamic abnormalities in 47%,¹⁴⁾ a mortality of up to 50% at 12 months,⁴⁾ such hemodynamic benefits may become relevant after orthotopic heart transplantation.

Certain limitations apply to this study. The confounding effects of length of OKT3 induction therapy on the

early postoperative measurements could not be determined. Potential benefits of newer immunosuppressive drugs like sirolimus and mycophenolate mofetil, e.g. reduced the incidence of humoral rejection, with a less severe course of rejection, could not be assessed. Furthermore, the diagnosis of humoral rejection can be established by newer methods than the ones described herein. However, in order to obtain a reasonable number of biopsies for further analysis we decided to rely on diagnostic studies used in a large number of patients. Fourthly, the severity of hemodynamic compromise would better be assessed by continuous cardiac output measurements after establishing the diagnosis of humoral rejection than by three injections of 5% dextrose. This provides the treating physician with a brief impression only. On the other hand, permanent cardiac output catheters in an immunosuppressed patient pose a considerable risk for infection and cannot be recommended for routine hemodynamic monitoring during the treatment of rejection events after cardiac transplantation.

In summary, the present study demonstrates improved cardiac output and index with lower right atrial mean and pulmonary capillary wedge pressure in patients undergoing humoral rejection after total orthotopic heart transplantation. This is in accordance with previous studies from our group indicating hemodynamic benefits after TOHT in patients without any kind of rejection.⁷⁾ In view of the restrictive physiology and the hemodynamic compromise frequently seen during humoral rejection after cardiac transplantation, this technique can be beneficial until that restrictive pattern has subsided following appropriate therapy with cyclophosphamide with or without additional plasmapheresis.

Acknowledgment

Ivan Aleksic is supported by the Deutsche Forschungsgemeinschaft, Bonn, Germany (DFG, grant Al 381/1-1) and Dov Freimark is supported by the Save-A-Heart Foundation, Los Angeles, CA.

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