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The Impact of Pacemaker Programming on Morbidity in Heart Transplant Recipients

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ABSTRACT: Pacemaker programming recommendations in patients post-heart transplant include a higher lower rate limit, activating rate response mode, maximising battery longevity and minimising ventricular pacing in patients without atrioventricular block. This study sought to investigate how variability in pacemaker programming following orthotopic heart transplant affects morbidity. We conducted a retrospective analysis of heart transplant recipients at a single transplant centre between 1991 and 2023. Patients requiring pacemaker implantation following transplantation were matched with non-pacemaker recipients by age, sex and height. Patient and device characteristics were reviewed. Clinical outcomes, programming and physiological parameters were compared within the pacemaker group and between subject and comparator groups. Forty-five heart transplant recipients were included: 15 with pacemakers and 30 without. Within the pacemaker group, 20% were programmed with LRL > 60 bpm, rate-response mode in 47% and algorithms minimising ventricular pacing in 27%. Fifty-three percent were NYHA class I, and 46% NYHA class II; resting heart rate was similar between the groups (85 (SD14.9) and 79 (SD8) bpm: $p = 0.33$). NYHA class I group achieved a higher workload (METS 9 (SD2.7) *vs.* 6.9 (SD1) mL/kg/min: $p = 0.21$), and peak heart rate (135 (18.8) *vs.* 123 (14.8) bpm: $p = 0.29$) during exercise stress echocardiogram (ESE). The pacemaker group was more symptomatic than the comparator group (NYHA class II 46% *vs.* 10%: $p = 0.016$) and exhibited higher rates of cardiac allograft vasculopathy (53% *vs.* 10%: $p = 0.005$). There is substantial variability in pacemaker programming in heart transplant recipients. Patients who require a pacemaker have a greater symptom and comorbidity burden than those without. No identifiable physiological or programming differences stratified the greater morbidity within the pacemaker cohort.

Keywords: Orthotopic heart transplantation; Permanent pacemaker; Chronotropic incompetence

1. Introduction

In orthotopic heart transplant (OHTx) recipients, the incidence of permanent pacemaker (PPM) requirement over long-term follow-up has been reported to be as high as 24% [1]. While pacing is modestly prevalent among these patients, there is a paucity of data to inform best programming practices in this distinct group. The limited existing publications have suggested various programming considerations specific to OHTx recipients, including utilisation of a higher lower rate limit (LRL) of >80 beats per min (bpm), activation of rate response mode, maximising battery longevity and minimising ventricular pacing in patients without atrioventricular nodal block [2–4]. However, the specific impact of these programming strategies on patient symptoms has not been clearly established, and there are no specific guideline recommendations for this cohort. In the present study, we sought to investigate how differences in PPM programming in OHTx recipients affect exercise capacity and quality of life.

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2. Methods

We retrospectively reviewed all OHTx recipients at a single quaternary metropolitan transplant centre in Melbourne, Australia, between August 1991 and October 2023. Ethics approval was obtained from the Alfred Health Medical Ethics Board (HREC/186/24). We first identified all OHTx recipients who received PPM implants (single chamber, dual chamber and cardiac resynchronisation devices—there were no leadless pacemakers) over long-term follow-up (PPM group). We then established a comparator group of OHTx recipients without PPM requirement (no PPM group); these patients were age-, sex- and height-matched (individual matching in this characteristic hierarchy) with each patient in the PPM group in a 1:2 ratio. A 1:2 ratio was chosen, given the relatively low number of patients in the PPM group. We specifically included patients with ongoing annual follow-up at our institution, including routine biennial stress testing to investigate coronary allograft vasculopathy (CAV). We excluded heterotopic heart transplant recipients as these patients have unique physiological and pacing considerations distinct from the OHTx cohort, and those with severe impairment due to non-cardiovascular or metabolic comorbidities which impacted their ability to undergo investigations, deceased patients, patients with an implantable cardioverter defibrillator and those attending transplant or pacing follow up at another centre.

