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Pacemakers are associated with a higher risk of late death and transplantation in the Fontan population

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ABSTRACT

Background: The need for permanent pacing has been identified as a predictor of poor outcomes in the late survivors of Fontan surgery. However, it is not clear if the need for a pacemaker is a surrogate marker of a declining Fontan state, or if pacing is deleterious to the Fontan circulation.
Objectives: We sought to compare the long-term outcomes of propensity-matched Fontan patients with and without a permanent pacemaker.
Methods: Patients who have survived Fontan completion with a documented history of cardiac arrhythmia were identified from the Australia and New Zealand Fontan Registry. Pacemaker insertion details, cardiac function and electrophysiological data were obtained for the patients with a permanent pacemaker. Survival analysis was performed with propensity score matching to compare late survival and outcomes in patients with versus without a pacemaker.
Results: There was a total of 310 patients with a history of cardiac arrhythmia, of which 126 (41%) had a permanent pacemaker. After propensity-score matching, 99 pairs were generated (n = 198). Patients with a permanent pacemaker had a higher risk of death (HR 3.32 95% CI 1.60–6.90, p = 0.001) and death or transplantation (HR 3.55 95% CI 1.87–6.73, p < 0.001). Patients who were only paced atrially were not at a significantly increased risk of death or transplantation. However, patients who were ventricular paced >50% of the time were much more likely to encounter late death or transplantation (HR 3.82 95% CI 1.64–8.95, p = 0.002).
Conclusions: Having a permanent pacemaker and needing ventricular pacing is likely associated with an increased risk of death and transplantation in patients with a Fontan circulation.

1. Introduction

The management of atrial arrhythmias is one of the most challenging tasks in the long-term care of patients post Fontan completion. The incidence of atrial arrhythmias increases over time with a Fontan circulation, with freedom from arrhythmia falling as low as 23–42% beyond 20 years post Fontan surgery [1,2]. A significant proportion of these patients receive a permanent pacemaker with the development of sinus node dysfunction or as a result of aggressive anti-arrhythmia therapy. The incidence of pacemaker insertion is between 13 and 38% in the contemporary population [3,4]. However, the effects of permanent pacing on the single ventricle circulation are still poorly understood. Having a pacemaker has previously been identified as a strong predictor for late death post Fontan surgery [5,6]. There has since been some limited description of significant ventricular dysynchrony and cardiac decompensation in Fontan patients associated with pacing

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[7,8]. However, we do not know whether needing a pacemaker is a surrogate marker of a declining state, or if pacing in itself affects ventricular function and outcomes.

Some have advocated for a lower threshold for pacemaker insertion in this population, either as prophylactic intervention before radiofrequency ablation [9] or during Fontan conversion [10]. However before we do so, we need to better understand the impact of pacing on the single ventricle circulation. Therefore, we sought to investigate the role of having a permanent pacemaker on late outcomes in the Australia and New Zealand Fontan population.

2. Methods

All patients who had survived the Fontan operation with a documented history of arrhythmia were identified from the Australia and New Zealand Fontan Registry. The initiation and data collection process of the Registry has been previously described [11] and currently includes 1524 patients living with a Fontan circulation. Ethical approval has been granted to each participating institution. The patients with a permanent pacemaker (PPM) were separately identified from the cohort. Patients who had a pacemaker implanted both before or after Fontan completion were included in this review. Of a total of 310 patients with a history of arrhythmia, 126 patients had insertion of a PPM.

Details including the patients' pre-Fontan baseline characteristics, Fontan surgery and late follow-up were collated for the purpose of propensity score matching. We sought to review the patients' transthoracic echocardiogram and electrocardiogram (ECG) at the time preceding PPM implantation and at latest follow-up. The PR and QRS durations were extracted at both time-points accordingly. Patients who were receiving only atrial pacing and those who had ventricular pacing >50% of the time were separately identified. This was assessed based on a pacemaker device check within 2 years of last follow-up. A separate analysis was performed for these 2 subgroups to determine the influence of mode of pacing on overall outcome. The cutoff for ventricular pacing of 50% was chosen for dichotomization of patients in reference to existing studies that have used the same threshold to evaluate the impact of chronic pacing on ventricular function and heart failure [12,13]. The main primary end-points were time to late death, and time to death or transplantation. Secondary end-points included progression of New York Heart Association classification (NYHA) and systemic ventricular heart function. The frequency of clinical review for follow-up was independently determined by each unit, but was usually annual or biannual assessment with second-yearly echocardiograms.

