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ORIGINAL ARTICLE

Severe right heart failure after heart transplantation. A single-center experience

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Summary

We reviewed our heart transplantation recipient population, using hard criteria defining severe right heart failure (RHF), and analyzed possible risk factors for outcome after RHF. Between 1983 and 1998 621 cardiac transplantations were performed at our institution. RHF was defined by the necessity to implant an assist device or echocardiographically confirmed right ventricular ballooning with concomitant end organ failure. RHF patients were compared with a matched control group. Thirty-five patients (5.9%) with severe RHF after transplantation fulfilled inclusion criteria. Of these, 32 patients died, while none of the control patients died ($P < 0.001$). Increased preoperative pulmonary capillary wedge ($P = 0.005$) and mean pulmonary artery pressure ($P = 0.006$) were identified as significant risk factors for severe RHF. Severe RHF as defined in our study is irreversible in almost every case without differences among therapeutical concepts. Hence, improvement of postoperative outcome necessitates avoidance or aggressive therapy of possible risk factors.

Introduction

Right ventricular dysfunction remains a common and potentially severe complication after heart and combined heart-lung transplantation or implementation of a left ventricular assist device and contributes significantly to morbidity and mortality in the early postoperative course [1]. Ischemia-reperfusion injury, incurred during organ harvest, distant procurement and subsequent reperfusion, is the principal underlying cause [2,3]. During transplantation, several risk factors make the right ventricle in particular susceptible for ischemic damage. Myocardial preservation during hypothermic cardioplegia has been shown to be less effective in the right ventricle as compared with the left ventricle [4]. Mechanical trauma during organ harvest and implantation, warm ischemia during surgery, air embolism of the right coronary artery, mechanical ventilation with positive end-expiratory pressure (PEEP) and high pulmonary vascular resistance (PVR) [5,6] might contribute to injury to the thin right ventricular myocardium.

In this retrospective chart review patients who developed severe right heart failure (RHF) in the early postoperative course after orthotopic heart transplantation were identified. To this date, no prospective studies and no generally accepted criteria for RHF in retrospective studies have been published. Hence, we set up restrictive inclusion criteria for severe RHF. We report on patient characteristics and clinical course in patients with RHF fulfilling our criteria. These patients were compared with case matched control patients who received their heart allografts during the same time period and who did not develop severe RHF. Potential risk factors for severe RHF after transplantation were analyzed.

Patients and methods

Patient selection

Patient charts from 591 heart transplant recipients operated during the time period from August 1983 to December 1998 were retrospectively reviewed to extract data on

patients demographics, disease leading to heart transplantation, waiting time from listing to heart transplantation, history of risk factors for cardiac disease, previous heart surgery, retransplantation, intraoperative data and criteria indicating severe RHF (explained below) in the early postoperative course. During the respective time period all transplants were performed according to the technique of Lower and Shumway [7]. Since 1999 a bicaval technique was used. To exclude different operative techniques as potential confounding variables for development of postoperative RHF, only patients having received a heart transplant using the technique of Lower and Shumway [7] as performed until the end of 1998 were included into the study.

Severe RHF was defined as: necessity of postoperative implementation of a mechanical assist device [intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO) or right ventricular assist device (RVAD)] or ballooned right ventricle (RV) verified by echocardiography and concomitant end organ failure of liver (GOT, GPT >200 U/l) and/or kidney (serum creatinine increase >30% of preoperative level) and/or intestine (serum lactate >6 mmol/l).

A matched pairs analysis was conducted by including all patients, who met the criteria of severe RV failure, in the study group. Gender, age (±5 years), height (±3 cm) and body mass index (BMI) (±2) matched heart transplant recipients operated during the same time period, who did not develop RHF, served as controls.

Data extraction

In the preoperative course, all patients received routine right and left heart catheterization to determine left ventricular ejection fraction, cardiac index, central venous pressure, pulmonary artery pressure (PAP) and pulmonary capillary wedged pressure (PCWP). The number, kind and duration of preoperative implanted assist devices were analyzed.

Intaoperative data, i.e. duration of ischemia and reperfusion, cardiopulmonary bypass time, intra- and perioperative complications (severe bleeding, cardiac arrhythmia and increased PAP), were extracted from surgery and anesthesiology protocols.

Data extracted in the postoperative course (30 days) included: duration of mechanical ventilation, stay on intensive care unit (ICU) and total length of stay in hospital, implantation and duration of IABP, ECMO or RVAD and postoperative complications (severe bleeding, rethoracotomy, infection, arrhythmia, renal failure and death). Mean and median survival times were calculated as of December 1998.