We then collected clinical data using the institutional transplant database and patient electronic medical record to evaluate patient demographics, comorbidities and transthoracic echocardiogram results. New York Heart Association (NYHA) symptom class was determined as reported at each outpatient follow-up visit and incorporated into this analysis; in patients with a pacemaker, symptom data was collected following pacemaker implantation [5]. Exercise capacity was determined using the results of treadmill exercise stress echocardiogram (ESE) utilising the Bruce protocol [6]. For the PPM cohort, we examined the most recent device interrogation reports to determine PPM programming, including LRL, upper-rate limit and rate responsiveness. Data was then analysed for pacemaker programming specifications and compared within the pacemaker group between those who were NYHA functional class I and those who were NYHA functional class II. Data was also compared between the PPM group and the matched group of heart transplant recipients without pacemakers. Heart rate score (HrSc) was defined as the percentage of atrial-sensed and paced events in the single tallest 10 bpm device histogram bin [7]. Heart rate response (HRR) was defined as peak heart rate—resting heart rate [8]. Chronotropic index (CIx) was calculated as HRR/(220—age—resting heart rate) [9].

Continuous parametric data are represented as mean ± standard deviation (SD) and compared using the Welch Two Sample *t*-test. Non-parametric data are presented as median and interquartile range and compared using the Mann-Whitney *U* test. Categorical data are represented as *n* (%) and compared using the Chi-squared test. Bivariate correlation was assessed with a Pearson's correlation coefficient (r). All p values ≤ 0.05 were considered statically significant. Statistical analyses were performed using R Statistical Software (version 4.3.2, The R Foundation for Statistical Computing, 2023).

3. Results

Records were retrospectively reviewed for 825 heart transplant recipients over a 22-year period. Within this cohort, we identified 15 subjects who required PPM implants after transplantation and met the specified inclusion and exclusion criteria. The comparator group consisted of 30 matched controls of OHTx recipients who did not require PPM over long-term follow-up.

The clinical characteristics of the two groups are shown in Table 1. Mean age in the pacemaker and non-pacemaker groups were 64.8 (SD 15.8) and 63.0 (SD 14.8) years ($p = 0.71$), one-third of patients in each group were female sex ($p = 1$), and height 171 cm (SD 11.5) and 170 cm (SD 11.4) ($p = 0.79$) and weight 73.9 kg (SD 15.0) and 78.2 kg (SD 15.5) ($p = 0.38$), respectively. There was a non-significant difference in time from heart transplant in the pacemaker and non-pacemaker groups (17.4 (SD 10.2) and 13.1 (SD 8.0) years: $p = 0.17$). In the pacemaker group, 53% were NYHA class I and 46% NYHA class II. The mean time to pacemaker implantation following heart transplantation was 12.3 years. Early post-OHTx pacing (<1-year post-transplant) was required in two patients. Within the pacemaker group, those who developed CAV were found to require pacemaker implantation later following transplantation compared to those without CAV (16.8 *vs.* 7.1 years: $p = 0.03$).

Table 1. Baseline Patient Characteristics.

	PPM: NYHA Class 1 (*n* = 8)	**PPM: NYHA Class 2 (*n* = 7)**	***p*-Value**
Female	3 (37.5)	2 (28.6)	1.0
Age, y	59.3 (17.0)	71.7 (12.0)	0.12
Height, cm	169.1 (13.1)	172.9 (10.1)	0.54
Weight, kg	76.0 (18.4)	71.6 (10.7)	0.57
Time following the transplant, y	14.9 (12.0)	20.8 (7.2)	0.27
Time to PPM following transplant, y	10.6 (10.1)	14.1 (7.9)	0.46
Time following PPM, y	4.3 (3.2)	6.6 (3.2)	0.18
	PPM (*n* = 15)	No PPM (*n* = 30)	
Female	5 (33.3)	10 (33.3)	1.0
Age, y	65.1 (15.8)	63.2 (14.8)	0.71
Height, cm	170.9 (11.5)	169.9 (11.4)	0.79
Weight, kg	73.9 (15.0)	78.2 (15.5)	0.38
Time following the transplant, y	17.6 (10.2)	13.4 (8.0)	0.17

Values are *n* (%) or mean ± SD. PPM = permanent pacemaker; NYHA = New York Heart Association.

