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TWENTY-SEVEN YEARS EXPERIENCE WITH HEART TRANSPLANTATION

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Abstract. *Background: The objective of this study was to evaluate long-term outcomes of cardiac transplantation (HTx) in different eras of innovation at a single center during a period of 27 years. Methods: We performed a retrospective analysis of 960 cardiac allograft recipients (40 re-HTx) between 1981 and 2008. The results of 6 different eras based on milestones in HTx were analyzed: Era1: the early years (n = 222, 1981 - 1992); era2: introduction of inhalative nitric oxide, prostanoids, University of Wisconsin solution (UW) replacing Bretschneider's solution (HTK, n = 118, 1992 - 1994); era3: statins (n = 102, 1994 - 1995); era4: tacrolimus (n=115,1995-1996); era5: mycophenolate mofetil (MMF, n = 143, 1997 - 2000) and era6: sirolimus (n = 300, 2000 - 2008). Outcome variables were survival, freedom from transplant vasculopathy (CAV) and from acute rejection episodes (ARE). Results: Differences in survival was found comparing era1 and era2 with era4 and era6 ($p < 0.001$). Organ preservation through UW demonstrated a significantly better survival compared to HTK ($p < 0.001$). Less ARE occurred in patients receiving tacrolimus-sirolimus or tacrolimus-MMF ($p < 0.001$). Patients receiving tacrolimus-MMF showed less CAV than treated with cyclosporine-MMF ($p < 0.005$). There were more ventricular assist device implantations and more re-HTx in era6 ($p < 0.0001$). Conclusions: Although the causes for improvement in survival over time are multifactorial, we believe that changes in immunosuppressive therapy have had a major impact on survival.*

Keywords: Heart transplantation, immunosuppression, survival, chronic allograft vasculopathy, acute rejection.

1. Introduction

On August 19, 1981, the first successful heart transplantation (HTx) was performed by Reichart and colleagues at our center and on July 8, 2008 the one-thousandth heart transplantation. During the last 27 years many advances have been made in the field of surgical care, organ preservation, perioperative management, immunosuppression, and infection control. These advances have contributed to establish heart transplantation as an effective therapy for patients with end-stage heart disease [1]. Nowadays, the patients who undergo HTx differ from those in earlier periods. There are an increasing proportion of older patients

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with multiple concomitant diseases, patients with mechanical circulatory support devices or re-transplantations (re-HTx). This results in a larger number of sensitized patients who are at high risk for the development of various adverse immunologic effects [2]. On the other hand a large variety of immunosuppressive protocols have been developed and the individualization of immunosuppression provides a powerful tool for the prevention of rejection and the avoidance of side effects [3]. In this study we summarize the data of our 27 year experience in 1000 HTx in order to correlate long-term patient outcomes with different eras of innovation.

2. Material and Methods

Patients

We reviewed the data of 960 patients who underwent HTx at our center between August 1981 and July 2008 for the treatment of end-stage heart disease. A total of 1000 transplants, including 40 re-transplants in 38 patients, have been performed.

Donor acceptance criteria

Recipients were selected based on ABO blood type compatibility and donor-recipient size matching (usually within 20% of body mass index). Until 2005 the prospective donor-specific HLA cross-matching was only performed when recipients were tested positive for panel reactive antibodies (PRAs) greater than 10%. Since 2005 PRA, ELISA and LUMINEX was performed for all patients. For pre-sensitized patients “virtual cross matching” according to donor HLA typing, prospective and retrospective B- and T-cell cross matching was realized. Donor hearts are accepted, when preformed antibodies have been ruled out by virtual cross matching [26, 27]. In highly pre-sensitized patients plasmapheresis or treatment with monoclonal antibodies was initiated in order to reduce the PRA positivity on retesting. Organ donation and transportation was organized by Eurotransplant International Foundation in Leiden (Netherlands).

Surgical methods

In most of the patients surgery was performed in the biatrial technique first described by Lower and Shumway except patients after atrial switch operations [4]. Furthermore 74 patients were bridged to transplantation by implantation of a ventricular assist device (VAD). The mean ischemic time was 3.43 ± 1.01 hours.

Organ preservation

We used Bretschneider’s solution (HTK) for cardioplegic arrest of the donor hearts until 1991 (n = 254). In 1992 we replaced Bretschneider’s solution by University of Wisconsin solution (UW, n = 628) [5]. Other preservation solutions, mostly Celsior (n = 107), were used in the remaining patients (n = 118). We did not modify the preservation technique and still use topical cooling with

infusion of cold saline via a left ventricular vent after the left atrial anastomosis is finished. The so called “hot shot” is not established at our centre.

Immunosuppressive therapy

In 1981 the standard triple immunosuppressive regimen consisted of cyclosporine (CyA), azathioprine (AZA) and methylprednisolone. Immunosuppression was initiated with administration of methylprednisolone (500 mg) intravenously approximately 20 minutes before releasing the aortic cross clamp. On arrival at the intensive care unit (ICU), CyA was added in order to achieve initial serum levels of 250 to 350 ng/mL for the first 3 months, and 200 to 250 ng/mL for the first year. The trough levels were tapered down individually with regard to acute rejection episodes (ARE), infections and renal function ending up at a maintenance target trough level of 100 ng/mL late after transplantation. Methylprednisolone therapy was continued postoperatively at a dose of 125 mg every 8 hours for 3 doses. The initial daily dosage of 1 mg/kg body weight was continuously tapered down to 0.1 mg/kg body weight in the first month. Since 1995 methylprednisolone was withdrawn 6 months after transplantation in all patients who did not suffer from multiple ARE.

