Original Article

Risk factors and survival of patients with permanent pacemaker implantation after heart transplantation

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Background: Permanent pacemaker (PPM) implantation after heart transplantation (HTX) may be required due to severe bradycardia. The aim of this study was to investigate the risk factors, indications, perioperative outcomes and complications of PPM implantation after HTX as well as the underlying effect on post-transplant mortality including causes of death.

Methods: This registry study included 621 patients receiving HTX at Heidelberg Heart Center between 1989 and 2018. Patients were stratified by PPM implantation after HTX. Data analysis of risk factors for PPM implantation included donor and recipient demographics, post-transplant medication, mortality, and causes of death.

Results: Thirty-six patients (5.8%) received PPM implantation after HTX, 12 (33.3%) with early PPM and 24 (66.7%) with late PPM. Indications for PPM implantation after HTX included sinus node dysfunction (SND) (n=15; 41.7%) and atrioventricular block (AVB) (n=21; 58.3%). Multivariate analysis revealed recipient body mass index (BMI) [hazard ratio (HR): 1.10; confidence interval (CI): 1.01–1.21; P=0.03], donor age (HR: 1.07; CI: 1.03–1.10; P<0.01), and biatrial HTX (HR: 2.63; CI: 1.22–5.68; P=0.01) as significant risk factors for PPM implantation after HTX. Kaplan–Meier estimator displayed a statistically significant inferior 5-year post-transplant survival among patients with early PPM after HTX in comparison to patients with late PPM or no PPM after HTX (P<0.01) along with a higher percentage of death due to infection (P<0.01).

Conclusions: Multivariate risk factors for PPM implantation after HTX include recipient BMI, donor age, and biatrial HTX. Early PPM implantation after HTX is associated with increased 5-year post-transplant mortality due to infection.

Keywords: Biatrial; sinus node dysfunction (SND); bradycardia; mortality; pacing

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Introduction

Cardiac rhythm disorders after heart transplantation (HTX) are frequent and may manifest in different ways either as tachyarrhythmias or as bradyarrhythmias (1-3). Common post-transplant bradyarrhythmias comprise sinus node dysfunction (SND) and atrioventricular block (AVB) which may require permanent pacemaker (PPM) (4,5). Bradycardic rhythm disorders after HTX are often transient and improve over time, with reported rates of PPM implantation after HTX varying between 3.5% and 20.5% (6,7). A large analysis of the United Network for Organ Sharing (UNOS) database showed that more than 10% of all patients received a PPM after HTX (5).

The initial standard technique for HTX, also known as the biatrial technique, has been associated with elevated rates of PPM implantation due to a continuous circular suture of the right donor and recipient atrium with possible sinus node injury (2,4,8-10). In contrast, the bicaval technique uses two donor-to-recipient vena cava anastomoses preserving the right atrial (RA) integrity and the sinus node (2,4).

Regarding the analysis of further risk factors, complications, and long-term outcomes of PPM implantation after HTX, there is only a minority of studies with a population of more than 500 patients and only one multi-center study investigating the need for PPM implantation after HTX (3-5,11-15). Additionally, studies yielded inconsistent results due to considerably differences in design, analyzed parameters, and length of follow-up. Moreover, the vast majority of the existing literature is outdated, as most studies were published in the 1990s (3,16-39) and in the 2000s (4,6,7,40-43).

Thus, given the need for new studies in this area of research, the aim of this large registry study was to investigate the risk factors, indications, perioperative outcomes and complications of PPM implantation after HTX as well as the underlying effect on post-transplant mortality including causes of death.

Methods

Patients

The performance of this study was in accordance with the ethical principles for medical research of the Declaration of Helsinki. Approval was given by the ethics committee of the University of Heidelberg (ethical approval number: S-286/2015, date of ethical approval: 22-06-2015). This study included all adult patients (≥18 years) receiving HTX at Heidelberg Heart Center between 1989 and 2018 except for patients with repeated HTX. Four patients with implantable cardioverter defibrillator (ICD) implantation after HTX due to ventricular tachycardia and no requirement for pacing were also excluded. Written informed consent was obtained from patients for inclusion in the Heidelberg HTX Registry allowing the clinical and scientific use of data. According to the ethical approval, no additional written informed consent was required for this registry study as only routine clinical data were analyzed (2,44-49).

All available medical records were screened for PPM implantation after HTX and patients were accordingly stratified into the following two groups: Patients with PPM implantation after HTX ("PPM after HTX") and patients without PPM implantation after HTX ("No PPM after HTX"). Then, patients with PPM implantation after HTX were further subdivided into patients with PPM implantation ≤1 year after HTX (early PPM after HTX) and patients with PPM implantation >1 year after HTX (late PPM after HTX).