Device programming settings in the 15 patients in the PPM group are shown in Table 2. Dual chamber devices were implanted in 74%, single chamber in 14% and biventricular devices in 13%. Indications for pacemaker implantation included atrioventricular node disease (53%), sinus bradycardia (13%), atrial fibrillation (7%) and sinus rhythm with pauses/ventricular standstill (27%). Only a minority (3/15, 20%) were programmed at a LRL > 60 bpm. Rate-response mode was programmed on in 47% and algorithms that minimise ventricular pacing in 27% of patients. RV pacing burden <1% was present in 53% of patients. High RV pacing burden (>20%) was present in 33% of patients; pacing was indicated in each of these patients for complete heart block. Thirteen percent were left ventricular paced >20% of the time.

Table 2. Comparison of patients with a pacemaker following heart transplantation by New York Heart Association Functional class.

Variable	**NYHA Class 1 (*n* = 8)**	**NYHA Class 2 (*n* = 7)**	***p*-Value**
Resting heart rate, bpm	85 (14.9)	79 (8.0)	0.33
CAV	5 (62.5)	3 (42.9)	0.8
Device details			
Type			
Single chamber	2 (25)	0 (0)	
Dual chamber	5 (62.5)	6 (85.7)	
Biventricular	1 (12.5)	1 (14.3)	
Programming mode			
Rate response	3 (37.5)	4 (57.1)	
Minimised ventricular pacing	1 (12.5)	3 (42.9)	
Lower rate limit, bpm	65.6 (11.2)	60.0 (0.0)	0.20
Upper rate limit, bpm	132.5 (8.8)	125.7 (7.9)	0.18
Underlying rhythm			
Sinus rhythm	4 (50)	5 (71.4)	
High-degree AVB	2 (25)	1 (14.3)	
No underlying rhythm	2 (25)	0 (0)	
Atrial-pacing percentage, %	25.8 (40.6)	8.7 (12.6)	0.41
Right ventricular-pacing percentage, %	43.3 (52.8)	28.3 (48.3)	0.59
HrSc median, bpm	83 (15.7)	79 (7.9)	0.54
HrSc mode, %	47 (12.5)	37.1 (4.9)	0.09
Transthoracic Echocardiogram			
LVEF, %	58.1 (9.9)	53.9 (13.1)	0.50
ESE			
METS, mL/kg/min	9 (2.7)	6.9 (1.0)	0.21
Peak heart rate, bpm	135 (18.8)	123 (14.8)	0.29
Heart rate response	45 (21.6)	41 (13.6)	0.75
Chronotropic index	0.7 (0.4)	0.6 (0.2)	0.58

Values are *n* (%) or mean ± SD. NYHA = New York Heart Association; CAV = cardiac allograft vasculopathy; AVB = atrioventricular nodal block; HrSc = heart rate score; LVEF = left ventricular ejection fraction; ESE = treadmill exercise stress echocardiogram; METS = metabolic equivalent of task.

When comparing patients with NYHA class I and NYHA class II symptoms in the pacemaker group, there were no statistically significant differences in frequency of atrial pacing (26% *vs.* 9%: $p = 0.41$) or right ventricular pacing (43% *vs.* 28%: $p = 0.59$) between the two groups. Resting heart rate was similar between the two groups (85 (SD 14.9) and 79 (SD 8) bpm: $p = 0.33$), so too was the median HrSc (83 (SD 15.7) and 79 (SD 7.9) bpm: $p = 0.54$); no patient in either group had a HrSc mode > 70%. The NYHA class I group achieved a statistically non-significant higher workload (metabolic equivalent of task (METS) 9 (SD 2.7) *vs.* 6.9 (SD 1) mL/kg/min: $p = 0.21$), and peak heart rate (135 (18.8) *vs.* 123 (14.8) bpm: $p = 0.29$) on ESE testing when compared to the NYHA class II group. There were no differences in left ventricular ejection fraction (58% (SD 9.9) and 54% (SD 13.1): $p = 0.5$), heart rate response (HRR) (45 (21.6) and 41 (13.6) bpm: $p = 0.75$), or CIx (0.7 (0.4) and 0.6 (0.2): $p = 0.58$) between symptomatic and asymptomatic patients with pacemakers. There was a positive linear correlation between HRR and METS (r = 0.53: $p = 0.09$), and CIx and METS (r = 0.74: $p = 0.009$), and a negative linear correlation between HrSc mode and METS (r = −0.36: $p = 0.28$).