Statistical analysis

Statistical analysis was performed using SPSS (SPSS Inc. Chicago, IL, USA). All Data are given as mean ± SD. Intragroup comparisons were performed using the paired *t*-test, while the unpaired *t*-test was used for intergroup comparisons after testing for normal distribution. Multiple regression analysis was performed to identify potential independent risk factors for RHF. All calculated *P*-values were two-sided and *P*-values <0.05 were considered statistically significant.

Results

From August 1983 to December 1998 621 heart transplantations in 591 patients were performed at Hannover medical school. Frequency of retransplantation was 5% (30 patients) during this time course. Gender distribution was 510 (86.3%) males and 81 (13.7%) females. Thirty-five (5.9%) patients met the criteria for severe RHF. With 82.9% males ($n = 29$) and 17.1% females ($n = 6$) in this group, the gender distribution of the overall patient population was well reflected.

To evaluate possible risk factors leading to RHF in the early postoperative course, data from RHF patients were compared with 35 matched pair control patients. General preoperative risk factors for cardiac disease did not differ significantly between study and control patients (Table 1). Analysis of underlying diseases in patients with RHF [dilatative cardiomyopathy (DCM): 20, ischemic cardiomyopathy (ICM): 11, valvular disease: one, hemangiothelioma: one, hypertrophic obstructive cardiomyopathy

Table 1. Demographic data and concomitant diseases.

	Right heart failure ($n = 35$)	Matched controls ($n = 35$)	Significance (*P*-value)
Age	47.3 ± 12.6	46.9 ± 13.1	0.865
Gender			0.383
Male	29	27	
Female	6	8	
Height (cm)	173.2 ± 8.9	172 ± 10.5	0.744
Weight (kg)	70.9 ± 13.9	71 ± 13.3	0.831
Body mass index (kg/m^2)	23.5 ± 3.5	23.7 ± 3.1	0.504
COPD	1	6	0.057
Diabetes mellitus	6	5	0.479
Hypertension	6	8	0.406
Hyperlipoproteinemia	5	9	0.202

Values given are mean ± SD.
Unpaired *t*-test. Group with right heart failure versus control group: $P = \text{NS}$.
COPD, chronic obstructive pulmonary disease.

(HOCM): one, acute graft failure: one] revealed no significant differences as compared with matched controls (DCM: 25, ICM: six, valvular disease: one, Ebstein's anomaly: one, undifferentiated left heart failure with intracardiac thrombus formation: one, HOCM: one; $P =$ NS). Fifteen patients with RHF after transplantation versus 23 matched controls had a history of previous open heart surgery ($P =$ NS). While none of the control patients had been subject to retransplantation, seven patients with RHF were already recipients of a second graft ($P = 0.001$). Of the retransplanted patients, three received a second graft because of acute graft dysfunction at day 1, 2 and 3 after an initial transplant and four received the second graft because of chronic allograft rejection.

Preoperative cardiac index did not differ among groups and the ejection fraction was even significantly higher in the RHF group (Table 2), indicating that preoperatively, the control group did not have a better left ventricular function as compared with the RHF group. However, preoperative PAP and PCWP were significantly higher in the RHF group, when compared with the control group (Table 2). Seven patients who developed postoperative severe RHF, preoperatively had received assist devices as follows: ECMO: two patients, RVAD: two patients, IABP: three patients.

Mean ischemic time of the graft was 177.1 ± 41.8 min vs. 181.5 ± 34.7 min (RHF group versus controls; $P =$ NS). Two patients with severe RHF died intraoperatively, none in the control group. Weaning time from cardiopulmonary bypass was significantly prolonged in patients with RHF as compared with matched controls (91.0 ± 66.7 min vs. 47.6 ± 22.6 min; $P < 0.05$). Frequency of postoperative complications was significantly higher in patients with severe RHF (Fig. 1). During or after transplantation, only patients from the study group required the implantation of mechanical assist devices: RVAD: three patients, ECMO: six patients, RVAD and ECMO: two patients, RVAD and IABP: two patients and RVAD, ECMO and IABP: four patients.

After exclusion of the two intraoperative deaths, the mean survival time in the RHF group was 242 ± 655 days vs. 1419 ± 1025 days in the control group as of December 1998. Median survival during the same time period was 8 ± 519 in RHF and 1169 ± 1040 days in control patients ($P < 0.0001$). Thirty-two of 35 patients with severe RHF died within 30 days after transplantation. No patient in the matched control group died during this early phase ($P < 0.001$) and as of December 1998 as the cut off date for data collection all but five matched control patients were alive. In our patient population early RHF contributes by 13.2% to all deaths after heart transplantation (Fig. 2a,b). With regard to the causes of death occurring during the entire study period (242 patients), RHF (13.2%) and acute allograft rejection (13.2%) were the second most frequent causes of death after transplant vasculopathy (19.8%).