In 1993, tacrolimus (Tac) was introduced and consecutively replaced CyA in most of the de novo patients. Starting with an intravenous dose ranging from 0.01 mg/kg/day to 0.03 mg/kg/day, the daily Tac dose was adjusted in order to reach target trough levels of 10 to 15 ng/mL. After the initial postoperative period Tac was administered orally aiming at the same trough levels of 10 to 15 ng/mL for the first three months. Then the target trough levels were tapered to 9 - 12 ng/mL until month 12 and to 7 - 10 ng/mL for the further course. Completing the triple regimen, azathioprine (AZA) was administered at a daily dose of 2 - 4 mg/kg body weight, depending on the patient’s white blood cell count. In 1997, mycophenolate mofetil (MMF) began to replace AZA, and its combination therapy with Tac was found to be associated with suppression of ARE [6]. Therapeutical drug monitoring for MMF was introduced in 1997 and the target levels for MMF were 1.5 to 4 µg/mL. In patients who suffered from ARE under target trough levels on a CyA-based immunosuppression regimen, the immunosuppressive regimen was switched from CyA to Tac. In 2000, sirolimus (Sir) was introduced because of its superior side effect profile in terms of calcineurin-inhibitor (CNI)-related renal failure which represents a frequent complication after cardiac transplantation. In a prospective study Groetzner et al. could show that conversion from CNI-based immunosuppression to MMF and Sir in heart transplant recipients with chronic renal failure was safe, preserved graft function and improved renal function [7].

Diagnosis and management of acute rejection

Endomyocardial biopsies were performed according to a standardized schedule to diagnose ARE. ARE with an ISHLT grade $\geq$ 2 were treated with 3 doses of 500 mg methylprednisolone intravenously for 3 days. The same treatment was considered in patients with ISHLT grade $\geq$ 1B and hemodynamic compromise or other clinical signs of rejection such as edema, dyspnea or cardiac rhythm disorders. When endomyocardial biopsy confirmed persistence of rejection after the first steroid pulse, a second intravenous treatment with methylprednisolone was administered or - depending on the severity of rejection - intravenous mono- or polyclonal antibody preparations such as orthoclone monoclonal antilymphocyte antibody (OKT3, until 1994) or antithymocyte globulin (ATG) were administered.

Antiinfective prophylaxis

Since 1994, cytomegalovirus (CMV) prophylaxis was initiated with ganciclovir in patients at high risk for CMV infection (donor CMV-positive, recipient CMV-negative). Patients presenting with other CMV constellations were scheduled for a preemptive approach with CMV-testing and ganciclovir-treatment only after proven CMV-viraemia. Starting with a daily dose of 2.5 to 5.0 mg/kg intravenously for 2 weeks, antiviral therapy was continued for another 3 months with oral ganciclovir and since 2001 with oral valganciclovir. Additionally, inhaled amphotericin B and oral nystatin were administered for 7 days for antifungal prophylaxis. Trimethoprim-sulfamethoxazole was administered at 960 mg twice per week for pneumocystis carinii prophylaxis for the first 6 months after HTx.

Perioperative management

In 1994 we implemented prophylactic and aggressive treatment of hyper-cholesterolemia with statins at our institution in order to reduce the incidence and development of transplant vasculopathy (TVP) [10]. In 1996 perioperative inhalative nitric oxide (NO) was introduced in order to prevent post operative right ventricular failure in patients with high pulmonary vascular resistance [8]. In the same year we started to use inhalative iloprost (prostacyclin analogue) for the treatment of pulmonary hypertension at our institution [9].

Follow-Up

In order to detect acute or chronic rejection and infectious complications, every patient underwent regularly detailed examination including coronary angiography, endomyocardial biopsy, echocardiography, chest x-ray, routine laboratory values, trough level-monitoring for immunosuppressive drugs and CMV-detection.

Definition of the eras

The entire group of 960 transplant recipients (with 40 re-HTx) was divided into 6 eras based on the introduction of new techniques or drugs in the field of HTx. The beginning of each era was set, whenever we used a new innovation for the first time:

Era 1: the early years of HTx at our center with cyclosporine (CyA) and azathioprine (AZA, n = 222, 1981 - 1992);

Era 2: introduction of inhalative nitric oxide (NO), prostanoids, and University of Wisconsin solution (UW) replacing Bretschneider's solution (HTK, n = 118, 1992 - 1994);

Era 3: introduction of statins (n = 102, 1994 - 1995);

Era 4: introduction of tacrolimus (Tac, n = 115, 1995 - 1996);

Era 5: introduction of mycophenolate mofetil (MMF, n = 143, 1997 - 2000) and Era 6: introduction of sirolimus (Sir, n = 300, 2000 - July 2008).

Statistical Analysis

For computer-assisted statistical data analysis the software package R was used (version 2.6.0; the R Project for Statistical Computing). Values of continuous variables are expressed as mean ± standard deviation. Survival estimates were calculated with the Kaplan-Meier method and the log-rank test (Mantel-Cox) was performed to calculate probability values. A Cox-proportional hazard model was calculated for multivariate analysis where appropriate. For multiple group comparisons in the demographic data an analysis of variance (ANOVA) was used to discriminate significant differences.

3. Results

Demographics

Between August 1981 and July 2008, 1000 patients underwent HTx at the Medical Center of the University of Munich, Grosshadern. There were 819 male (81.9%) and 181 female patients (18.1%). At the time of transplantation, 91 patients were younger than 18 years (9.1%), 758 patients were aged between 18 and 60 years (75.8%), and 151 patients were older than 60 years (15.1%). In this study group, end-stage heart disease was caused by dilative cardiomyopathy (DCM) in 540 patients (54.0%), by ischemic cardiomyopathy (ICM) in 276 patients (27.6%), and by other diseases such as congenital heart disease, cardiac tumors, or advanced valvular disease in 184 patients (others=18.4%). The mean patient age was 45.9 ± 16.3 years, ranging from 1 month to 73.4 years, with a mean donor age of 32.3 ± 14.4 years, ranging from 1 month to 66.7 years at the time of transplantation. In the entire study group 36 patients received a second transplant and 2 patients received 3 transplants. The mean follow-up time was 7.22 ± 6.2 years. In most of the patients surgery

was performed in the biatrial technique first described by Lower and Shumway except patients after atrial switch operations [4]. We found only 15 patients with severe tricuspid valve insufficiency and necessity of surgery (1.5%). 7% of the patients required a pacemaker implantation after HTx (70 patients). Heterotopic heart transplantation was performed in 2 patients (0.2%).