2.1. Statistical analysis

Continuous variables were described using mean and standard deviation and categorical variables were reported in percentages. A Cox proportional hazard model was used to examine the variables associated with death or death and transplantation amongst the patients with PPMs, from which the hazard ratios and associated 95% confidence intervals were generated. The proportional hazards assumption was assessed based on the method of Harrell-Lea and via diagnostic plots. All statistical analyses were performed using Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

We then separately analysed the impact of having a PPM on prognosis, adjusting for the confounding effects of baseline heterogeneity associated with the patients' clinical status. Propensity score matching was performed to match the 126 patients with a PPM to controls from the pool of consecutive Fontan patients with a history of arrhythmia but without a PPM (n = 184). For the calculation of propensity scores, clinically relevant factors were included a prior when determined to likely be related to the outcome, as suggested by Rubin and Thomas [14,15]. Additional factors were included if bivariate logistic regression demonstrated an association with treatment assignment, as defined by a 10% change in the odds ratio for the treatment variable following addition of the confounder. The variables used for matching included baseline demographics (male, Hypoplastic Left Heart syndrome, dominant right ventricle), Fontan-related factors (age at Fontan procedure, having an Atriopulmonary Fontan, prolonged pleural effusions post Fontan procedure (>30 days)), and late risk factors (protein-losing enteropathy, duration of arrhythmia, radiofrequency ablation and Fontan conversion). Prior to propensity score matching, 7 of the 10 included baseline covariates demonstrated significant imbalance, with standardized mean differences exceeding 0.1 [16].

Matched pairs were constructed using 1:1 nearest neighbour matching via caliper matching, using a caliper of width equal to 0.2 of the standard deviation of the logit of the propensity score. Residual bias for a covariate was considered significant when the absolute standardized mean difference remained >0.1 post-matching. The discriminative power of the model was assessed by determining the c statistic, area under the receiver operating curve. The overall bias of the model was assessed using overall mean standardized bias, and was considered to have an acceptable level of bias if the mean bias was ≤5%. The proportional hazards assumption was tested on the basis of Schoenfeld residuals and using diagnostic plots. Propensity scores were first used to account for the heterogeneity between the two groups and then used to match patients of similar propensity scores. As such, two survival models were constructed for each end-point: (i) using propensity as a covariate for all individuals in a multivariable model and (ii) restrictive analysis using only propensity-score matched pairs. The end points were time to death and time to death or transplantation. Entry to the survival model occurred on survival to hospital discharge after Fontan completion. A subgroup analysis was performed by separately matching patients with atrial and ventricular pacing with patients from the same cohort of patients without a PPM in a similar fashion. Survival analysis was performed using the Kaplan-Meier method for the 3 groups (matched pairs for all patients with a PPM, patients who were only atrially paced and patients with >50% ventricular pacing). Analysis of the association between having a PPM and the primary endpoints were performed using Cox proportional hazards regression analysis.

A sensitivity analysis of the estimated treatment effects was also performed based on the bounding approach as proposed by Rosenbaum [17]. The Mantel-Haenszel bounds were calculated using the *mhbounds* package to examine the sensitivity of our findings to the assumption of no unmeasured confounders.

3. Results

Of the 1524 patients recruited in the Australia and New Zealand Fontan registry, there was a total of 126 patients (8%) identified who had received a PPM between 1981 and 2017: 7 before Fontan surgery at a median of 1.0 (IQR 0.5–3.6) years of age; 30 who had PPMs inserted during concomitant surgery and 35 patients who had PPM insertion in the peri-operative period. Of the perioperative PPM insertions, 21 patients were post Fontan completion and 8 were post Fontan conversion. The remaining patients had PPM insertion at median duration of 10.0 years (IQR 3.3–17.3) post Fontan completion. Sixty-two (50%) of the patients had atriopulmonary Fontans and 80 patients (64%) had dominant right ventricles. The indications for PPM insertion were sick sinus syndrome (58), complete heart block (42), anti-tachycardia management (18), ventricular tachycardia (2), cardiac resynchronisation (1) and unknown (5). Mean duration from first onset of arrhythmia to insertion of PPM was 3.8 ± 6.1 years. Twenty-five patients (20%) had a history of previous radiofrequency ablation.

