Int Cardiovasc Res J.2018;**12**(3):90-98.icrj.69785

International Cardiovascular Research Journal

www.ircrj.com

Right Ventricular Septal Pacing vs. Right Ventricular Apical Pacing Following Atrioventricular Node Ablation: A 10-Year Follow-up

William Eysenck [1,*], Neil Sulke [1], Angela Gallagher [1], Fadi Jouhra [1], Nikhil Patel [1], Stephen Furniss [1], Rick Veasey [1]

[1] Cardiology Research Department, Eastbourne General Hospital, East Sussex, United Kingdom

ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 23 Apr 2018
Revised: 20 Jun 2018
Accepted: 1 Jul 2018

Keywords:
Heart Failure
Heart Ventricles
Ablation

ABSTRACT

Background: Right Ventricular Septal (RVS) pacing is often recommended as a more physiological alternative to Right Ventricular Apical (RVA) pacing.
Objectives: This study aimed to determine the long-term outcomes in patients persistently paced following Atrioventricular Node (AVN) ablation.
Materials and Methods: This study was conducted on 200 patients who underwent Permanent Pacemaker (PPM) implantation prior to AVN ablation with either RVA- or RVS-pacing. Primary endpoints were hospitalization due to Heart Failure (HF) and death. Secondary endpoints included changes in Ejection Fraction (EF), inter- and intra-ventricular dyssynchrony measures, and paced QRS duration. Demographic data were obtained from all patients. In addition, CT chest examinations were analyzed to confirm RVS lead position.
Results: The mean survival time from AVN ablation was 6.32 ± 4.294 years in the RVA group and 3.00 ± 2.546 years in the RVS group (hazard ratio = 3.512, P = 0.0001). The results showed no significant differences between the two sites regarding hospitalization due to HF. Baseline and follow-up EFs were respectively 48.4 ± 13.8% and 53.1 ± 8.5% for RVA pacing and 52.0 ± 10.6% and 55.2 ± 11.3% for RVS pacing (P = 0.911). Moreover, 76% of the patients in the RVS group had a septal lead confirmed on CT chest review. Twenty-four percent of the RVS leads were in alternate sites, including the RVA and free wall.
Conclusions: The results revealed was no diminution in EF with either lead position at long-term follow-up. The mortality rate was significantly less in RVA pacing compared to documented septal pacing although a quarter of the RVS leads were found in alternate sites on CT chest review.

1. Background

Permanent Pacemaker (PPM) insertion combined with radiofrequency ablation of the Atrioventricular Node (AVN) resulted in improved quality of life, symptoms, and functional capacity in patients with drug-refractory Atrial Fibrillation (AF) and an uncontrolled ventricular rate (1). Indications for AVN ablation included AF and poorly controlled ventricular rates despite maximal medical therapy and control of ventricular rate in patients with AF and a Cardiac Resynchronization Therapy (CRT) device to maximize biventricular pacing (1). Optimal ventricular lead position is relevant in this patient cohort due to the high percentage of ventricular pacing involved. Right Ventricular Apical (RVA) pacing can result in pacing-induced dyssynchrony, which may result in Left Ventricular (LV) systolic dysfunction (2-5), potentially leading to heart failure admission and increased morbidity and mortality. Right Ventricular Septal (RVS) pacing is theoretically associated with a more physiological ventricular activation. Studies have suggested that RVS pacing could improve short-term outcomes and LV systolic performance (6). However, there is no definitive evidence that RVS pacing is superior to RVA pacing in the long run (7). In patients with normal ventricular function, the negative remodeling effect of RVA pacing could take a year or more to manifest (8-10). Few studies have evaluated the two pacing sites at

*Corresponding author: William Eysenck, Cardiology Department, Eastbourne General Hospital, Kings Drive, Eastbourne, BN21 2UD.
Tel: +44-01323417400, Ext: 4132, Fax: +44-01323435821,
E-mail: William.eysenck@nhs.net.

more than 18 months of follow-up (5, 9).