The distribution of age, gender, and pre-transplant diagnosis showed statistically significant changes through the different eras, as shown in **table 1**.

	Era 1 1981 – 1992 n = 222	**Era 2 1992 – 1994 n = 118**	**Era 3 1994 – 1995 n = 102**	**Era 4 1995 – 1996 n = 115**	**Era 5 1997 – 2000 n = 143**	**Era 6 2000 – 2006 n = 300**	**p Value**
Recipient age (years)	45.2 ± 11.9	46.3 ± 15.2	42.9 ± 18.9	49.6 ± 12.8	49.0 ± 17.1	44.1 ± 19.2	< 0.004
Donor age (years)	27.8 ± 10.4	30.8 ± 12.8	28.2 ± 14.0	32.5 ± 13.1	37.6 ± 15.8	34.7 ± 16.0	**< 0.0001**
Recipient gender in % (m/f)	87.9 / 12.1	81.5 / 18.5	83 / 17	83.3 / 16.7	81 / 19	77.6 / 22.4	0.01
Donor gender in % (m/f)	72.5 / 27.5	67.8 / 32.2	63.8 / 36.2	67 / 33	54.9 / 45.1	72.4 / 27.6	0.09
Age distribution							
< 19 years	2.2 %	9.2 %	11.3 %	4.2 %	10.3 %	14.7 %	
19 – 60 years	90.5 %	77.7 %	71.7 %	84.2 %	71.4 %	64.4 %	
> 60 years	7.4 %	13.1 %	17 %	11.7 %	18.3 %	20.9 %	
Diagnosis							
DCMP	41.5 %	50.8 %	52.8 %	56.7 %	60.3 %	60.3 %	
ICMP	42 %	33.8 %	20.8 %	25 %	32.5 %	25.9 %	ns
Others	16.5 %	15.4 %	26.4 %	18.3 %	7.1 %	13.8 %	
VADs (n=74)	3 (6.6 %)	7 (5.9 %)	5 (4.9 %)	6 (5.2 %)	10 (6.9 %)	**43 (14.3%)**	**< 0.0001**
Retransplants (n=40)	7 (3.2 %)	3 (2.5 %)	4 (3.9 %)	4 (3.5 %)	4 (2.8 %)	**18 (6 %)**	**< 0.0001**
Ischemic time (hours)	2.50 ± 0.51	3.08 ± 0.54	3.02 ± 0.54	3.39 ± 0.49	3.22 ± 0.59	**4.00 ± 0.51**	**< 0.0001**

Table 1. Distribution of demographic variables among different eras of innovation.
DCMP = dilated cardiomyopathy, ICMP = ischemic cardiomyopathy,
Others = congenital heart disease, cardiac tumors, advanced valvular disease etc.,
VAD = ventricular assist device.

There was an increase in the proportion of donors with advanced age ($p < 0.0001$) and of female recipients ($p < 0.01$) in the later eras. The proportion of patients requiring a ventricular assist device (VAD) increased significantly in the later eras (6.6% vs. 14.3%, $p < 0.0001$). Moreover, in era 6 significantly more patients were re-transplanted (6%, $p < 0.0001$) and ischemic time increased up to 4.00 ± 0.51 hours ($p < 0.0001$).

Patient survival

The actuarial survival of the entire study group was 75.9%, 68.5%, 56.3%, 44.0%, 38.2% and 28.2% at 1, 5, 10, 15, 20 and 25 years, respectively **(figure 1a-c)**.

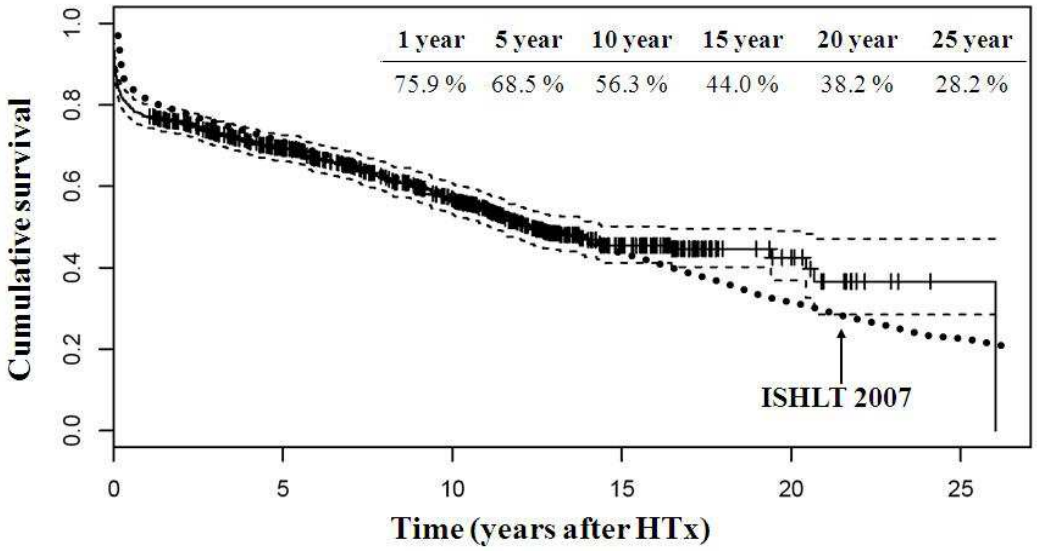

Figure 1a. Cumulative survival of 960 patients undergoing heart transplantation between August 1981 and July 2008

We could show a better cumulative survival 20 and 25 years after HTx comparing with the ISHLT data **(figure 1a)**. The patient with the longest survival of 27 years is still alive.