The modality of PPM insertion was known for 105 patients (84%). Of the 105 patients, 33 (31%) had single chamber pacemakers, of which 20 were atrial pacemakers and 13 ventricular, while 72 (69%) had dual chamber pacemakers. Besides the 30 patients who had PPM insertion with concomitant surgery, 66 patients (63%) needed surgical access namely via sternotomy (35), anterior thoracotomy (25) and subxyphoid incision (6). Only 9 patients had PPM insertion via transvenous access. A total of 93 patients had pre- and post-procedural transthoracic echocardiograms. Seven out of the 93 patients (8%) were noted to have deterioration of ventricular function post PPM insertion, of which 2 patients needed urgent reintervention for cardiac resynchronisation. Two of the 7 patients had return of baseline heart function at latest follow-up.

One patient was lost to follow-up post PPM insertion and was excluded from subsequent analysis. The remaining 125 patients were followed up for a median duration of 19.9 years (IQR 13.5–27.3). Forty-four patients (36%) needed pacemaker lead revision over the course of follow-up, with mean number of 1 ± 1 (range 1–3) re-implantations, while 41 patients (33%) needed a mean of 1 ± 1 (range 1–2) pacemaker generator change. There were 30 deaths (24%) at median 4.5 years (IQR 2.0–10.0) post PPM insertion and 13.8 years (IQR 9.7–23.8) post Fontan completion. Seventeen patients had heart transplantation at median 12 years (6.8–26.9) post Fontan completion, of which 11 were alive at latest follow-up. Of the 84 patients who were alive and free from heart transplantation, 81 patients (96%) were of NYHA class 2 or less. Thirteen patients (15%) had moderate to severe systemic ventricular dysfunction. Twenty-seven patients (22%) had documented thromboembolic events during the course of follow-up. Of the 9 patients with transvenous pacing leads, 4 patients were anticoagulated with warfarin and 2 patients were on anti-platelet therapy. Only one of the patients had a thromboembolic event during follow-up on warfarin. On univariable analysis, having Hypoplastic left heart syndrome (HR 5.22 95% CI 1.19–22.9, p = 0.03) and ventricular pacing >50% of the time were the only significant predictors of death (HR 3.62 95% CI 1.30–10.1, p = 0.01) (Table 1).

3.1. Ventricular-pacing

Of the 125 patients with a permanent pacemaker, 98 patients had recent pacemaker checks (within 2 years of last follow-up). Pacing

Table 1
Univariable analysis of predictors of death amongst patients with a pacemaker (n = 125).

Variable		Total no. of patients (n = 125)	Total deaths (%)	HR (95% CI)	p-Value
Male		65	18 (28%)	1.54 (0.74–3.21)	0.25
Hypoplastic left heart syndrome	Yes	6	2 (33%)	5.22 (1.19–22.9)	0.03
	No	119	28 (24%)		
Age at Fontan				0.98 (0.92–1.05)	0.55
Atriopulmonary Fontan	Yes	62	18 (29%)	0.70 (0.32–1.52)	0.37
	No	63	12 (19%)		
Right ventricular dominance	Yes	33	8 (24%)	1.24 (0.55–2.78)	0.61
	No	92	22 (24%)		
Complete heart block	Yes	42	9 (21%)	1.04 (0.47–2.30)	0.91
	No	83	21 (25%)		
Radiofrequency ablation	Yes	25	6 (24%)	0.62 (0.25–1.53)	0.30
	No	100	24 (24%)		
Fontan conversion	Yes	30	6 (20%)	0.51 (0.21–1.25)	0.14
	No	95	24 (25%)		
Age at PPM implantation				0.97 (0.94–1.01)	0.10
Time from 1st arrhythmia to PPM				0.98 (0.92–1.04)	0.44
Atrial pacing >50% of time	Yes	37	6 (16%)	0.70 (0.27–1.84)	0.47
	No	62	13 (21%)		
Ventricular pacing >50% of time	Yes	45	14 (31%)	3.62 (1.30–10.1)	0.01
	No	50	5 (10%)		

modes were AAI in 31 patients (32%), VVI in 21 patients (21%) and DDD in 46 patients (37%). Both sensing and pacing thresholds were satisfactory in 91 patients (93%). Forty-five patients (46%) had ventricular pacing >50% of the time. Patients who had ventricular pacing >50% of the time were more likely, albeit not statistically significant, to have systemic ventricular dysfunction at time of PPM insertion (16% vs 8%, p = 0.14). Patients who had ventricular pacing >50% of the time had a smaller increase in PR interval on latest ECG as compared to those who were ventricular-paced <50% of the time (mean 8.6 ± 61.2 ms vs 43.9 ± 67.1 ms, p = 0.24). However, mean increase in QRS duration at time of follow-up was significantly greater in patients who were mostly receiving ventricular pacing (37.5 ± 28.7 ms vs 4.6 ± 15.6 ms, p < 0.001). Amongst all patients receiving permanent pacing, patients with QRS interval >130 ms on ECG at latest follow-up were at greater risk of late death and transplantation (HR 3.12, 95% CI 1.09–8.90, p = 0.03).

