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Permanent pacing and conduction recovery in patients undergoing cardiac surgery for active infective endocarditis in an Australian Tertiary Centre

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Abstract

Background: Postoperative heart block is common amongst patients undergoing surgery for infective endocarditis (IE). Limited data exists allowing cardiologists to predict who will require permanent pacemaker (PPM) implantation postoperatively. We aimed to determine the rate of postoperative PPM insertion, predictors for postoperative PPM, and describe PPM utilization and rates of device related infection during follow up.

Methods: A retrospective analysis was performed of 191 consecutive patients from a single institution who underwent cardiac surgery for IE between 2001 and 2017. Preoperative and operative predictors for postoperative PPM were evaluated using univariate and multivariate logistic regression.

Results: The rate of postoperative PPM implantation was 11% (17/154). The PPM group had more preoperative prolonged PR interval alone (33% vs 12%, p=0.03), coexistent prolonged PR and QRS durations (13% vs 2%, p=0.01), infection beyond the valve leaflets (82% vs 41%, p=0.001), aortic root debridement (65% vs 23%, p=<0.001), patch repair (47% vs 20%, p=0.01), postoperative prolonged PR interval (50% vs 24%, p= 0.01), and prolonged QRS duration (47% vs 15%, p= 0.001). On multivariate analysis, infection beyond the valve leaflets emerged as an independent predictor for postoperative PPM (OR 1.94, 95% CI 1.14-3.28, p=0.014). A reduction in PPM utilization was observed in 5 patients whilst 8 patients continued to show significant ventricular pacing with no underlying rhythm at 12 months. There were no device related infections.

Conclusion: Postoperative PPM was required in 11% of patients undergoing surgery for infective endocarditis over a 16-year period. Infection beyond the valve leaflet was an independent predictor for postoperative PPM insertion.

Keywords: Infective endocarditis, postoperative heart block, conduction recovery

Introduction

Infective endocarditis (IE) is a disease of high morbidity and mortality.[1] Cardiac valve surgery is potentially lifesaving and is required in up to 50% of cases during their acute infection.[2] Postoperative heart block is a common complication and is an

independent predictor of mortality.[3] Approximately 12% of patients with IE require a PPM to be inserted postoperatively.[4,17] The etiology of heart block in patients with IE undergoing surgery is likely multifactorial, including both infective destruction and surgical debridement of valvular tissue and the intrinsic conduction system. Heart block may also be transient due to trauma and edema from surgical manipulation in close proximity to the conduction system. Although the potential for conduction recovery exists, the optimal time to wait for conduction recovery is unclear. Placement of transvenous PPM systems in patients with IE carries the risk of endovascular device-related infection and therefore avoiding implantation in patients in whom early conduction recovery is likely would be preferable. Observational studies have evaluated the frequency of pacemaker dependency after pacemaker insertion for patients with heart block after cardiac surgery with variable results.[5,6] Amongst patients requiring surgery for IE, limited data are available on the predictors for PPM insertion, PPM utilization post implantation, and rate of device related infection. As such, deciding in whom and when to implant a PPM continues to pose a challenge for treating physicians.

We sought to retrospectively study a cohort of consecutive patients who underwent surgery for active IE at an Australian Tertiary Centre to determine:

1. The rate of postoperative PPM.
2. Clinical characteristics of the pacemaker group and predictors for postoperative PPM insertion.
3. Any change in percentage pacing or underlying rhythm at VVI 30 in the pacemaker group over 12 months.
4. The rate of device related infection after pacemaker insertion.