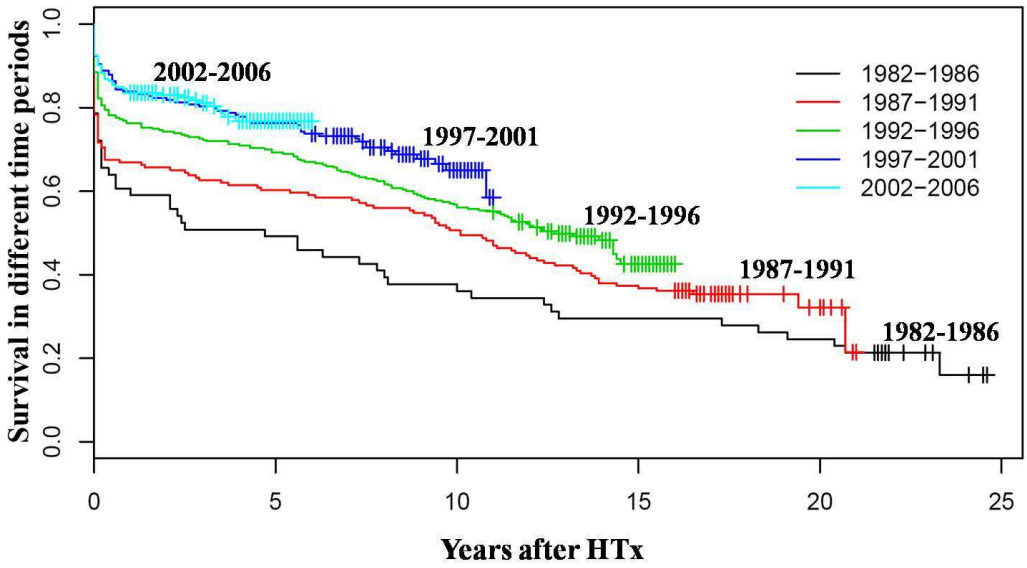

Figure 1b. Cumulative survival improved with every 5 year report

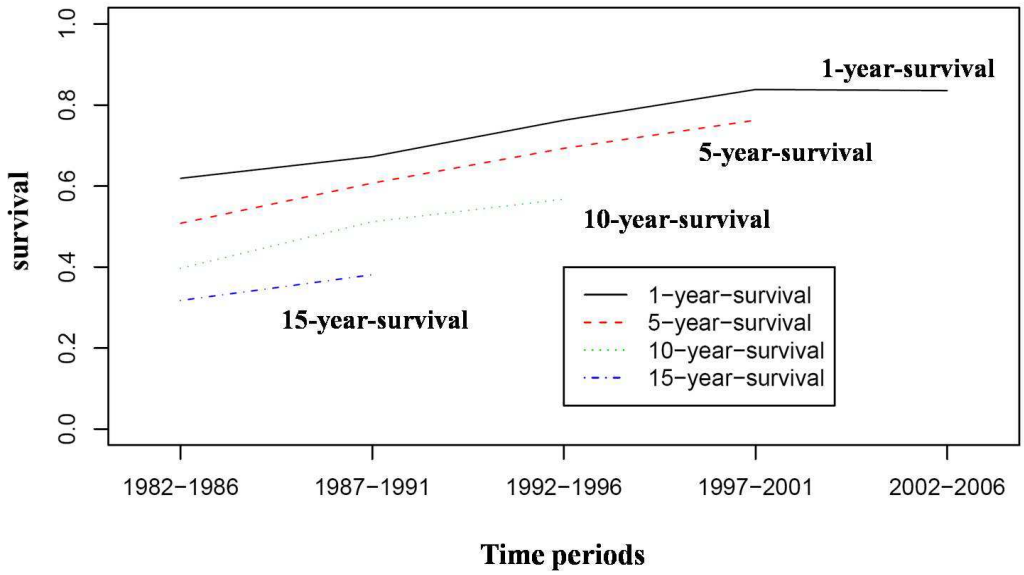

Figure 1c. The improvements of the 1-, 5-, 10- and 15-year survival

With regard to the eras, actuarial survival at 1, 5, 10, 15, 20 and 25 years for era 1 was 65.3%, 57.7%, 46.8%, 35.6%, 30.8 and 22.8; survival at 1, 5, 10 and 15 years for era 2 was 70.3%, 64.4%, 46.6 and 31.4%; survival at 1, 5 and 10 years for era 3 was 70.2%, 68.1% and 61.7%; for era 4 was 83.5%, 73.9% and 61.7% and for era 5, 80.5%, 73.5%, 62.1%. For era 6 the actuarial survival at 1, 5 and 10 years was 82.3%, 74.3% and 61.7%. Significant differences in survival were found when comparing era 1 and era 2 with the tacrolimus-era (era 4) and the sirolimus-era (era 6, $p < 0.001$, **figure 2**).

