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Permanent pacemaker implantation early and late after heart transplantation: Clinical indication, risk factors and prognostic implications

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BACKGROUND: Permanent pacemaker implantation (PPM) early after cardiac transplantation has been shown not to predict a worse outcome. However, the requirement for pacing late after transplantation and its prognostic implications are not fully known. We describe the clinical indications, risk factors and long-term outcome in patients who required pacing early and late after transplantation.

METHODS: The transplant database, medical records and pacing database/records were reviewed for all patients undergoing de novo orthotopic cardiac transplantation ($n = 389$) at our institution between January 1995 and May 2006.

RESULTS: A total of 48 patients (12.3%) received a pacemaker after transplantation. Of these patients, 30 were paced early, pre-hospital discharge (25 ± 19 days post-transplantation), and 18 patients had late pacing (3.0 ± 3.3 years post-transplantation). There were no differences in clinical characteristics, use of anti-arrhythmic drugs or length-of-stay post-transplantation between early and late groups. Early indications for pacing were more often sino-atrial (SA) disease (24 of 30, 80%), whereas atrio-ventricular (AV) disease was more likely to occur later ($p = 0.03$). Risk factors for PPM included use of biatrial anastomosis ($p = 0.001$) and donor age ($p = 0.002$). Prior rejection was a univariate but not multivariate ($p = 0.09$) predictor of the need for PPM. Development of cardiac allograft vasculopathy was not predictive. There was no significant difference in mortality between late and early PPM patients or between late PPM patients and the non-paced patients who survived transplantation and initial stay.

CONCLUSIONS: Patients who required PPM late after orthotopic cardiac transplantation had a prognosis comparable to those paced early and those who did not require PPM. The independent risk factors for PPM were biatrial anastomosis and increasing donor age. SA-nodal dysfunction as an indication for PPM was more prevalent early after transplantation, whereas atrioventricular (AV) disease more commonly presented late. The requirement for pacing late after transplantation was not associated with rejection or cardiac allograft vasculopathy.

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Bradycardia is common in the early phase after orthotopic cardiac transplantation, occurring in 14% to 44% of patients.[1] In the 1990s, the need for permanent pacemaker (PPM) implantation after transplantation declined, following a trend away from the earlier biatrial surgical implant technique toward a newer, bicaval technique.[2–4] Other changes, such as the short-term use of positive chronotropic drugs like theophylline in the management of post-operative bradycardia, may have also played a role in the reduced need for pacing.[5,6] However, in the current era of extended

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donor criteria, post-operative bradyarrhythmia remains a significant issue regardless of operative technique.[7]

Early need for pacing due to sinus-node disease has been shown not to predict a worse outcome.[8] The pathogenesis, natural history and optimal management for this has been described elsewhere.[1] However, the need for pacing in patients who develop an indication late after transplantation could possibly be a marker for worse outcome, through graft vasculopathy or rejection.[9]

We investigated cardiac transplant patients who received a PPM, either during the index hospital admission for transplantation, or later when symptomatic bradycardia or other pacing indications arose. The aim was to establish whether there are differences in the baseline or follow-up characteristics of these patients, and whether need for late pacemaker implantation is associated with adverse events or a poor outcome.

Methods

Design and subjects

Between January 1995 and May 2006, 389 consecutive patients underwent de novo orthotopic cardiac transplantation at our institution. Heterotopics and "re-do" orthotopic transplantations were excluded from analysis in this study. Forty-eight (12.3%) patients had received a PPM after transplantation. The study involved retrospective analysis of the paced cohort, using case-notes and database records from the transplant and pacing departments. Patients were allocated to the "early-paced" (EP) group if they underwent insertion of a pacemaker prior to discharge from hospital after transplantation, and "late-paced" (LP) if insertion occurred separately after the index admission. For comparison, basic demographics, donor ischemia time, surgical technique and survival data were available for the 341 non-paced (NP) patients within the whole cohort. A sub-group was defined for those who survived initial post-operative hospital stay (late non-paced, LNP) to account for bias in the total cohort from early deaths in patients who did not survive long enough to require a pacemaker.

Statistical methods

Statistical analysis was conducted using STATA software, version 10.1 (StataCorp LP, College Station, TX). Continuous variables are summarized by mean ± standard deviation and analyzed by *t*-test or analysis of variance (ANOVA). Categorical variables are represented by frequencies and percentages, and analyzed by chi-square or Fisher's exact test. Survival data were analyzed using the log-rank test and Cox regression, expressed as odds ratios (ORs) and 95% confidence intervals (CIs) as appropriate. Kaplan–Meier survival curves were constructed from log-rank test data.

Results

Demographics

In the whole cohort, indications for transplantation were ischemic heart disease (45%), dilated cardiomyopathy (37.5%), genetic/congenital (14.1%) and other (3.4%). Of the paced cohort, the indications were ischemic heart disease (47.9%), dilated cardiomyopathy (41.7%) or genetic/congenital (10.4%). Thirty patients received a PPM prior to discharge (EP) and 18 afterward (LP). Demographic and background data for the EP, LP and non-paced groups are presented in Table 1. No significant differences were found in baseline characteristics between the EP and LP groups, including pre- or post-transplant medication (including amiodarone, 2 in each group), donor profile (gender, diabetes, smoking, hypercholesterolemia, hypertension) and ischemia time. The age distribution of the NP cohort was similar (46.9 ± 11.6 years). Further

Table 1 Demographic Characteristics of Cardiac Transplant Patients Undergoing Pacemaker Implantation

	Early-paced	Late-paced	All non-paced
N	30	18	341
Male (%)	24/30 (80%)	14/18 (83.3)	67/341 (80.4)
Age (years)	46.3 ± 12.3	47.2 ± 9.8	46.9 ± 11.6
Biatrial anastomosis (%)	28/30 (93.3%)	18/18 (100%)	108/317 (34%)[a]
Total ischemic time (minutes)	150.7 ± 61.2	145.9 ± 55.5	168.5 ± 60.1
Donor age (years)	36.7 ± 11.8	38.2 ± 15.2	34.6 ± 11.7
Diabetes in recipient (%)	4/30 (13.3)	0/19 (0)	40/338 (11.8)
Creatinine (μmol)	106.0 ± 20.6	113.2 ± 33.4	NA
LVEF before discharge (%)	75.1 ± 4.9	74.5 ± 5.5	NA
Transplant indication			
Dilated cardiomyopathy (%)	13/30 (43.3)	7/18 (38.8)	126/341 (37.0)
Ischemic heart disease (%)	12/30 (40.0)	11/18 (61.1)	148/341 (43.4)
Other (%)	5/30 (16.7)	0/18 (0)	66/341 (19.4)

There were no statistically significant differences between the early-paced and late-paced groups. LVEF, left ventricular ejection fraction (biplane method of disks); NA, not available.

[a] $p < 0.001$.