Methods

The Austin Health Human Research Ethics Committee (HREC) approved the study protocol. From January 2001 to July 2017, 191 patients who underwent cardiac

surgery for IE at The Austin Hospital were identified from a national registry, the Australia New Zealand Society of Cardiothoracic Surgery National database (ANZSCTS). Patients were excluded if they had a PPM inserted preoperatively or had surgery for healed IE. Healed IE was defined as patients who responded to antibiotic therapy but required surgery in the convalescent period for ongoing symptomatic valve stenosis or regurgitation. A pre-specified range of baseline characteristics, preoperative, operative and postoperative details were available from the ANZSCTS database in addition to extensive review of individual patient medical records and operative notes. We collected preoperative data including demographics, comorbidities, baseline serum creatinine, the responsible microorganism, use of antiarrhythmic and atrio-ventricular node blockers (beta blocker and calcium channel blockers) and electrocardiographic features including conduction disorder. A conduction disorder was defined as the presence of a prolonged PR interval >200 milliseconds alone, prolonged QRS duration >120 milliseconds alone, or coexistent prolonged PR and QRS durations on 12-lead surface electrocardiogram. Operative variables included type and number of valves infected, extent of infection, type of surgery, cross clamp time, and bypass time. The extent of infection was documented in the operative notes at the time of surgery and it was classified as either involving the valve leaflet only, or extending beyond the

leaflet into the annulus or extra valvular structures. The need for extra valvular surgery including patch repair, aortic root debridement or total root replacement was documented. Postoperative variables included type of arrhythmias, electrocardiographic abnormalities on day 1 post-operatively, use of anticoagulation, pacemaker insertion, in-hospital mortality, 30-day mortality, and length of stay.

The indication and timing of PPM insertion were at the discretion of the treating cardiac surgery and cardiology teams and was classified as either heart block or sinus node dysfunction. Patients who required a PPM for sinus node dysfunction (SND) were excluded from further analyses, as cardiac surgery and IE are more mechanistically associated with heart block than SND. Devices were implanted by cardiac electrophysiologists and programmed routinely. Interrogation reports at day 1, 3 months and 12 months post insertion were reviewed and pacemaker utilization was described for the patients who required a PPM postoperatively. This included intrinsic rhythm assessments at VVI mode at a rate of 30 beats per minute (bpm) in addition to atrial and ventricular pacing percentages over the 12 months period.

Statistical analysis

Continuous data are presented as medians with ranges. Categorical data are presented as absolute numbers and percentages. Categorical variables were compared using Pearson's $\chi 2$ test, while continuous variables were compared using

Student's t-test. We performed logistic regression to determine predictors of post-operative PPM, with results presented as odds ratios (OR) with respective 95% confidence interval (CI). Only preoperative and operative variables were included in these analyses. Significant variables identified on univariate analysis were included in the subsequent multivariate model. Statistical significance was established at $P<0.05$. All data were analysed using Stata MP 13.0 (Stata Corp LP, College Station, TX).

Results

Between January 2001 and July 2017, a total of 191 consecutive patients underwent surgery for IE. A total of 37 patients with preoperative PPM or healed IE were excluded. Out of the remaining 154 patients, a total of 19 patients required a PPM postoperatively. Postoperative heart block was the main indication in 17 patients (11%) compared to sinus node dysfunction in 2 patients. The median time for PPM insertion of 8 days (95% CI, 18).

Baseline and preoperative characteristics

Table 1 demonstrates the baseline characteristics and preoperative clinical and electrocardiographic details of the pacemaker and the non-pacemaker groups. Overall, 10% (15/154) of patients were on dialysis preoperatively. There were no significant differences in the baseline characteristics between the groups. However,

significant differences were seen in the preoperative electrocardiographic details. The PPM group had more preoperative prolonged PR interval alone (33% vs 12%, *p*=0.03), and coexistent prolonged PR and QRS durations (13% vs 2%, *p*=0.01).

Operative details

Table 2 shows procedural details of both groups. All 17 patients in the PPM group and 128/135 patients in the non-PPM group had their operative notes available for review. The pacemaker group had a higher incidence of infection beyond the valve leaflet (82% vs 41%, *p*=0.001), aortic root debridement (65% vs 23%, *p*=<0.001) and patch repair (47% vs 20%, *p*=0.01). There were, no significant differences in number or type of valves involved, cumulative cross clamp and bypass time.