Follow-up

Follow-up after HTX was performed according to the usual standard of care at Heidelberg Heart Center. As part of HTX surgery, patients received a temporary pacemaker system consisting of an external pacing box and two epicardial pacing leads which were placed on the right atrium and ventricle. The epicardial pacing leads routinely remained *in situ* for around 10 days after HTX. During the initial hospital stay, 12-lead electrocardiography (ECG) was regularly performed and in case of any suspected arrhythmic disorder. Before discharge, patients routinely had a 24-hour-holter-recording (2,44-49).

After the initial hospital stay, patients were followed-up monthly during the first 6 months after HTX, then bimonthly between month 6 to 12 after HTX, and thereafter routinely three to four times annually. Routine follow-up included medical history, physical examination, ECG, echocardiography, endomyocardial biopsy, and blood tests including immunosuppressive drug monitoring (2,44-51).

Post-transplant medication

Patients after HTX initially received an anti-thymocyte globulin-based immunosuppression induction therapy. The

initial standard immunosuppressive drug regimen at the beginning of the study period consisting of cyclosporine A (CsA) and azathioprine (AZA) was subsequently switched to CsA and mycophenolate mofetil (MMF) from 2001 onward. Since 2006, tacrolimus (TAC) and MMF were routinely used as initial immunosuppressive drug therapy. Steroids (prednisolone) were tapered incrementally during the first post-transplant months and discontinued finally 6 months after HTX if possible (2,44-49).

Statistical analysis

SAS statistical software (Version 9.4, SAS Institute, Cary, NC, USA) was used for analysis of data. Data were given as mean ± standard deviation (SD) or as count (n) and percentage (%). Measures of association [mean difference (MD) or hazard ratio (HR)] with 95% confidence interval (CI) were applied for results. Student's *t*-test was used for continuous variables and chi-squared test was applied for categorical variables. Kaplan-Meier estimator was employed to graphically display 5-year survival after HTX. Extensive univariate analyses were performed to test for differences between groups covering recipient data, previous open-heart surgery, principal diagnosis for HTX, donor data, perioperative data, and medication after HTX including immunosuppressive drug therapy (2,44-49).

In addition, a multivariate analysis (Cox regression model) was conducted to analyze the influence of the following five clinically relevant parameters which were statistically significant in the univariate analysis between patients with and without PPM implantation after HTX: recipient age, recipient body mass index (BMI), recipient arterial hypertension, donor age, and biatrial HTX. In order to avoid biased regression coefficients and to ensure a stable number of events (patients with PPM implantation after HTX) per analyzed variable, we did not include further parameters in this multivariate analysis (2,44-49).

In patients with PPM implantation after HTX, data regarding device surgery and outcomes of PPM implantation after HTX were further investigated including type and position of PPM, perioperative data, perioperative complications, and causes of death within 5 years after HTX. Furthermore, a sensitivity analysis was carried out to test the robustness of the study results using a subgroup of patients with TAC and MMF as immunosuppressive drug regimen as the immunosuppressive drug therapy was switched from 2006 (2,44-49).

Results

Baseline characteristics

In this registry study including 621 patients, 36 patients (5.8%) required PPM implantation after HTX. Hereof, 12 patients (33.3%) had a PPM ≤1 year after HTX (early PPM after HTX) and 24 patients (66.7%) received a PPM >1 year after HTX (late PPM after HTX).

Patients with PPM implantation after HTX had a higher recipient age (55.0±6.5 versus 51.8±10.5 years; MD: 3.2 years, 95% CI: 0.8–5.6 years, P=0.01), a higher recipient BMI (26.4±4.1 versus 24.8±3.9 kg/m^2; MD: 1.6 kg/m^2, 95% CI: 0.2–3.0 kg/m^2, P=0.03), and a higher rate of recipient arterial hypertension (72.2% versus 53.5%; MD: 18.7%; 95% CI: 3.5–33.9%, P=0.03) than patients without PPM after HTX. In terms of donor data, patients with PPM implantation after HTX showed a higher donor age (46.7±11.8 versus 40.7±13.5 years; MD: 6.0 years, 95% CI: 1.8–10.2 years, P<0.01), whereas there was no significant difference regarding male donor sex or donor BMI. No further donor data were available for this study.

Analysis of perioperative data revealed a higher percentage of biatrial HTX in patients with PPM implantation after HTX (41.7% versus 25.1%; MD: 16.6%, 95% CI: 0.2–33.0%, P=0.03) and accordingly a higher degree of bicaval HTX in patients without PPM implantation after HTX (74.9% versus 58.3%; MD: 16.6%, 95% CI: 0.2–33.0%, P=0.03). No statistically significant differences between groups could be detected in the remaining parameters. Baseline characteristics are presented in *Table 1*.