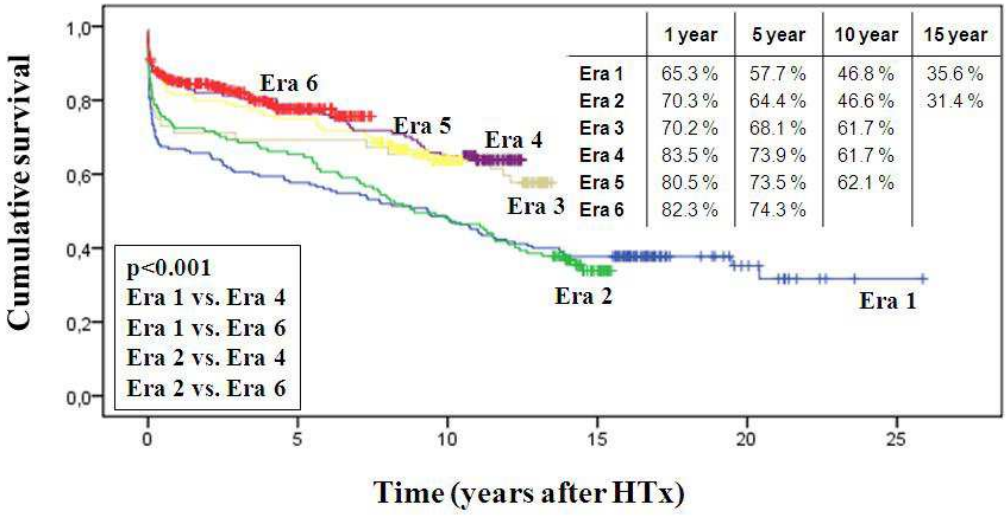

Figure 2. Cumulative survival of patients undergoing heart transplantation between 1981 and 2008 in six different eras of innovation. Era 1: early years of HTx at our center (1981 - 1992); era 2: introduction of NO, prostanoids, and UW replacing HTK (1992 - 1994); era 3: introduction of statins (1994 - 1995); era 4: introduction of Tac (1995 - 1996); era 5: introduction of MMF (1997 - 2000); era 6: introduction of Sir (2000 - 2008), $p < 0.001$.

Actuarial survival at 1, 5, 10, 15 and 20 years based on pre-transplant diagnosis was 80.6%, 74.4%, 64.2%, 54.5 and 48.9% at 20 years for DCM, and 73.5%, 65.1%, 48.1% and 31.1 at 15 years for ICM and 65.1%, 53.4%, 42.1% and 31.1% at 15 years for other diseases (e.g. congenital heart disease, cardiac tumors, or advanced valvular disease). Long-term survival in patients with DCM was superior compared to patients with ICM ($p < 0.001$). When compared to patients with other diseases, ICM patients revealed a trend towards inferior survival (figure not shown).

Furthermore, there was no significant difference in survival for male patients compared with female patients ($p = 0.135$, data not shown), but there was a trend towards a better long-term-survival for female patients. Comparing the gender

from donors and recipients revealed a trend towards a better long-term-survival for female recipients with male donor hearts ($p = 0.238$, figure not shown).

Comparing the different groups of age showed that survival of recipients younger than 18 years was significantly better than survival of recipients aged between 18 and 60 years ($p < 0.001$) and also better than survival of patients older than 60 years ($p < 0.001$, figure not shown).

There was a superior early and long term survival in patients, who were transplanted after 1992, when UW preservation solution replaced Bretschneider's solution at our institution ($p < 0.001$, **figure 3**). Actuarial survival at 1, 5, 10 and 15 years was 80.1%, 72.3%, 58.5% and 46.4%, respectively, when UW was used for preservation, and 66.1%, 58.7%, 47.3% and 36.4%, respectively, when HTK was used.

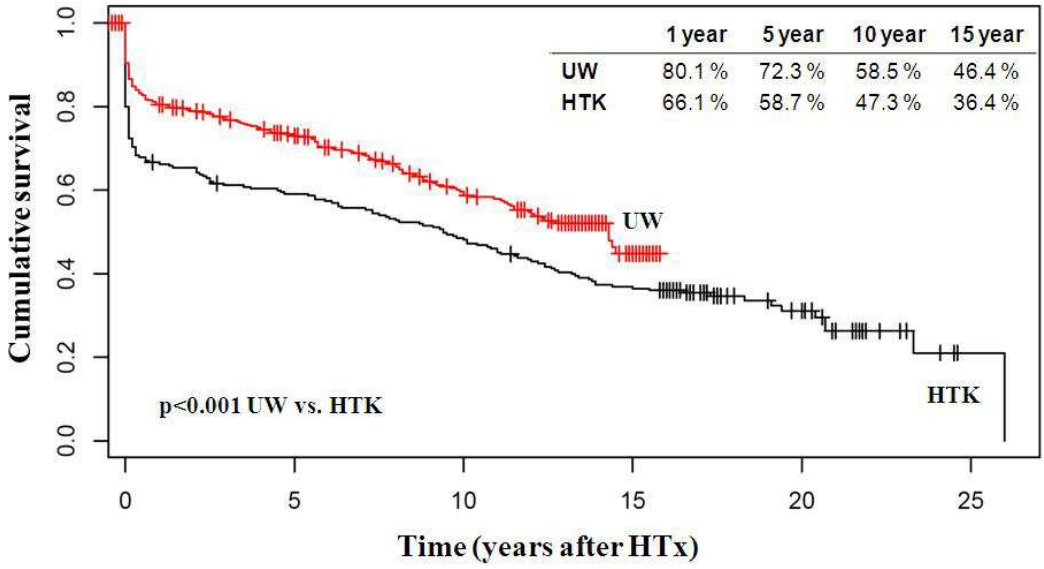

Figure 3. Cumulative survival of patients undergoing heart transplantation between 1981 and 2007 comparing University of Wisconsin preservation solution (UW) versus Bretschneider's solution (HTK), $p < 0.001$.

The survival of patients undergoing re-HTx was inferior to the survival of patients, who were not re-transplanted ($p < 0.001$, figure not shown). Actuarial survival at 1, 5, 10 and 15 years of re-transplanted patients was 56.5%, 36.9%, 17.6% and 8.8%, respectively, and 76.7%, 69.8%, 57.4% and 45.3%, respectively, in patients, who were not re-transplanted.