Postoperative outcomes

Table 3 presents postoperative clinical, electrocardiographic, and outcomes details of both groups. There was no significant difference in the prevalence of atrial fibrillation. In terms of electrocardiographic variables, the PPM group was more likely to have a prolonged PR interval (50% vs 24%, *p*=0.01), and prolonged QRS duration (47% vs 15%, *p*=0.001) compared with those who did not receive a PPM. Overall in-hospital mortality was 10% whilst 30-day mortality was 10% (16/154) with no significant difference in mortality between the two groups. There was no difference in the hospital length of stay (28 ± 11 vs 24.9 ± 14, *p*=0.37).

Predictors of postoperative pacemaker implantation

On univariate analysis, preoperative prolonged PR interval (p= 0.04*),* coexistent prolonged PR and QRS durations (p= 0.03), and extent of infection beyond valve leaflet (*p*=0.001) were identified as predictors for postoperative PPM. On multivariate analysis, the only significant independent predictor for PPM was the extent of infection beyond the valve leaflet (OR 1.94, 95% CI 1.14-3.28, *p*=0.014) (**Table 4**).

Pacemaker follow-up

Tables 5 present the timings of PPM insertion together with the PPM interrogations for the study cohort. Two patients died in the first 12 months. There were no documented device related infections at 12 months follow up. In 8 patients, the absence of an underlying rhythm together with significant ventricular pacing continued during follow up. A reduction in PPM utilization was noted in 5 patients over 12 months. In 2 patients, no significant PPM utilization was documented from day 1 and in one patient, pacing requirements increased. There was no significant difference between PPM utilization at 12 months and postoperative day of implantation (p= 0.35)

Discussion

Our study provides a novel insight into permanent pacing for heart block in the context of heart surgery for active IE in an Australian Tertiary Centre over a 16 year period. Our main findings are:

1. Postoperative PPM insertion was required in 11% of patients who underwent surgery for active endocarditis.
2. The patients who required a PPM postoperatively were more likely to have preoperative prolonged PR interval, preoperative coexistent PR and QRS prolongation, infection extending beyond the valve leaflet, patch repair, aortic root debridement, and postoperative prolonged PR interval and QRS duration. Infection beyond the valve leaflet was an independent predictor for postoperative PPM.
3. A reduction in pacing requirements suggesting conduction recovery was noted in 5 patients.
4. There were no significant device related infections at 12 months post insertion in the setting of treated IE.

Amongst patients who undergo cardiac surgery for IE, the reported rate of PPM implantation post operatively is about 12%, which is consistent with our incidence of 11%.[4,17] Conversely, in the absence of IE, the rate of postoperative PPM is low at

6%.[18,19] The higher rate of PPM in patients undergoing surgery of endocarditis likely relates to infective destruction of the conduction system by the organism itself in addition to the extensive surgical debridement required sterilizing the infected tissue. In our cohort, more preoperative conduction disorder, infection beyond the valve leaflet, and extravalvular surgery (patch repair and aortic root debridement) was observed in the PPM group.

Postoperatively, earlier PPM implantation leads to earlier patient mobilization, improved surgical outcomes, shorter length of stay, and reduced costs.[15] This is counterbalanced by evidence that more liberal PPM insertion postoperatively is associated with increased risk of device related complications such as infections, need for lead repositioning and long term right ventricular pacing.[16] Furthermore, waiting may allow for resolution of tissue edema and conduction recovery and could prevent unnecessary PPM implantation. The American College of Cardiology and the American Heart Association has no current guidelines regarding timing of PPM insertion in these patients.[14] Additionally, certain scenarios require consideration of intraoperative epicardial instead of transvenous systems such as the setting of surgery for tricuspid valve IE and patients with recurrent blood infections. From here the need for reliable predictors of PPM implantation emerges.