Patients with pacemakers following OHTx were more symptomatic than those without pacemakers (NYHA class II 46% *vs.* 10%: $p = 0.016$) [Table 3]. With higher rates of patient-reported exertional dyspnoea (26% *vs.* 0%: $p = 0.016$), lethargy (40% *vs.* 3%: $p = 0.005$), and reduced exercise tolerance (26% *vs.* 3%: $p = 0.065$) during clinic evaluation in the PPM group. The groups exhibited similar resting heart rates (82.5 (SD 12.2) and 82.6 (SD 13.2) bpm: $p = 0.97$), but significantly higher rates of CAV (8/15, 54% *vs.* 3/30, 10%: $p = 0.005$) and anaemia (5/15, 33% *vs.* 1/30, 3%: $p = 0.02$) were found in the pacemaker group. Prevalence of other comorbidities was balanced between the PPM and non-PPM groups, and there were no significant differences in specific cardiovascular medication administration. The pacemaker group had a trend towards lower left ventricular ejection fraction on transthoracic echocardiogram than the non-pacemaker group (56% (SD 11.3) and 62% (SD 7.9): $p = 0.066$), however during ESE testing, the groups achieved similar METS (7.9 (SD 2.6) and 8.1 (SD 2.5) mL/kg/min: $p = 0.8$).

Table 3. Comparison of patients with and without a pacemaker following heart transplantation.

Variable	PPM (*n* = 15)	No PPM (*n* = 30)	*p*-Value
NYHA class			**0.016**
1	8 (53.3)	27 (90.0)	
2	7 (46.7)	3 (10.0)	
Clinical symptoms			
Palpitations	0 (0.0)	2 (6.7)	0.80
Dyspnoea	2 (13.3)	0 (0.0)	0.20
Exertional dyspnoea	4 (26.7)	0 (0.0)	**0.016**
Reduced exercise tolerance	4 (26.7)	1 (3.3)	0.065
Dizziness	1 (6.7)	2 (6.7)	1
Lethargy/fatigue	6 (40.0)	1 (3.3)	**0.005**
Resting heart rate, bpm	82.5 (12.2)	82.6 (13.2)	0.97
Comorbidities			
Hypertension	9 (60.0)	10 (33.3)	0.17
Atrial fibrillation/flutter	4 (26.6)	2 (6.7)	0.20
CAV	8 (53.3)	3 (10.0)	**0.0048**
Allograft dysfunction	1 (6.7)	0 (0.0)	0.72
Diabetes	2 (13.3)	9 (30.0)	0.39
Hypercholesterolaemia	5 (33.3)	10 (33.3)	1
Malignancy	7 (46.7)	11 (36.7)	0.75
Anaemia	5 (33.3)	1 (3.3)	**0.02**
Chronic kidney disease	11 (73.3)	18 (60)	0.58
Biochemistry			
Hb, g/L	125.0 (22.9)	130.1 (14.7)	0.50
Creatinine, μmol/L	137.3 (43.9)	124.9 (60.9)	0.46
Medications			
Beta-blocker	4 (26.7)	7 (23.3)	1
DHP CCB	2 (13.3)	8 (26.7)	0.53
Non-DHP CCB	1 (6.7)	3 (10.0)	1
Alpha-blocker	2 (13.3)	1 (3.3)	0.53
Transthoracic Echocardiogram			
LVEF, %	56.1 (11.3)	62.4 (7.9)	0.066
ESE			
METS, mL/kg/min	7.9 (2.6)	8.1 (2.5)	0.8