Initial medication after HTX

Comparison of immunosuppressive medication displayed no statistically significant differences between both groups regarding the use of CsA, TAC, Aza, or MMF. Additionally, there were no statistically significant differences in the administration of acetylsalicylic acid, beta-blockers, ivabradine, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors/sartans, or statins. An overview of the initial medication after HTX is given in *Table 2*.

Multivariate analysis of risk factors for PPM implantation after HTX

Multivariate analysis of risk factors for PPM implantation

Table 1 Baseline characteristics

Parameter	PPM (n=36)	No PPM (n=585)	Difference	95% CI	P value
Recipient data					
Age (years), mean ± SD	55.0±6.5	51.8±10.5	3.2	0.8–5.6	0.01*
Male sex, n (%)	27 (75.0)	460 (78.6)	3.6	–10.9–18.1	0.61
Body mass index (kg/m^2), mean ± SD	26.4±4.1	24.8±3.9	1.6	0.2–3.0	0.03*
Coronary artery disease, n (%)	15 (41.7)	239 (40.9)	0.8	–15.8–17.4	0.92
Arterial hypertension, n (%)	26 (72.2)	313 (53.5)	18.7	3.5–33.9	0.03*
Dyslipidemia, n (%)	26 (72.2)	368 (62.9)	9.3	–5.8–24.4	0.26
Diabetes mellitus, n (%)	14 (38.9)	196 (33.5)	5.4	–11.0–21.8	0.51
Renal insufficiency^, n (%)	21 (58.3)	335 (57.3)	1.0	–15.5–17.5	0.90
GFR (mL/min/1.73 m^2), mean ± SD	58.6±16.6	60.4±21.5	1.8	–4.2–7.8	0.54
Previous open heart surgery					
Overall open heart surgery, n (%)	10 (27.8)	171 (29.2)	1.4	–13.7–16.5	0.85
CABG surgery, n (%)	5 (13.9)	72 (12.3)	1.6	–10.0–13.2	0.78
Congenital, valvular or ventricular surgery, n (%)	5 (13.9)	65 (11.1)	2.8	–8.8–14.4	0.61
VAD surgery, n (%)	3 (8.3)	44 (7.5)	0.8	–8.5–10.1	0.86
Principal diagnosis for HTX					
Ischemic CMP, n (%)	12 (33.3)	194 (33.2)	0.1	–15.8–16.0	0.98
Non-ischemic CMP, n (%)	21 (58.3)	309 (52.8)	5.5	–11.1–22.1	0.52
Valvular heart disease, n (%)	2 (5.6)	32 (5.5)	0.1	–7.6–7.8	0.98
Cardiac amyloidosis, n (%)	1 (2.8)	50 (8.5)	5.7	–0.2–11.6	0.22
Donor data					
Age (years), mean ± SD	46.7±11.8	40.7±13.5	6.0	1.8–10.2	<0.01*
Male sex, n (%)	19 (52.8)	248 (42.4)	10.4	–6.4–27.2	0.22
Body mass index (kg/m^2), mean ± SD	25.0±4.2	24.8±4.1	0.2	–1.3–1.7	0.75
Perioperative data					
Transplant sex mismatch, n (%)	16 (44.4)	263 (45.0)	0.6	–16.2–17.4	0.95
Ischemic time (min), mean ± SD	217.8±72.9	222.8±68.3	5.0	–20.6–30.6	0.70
Ischemic time ≥240 min, n (%)	15 (41.7)	241 (41.2)	0.5	–16.1–17.1	0.96
Biatrial HTX, n (%)	15 (41.7)	147 (25.1)	16.6	0.2–33.0	0.03*
Bicaval HTX, n (%)	21 (58.3)	438 (74.9)	16.6	0.2–33.0	0.03*

^, GFR <60 mL/min/1.73 m^2; *, statistically significant (P<0.05). CABG, coronary artery bypass graft; CMP, cardiomyopathy; CI, confidence interval; GFR, glomerular filtration rate; HTX, heart transplantation; n, number; PPM, permanent pacemaker; SD, standard deviation; VAD, ventricular assist device.