In patients undergoing valve surgery without IE, various preoperative and operative predictors have been studied to identify patients more likely to need PPM postoperatively earlier to reduce their hospital stay and improve the usage of hospital resources; these studies have yielded inconsistent findings.[7-11,18] Examples of predictors included baseline conduction disorder, advanced age, prolonged cardiopulmonary bypass time, aortic valve surgery, and postoperative cardiac arrest. In our univariable analysis, the pacemaker group was more likely to have had a preoperative prolonged PR interval (either in isolation or in combination with prolonged QRS duration), infection beyond the valve leaflets, patch repair, aortic root debridement, postoperative prolonged PR interval and QRS duration. We only included the preoperative and operative variables in the multivariate analysis in order to determine the independent predictors for pacemaker implantation that would guide decision making at time of surgery or the early post operative period. Infection beyond the valve leaflet at the time of surgery was the only independent predictor for postoperative PPM insertion. These findings could be explained by the infective destruction of conduction system as the infection extends beyond the leaflets into the annulus and other extra valvular structures. As this is usually associated with the need for surgical procedures such as patch repair and aortic root debridement, these procedures were not included in regression modelling due to the significant likelihood

of co-linearity with the indication for surgery being extent of infection beyond leaflets. The presence of infection beyond valve leaflets at time of surgery can help with decision making on the timing of permanent pacing as conduction recovery seems to be unlikely in this group of patients. This approach could be advantageous when epicardial systems are considered at the time of surgery in patients where a transvenous system could pose a risk such as tricuspid valve surgery and recurrent infections.

In recent years, the issue of conduction recovery and pacemaker dependency after PPM implantation has gained significant interest. Conduction recovery in an IE cohort could be explained by the reversibility of the extensive surgical edema and infective inflammation that is unique within this group of patients. However, the natural history for postoperative conduction disturbance remains poorly understood. Identifying patients with who will likely have conduction recovery would allow for considerations of a longer monitoring period or alternatively a temporary form of pacing prior to implantation of a PPM. Several observational cohorts have studied patients who underwent PPM implantation postoperatively to assess the rate of pacemaker dependency and understand the characteristics of the group who recover conduction with variable results. The rate of pacemaker dependency varied between 40-91% with inconsistent predictors such as pre-operative left bundle branch block,

pre-operative 1st degree heart block and persistent post-operative 3rd degree heart block.[5,6,9,10,12] These inconsistencies have been attributed partly to the absence of a universal definition for pacemaker dependency and conduction recovery.[20] In our cohort, 8 patients continued to demonstrate high ventricular pacing percentage with no underlying rhythm during follow up suggesting no conduction recovery. Moreover, pacing requirements increased over 12 months in one patient, which could have been due to progressive atrioventricular conduction disease. On the other hand, a reduction in PPM utilization was documented in 5 patients. Three out of 5 had no underlying rhythm and significant ventricular pacing on day 1 which improved to sinus rhythm with <1% ventricular pacing at either 3 or 12 months, suggesting conduction recovery. One patient had significant pacing requirements on day 1 followed by emergence of an underlying rhythm (atrial fibrillation) together with a reduction in ventricular pacing of about 50% suggesting some conduction recovery. In one patient, atrial fibrillation was the underlying rhythm during follow up, however significant ventricular pacing was noted on day 1 and 3 months followed by a reduction of ventricular pacing <1% at 12 months. This could have been due to conduction recovery.

Limited data are available on rate and predictors of conduction recovery in an IE cohort. Jassal et al documented an ongoing need for pacing in 90% at 12 months

using serial ECG assessments.[13] Additionally, Kiehl et al demonstrated that in a cohort of IE patients who required a PPM (n=31), the rate of late conduction recovery (defined as ventricular pacing percentage <10% after 1 month of implantation) was 9% and the presence of pre operative AV conduction abnormalities (prolonged PR and QRS intervals) was associated with decreased recovery.[22] Using the same criteria defined by Kiehl et al to define conduction recovery in our cohort would yield a rate of 25%. The higher rate in our study cohort despite having a conservative median implant time of 8 days could be due to differences in patient demographics, surgical technique or a combination of early surgery and aggressive antibiotics reducing permanent damage to the conduction system.