Values are *n* (%) or mean ± SD. Significant differences are bolded. Allograft dysfunction was defined as Left Ventricular Ejection Fraction < 40%; Anaemia was defined as Hb < 128 g/L; Chronic kidney disease was defined as eGFR < 60 mL/min/1.73m^2; PPM = permanent pacemaker; NYHA = New York Heart Association; CAV = cardiac allograft vasculopathy; DHP CCB =

Dihydropyridine calcium channel blocker; LVEF = left ventricular ejection fraction; ESE = treadmill exercise stress echocardiogram; METS = metabolic equivalent of task.

4. Discussion

We have demonstrated that there is substantial variability in pacemaker programming following heart transplantation at our centre. However, this does not correlate with symptom burden (Figure 1). Additionally, patients who require PPM implantation following transplantation had higher rates of CAV and anaemia than those without PPM, chronic comorbidities that likely contribute to their greater symptom burden (Graphical Abstract).

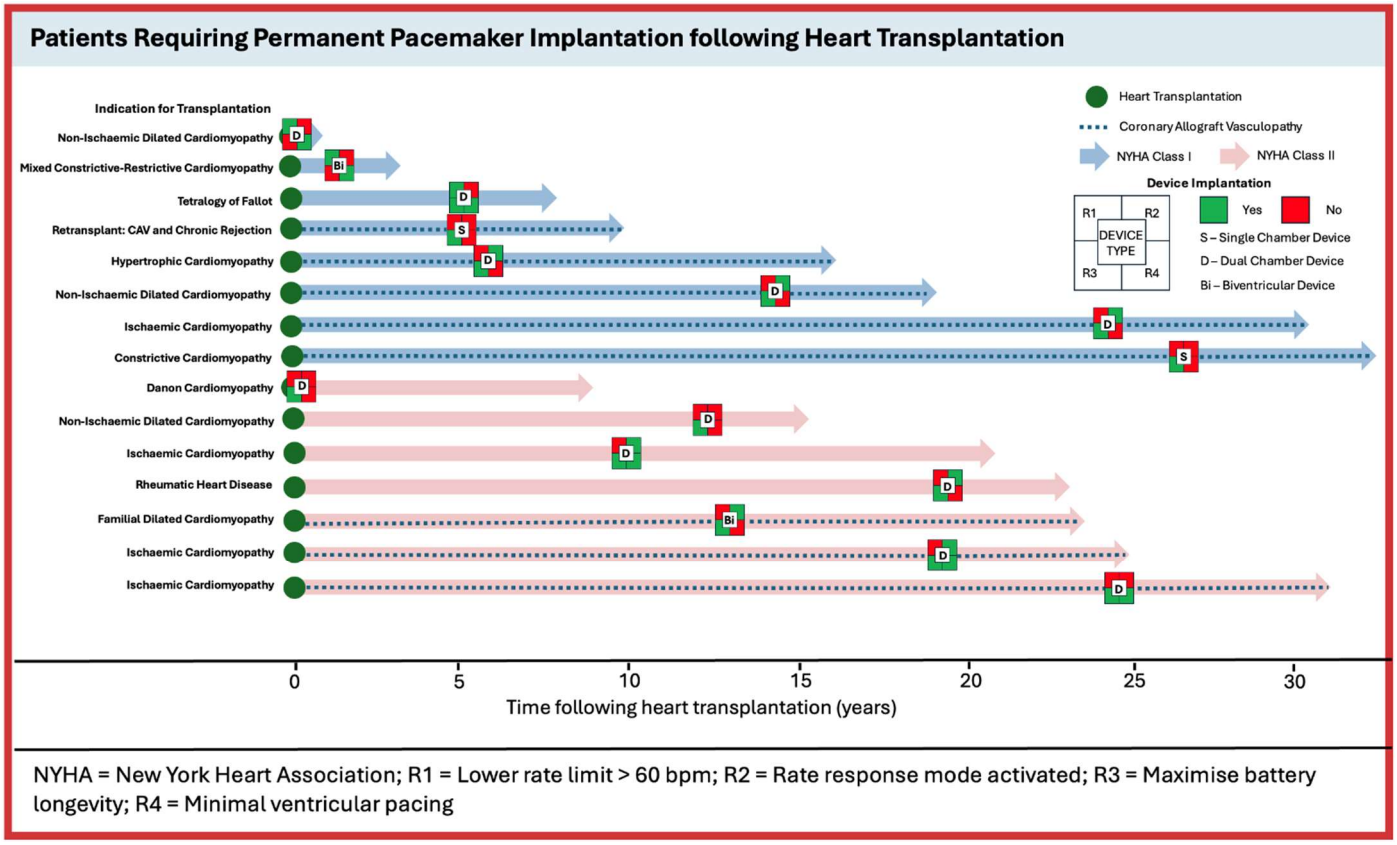

Figure 1. The timeline of events from orthotopic heart transplantation to study date for each subject requiring permanent pacemaker implantation following heart transplantation as stratified by New York Heart Association function class status. The indication for transplantation is listed for each subject before the green circle, which indicates the time of transplantation, and the dotted lines indicate the status of coronary allograft vasculopathy following transplantation. Timing of device implantation is indicated by a flag, device type is exhibited in the central box of each flag and programming recommendation status is represented by the colour in each flag quadrant; green indicates programmed as per recent recommendations, and red indicates not programmed as per recent recommendations.

In our study, a minority of patients in the pacemaker cohort were paced with a LRL > 60 bpm. These patients had a pacemaker implanted within the last two years in the setting of complete heart block and subsequently were clinically NYHA class I. Heart transplant recipients commonly have blunted chronotropic response, decreased heart rate variability and reduced augmentation in cardiac output to exercise [10]. In this population, programming a higher LRL, >80 bpm, is one recommendation made in the limited literature available to optimise cardiac