Actuarial survival based on immunsuppressive regimen at 1, 5, and 10 years were as follows: 69.5%, 61.3% and 47.6% respectively for CyA-AZA, 87.9%, 83.1%,

and 77.0%, respectively for the combination of CyA-MMF, 77.5%, 74.6%, and 68.8%, respectively for Tac combined with AZA, 79.9%, 72.7%, and 63.1%, respectively for the combination of Tac-MMF. Actuarial survival at 1 and 5 years was 92.4%, and 85.5%, respectively for Tac-Sir. Finally, actuarial survival at 1 year was 90.9%, respectively for Sir-MMF (**figure 4**).
Patients under immunosuppressive therapy with CyA-MMF, Tac-MMF or Tac-Sir had a significantly better survival than patients receiving CyA-AZA ($p < 0.001$, **figure 4**).

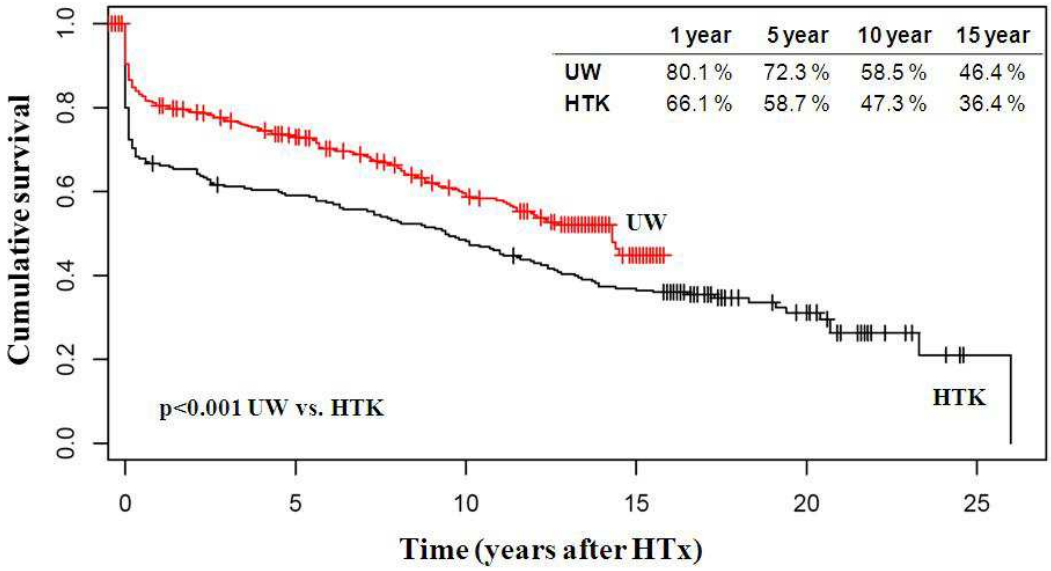

Figure 4. Cumulative 1-, 5-, and 10 year survival of patients undergoing heart transplantation between 1981 and 2007 comparing different immunosuppressive regimen, $p < 0.001$.

Furthermore patients receiving Tac-MMF had an inferior survival when compared to patients receiving Sir-MMF, TAC-Sir and CyA-MMF. This is likely due to the fact that in the Tac-MMF group there were significantly more patients with diabetes than in the other groups (Hazart-ratio 2.1, $p = 0.0009$). The survival of patients receiving MMF in their immunosuppressive regimen was significantly better than patients receiving AZA ($p < 0.001$, data not shown).

Acute Rejection

Freedom from ARE based on different immunosuppressive regimen is shown in **figure 5**. Freedom from ARE at 1, 5, and 10 years were as follows: 43.5%, 39.7%, and 38.7% for CyA-AZA, 55.0%, 49.1%, and 47.1% for the combination of CyA-MMF, 30.4% and 27.0% for Tac-AZA, 80.4%, 77.5%, and 75.6% for the combination of Tac-MMF. Freedom from ARE at 1 and 5 years was 94.5%, and 87.9%, respectively for the combination of Tac-Sir and 70.0% and 58.3% for

Sir-MMF. CyA-MMF and Tac-MMF was significantly better regarding ARE than CyA-AZA and Tac-AZA ($p < 0.001$). The best combination regarding ARE was Tac-Sir ($p < 0.001$ vs. all groups, except Tac-MMF).

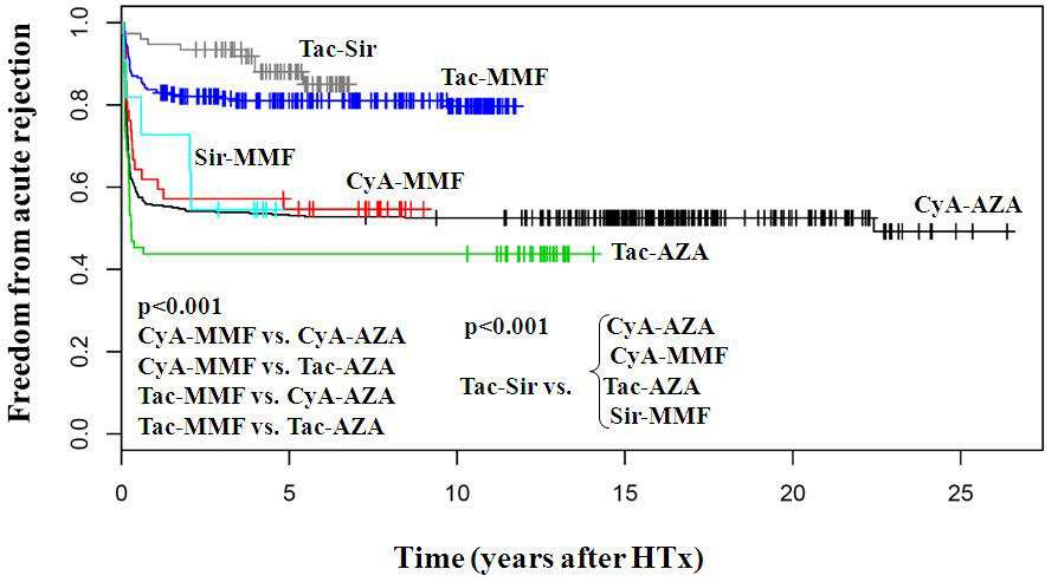

Figure 5. Freedom from acute rejection (ARE) based on different immunosuppressive regimens, $p < 0.001$.