The prevalence of device related infection is increasing with more devices implanted every decade. The rate of PPM related infection is about 1-2% in the first 12 months after PPM insertion.[21] To our knowledge, this is the first study to report the rate of device related PPM infection in patients undergoing surgery for IE. In our cohort, none of the 19 patients had device related infections during the follow up period. Despite few patients, the data are reassuring given the perceived high risk of device related infections in this high-risk group.

Limitations

We acknowledge certain limitations in this study. As a retrospective analysis, results should be interpreted with caution and further prospective validation of results is needed. The relatively small cohort of patients limits certain statistical analyses, in particular evaluation of predictors in multivariable modeling. Additionally, over the 16 years of cardiac surgery, operative techniques, medical treatments, and PPM implantation decisions for IE may have evolved leading to possible treatment biases.

Conclusion

Postoperative PPM insertion was required in 11% of patients undergoing surgery for infective endocarditis over a 16-year period. Infection beyond the valve leaflet was an independent predictor for postoperative PPM insertion. Reduction in PPM utilization was observed in 5 patients over 12 months. There were no device related infections documented over 12 months follow up.

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Table 1: Baseline characteristics and pre-operative details

Variables	PPM (n=17)	Non-PPM (n=135)	p-value
Baseline characteristics			
Age, mean (SD)	55.2 (15)	50.6 (16)	0.26
Gender, Male, N (%)	13 (76)	93 (69)	0.94
Smoking, N (%)	9 (53)	76 (56)	0.79
Diabetes, N (%)	4 (24)	19 (14)	0.31
Dialysis, N (%)	3 (18)	12 (9)	0.25
Hypertension, N (%)	7(41)	44 (33)	0.48
Prior stroke, N (%)	6 (35)	28 (21)	0.18
Peripheral vascular disease, N (%)	1 (6)	4 (3)	0.53
Chronic lung disease, N (%)	0	15 (11)	0.22
Ischemic heart disease, N (%)	0	14 (10)	0.16
Pre-operative details			
Pre-operative Cr > 200 μmol/l, N (%)	3 (18)	15 (11)	0.50

Organism (Staph. Aureus), N (%)	8 (47)	60 (44)	0.84
Pre-operative atrial fibrillation, N (%)	2 (12)	8 (6)	0.45
Prolonged PR >200 msec alone, N (%)	5 (33)	14 (12)	0.03
Prolonged QRS >120 msec alone, N (%)	0	6 (4)	0.30
Prolonged PR and QRS present, N	2 (13)	2 (2)	0.01
Pre-operative antiarrhythmic, N (%)	0	5 (4)	0.42
Pre-operative AV blockers (BB, CCB), N (%)	5 (29)	19 (14)	0.08

BB = Beta Blockers, CCD = Calcium Channel Blockers, Cr = Creatinine, PPM = Permanent Pacemaker, SD = Standard Deviation

Table 2: Operative details

Variables	PPM (n=17)	Non- PPM (n=135)	p-value
Type of surgery			
Single valve, N (%)	12 (70)	103 (76)	0.60
Multiple valves, N (%)	5 (29)	28 (21)	0.66
Vegetectomy only, N (%)	0	4 (3)	

Extent of infection			
Leaflet only, N (%)	3 (18)	75 (59)	
Beyond valve leaflet , N (%)	14 (82)	53 (41)	0.001
Valve surgery (repair & replacement)			
Aortic valve, N (%)	11 (65)	74 (55)	0.30
Mitral valve, N (%)	8 (47)	72 (53)	0.31
Tricuspid valve, N (%)	3 (18)	15 (11)	0.79
Pulmonary valve, N (%)	0	8 (6)	0.30
Extra valve surgery			
Aortic root debridement, N (%)	11 (65)	29 (23)	<0.001
Patch repair, N (%)	8 (47)	25 (20)	0.01
Aortic root reconstruction, N (%)	4 (24)	18 (14)	0.26
Cumulative cross clamp time, mean (range)	170.6 (85-362)	138.8 (28-524)	0.10