Table 2 Initial medication after HTX

Parameter	PPM (n=36)	No PPM (n=585)	Difference	95% CI	P value
Cyclosporine A, n (%)	22 (61.1)	322 (55.0)	6.1	–10.3–22.5	0.48
Tacrolimus, n (%)	14 (38.9)	263 (45.0)	6.1	–10.3–22.5	0.48
Azathioprine, n (%)	19 (52.8)	245 (41.9)	10.9	–5.9–27.7	0.20
Mycophenolate mofetil, n (%)	17 (47.2)	340 (58.1)	10.9	–5.9–27.7	0.20
Steroids, n (%)	36 (100.0)	585 (100.0)	0.0	NA	NA
Acetylsalicylic acid, n (%)	3 (8.3)	61 (10.4)	2.1	–7.3–11.5	0.69
Beta blocker, n (%)	6 (16.7)	106 (18.1)	1.4	–11.2–14.0	0.83
Ivabradine, n (%)	2 (5.6)	52 (8.9)	3.3	–4.5–11.1	0.49
Calcium channel blocker	12 (33.3)	153 (26.2)	7.1	–8.7–22.9	0.34
ACE inhibitor/sartan, n (%)	18 (50.0)	256 (43.8)	6.2	–10.6–23.0	0.46
Diuretic, n (%)	36 (100.0)	585 (100.0)	0.0	NA	NA
Statin, n (%)	11 (30.6)	228 (39.0)	8.4	–7.2–24.0	0.31
Gastric protection (PPI/H_2 blocker), n (%)	36 (100.0)	585 (100.0)	0.0	NA	NA

ACE inhibitor, angiotensin-converting-enzyme inhibitor; CI, confidence Interval; HTX, heart transplantation; H_2 blocker, histamine receptor blocker; n, number; NA, not applicable; PPI, proton pump inhibitor; PPM, permanent pacemaker.

Table 3 Multivariate analysis of risk factors for PPM implantation after HTX

Variable	Hazard ratio	95% confidence interval	P value
Recipient age (years)	1.03	0.98–1.08	0.20
Recipient body mass index (kg/m^2)	1.10	1.01–1.21	0.03*
Recipient arterial hypertension (in total)	1.43	0.65–3.14	0.37
Donor age (years)	1.07	1.03–1.10	<0.01*
Biatrial HTX (in total)	2.63	1.22–5.68	0.01*

*, statistically significant (P<0.05). HTX, heart transplantation; PPM, permanent pacemaker.

after HTX included the following five parameters: recipient age in years (HR: 1.03; 95% CI: 0.98–1.08; P=0.20), recipient BMI in kg/m^2 (HR: 1.10; 95% CI: 1.01–1.21; P=0.03), recipient arterial hypertension (HR: 1.43; 95% CI: 0.65–3.14; P=0.37), donor age in years (HR: 1.07; 95% CI: 1.03–1.10; P<0.01), and biatrial HTX (HR: 2.63; 95% CI: 1.22–5.68; P=0.01). Multivariate analysis of risk factors for PPM implantation after HTX is provided in *Table 3*.

Indications, perioperative data and complications of PPM implantation after HTX

Indications for PPM implantation after HTX included 15 patients with SND (41.7%) and 21 patients with AVB (58.3%). Patients with early PPM after HTX had a significantly higher rate of SND (66.7% versus 29.2%; P=0.03), whereas patients with late PPM after HTX showed a higher percentage of AVB (70.8% versus 33.3%; P=0.03) as indication for PPM after HTX.

Perioperative data and complications showed no significant differences between patients with early and late PPM after HTX. Indications, perioperative data and complications of PPM implantation after HTX are shown in *Table 4*.

Follow-up measures of PPM implantation after HTX

Patients with early PPM after HTX revealed a significantly

Table 4 Indications, perioperative data and complications of PPM implantation after HTX

Parameter	All PPM (n=36)	Early PPM (n=12)	Late PPM (n=24)	P value
PPM indication				
Sinus node dysfunction, n (%)	15 (41.7)	8 (66.7)	7 (29.2)	0.03*
Atrioventricular block, n (%)	21 (58.3)	4 (33.3)	17 (70.8)	0.03*
Perioperative data				
Single chamber pacemaker, n (%)	2 (5.6)	0 (0.0)	2 (8.3)	0.30
Dual chamber pacemaker, n (%)	34 (94.4)	12 (100.0)	22 (91.7)	0.30
DDD/R pacing mode, mean ± SD	34 (94.4)	12 (100.0)	22 (91.7)	0.30
VVI/R pacing mode, mean ± SD	2 (5.6)	0 (0.0)	2 (8.3)	0.30
Left sided implantation, n (%)	26 (72.2)	8 (66.7)	18 (75.0)	0.60
Right sided implantation, n (%)	10 (27.8)	4 (33.3)	6 (25.0)	0.60
Operation time (min), mean ± SD	74.8±19.6	77.2±20.8	73.6±18.9	0.63
Fluoroscopy time (min), mean ± SD	3.1±1.8	3.1±2.1	3.2±1.6	0.90
Radiation dose (Gy·cm^2), mean ± SD	2.6±1.2	2.6±1.0	2.7±1.4	0.85
Perioperative complications				
Haemothorax/pneumothorax, n (%)	1 (2.8)	1 (8.3)	0 (0.0)	0.15
Pericardial effusion, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Prolonged RA lead implantation, n (%)	19 (52.8)	5 (41.7)	14 (58.3)	0.35
RA lead dislodgement during surgery, n (%)	10 (27.8)	4 (33.3)	6 (25.0)	0.60
RA lead position, n (%)				
Right atrial appendage	24 (66.7)	8 (66.7)	16 (66.7)	0.55
Other than right atrial appendage	10 (27.8)	4 (33.3)	6 (25.0)	0.55
RA lead implantation not possible	2 (5.6)	0 (0.0)	2 (8.3)	0.55