Patients who had ventricular pacing >50% of the time were at higher risk of death (HR 3.62 95% CI 1.30–10.1, p = 0.01) and death or transplantation (HR 3.33 95% CI 1.46–7.60, p = 0.004). Survival at 10 and 20 years was 87% (95% CI 72–94) and 77% (95% CI59–88) for these patients, and 96% (95% CI 85–99) and 91% (95% CI 71–97) for those who had ventricular pacing <50% of the time. Freedom from death and transplantation at 10 and 20 years was 75% (95% CI 59–86) and 64% (95% CI 46–77) for patients who had ventricular pacing >50% of the time, and 94% (95% CI 82–98) and 86% (95% CI 72–94) for those who did not. Patients who had ventricular pacing >50% of the time were also more likely to have moderate or severe systemic ventricular dysfunction at latest follow-up (44% vs 20%, p = 0.01). However, compared to patients without ventricular pacing, patients with ventricular pacing ≤25% of the time did not have a greater risk of death and transplantation (22% vs 0%, p = 0.17) or significant ventricular dysfunction (0% vs 24%, p = 0.18).

Table 3
Results of Cox regression analysis with propensity score adjustment and propensity score matching for risk of death and death and transplantation for patients with a PPM versus those without.

	HR	95% CI	p-Value
Death			
Unadjusted	1.84	1.09–3.12	0.02
Propensity score adjusted (n = 310)	3.07	1.76–5.38	<0.001
Propensity score matched (n = 198)	3.32	1.60–6.90	0.001
Death and transplantation			
Unadjusted	2.16	1.34–3.48	0.001
Propensity score adjusted (n = 310)	3.33	2.01–5.52	<0.001
Propensity score matched (n = 198)	3.55	1.87–6.73	<0.001

3.2. Propensity-matched analysis

The 125 patients with a PPM were matched to all patients with a history of atrial arrhythmia in the Fontan Registry. There was a total of 198 patients (99 pairs) included in the analysis after propensity-score matching (Table 2). The mean propensity scores for patients who had received a PPM and those who did not were 0.47 (95% CI 0.32–0.59) and 0.35 (95% CI 0.26–0.43) respectively. The mean standardized biases before and after matching were 18% and 4% respectively. Median duration of follow-up for the total matched cohort was 21.0 years (IQR 13.8–26.9); 17.7 years (IQR 11.6–25.6) for patients with a PPM, and 22.8 (IQR 15.0–28.1) for patients without a PPM.

Cox-regression analysis performed with propensity score adjustments demonstrated a higher risk of late death associated with having a PPM. The estimated hazard ratio for late death was 3.32 (95% CI 1.60–6.90, p = 0.001) in the matched cohort. Patients with a PPM also had higher risk of death and transplantation (HR 3.55 95% CI 1.87–6.73, p < 0.001). The results of the propensity-score derived models are presented in Table 3. Late survival in the matched cohort is

Table 2
Patient demographics in pre-matched cohort (n = 310) and paired cohort post propensity score matching (n = 198).