Duration of stay on ICU was significantly prolonged in patients with severe RHF (9.5 ± 9.0 day vs. 2.3 ± 2.2 day; $P < 0.001$), as was the duration of mechanical ventilation (9.2 ± 8.9 day vs. 1.6 ± 1.5 day; $P < 0.001$).

Table 2. Cardiac status before transplantation.

	Right heart failure ($n = 35$)	Matched controls ($n = 35$)	Significance (P-value)
Left ventricular ejection fraction (%)	26.3 ± 16.1	17.0 ± 6.3	0.005*
Cardiac index (l/min/m^2)	1.9 ± 0.5	2.1 ± 0.5	0.654
PAP (mm Hg)	33.1 ± 8.3	20.2 ± 5.6	0.006*
PCWP (mm Hg)	23.5 ± 4.9	14.3 ± 4.5	0.005*
PVR_i (dyn/s^1/cm^5)$_i$	404.21 ± 137.4	224.8 ± 75.2	0.02*
Preoperative mechanical ventilation	3	0	0.12
Preoperative assist device (n)			
IABP	3	0	0.120
ECMO	2	0	0.246
RVAD	2	0	0.246
Total mechanical assist devices	7	0	<0.001

Values given are mean ± SD.
Group with right heart failure versus control group: *$P < 0.05$.
PAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedged pressure; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; RVAD, right ventricular assist device.

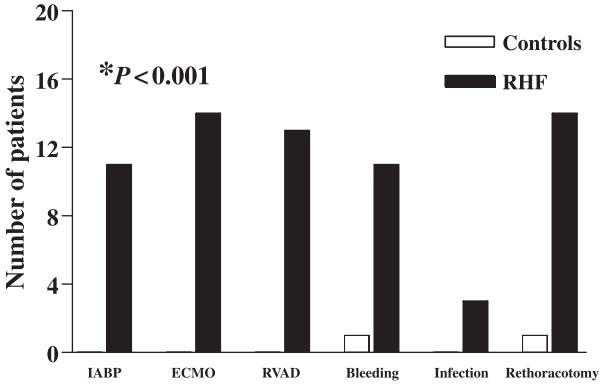

Figure 1 Morbidity after heart transplantation. Right heart failure (RHF) versus matched controls. IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; RVAD, mechanical right ventricular assist device. Significant difference between the RHF group and controls for all above parameters; *$P < 0.001$.

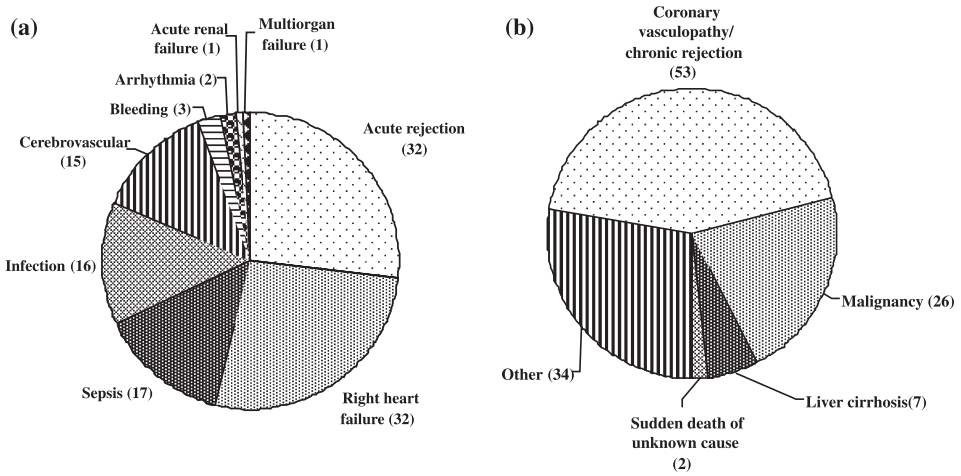

Figure 2 Early (a) and late (b) mortality after heart transplantation, absolute number of deaths in our heart transplantation recipient population during the entire study period is given (numbers in parentheses).