*, statistically significant (P<0.05). HTX, heart transplantation; n, number; NA, not applicable; PPM, permanent pacemaker; RA, right atrium; RV, right ventricle; SD, standard deviation.

lower percentage of atrial and ventricular pacing than patients with late PPM after HTX at baseline (atrial: 8.0%±4.8% versus 20.9%±26.9%; P=0.04; respectively ventricular: 19.4%±21.5% versus 42.5%±41.9%; P=0.04), at 6-month follow-up (atrial: 2.0%±1.7% versus 25.0%±30.2%; P<0.01; respectively ventricular: 0.5%±0.8% versus 34.0%±43.0%; P<0.01), and at 24-month follow-up (atrial: 1.3%±1.1% versus 21.9%±29.2%; P=0.03; respectively ventricular: 0.3%±0.3% versus 45.6%±47.5%; P<0.01).

No statistically significant differences could be observed between groups in regard to stimulation threshold, sensitivity, or impedance during follow-up. Follow-up measures of PPM implantation after HTX are provided in *Table 5*.

Survival after HTX

Patients with and without PPM implantation after HTX showed a similar 5-year post-transplant survival in the Kaplan-Meier estimator indicating no effects of PPM implantation after HTX on post-transplant survival (P=0.85). Stratified by early PPM (PPM ≤1 year after HTX), late PPM (PPM >1 year after HTX), and no PPM after HTX, the Kaplan-Meier estimator displayed a statistically significant inferior 5-year post-transplant survival of patients with early PPM after HTX in comparison to patients with late PPM or no PPM after

Table 5 Follow-up measures of PPM implantation after HTX

Parameter	All PPM (n=36)	Early PPM (n=12)	Late PPM (n=24)	P value
Baseline after implantation				
Pacing (%)				
RA lead, mean ± SD	16.4±22.7	8.0±4.8	20.9±26.9	0.04*
RV lead, mean ± SD	34.8±38.0	19.4±21.5	42.5±41.9	0.04*
Stimulation threshold (V at 0.4 ms)				
RA lead, mean ± SD	0.9±0.3	0.9±0.3	0.9±0.3	0.86
RV lead, mean ± SD	0.7±0.2	0.8±0.3	0.7±0.2	0.45
Sensitivity (mV)				
RA lead, mean ± SD	2.2±1.6	2.4±1.6	2.2±1.6	0.75
RV lead, mean ± SD	10.4±4.0	11.0±4.2	10.0±3.8	0.51
Impedance (Ω)				
RA lead, mean ± SD	493.7±103.8	495.8±74.3	492.5±116.7	0.92
RV lead, mean ± SD	577.7±104.0	569.7±125.9	581.7±90.8	0.78
At 6-month follow-up				
Pacing (%)				
RA lead, mean ± SD	20.4±28.6	2.0±1.7	25.0±30.2	<0.01*
RV lead, mean ± SD	27.8±40.9	0.5±0.8	34.0±43.0	<0.01*
Stimulation threshold (V at 0.4 ms)				
RA lead, mean ± SD	1.0±0.3	0.9±0.3	1.0±0.3	0.69
RV lead, mean ± SD	0.7±0.2	0.7±0.2	0.7±0.2	0.64
Sensitivity (mV)				
RA lead, mean ± SD	2.4±1.9	2.6±1.6	2.2±1.8	0.66
RV lead, mean ± SD	9.7±3.5	10.4±1.5	9.5±3.8	0.43
Impedance (Ω)				
RA lead, mean ± SD	460.4±87.0	436.6±79.6	466.4±87.7	0.53
RV lead, mean ± SD	557.1±117.4 Ω	512.4±121.0	567.2±114.2	0.44
At 24-month follow-up				
Pacing (%)				
RA lead, mean ± SD	18.0±27.5	1.3±1.1	21.9±29.2	0.03*
RV lead, mean ± SD	37.6±46.5	0.3±0.3	45.6±47.5	<0.01*
Stimulation threshold (V at 0.4 ms)				
RA lead, mean ± SD	1.0±0.3	1.2±0.3	1.0±0.3	0.43
RV lead, mean ± SD	0.7±0.2	0.6±0.1	0.7±0.2	0.54
Sensitivity (mV)				
RA lead, mean ± SD	2.2±1.5	2.1±0.8	2.2±1.6	0.90
RV lead, mean ± SD	10.1±3.8	10.6±0.8	10.0±4.2	0.63
Impedance (Ω)				
RA lead, mean ± SD	445.8±78.0	453.0±58.4	435.2±62.8	0.72
RV lead, mean ± SD	568.5±145.5	560.0±127.8	570.3±149.0	0.92