	Overall cohort (unmatched n = 310)				Matched cohort (caliper matching n = 198)			
	PPM (n = 125)	No PPM (n = 185)	Standardized mean difference	p-Value	PPM (n = 99)	No PPM (n = 99)	Standardized mean difference	p-Value
Baseline demographics								
Male	65 (52%)	107 (58%)	−0.12	0.31	55 (56%)	57 (58%)	−0.04	0.78
HLHS	4 (3%)	10 (5%)	−0.11	0.36	4 (4%)	3 (3%)	0.05	0.70
Dominant right ventricle	80 (64%)	114 (62%)	0.05	0.68	63 (64%)	62 (63%)	0.02	0.89
Fontan procedure								
Age at Fontan (mean, years)	7.5 ± 5.6	7.1 ± 5.9	0.07	0.90	7.1 ± 5.1	7.1 ± 6.3	0.05	0.97
AP Fontan	63 (50%)	82 (44%)	0.12	0.29	44 (44%)	47 (47%)	−0.06	0.67
Prolonged pleural effusions	9 (7%)	15 (8%)	−0.03	0.77	7 (7%)	7 (7%)	0.00	1.00
Late follow-up factors								
Protein-losing enteropathy	11 (9%)	7 (4%)	0.21	0.06	5 (5%)	6 (6%)	−0.04	0.76
Radiofrequency ablation	25 (20%)	32 (17%)	−0.13	0.55	19 (19%)	18 (18%)	0.03	0.86
Duration from 1st arrhythmia to latest follow-up (mean, years)	14.1 ± 8.6	9.8 ± 7.7	0.52	<0.001	12.7 ± 8.2	13.4 ± 7.9	−0.08	0.56
Fontan conversion	30 (24%)	12 (6%)	0.50	<0.001	8 (8%)	12 (13%)	−0.12	0.35

estimated as 89% (95% CI 80–94), 79% (95% CI 68–86%) and 57% (95% CI 40–71%) in patients with a PPM; and 99% (95% CI 92–100%), 95% (95% CI 87–98%) and 85% (95% CI 72–92%) without a PPM at 10, 20 and 30 years post-Fontan surgery. Freedom from death and transplantation at 10, 20 and 30 years post-Fontan surgery were 82% (95% CI 72–88%), 69%(95% CI 58–78%) and 45% (95% CI 30–60%) for the patients with a PPM; 98% (95% CI 92–99%), 93% (95% CI 84–97%) and 83% (95% CI 70–90%) for the patients without a PPM (Fig. 1). The model was adequately saturated with an area under the ROC curve of 0.70.

3.3. Propensity-matched subgroup analysis

A subgroup analysis was conducted based on mode of pacing, with propensity matching of patients with predominant atrial and ventricular pacing. There were 35 matched pairs generated for patients who were solely receiving atrial pacing. Patients who were being atrially paced >50% of the time were not at a significantly increased risk of death or transplantation as compared to patients without a PPM (HR 0.42 95% CI 0.11–1.62, p = 0.21). (Fig. 1) Forty-three matched pairs were generated for patients who had ventricular pacing >50% of the time and a similar analysis performed. Patients with predominant ventricular pacing were significantly more likely to encounter death or transplantation (HR 3.82 95% CI 1.64–8.95, p = 0.002) (Fig. 1).

Sensitivity analysis was performed to examine the assumption of no unmeasured confounders. The effect of treatment (having a PPM) on survival is insensitive to the bias of an unmeasured confounder unless it increased the odds of exposure by more than or equal to 60% (Γ = 1.55, HR 1.61 p = 0.05; Γ = 1.60, HR 1.52 p = 0.06).