Long-term lead performance is another consideration. Studies including up to 24 months of follow-up have suggested no significant differences in the mean pacingthreshold, R-wave sensing, and lead impedance (11). However, long-term performance with up to 10 years of follow-up has not been assessed.

2. Objectives

The present study aims to compare the long-term clinical outcomes of RVS and RVA lead positions in patients ≥ 98% ventricular paced following AVN ablation.

3. Materials and Methods

3.1. Study Design and Population

This study complied with the Declaration of Helsinki and was approved by the appropriate national Ethics Committee and institutional review board. The study was performed at Eastbourne General Hospital, UK.

In this retrospective cohort study, consecutive patients who had undergone an AVN ablation between 1996 and 2015 were identified using Tomcat coding software (Royal Philips Electronics, Eindhoven, the Netherlands). Indications for AVN ablation included drug refractory AF, failed left atrial tachycardia ablation, and control of ventricular rate in patients with AF. All clinical records for every outpatient encounter and hospital admission were reviewed. Patients were censored at time of death or time of last hospital review. If the patients could not be censored according to these criteria (for example, if they had moved to a different geographical location), they were excluded.

Demographic data were gained by case note review. The gathered information included presence of co-morbidities, cardiac medication usage, and echocardiographic data. PPM diagnostic data were reviewed at least every 12 months. The recorded data included ventricular pacing percentage, ventricular stimulation threshold, and lead impedance. Finally, mortality data were obtained from death certificates and post-mortem analyses.

This study was performed on 200 consecutive patients undergoing AVN ablation between January 1996 and December 2015. The two primary endpoints were death and hospitalization for heart failure. Secondary endpoints were change in Left Ventricular Ejection Fraction (LVEF), echo dyssynchrony measures, QRS duration, and pacing parameters over time. The following exclusion criteria were applied:

- Cumulative ventricular pacing < 98%, indicative of recovery of AV node conduction.
- Patients who moved to another location and could not be censored due to passing away or undergoing local follow-up appointments.

3.2. Permanent Pacemaker Implantation Techniques

The decision regarding ventricular lead site was made by the operator in each case. In the RVA group, the Right Ventricular (RV) lead was placed via the cephalic, axillary, or subclavian vein. Passive or active fixation electrodes were passed across the tricuspid valve using a curved stylet and into the RV apex, guided by fluoroscopy. A straight stylet was used to position the electrode into the standard apical position using the Posteroanterior (PA) fluoroscopic view (Figure 1).

For RVS placement, first a large curve was created using the distal 5 - 6 cm of the wire allowing advancement of the active fixation lead across the tricuspid valve and into the pulmonary artery. Next, the lead was withdrawn onto the RV septum. The stylet was then shaped with an oblique smaller curve to position the lead onto the septum. This technique has been described by Mond (8). The pacing site in the ventricular septum was determined by fluoroscopy. The PA view was used to guide the lead into the Right Ventricular Outflow Tract (RVOT). The septal direction was confirmed with a rightward and posterior pointing directionality towards the spine of the ventricular lead away from the anterior free wall in the Left Anterior Oblique (LAO) view (8). Once the lead tip made contact with the septal wall, the fixation screw was deployed under fluoroscopy according to manufacturers' instructions. The ventricular R-wave amplitude, lead impedance, and stimulation threshold were measured after screw deployment and at the end of the procedure.

3.3. Determination of the Ventricular Lead Site

Chest X-Rays (CXRs) were reviewed for all patients. If available, CT scans of the chest post PPM implant were reviewed by two blinded physicians to confirm the documented ventricular lead site.

3.4. QRS Duration and Pacemaker Follow-up

All available electrocardiograms (ECGs) in patients' case notes were reviewed. ECGs were obtained at baseline, after PPM implantation, at outpatient clinics, and during hospital admissions. The QRS interval, defined as the length of time from the onset of the pacing spike until the end of the QRS complex, was measured and confirmed by two investigators.