*, statistically significant (P<0.05). HTX, heart transplantation; PPM, permanent pacemaker; RA, right atrium; RV, right ventricle; SD, standard deviation.

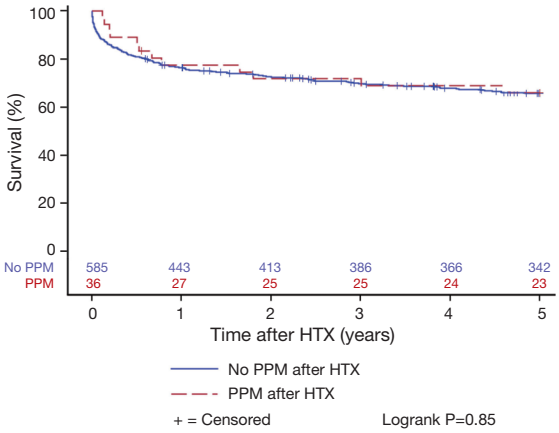

Figure 1 Post-transplant survival of patients with and without PPM after HTX (Kaplan-Meier estimator). There was no statistically significant difference in 5-year post-transplant survival between patients with and without PPM after HTX (P=0.85). HTX, heart transplantation; PPM, permanent pacemaker.

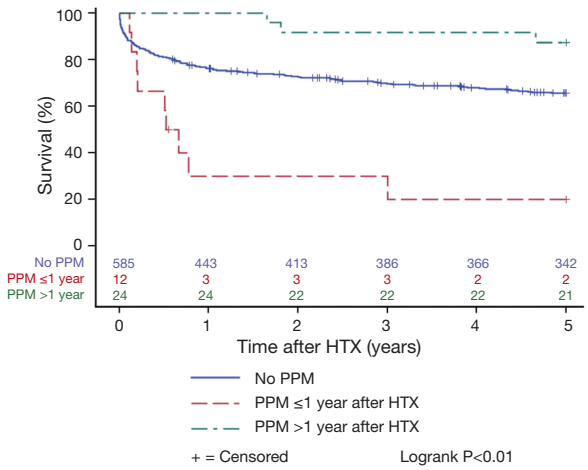

Figure 2 Post-transplant survival of patients with early PPM, late PPM, and no PPM after HTX (Kaplan-Meier estimator). Overview of 5-year post-transplant survival of patients stratified by early PPM (PPM ≤1 year after HTX), late PPM (PPM >1 year after HTX), and no PPM after HTX. Patients with early PPM after HTX showed a statistically significant inferior 5-year post-transplant survival in comparison to patients with late PPM or no PPM after HTX (P<0.01). HTX, heart transplantation; PPM, permanent pacemaker.

HTX (P<0.01). Kaplan-Meier estimators are presented in *Figures 1* and *2*.

Causes of death after HTX

A total of 12 patients with PPM implantation after HTX (33.3%) deceased within five years after HTX. In the early PPM after HTX group, 9 patients (75.0%) passed away, while 3 patients (12.5%) deceased in the late PPM group after HTX. With regard to the causes of death, significantly more patients in the early PPM after HTX group died from infection/sepsis following chest infection than patients in the late PPM after HTX group (58.3% versus 8.3%; P<0.01), while there was no significant difference in left ventricular ejection fraction. Moreover, there was no difference between groups in terms of transplant failure, acute rejection, malignancy, or thromboembolic event/bleeding. Causes of death after HTX are given in *Table 6*.

Sensitivity analysis

A sensitivity analysis to test the robustness of the study results was performed with a subgroup of patients receiving TAC and MMF as immunosuppressive medication (277 of 621 patients, 44.6%). The robustness of the study results was confirmed as similar results were observed concerning risk factors and survival of patients with PPM after HTX.

Discussion

Indications for and timing of PPM implantation after HTX

More than 50% of patients after HTX experience bradyarrhythmias within the first few post-transplant weeks (6,20,36). SND is the most common cause of bradyarrhythmia in the initial post-transplant period while AVB tends to present later after HTX (1,6,8,13,37).