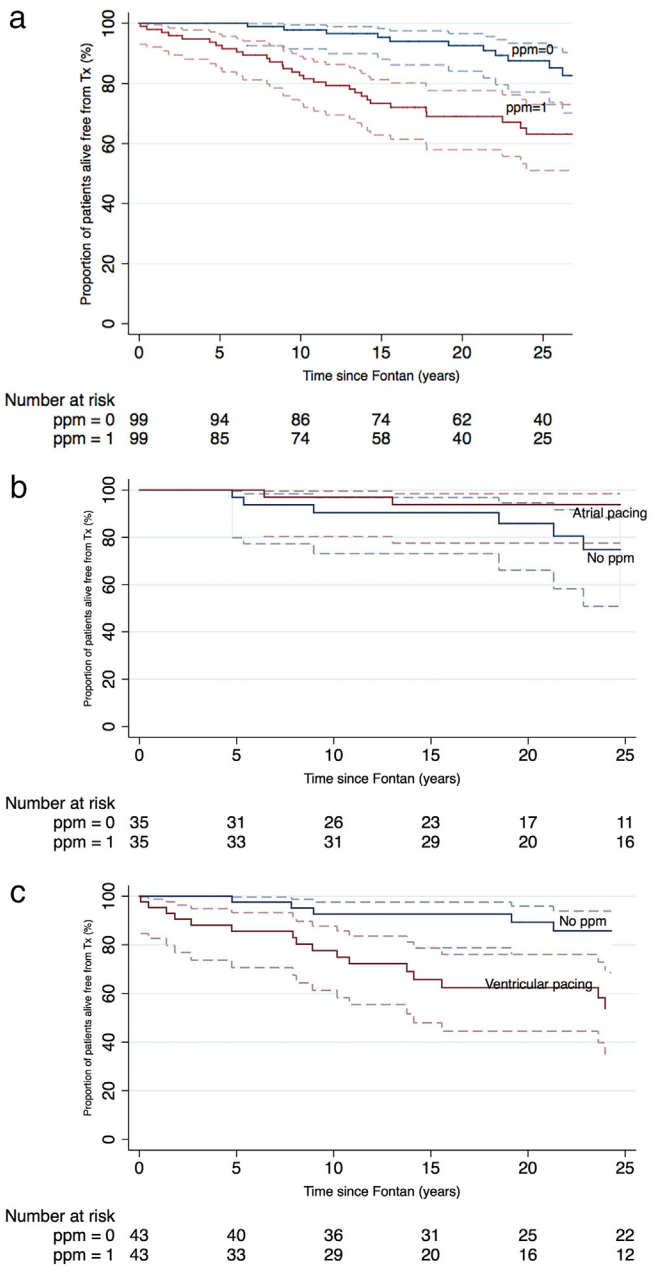

Fig. 1. Kaplan-Meier curves for freedom from death and transplantation for propensity matched patients (a) with a pacemaker (ppm = 1) and without a permanent pacemaker (ppm = 0); (b) with atrial pacing >50% of time vs without; (c) with ventricular pacing >50% of time vs without.

4. Discussion

Atrial arrhythmia remains the most significant cause of morbidity post-Fontan surgery, affecting over 50% of patients at 20 years post-op [1,2]. Sinus node dysfunction is also prevalent in this cohort, likely related to surgical manipulation near the sinoatrial node. The incidence of sinus node dysfunction has been highly variable amongst centres, reported to be between 22 and 44% [18,19]. It is hence predictable that the most common intervention during late follow-up post-Fontan completion is the insertion of a permanent pacemaker [18,20]. In fact, atrioventricular nodal ablation with concomitant pacemaker implantation has even been advocated as a management option for treatment-resistant tachyarrhythmias [9]. Cardiac resynchronization therapy has also been used to improve the hemodynamics in decompensated Fontan failure [21,22]. However, permanent pacing may have potential detrimental effects on the Fontan circulation. The Fontan Cross-Sectional Study by the Pediatric Heart Network demonstrated that patients with a Fontan circulation and living with a pacemaker had significantly poorer functional status and ventricular systolic function compared to those without [23]. Despite so, it was not possible to distinguish whether having a pacemaker was a surrogate marker for more severe disease, or whether a causative relationship existed between being paced and poorer outcomes.

In this study, we propensity-matched Fontan patients for known risk factors of late mortality and duration of arrhythmia, in an attempt to evaluate the impact of having a pacemaker without the confounding factors of patient complexity. Patients with a pacemaker who were ventricular-pacing dependent had a profoundly greater risk of late death and transplantation. This relationship had been previously described in a small study, where single-ventricle patients with equal or >50% ventricular pacing had 5 times the risk of having heart transplantation or death. They also more often had significant ventricular dysfunction and atrioventricular valve regurgitation compared to their counterparts without pacemakers [8]. This has been hypothesized to be due to the loss of atrioventricular synchrony, leading to ineffective ventricular filling and reduced cardiac output. The volume and pressure loaded systemic ventricles of a Fontan circulation have been shown to be more prone to mechanical dyssynchrony than a normal biventricular circulation over time [24]. This may account for the variable response to resynchronization therapy in this cohort [21,25,26]. On the contrary, atrial pacing on its own did not seem to have any negative influence on the Fontan circulation. As such, more effort should be made to preserve native atrioventricular conduction during surgical interventions and in the management of late arrhythmia in this group.

Cardiac pacing is challenging after Fontan palliation, due to the limited access often precluding endocardial lead insertion. Majority of the patients require insertion of pacemaker leads via a surgical approach, with over 90% of our group needing access via a sternotomy or thoracotomy. Such access remains challenging due to adhesions from previous operations. Hence, the optimisation of lead placement site is rarely prioritised under such circumstances. However, the preservation of “normal” electro-mechanical conduction may be more

important in the single ventricle circulation than in biventricular hearts. A narrow QRS duration on ECG with pacing has been shown to be a useful marker for the preservation of physiological ventricular activation [27]. In our study, patients with a prolonged QRS duration had a significantly greater risk of late death or transplantation. Having a longer QRS duration has also been associated with a greater systemic ventricle end-diastolic volume and lower peak oxygen uptake (VO_2) in previous studies [28], all known predictors of late Fontan failure. Hence, we believe that the QRS duration post PPM implantation should be carefully monitored. There should also be a low threshold for reintervention if early QRS prolongation is observed post-pacing, to reduce the likelihood of permanent ventricular dysfunction.