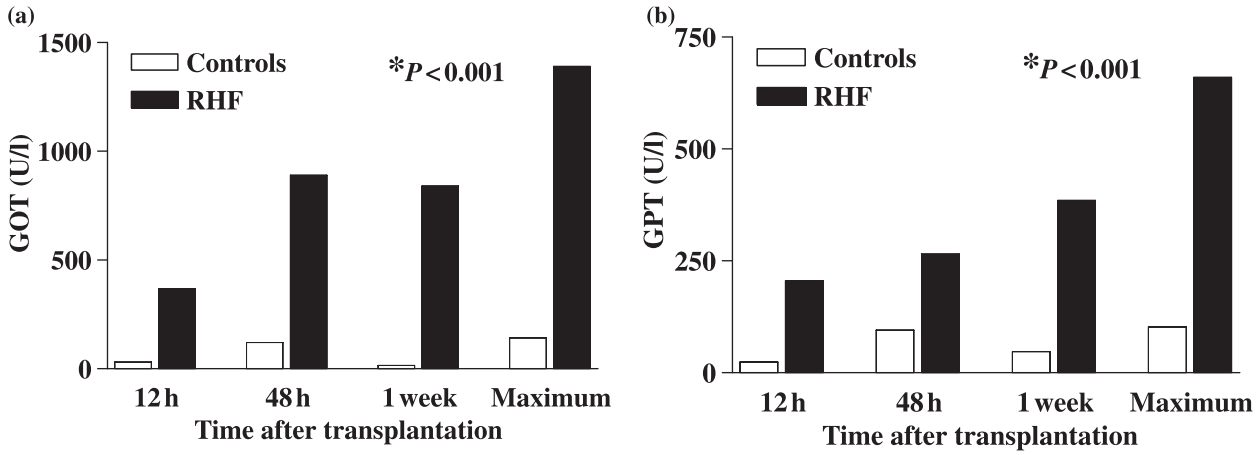

Figure 3 Glutamate oxalacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) serum levels in U/l are given in panel (a) and (b), respectively. Samples drawn 12 h, 48 h and 1 week after heart transplantation and, above that, the detected post-transplant maximum were analyzed. Serum transaminase activities were significantly higher in the RHF group at every time point after transplantation; $*P < 0.001$.

As an indirect marker of right ventricular failure the end organ function of liver, kidney and intestine were analyzed. GOT and GPT serum levels were significantly higher during the postoperative period in RHF patients at all time points as compared with matched controls (Fig. 3), as were creatinine serum levels (210 ± 55 μmol/l vs. 95 ± 42 μmol/l; $P < 0.001$) and lactate plasma levels (10.8 ± 3.2 mmol/l vs. 1.4 ± 0.6 mmol/l; $P < 0.001$) both 12 h after transplantation.

Discussion

Right heart failure is a severe complication after heart or combined heart-lung transplantation [8], after lung transplantation [9] or after implementation of a left ventricular assist device. Failure of the right ventricle is the underlying cause for a large fraction of the 30-day morbidity and mortality after heart transplantation and, besides acute rejection, the single most important cause of death in the early postoperative period [1].

As of today no prospective study for RHF has been conducted, but numerous retrospective analyses were performed. However, the comparability of these studies is limited as multiple different criteria were used to define RHF. Hence, we defined severe RHF in that way, that patients had to fulfill restrictive inclusion criteria set at arbitrary chosen, but clinically relevant levels. Strictly following the inclusion criteria, the incidence, possible risk

factors and clinical outcome of severe RHF after heart transplantation at our institution were analyzed.

Patients with RHF showed significantly increased incidences of all complications that were analyzed, including an extremely high mortality, in our study population. This demonstrates the clinical importance of RHF after heart transplantation. Hereby RHF was already evident during surgery in most patients, indicated by some degree of right ventricular ballooning, significantly increased weaning time from cardiopulmonary bypass and the need to implant assist devices in some patients. Our data show that early high GOT, GPT, creatinine or lactate serum levels after heart transplantation are a reliable indicator of RHF and are because of systemic congestion and subsequent organ damage. However, the therapeutic relevance of these parameters is low, as the outcome of patients with manifest peripheral organ damage is markedly impaired, as is shown by our data for our RHF population.

As preoperative risk factors for RHF after heart transplantation an elevated pulmonary artery and PCWP were identified, indicating the importance of an elevated PVR in the potential heart graft recipient. This result is in line with numerous other studies [8,10].