Cumulative bypass time, mean (range)	236.8 (110-503)	194.6 (48-689)	0.15

Table 3: Post-operative details

Variables	PPM (n=17)	Non-PPM (n=135)	p-value
Post-operative AF, N (%)	3 (18)	44 (33)	0.20
Post-operative Prolonged PR > 200, N (%)	7 (50)	22 (24)	0.01
Post-operative prolonged QRS >120, N (%)	8 (47)	20 (15)	0.001
Post-operative anticoagulation, N (%)	8 (47)	50 (37)	0.49
Median post op day of PPM insertion	8 (18)		
In Hospital mortality, N (%)	1 (6)	14 (10)	0.55
30-day mortality, N (%)	1 (6)	15 (11)	0.55
Length of Stay, mean (SD)	28 (11)	24.9 (14)	0.37

AF = Atrial Fibrillation, PPM = Permanent Pacemaker, SD = Standard Deviation

Table 4: Univariate and multivariate analysis of predictors for PPM

Variable	Univariate analysis		Multivariate analysis	
	Odds Ratio	*P*	Odds Ratio (95% CI)	*P*

	(95% CI)			
Preoperative prolonged PR >200 msec	3.43 (1.04-11.35)	**0.04**	1.84 (0.48-6.98)	0.37
Preoperative prolonged PR + QRS	8.87 (1.16-67.6)	**0.03**	3.71 (0.42-32.62)	0.24
Extent of infection-beyond leaflets	2.13 (1.36-3.36)	**0.001**	1.94 (1.14-3.28)	**0.014**
Aortic valve surgery	1.30 (0.79-2.14)	0.30		

Table 5: PPM indications, timing, and detailed checks during follow up.

ID	**Days awaited**	**Day 1 PPM check**			**3 months PPM check**			**12 months PPM check**		
		% Apacing[1]	% Vpacing[2]	Underlying rhythm at VVI 30	% Apacing[1]	% Vpacing[2]	Underlying rhythm at VVI 30	% Apacing[1]	% Vpacing[1]	Underlying rhythm at VVI 30
1	14	<1	100	Consistent	<1	100	Consistent	<1	100	Consistent

				pacing			pacing			pacing
2	1	<1	<1	Sinus rhythm	<1	<1	Sinus rhythm	<1	<1	Sinus rhythm
3	3	3	100	Consistent pacing	<1	100	Consistent pacing	<1	98	Consistent pacing
4	11	93	20	Sinus rhythm	<1	20	Sinus rhythm	78	78	Consistent pacing
5	0	<1	100	Consistent pacing	<1	100	Consistent pacing	<1	100	Consistent pacing
6	18	<1	100	Consistent pacing	<1	100	Consistent pacing	<1	100	Consistent pacing
7	13	<1	100	Consistent paci	<1	100	Consistent paci	7	100	Consistent paci

				ng			ng			ng
8	8	<1	100	Consistent pacing	<1	<1	Sinus rhythm	<1	<1	Sinus rhythm
9	7	<1	100	Consistent pacing	<1	38	Atrial Fibrillation	8	50	Atrial Fibrillation
10	12	<1	65	Consistent pacing	<1	85	Atrial Fibrillation	<1	<1	Sinus rhythm
11	4	<1	100	Consistent pacing	Died during follow up					
12	6	<1	100	Consistent pacing	<1	100	Consistent pacing	3	100	Consistent pacing
13	14	<1	100	Consistent paci	<1	<1	Sinus rhyt	<1	<1	Sinus rhyt

				ng			hm			hm
14	1	8	100	Consistent pacing	5	100	Consistent pacing	<1	100	Consistent pacing
15	10	<1	<1	Atrial Fibrillation	<1	<1	Atrial Fibrillation	<1	<1	Atrial Fibrillation
16	7	100	100	Consistent pacing	10	87	Consistent pacing	Died during follow up		
17	11	<1	20	Atrial Fibrillation	<1	33	Atrial Fibrillation	<1	<1	Atrial Fibrillation