Graft Coronary Artery Disease

Freedom from CAV at 1, 5, 10, 15 and 20 years were as follows: 97.3%, 82.4%, 69.8%, 50.9% and 37.3% for CyA-AZA; 86.5%, 69.8%, and 43.2%, for CyA-MMF; 90.0%, 73.6%, and 61.1% for Tac-AZA; 95.9%, 82.9%, and 69.0% for Tac-MMF. Freedom from CAV at 1 and 5 years was 96.8% and 87.6% for Tac-Sir; 97.2%, and 93.0%, respectively for Sir-MMF (**figure 6**). Patients receiving Tac-MMF showed significantly less CAV than patients treated with CyA-MMF ($p < 0.005$).

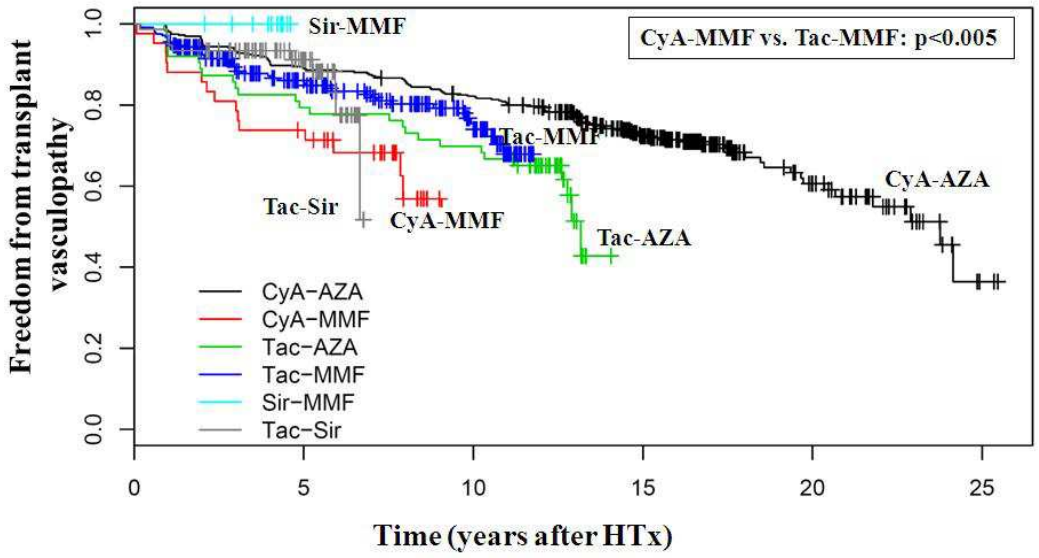

Figure 6. Freedom from cardiac allograft vasculopathy (CAV) based on different immunosuppressive regimen, $p < 0.005$.

4. Discussion

This study represents a large series of patients undergoing HTx at a single center by a team whose core members have not changed over time. Even if it seems that the division in 6 different eras did not allow individualized therapy, our patients received an individualized immunosuppressive regimen according to age, co-morbidities and time after HTx. Especially older patients with increased risk for infectious complications, renal failure and neoplasms necessitate a tailored immunosuppression [3]. This division in eras allows to examine trends and study changes which have occurred in the management of patients with end-stage heart disease over a period of 27 years. Here we could show subsequent improvement in survival with each era of innovation **(figure 2)**. Although the reasons for improved survival are of multifactorial origin, we ascribe the main advancements to evolving immunosuppressive therapy and improvements in immunologic monitoring. This hypothesis is supported by the subsequent diminishing incidence of ARE in relation to the gradual refinements in immunosuppressive therapy **(figure 5)**.

Patients Survival

The cumulative survival of 38.2% at 20 and 28.2 % at 25 years after HTx (**figure 1a**) was higher than shown in the ISHLT data [24]. The most likely reasons for these good results are the high rate of freedom from ARE, the use of UW preservation solution and the very experienced team whose core members have

not changed over time. Cumulative survival improved significantly during the different time periods (**figure 1b**) and was lower in the early phase of our HTx program (era 1, 1981 to 1992, **figure 2**). In this era the immunsuppressive regimen consisted of CyA and AZA. The next era (era 2, from 1992 to 1994) was heralded by the introduction of UW, which replaced HTK-solution because UW had shown superior results for cardiac perfusion in experimental studies [5]. Comparing the cumulative survival of patients receiving organ preservation with HTK vs. UW, we found a significant better survival in the UW group (**figure 3**). As it is displayed in the survival curve the UW group showed not only a decreased early mortality, but also a better long term survival. The 1 year survival was 80.1% in the UW group versus 66.1% in the HTK group. The long term survival 15 years after HTx was 46.4% in the UW group and 36.4% in the HTK group. As expected the organ preservation solution plays a significant role in early graft survival. Reichenspurner et al could show a decrease in the incidence of early, ischemic time-dependent graft failure [19]. Nevertheless also long term survival improved. In an experimental study from Kajihara et al. UW solution led to a better left ventricular function and a greater potential for long term preservation [20]. Furthermore Michel et al showed in rat hearts that UW resulted in better heart contractility, lower LDH and CK levels during perfusion then HTK [21]. The multivariate analysis we made, did not show differences between the groups regarding age, diabetes, infections or ARE. It is also noteworthy that the use of UW coincided with the introduction of perioperative inhalative nitric oxide (NO) and aerosolized iloprost both to prevent post operative right ventricular failure in patients with high pulmonary vascular resistance [8, 9]. Era 1 and 2 showed an improved survival at 1, 5, and 10 years against era 4 and 6 (**figure 2**).