output and emulate the altered post-transplant physiology whereby cardiac vagal denervation drives a catecholamine-induced baseline sinus rate of 90 to 110 bpm [2]. Interestingly, the recent myPACE trial found that patients with HFpEF, who share some similar physiology to the transplanted heart, benefit from moderately accelerated pacing rates due to enhancement of myocardial contractility and relaxation kinetics resulting in an increase in cardiac output [4,11]. The remaining patients in this cohort were paced at or below the nominal LRL, 60 bpm. Those with complete heart block underwent pacemaker implantation pre-2020, prior to the publication of the recent recommendations. While many patients in the pacemaker cohort were programmed in line with the limited published recommendations, clinically asymptomatic patients were not necessarily programmed with greater alignment to these recommendations.

Assessing contemporary markers of chronotropic incompetence, including HrSc, HRR and CIx, we demonstrated a positive relationship between both HRR and CIx, and METS, and a negative relationship between HrSc and METs, in keeping with the current literature [8,9,12]. There is a plenitude of data demonstrating improved cardiac output or increased exercise tolerance and peak VO_2 with rate-responsive atrial demand or dual-chamber pacing in heart transplant recipients, supporting the recommendation to program rate response mode in transplant recipients with pacemakers [2,3,13–15]. However, contemporary markers of chronotropic incompetence (HrSc, HRR and CIx), have not been validated in this specialised cohort. HrSc has been validated as a measure of chronotropic incompetence in the pacemaker population, and HRR as a marker of exercise tolerance in heart transplant recipients [7,8,12]. Additionally, CIx has been validated as a measure of chronotropic incompetence in patients with heart failure and found to infer prognostic implications [9,16]. Rate response mode was programmed in 47% of paced patients in our study: three patients at NYHA class I and four at NYHA class II. Our findings contribute to the validation of these measures of chronotropic incompetence in the transplant cohort. Further validation of these variables would provide additional clarity regarding the indication for programming rate response mode in transplant recipients.