Despite implementation of assist devices, most patients with severe RHF died in the early postoperative course. The benefit of assist device implementation in right ventricular failure remains controversial [11–13]. In our study, patients did not benefit from assist device implementation. A potential bias might be, that assist device implantation was usually indicated after the patient had already developed manifest severe RHF, and therefore might have been to late to effectively improve prognosis. While several patients received an assist device already prior to heart allografting, it has to be taken into consideration that these patients received their assist device as an emergency bridge to transplantation with a consecutive emergency transplant. It is well known, that the perioperative risk is much higher using this concept as compared with an elective approach as usually recommended in heart transplantation and as also recommended in assist device implantation as bridge to transplantation. Preoperative assist devices were implemented in several RHF, but not in control patients. While this potentially could compromise results selectively in the RHF group, it has been postulated by various authors, that preoperative implementation of a mechanical assist device might improve outcome after heart transplantation by preoperative stabilization of hemodynamics [14,15]. In these studies postoperative RHF and kidney failure were less frequent, and overall morbidity and mortality were decreased in heart transplant recipients that received a preoperative assist device as compared with patients without assist device [14]. This explains why a preoperative assist device not necessarily accounts for an increased risk, and therefore we decided to also include patients with pretransplant assist device implantation in our analysis. Above that, rate of emergency procedures in general with or without assist device implantation was identical in both groups.

Different additional intraoperative risk factors can lead to early postoperative RHF and should therefore be considered in heart transplantation. Numerous studies evaluating different preservation solutions, influence of the duration of cold and warm ischemia and influence of PEEP in the recipient have been performed [4,16–21]. Patients might benefit from consideration of these results and therefore carefully chosen preservation solutions and well established surgical techniques to reduce duration of ischemia are believed to be mandatory in heart transplantation. As there is not much room left for further improvement of ischemic time or surgical technique, any progress that might be expected has to evolve from innovative preservation techniques. We previously reported on experimental improvement of right heart function after transplantation using a C1-Esterase Inhibitor [22] and the calcium-desensitizing compound BDM [23] in a porcine model. However, it remains to be proven that clinical application of these techniques has a beneficial effect on the incidence of RHF.

Limitations of the study

Several important limitations of the study have to be considered. The disadvantages of a retrospective approach lie in the relative difficulty to standardize inclusion criteria in the RHF group. While we decided to set up very restrictive criteria for severe RHF to avoid a potential bias by subjective impressions by the surgeon of the degree of failure, it is obvious that the actual proportion of patients with transient postoperative right ventricular failure is much higher than the 5.9% in our study. To evaluate RHF more sensitively a prospective approach would have been required. The RHF group is of heterogenous composition. While this would be natural because of its definition by a symptom, the fact of a much higher proportion of retransplantation recipients might potentially influence the results and bias the analysis of potential independent risk factors. Patients with a redo heart transplantation were not excluded from our retrospective study. Analysis of preliminary data revealed, that in two of the retransplantation recipients the second procedure was performed more than 6 months after the primary grafting. It has been shown, that this would not increase the early risk as compared with patients with a primary heart transplantation [15,24]. Above that, our data showed, that of the three survivors of the severe RHF,

one was a recipient of an emergency retransplantation. Within the RHF group, there was no difference with respect to morbidity and mortality between recipients of a primary or a secondary (re-)transplantation. Multivariate regression analysis showed, that retransplantation is not a significant risk factor for development of severe RHF. Hypothetical exclusion of recipients of a retransplantation from analysis would not have changed our results with respect to morbidity and mortality as well as to associated parameters in general. Taken all these considerations together, we decided to include retransplantation into our study groups. Another important limitation of the study is the lack of donor data. While consistent common sense acceptance criteria were applied for the donor hearts in general, reliable specific data on such important measures as donor management, mechanism of brain death or hemodynamic condition of the donor were not available retrospectively for a large fraction of patients. This data was thus excluded from the study. The potential influence of brain death associated parameters or other donor factors might therefore remain undetected in our study.

It has been previously shown, that early aggressive treatment of increased postoperative pulmonary artery resistance with intravenous or intrabronchial application of vasodilators of the pulmonary vasculature could prevent manifest RHF [25–27]. As right heart function not only depends on intrinsic factors like myocardial contractility and compliance, but also on extrinsic factors, i.e. preload, afterload, perfusion pressure of the right coronary artery and also left ventricular volume load [28], it should be considered, that despite acceptable basic myocardial function, the patient after cardiac transplantation might still be at risk to develop severe RHF.

As has been described previously, our data confirm that RHF is the most important cause of death in the early postoperative course [1], and the second most frequent cause of death after heart transplantation in general. Prevention of RHF after cardiac transplantation requires careful evaluation of recipient pulmonary hypertension and its effective treatment not only intraoperatively, but also preoperatively.

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