No significant increase in actuarial survival was observed after introduction of statins for the treatment of hypercholesterolaemia after HTx in era 3. Nevertheless the aggressive treatment of hypercholesterolemia had proved to lower the incidence and development of CAV in adults [10] as well as in children [11] and survival improved in the following periods also as result of the statin treatment. The next major periods began with the introduction of Tac (era 4), MMF (era 5) and Sir (era 6) as main immunosuppressant agents (**figure 2**). The survival and freedom from ARE and TVP of patients receiving MMF was significantly higher than patients receiving AZA. A review of major clinical trials with MMF in HTx from Kobashigawa and Meiser demonstrated that MMF provided long-term benefits in reducing CAV and increasing survival [23].

Nevertheless there was no significant difference in survival between era 4, 5 and 6. The multivariate analysis did show differences between these 3 groups regarding age, diabetes, ventricular assist devices, ischemic time and re-HTx. Donor and recipient age increased continuously over time. The patients had significantly more ventricular assist devices during their waiting time. The

ischemic time was longer and we had more retransplanted patients (see table 1). Furthermore we accepted more co-morbidities (diabetes, renal insufficiency) in recent eras. Therefore, even with the newer generation of immunosuppressive agents no better survival was observed between era 4, 5 and 6.

In most of our patients surgery was performed in the biatrial technique by Lower and Shumway. This method is easier to perform and does not lead to caval stenoses. On the other hand this technique might result in more tricuspid regurgitations. Nevertheless the data did not support any definite mandate for either of the surgical techniques. Grande et al. observed that tricuspid regurgitation occurs in 53.1% of the patients transplanted with the Lower/Shumway technique and in 41.9% of patients operated in the bicaval technique without significant difference [28]. The largest study examining bicaval vs. biatrial anastomosis techniques, the United Network for Organ Sharing (UNOS) database identified 14.418 patients undergoing heart transplantation between the years 1999 and 2005. Weiss et al. found no difference in survival between the two groups, although the bicaval technique was associated with a shorter lengh of hospital stay and less pacemaker placement [29]**.** In our group 70 patients required a pacemaker implantation after HTx (7%). If we look at the actual literature, pacemaker implantation after HTx occurred between 5-10% [29, 30, 31].

An increasing problem is the organ shortage with extended waiting lists and increased mortality on the waiting list. Evidence exists that certain “standard” donor criteria can be significantly liberalized to increase the available donor pool by accepting “marginal donors” who would, under conventional transplant guidelines, be declined as potential organ donors [32, 33]. In the last 27 years we accepted marginal donors in high urgent patients. In the future we might have to adjust this policy to organ shortage with extended waiting lists and increased mortality on the waiting list.

Acute rejection

As seen in **figure 5**, the use of new immunosuppressive drugs plays the key role in the prevention of ARE, especially the use of calcineurin inhibitors such as CyA and Tac. We demonstrated that Tac is superior to CyA in prevention of ARE. Grimm et al. showed in a large European trial that biopsy proven ARE of grade $\geq$ 3A at month 6 after HTx was significantly lower for Tac vs. CyA [13]. Additionally Kobashigawa et al. found significant differences in the incidence of treated ARE in their Tac/MMF group vs. the CyA/MMF group at 1 year after HTx [24]. In 1997, era 5 began with the addition of MMF to our program. Freedom from ARE was significantly higher in the MMF-based immunosuppression compared with immunosuppression based on AZA. Kobashigawa et al. showed in a randomized double-blind, and active-controlled

trial that the use of MMF as part of a triple immunosuppressive therapy was associated with a significant reduction in ARE and mortality when compared to the use of AZA [14]. Furthermore, the ability of MMF to reduce recurrent and refractory rejection episodes was shown in previous studies [15, 16].
After the introduction of Sir in 2000 a trail either in combination with Tac or MMF started. Patient treated with Tac-Sir showed the best results regarding ARE **(figure 5)**. De-novo Sir-MMF therapy revealed significant more ARE than the combination Tac-Sir. We introduced Sir because of its superior side effect profile in terms of CNI-related renal failure as a common problem after cardiac transplantation. In a prospective study at our center Groetzner et al. could show that conversion from CNI-based immunosuppression to MMF and Sir in heart transplant recipients with chronic renal failure was safe, preserved graft function and improved renal function [7].

Transplant Vasculopathy

When comparing the immunosuppressive therapies CyA-MMF and Tac-MMF, freedom from ARE as well as freedom from CAV ($p < 0.005$) were significantly higher in the Tac-MMF-group (**figure 6**). Weis et al. demonstrated that tacrolimus is superior to cyclosporine with respect to microvascular endothelial function, intimal thickening and vascular remodeling [25].

5. Limitations

Comparing outcomes of the different eras, we assumed that all events were mutually exclusive. Of course, this was not always the case. It is very difficult to evaluate outcome results in the field of transplantation for each defined milestone because some inventions overlapped.

6. Conclusions

This study clearly demonstrates that continued efforts in developing surgical care, perioperative management, organ preservation, immunosuppression, and infection control have improved early and long-term survival after cardiac transplantation. however, cardiac transplantation continues to evolve and mature, but many limitations still remain. in the future, highly specific immunosuppression or the achievement of tolerance induction is needed to further improve the results.

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