The ventricular stimulation threshold was measured at a 0.4 ms pulse width and the R-wave amplitude was performed during PPM implantation. Follow-up PPM interrogation downloads were performed 6 weeks following implantation and every 12 months at the outpatient clinic.

3.5. Evaluation of Cardiac Structure and Function

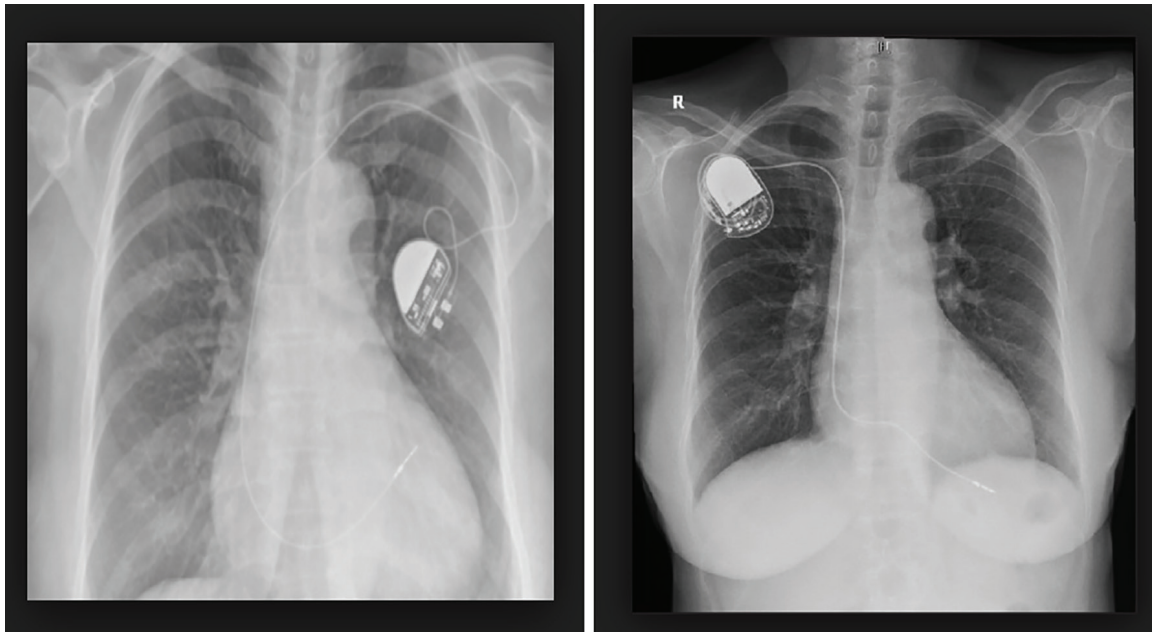
Baseline LVEF and underlying structural heart disease were assessed in all patients by echocardiography according to the current British Society of Echocardiography (BSE) standards prior to pacing. All patients with a history of ischemic heart disease, reduced LVEF, and valvular heart disease were identified using Healthcare Resource Group (HRG) codes and clinical review.

3.6. Echocardiography

Two-dimensional and M-mode echocardiograms were performed using a Vivid I System (GE Healthcare, Chicago, Illinois, USA). The following parameters were obtained: (i) LVEF assessed via biplane Simpson's equation and visual estimation, (ii) RV function, (iii) pulmonary artery systolic pressures, (iv) mitral regurgitation, and (v) inter-ventricular and intra-ventricular dyssynchrony.