5. Study limitations

There are important limitations in this study. Firstly, the propensity score matching analysis attempts to account for confounders that predict for the need for pacemaker therapy, as well as risk factors for poorer long-term prognosis. However, due to the heterogeneity of the patient cohort, we were not able to consider variables including protein-losing enteropathy, Fontan conversion and radiofrequency ablation as time-dependent variables in the generation of the propensity score. Moreover, in order to assess pacemaker therapy as a time-dependent variable, it would require patient matching based on their status of each individual variable at the time of device implantation. This was not achievable with the small patient cohort. As such, a simpler approach was adopted where exposure status (having a PPM) was treated as a binary event for the analysis.

The variables chosen for propensity score matching were selected based on factors that have been established in current literature as significant predictors of late mortality in the Fontan population. However, it is important to acknowledge that the current understanding of the physiology leading to late Fontan failure remains sparse. The need for a PPM may be associated with other unknown factors representing a later stage of Fontan failure that was not accounted for in the analysis. Factors gaining recent recognition such as atrioventricular valve incompetency, functional capacity and hepatorenal function were not accounted for in this analysis. However, this study attempts to address the impact of permanent pacing in a complex and heterogenous population, and suggests an important possibility that pacing could be deleterious in the Fontan circulation.

6. Conclusion

In conclusion, the need for ventricular pacing via a permanent pacemaker likely increases the risk of late death and need for heart transplantation in patients living with a Fontan circulation. More effort should be made to preserve physiological atrioventricular function in order to avoid the hazardous effects of permanent pacing on long-term outcomes.