Our cohort had various approaches to minimising ventricular pacing. Four patients were programmed with algorithms that limit ventricular pacing, three of which were without atrioventricular nodal block. Turning on modes that manage minimal ventricular pacing is recommended for patients without atrioventricular nodal block to avoid left ventricular deterioration due to chronic right ventricular pacing [2]. Of those with alternate programming, two had right ventricular single lead devices, and six had an atrioventricular nodal block and, therefore, inappropriate for limited ventricular pacing. On recent device checks, the remaining three patients were inherently minimally ventricularly paced (0, 0 and 4%).

Maximising battery longevity is recommended to minimise the frequency of invasive procedures, for example, generator changes, and therefore limit infection risk in this vulnerable immunosuppressed population [2].

Considering the substantial variability in pacemaker programming within our cohort, no definitive physiological or programming-dependent differences were identified when comparing patients within the pacemaker group stratified by symptom burden. Curiously, those who were programmed to pace at a higher lower rate limit were all NYHA class I, however, when comparing resting and peak heart rates between the two groups, there was no clinically significant difference. A prospective study interrogating the benefit of accelerated pacing in this specialised cohort would be of great value, however, the findings of our study portend to a result that garners no significant improvement in symptoms with accelerated pacing.

When we compared those with pacemakers following heart transplantation with the matched group without pacemakers, we found that transplant recipients with pacemakers have a greater symptom burden than their non-paced counterparts. This finding appeared to have no correlation with resting heart rate, and no patient with a pacemaker exhibited chronotropic incompetence as defined by a HrSc mode > 70% on device histogram [7,8]. The pacemaker group did, however, exhibit a greater frequency of comorbidities, particularly CAV and anaemia, and a trend towards lower left ventricular ejection fraction, which certainly are chronic factors that may contribute directly to their amplified symptomatology and should be considered for confounding adjustment in future research. Those who developed CAV required pacemaker implantation later following transplantation than those without, which is in alignment with existing literature that describes conduction disease due to CAV-related ischaemia [1]. Our data supports the notion that patients with pacemakers following orthotopic heart transplantation generally have a greater symptom burden than those without.

Our study is a retrospective analysis and, therefore, subject to Study Limitations. The study cohort was from a single transplant centre with a subsequent small number of patients in each study group, therefore, data may be statistically underpowered with a reduced ability to adjust for confounding factors. Ideally, we would have sought to compare patients with pacemakers utilising propensity score matching based on physiological or programming parameters; however, this would have been prohibitively underpowered due to limited patient numbers. Some data were unavailable, for example, specific ECGs from ESEs, which limited further analysis. The merits of this paper include that it is a detailed description of an entire single-centre experience and, considering the small patient population that includes patients with pacemakers following heart transplantation, there remains value in studying our cohort. We also integrated a non-pacemaker group as a descriptive comparator to illustrate differences. Further studies, ideally prospective, across multiple centres utilising larger study groups, are required for further verification of results.

5. Conclusions

Pacemaker programming following orthotopic heart transplantation is highly variable, and no identifiable physiological or programming differences stratified morbidity within the pacemaker cohort. Those requiring a pacemaker, however, had a greater symptom burden and rate of chronic comorbidities than those without a pacemaker following transplantation, which did not correlate with resting heart rate. Careful consideration should, therefore, be made when deliberating the implementation of a universal pacemaker programming guideline in patients with pacemakers following orthotopic heart transplantation. We recommend an individualised approach, noting this specialised cohort's unique post-transplant physiology.

Author Contributions

Conceptualisation and Design: M.R., E.N.T., H.C.P.; Acquisition, analysis, or interpretation of data: M.R., E.N.T., J.W., D.M.K., S.J.G. and H.C.P.; Drafting of the manuscript: M.R., E.N.T., J.W. and H.C.P.; Critical revision of the manuscript for important intellectual content: M.R., E.N.T., J.W., C.C., J.L.H., J.A.M., D.M.K., S.J.G. and H.C.P.; Supervision: H.C.P.

Ethics Statement

We received ethics approval from the Alfred Hospital Ethics Committee, Project No: 186/24.

Informed Consent Statement

This was a retrospective study, therefore ethics waived the need for individual patient consent.

Data Availability Statement

Data is stored. There is no ethics approval in place to share data with other organizations.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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