In the event of bradyarrhythmias after HTX, reversible causes such as negative chronotropic drugs, electrolyte imbalance, or hypothyreosis should be addressed first, followed by heart rate stimulating agents and temporary pacing considering PPM implantation as last option (6,12,28,36). If inevitable, the optimal timing of PPM implantation is essential in managing the balancing act between the early need for pacing and the risk of potential complications (6,12). The extended use of epicardial temporary pacing may be an adequate solution to bridge patients over transient bradyarrhythmias during the initial period after HTX (6,12,36). This could—in combination with other measurements such as the use of

Table 6 Causes of death within 5 years after HTX

Parameter	All PPM (n=36)	Early PPM (n=12)	Late PPM (n=24)	P value
Transplant failure, n (%)	3 (8.3)	2 (16.7)	1 (4.2)	0.20
Acute rejection, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Infection/sepsis, n (%)	9 (25.0)	7 (58.3)	2 (8.3)	<0.01*
Malignancy, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Thromboembolic event/bleeding, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
All causes, n (%)	12 (33.3)	9 (75.0)	3 (12.5)	<0.01*

*, statistically significant (P<0.05). HTX, heart transplantation; n, number; NA, not applicable; PPM, permanent pacemaker.

bicaval HTX instead of biatrial HTX—effectively reduce the incidence of PPM implantation due to SND in the early period after HTX. Additionally, regarding long term follow-up, the focus of PPM implantation after HTX could consequently change from SND early after HTX towards AVB in a later post-transplant setting. However, temporary pacing comes at a price such as an increased risk for infection, lead dislodgement, inadequate pacing, and may not always be possible in patients with rejection or voluminous fibrosis (6).

In this study, the need for overall PPM implantation after HTX (5.8%) was comparatively lower in patients with an extended use of epicardial temporary pacing combined with a predominant use of bicaval HTX. Additionally, the rate of early PPM implantation after HTX could be reduced to 1.9% (33.3% of all PPM implantations after HTX).

Risk factors for PPM implantation after HTX

As the causes for PPM implantation after HTX are still not fully understood, this large registry study with 621 patients investigated potential risk factors in detail. Our multivariate analysis showed an elevated recipient BMI, a higher donor age, and the performance of biatrial HTX as significant risk factors for PPM implantation after HTX. This is in line with findings by Cantillon *et al.* (5) who identified biatrial surgical technique and increasing donor age as important associations with the occurrence of bradyarrhythmias and requirement for PPM implantation after HTX in a large multi-center study.

To our knowledge, this is the first study to show an elevated recipient BMI as an independent risk factor for PPM implantation after HTX. The occurrence of bradyarrhythmias has been linked to obesity and sleep apnea (52,53). Cessation of breathing and hypoxemia are postulated to be essential factors in the emergence of bradyarrhythmias (53). Additionally, due to cardiac denervation in patients after HTX, the autonomous control of the heart is affected making these patients more vulnerable to changes in chronotropic function (45).

During the study period from 1989 to 2018, we found no relevant imbalance in PPM implantations after HTX reducing the likelihood of a potential era effect.

Prolonged ischemic time has previously been reported to be associated with bradyarrhythmias after HTX as hypoxia during surgery can cause damage to the sinus node and the electrical conduction system of the cardiac allograft (1,4,28). However, we and other recent studies could not detect a significant association between ischemic time and PPM implantation after HTX (5,7,11-13).

Pre-transplant use of amiodarone has been suggested to be another potential risk factor for PPM implantation after HTX (6). In a recent study, our group could show that neither short-term nor long-term amiodarone use before HTX was related to post-transplant bradycardia or PPM implantation after HTX (47). These results were supported by findings by Zieroth *et al.* (7) and by Woo *et al.* (43) who found no statistically significant association between pre-transplant amiodarone use and the requirement for PPM implantation after HTX. In addition, negative chronotropic drugs may cause a relevant heart rate reduction. However, we could not detect statistically significant differences between patients with and without PPM implantation after HTX regarding the administration of beta blockers, calcium channel blockers or ivabradine in this study.

Post-transplant survival and causes of death

Due to the lack of organ donation, it is essential to continuously improve quality of life and to search for

risk factors which may impair survival after HTX (11). Patients after HTX require an immunosuppressive drug regimen to prevent acute rejection episodes (50,51). These patients are consequently more vulnerable to infections especially in the initial post-transplant period when they require higher levels of immunosuppressive drugs (44,50,51). Hence, it is clinically very important to know whether PPM implantation after HTX is associated with increased post-transplant mortality. We observed a similar 5-year post-transplant survival between patients with and without PPM implantation after HTX in general. In accordance with our findings, several other authors found no significant association between overall PPM implantation after HTX and post-transplant mortality (3,4,13,15,27,28).