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Disclosures

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References

[1] C. Poh, D. Zannino, R. Weintraub, D. Winlaw, L. Grigg, R. Cordina, et al., Three decades later: the fate of the population of patients who underwent the Atriopulmonary Fontan procedure, Int. J. Cardiol. 231 (2017) 99–104.
[2] K. Pundi, K. Pundi, J. Johnson, J. Dearani, L. Zhuo, D. Driscoll, et al., Sudden cardiac death and late arrhythmias after the Fontan operation, Congenit. Heart Dis. 12 (2017) 17–23.
[3] E. Stephenson, M. Lu, C. Berul, S. Etheridge, S. Idriss, R. Margossian, et al., Arrhythmias in a contemporary Fontan cohort: prevalence and clinical associations in a multi-center cross-sectional study, J. Am. Coll. Cardiol. 56 (2010) 890–896.
[4] A. Egbe, G. Huntley, H. Connolly, N. Ammash, A. Deshmukh, A. Khan, et al., Outcomes of cardiac pacing in adult patients after a Fontan operation, Am. Heart J. 194 (2017) 92–98.
[5] T. Gentles, J. Mayer Jr., K. Gauvreau, J. Newburger, J. Lock, J. Kupferschmid, et al., Fontan operation in five hundred consecutive patients: factors influencing early and late outcome, J. Thorac. Cardiovasc. Surg. 114 (1997) 376–391.
[6] C. Poh, Y. d'Udekem, Life after surviving Fontan surgery: a meta-analysis of the incidence and predictors of late death, Heart Lung Circ. 27 (2018) 552–559.
[7] T. Higaki, C. Kondo, H. Tomimatsu, E. Yamamura, E. Yamamoto, K. Konishi, et al., Asynchronous contraction of the 2 ventricles caused by ventricular pacing after a Fontan-type operation in a patient with a biventricular heart, Int. J. Cardiol. 150 (2011) e116–e118.
[8] A. Bulic, F. Zimmerman, S. Ceresnak, I. Shetty, K. Motonaga, A. Freter, et al., Ventricular pacing in single ventricles—a bad combination, Heart Rhythm. 14 (2017) 853–857.
[9] R. Friedman, J. Will, A. Fenrich, N. Kertesz, Atrioventricular junction ablation and pacemaker therapy in patients with drug-resistant atrial tachyarrhythmias after the Fontan operation, J. Cardiovasc. Electrophysiol. 16 (2005) 24–29.
[10] T. Terada, H. Sakurai, T. Nonaka, T. Sakurai, J. Sugiura, T. Taneichi, et al., Surgical outcome of Fontan conversion and arrhythmia surgery: need a pacemaker? Asian Cardiovasc. Thorac. Ann. 22 (2014) 682–686.
[11] A. Iyengar, D. Winlaw, J. Galati, T. Gentles, R. Weintraub, R. Justo, et al., The Australia and New Zealand Fontan Registry: description and initial results from the first population-based Fontan registry, Intern. Med. J. 44 (2014) 148–155.
[12] A. Barsheshet, A. Moss, S. McNitt, C. Jons, M. Gilkson, et al., Long-term implications of cumulative right ventricular pacing among patients with an implantable cardioverter-defibrillator, Heart Rhythm. 8 (2011) 212–218.
[13] J. Steinberg, A. Fischer, P. Wang, C. Schuger, J. Daubert, et al., The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II, J. Cardiovasc. Electrophysiol. 16 (2005) 359–365.
[14] D. Rubin, N. Thomas, Matching using estimated propensity score: relating theory to practice, Biometrics 52 (1996) 249–264.
[15] M. Brookhart, S. Schneeweiss, K. Rothman, R. Glynn, J. Avorn, T. Sturmer, Variable selection for propensity score models, Am. J. Epidemiol. 163 (2006) 1149–1156.
[16] P. Austin, Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples, Stat. Med. 28 (2009).
[17] P. Rosenbaum, Observational Studies, Springer, New York, 2002.
[18] R. Kaultiz, G. Ziemer, T. Paul, M. Peuster, H. Bertram, G. Hausdorf, Fontan-type procedures: residual lesions and late interventions, Ann. Thorac. Surg. 74 (2002) 778–785.
[19] M. Cohen, G. Wernovsky, V. Vetter, T. Weiand, J. Gaynor, M. Jacobs, et al., Sinus node function after a systematically staged Fontan procedure, Circulation 98 (1998) II358–9.
[20] C. Van Dorn, S. Menon, J. Johnson, R. Day, J. Hoffman, A. Yetman, Lifetime cardiac reinterventions following the Fontan procedure, Pediatr. Cardiol. 36 (2015) 329–334.
[21] F. Zimmerman, J. Starr, P. Koenig, P. Smith, Z. Hijazi, E. Bacha, Acute hemodynamic benefit of multisite ventricular pacing after congenital heart surgery, Ann. Thorac. Surg. 75 (2003) 1175–1180.
[22] A. Dodge-Khatami, M. Rahn, R. Prêtre, U. Bauersfeld, Dual chamber epicardial pacing for the failing atriopulmonary Fontan patient, Ann. Thorac. Surg. 80 (2005) 1440–1444.
[23] R. Williams, T. Travison, J. Kaltman, F. Cecchin, S. Colan, S. Idriss, et al., Comparison of Fontan survivors with and without pacemakers: a report from the pediatric heart network Fontan cross-sectional study, Congenit. Heart Dis. 8 (2013) 32–39.
[24] K. Motonaga, C. Miyake, R. Punn, D. Rosenthal, A. Dubin, Insights into dyssynchrony in Hypoplastic Left Heart Syndrome, Heart Rhythm. 9 (2012) 2010–2015.
[25] F. Cecchin, P. Frangini, D. Brown, F. Fynn-Thompson, M. Alexander, J. Triedman, et al., Cardiac resynchronization therapy (and multisite pacing) in pediatrics and congenital heart disease: five years experience in a single institution, J. Cardiovasc. Electrophysiol. 20 (2009) 58–65.
[26] A. Dubin, J. Janousek, E. Rhee, M. Strieper, F. Cecchin, I. Law, et al., Resynchronization therapy in pediatric and congenital heart disease patients: an international multicenter study, J. Am. Coll. Cardiol. 46 (2005) 2277–2283.
[27] S. Kim, Y. Oh, G. Nam, K. Choi, J. Park, S. Park, et al., Paced QRS axis as a predictor of pacing-induced left ventricular dysfunction, J. Interv. Card. Electrophysiol. 41 (2014) 223–229.
[28] H. Ohuchi, A. Miyazaki, Y. Wakisaka, K. Watanabe, K. Kishiki, O. Yamada, et al., Systemic ventricular morphology-associated increased QRS duration compromises the ventricular mechano-electrical and energetic properties long-term after the Fontan operation, Int. J. Cardiol. 133 (2009) 371–380.