Although overall PPM implantation does not seem to be related to increased post-transplant mortality, further stratification into patients with early and late PPM after HTX may reveal relevant differences which may have an impact on post-transplant survival. Unfortunately, as a result of sample sizes, only a couple of studies adopted this approach (4,8). Cantillon *et al.* (4) detected no significant difference in 5-year post-transplant survival between patients with early (61 patients), late (45 patients) and no (1,201 patients) PPM implantation after HTX. Likewise, Jones *et al.* (8) reported no significant difference in 5-year post-transplant survival between patients with early (30 patients), late (18 patients) and no (341 patients) PPM implantation after HTX. In contrast, we found a statistically significant inferior 5-year post-transplant survival of patients with early (12 patients) PPM after HTX in comparison to patients with late (24 patients) or no (585) PPM after HTX (P<0.01) along with a higher percentage of death due to infection (P<0.01).

When comparing these three large studies, differences in the overall rate of PPM implantation after HTX (Cantillon: 8.1%; Jones: 12.3%, this study: 5.8%), the ratio of early versus (*vs.*) late PPM implantation after HTX (Cantillon: 57.5% *vs.* 42.5%; Jones: 62.5% *vs.* 37.5%, this study: 33.3% *vs.* 66.7%), the definition of early PPM implantation after HTX (Cantillon: ≤30 days after HTX; Jones: ≤30 days after HTX, this study: ≤1 year after HTX), and the location of study (Cantillon: USA; Jones: UK, this study: Germany) should be carefully considered (4,8). Therefore, given the few numbers of studies analyzing differences in mortality between early and late PPM implantation after HTX, further large multi-center trials are necessary.

Study limitations

Our findings were derived from a single-center registry study (Heidelberg HTX Registry) with 621 adult patients receiving HTX at Heidelberg Heart Center. Based on the study design, results should be treated with caution as it carries certain limitations. However, our study provides an excellent granularity which most multi-center studies lack. Further, patients received a standardized center-specific pre-, peri-, and post-transplant course of treatment and follow-up reducing the likelihood of potential selection bias and confounders (2,44-51).

This study analyzed data from patients receiving HTX at the Heidelberg Heart Center between 1989 and 2018. Due to this long study period, a possible era effect as a result of changes in medical care cannot be ruled out. In order to test the robustness of the study results, a sensitivity analysis including patients with TAC and MMF was carried out as the immunosuppressive drug therapy was subsequently switched from CsA and MMF to TAC and MMF from 2006 onward. Here, similar results were observed. A further change of medical treatment within the study period was the use of ivabradine instead of beta blockers or calcium channel blockers for heart rate reduction in patients after HTX from 2006 onward. However, there were no significant differences between patients with and without PPM implantation after HTX regarding the use of ivabradine, beta blockers or calcium channel blockers (45).

Our results should be regarded as hypothesis-generating, especially with respect to survival as multiple factors may influence survival. Hence, our data cannot proof or disproof a causal relationship between early PPM implantation after HTX and impaired post-transplant survival but merely indicate an association, especially in view of the relatively small number of patients with PPM implantation after HTX (2,44-51). Hence, to confirm our results, further large multi-center trials are desirable to investigate risk factors and survival of patients with PPM implantation after HTX.

Conclusions

Our data showed a comparatively lower need for PPM implantation after HTX in patients with an extended use of epicardial temporary pacing for up to 10 days combined with a predominant use of bicaval HTX. Overall PPM implantation after HTX was necessary in only 5.8% of patients. Additionally, the rate of early PPM implantation after HTX (≤1 year after HTX) could be reduced to 1.9%

(33.3% of all PPM implantations after HTX).

Multivariate analysis indicated a higher recipient BMI, an increased donor age, and the use of biatrial HTX as significant risk factors for PPM implantation after HTX. Kaplan-Meier estimator showed a significant inferior 5-year post-transplant survival of patients with early PPM after HTX in comparison to patients with late PPM or no PPM after HTX along with a higher percentage of death due to infection.

In summary, multivariate risk factors for PPM implantation after HTX include recipient BMI, donor age, and biatrial HTX. Early PPM implantation after HTX is associated with increased 5-year post-transplant mortality due to infection.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This work complies with the Declaration of Helsinki. The study was approved by the ethics committee of the University of Heidelberg (S-286/2015). Written informed consent was obtained from patients for inclusion in the Heidelberg HTX Registry allowing the clinical and scientific use of data.

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