Echocardiography was undertaken in the semi-recumbent

Figure 1. Right Ventricular Pacing Sites



Panel 1, right ventricular septal lead position; Panel 2, Right ventricular apical lead position

position. All data were recorded on digital cineloops and analyzed offline using dedicated software (Echopac, Version 6.4.3f6). Five consecutive beats were averaged for all variables. R-R intervals were recorded for each Doppler or tissue Doppler trace to allow adjustment for variation in heart rate. Echocardiographic assessments of dyssynchrony were undertaken, as well.

3.6.1. Inter-Ventricular Dyssynchrony

Inter-ventricular dyssynchrony was characterized by a prolonged delay between mechanical activations of the right and the left ventricles. This was measured by echo Doppler acquisition of aortic and pulmonic outflow velocities. Our data set considered a difference in time of onset between the two velocities of > 40 ms to be abnormal.

3.6.2. Intra-Ventricular Dyssynchrony

M-mode images of the parasternal short-axis view were used to measure mechanical dyssynchrony. A difference of more than 130 ms between the maximal inward movements of the basal septal and lateral walls was used to identify dyssynchrony.

3.7. Statistical Analysis

The data have been presented as mean with standard deviations of median with ranges where appropriated. Chi-square test was used to analyze the differences between categorical variables. For normally distributed continuous variables, Student's t-test was applied. If the variables did not follow normal distribution, Mann-Whitney test was performed to compare different groups.

Survival was estimated from the date of AVN ablation to that of death. It should be noted that living patients were censored at the date of the last follow-up. The Kaplan-Meier method was used to calculate survival rates, and the results were compared by the log-rank test. Additionally, Cox proportional hazard regression method was applied to identify the variables that independently predicted overall mortality. Predictors with univariate P values ≤ 0.2 were included in the multivariate Cox regression model. The analyses were adjusted for sex, age, and total follow-up time. The Cox proportional hazards regression models were used to calculate Hazard Ratios (HRs) and their 95% Confidence Intervals (CIs). All statistical analyses were performed using IBM SPSS Statistics 20 software.

4. Results

4.1. Patient Characteristics

The patients' demographic data have been summarized in Table 1. The mean ages of the 77 patients with RVS and 123 patients with RVA pacing were 72.7 ± 9.30 and 74.8 ± 11.86 years, respectively at the time of AVN ablation. The mean follow-up period was 3.82 ± 13.7 years in the patients undergoing RVS pacing and 8.5 ± 19.4 years in those with RVA pacing. There were no significant differences between the two groups regarding age, gender, history of heart failure, underlying heart disease (defined as ischemic heart disease, LVEF moderately impaired or worse, and valvular heart disease (defined as moderate to severe valvular dysfunction)), QRS duration, medication at the time of pacemaker implantation, and major co-morbidity (defined as Cerebrovascular Accident (CVA)/Transient Ischemic Attack (TIA), diabetes, malignancy, Chronic Obstructive Pulmonary Disease (COPD), and hypertension). The only co-morbidity that independently predicted mortality was malignancy with 25/72 (35%) of the dead patients compared to 23/128 (18%) of the alive ones having a diagnosis of cancer (P = 0.047). The rates of malignancy were similar in the two groups and did not reach statistical significance.

During follow-up, two patients had an upgrade of their device to CRT (1 with an RVS lead and 1 with an RVA lead). These patients were excluded from further analyses

Table 1. Patients' Demographics at Baseline

Pacing Site	RVS Pacing	RVA Pacing	P value
N	77	123	ns
Age at study AVN ablation	72.69 (± 9.30)	74.82 (± 11.86)	ns
Gender (male%)	34 (45%)	65 (53%)	ns
No underlying heart disease	36 (47%)	53 (43%)	ns
Ischaemic heart disease	12 (16%)	25 (20%)	ns
Reduced ejection fraction < 40%	18 (23%)	41 (33.3%)	ns
Valvular heart disease	27 (35%)	41 (33.3%)	ns
CVA/TIA	12 (15%)	10 (8%)	ns
Diabetes	9 (11%)	18 (15%)	ns
Malignancy	18 (24%)	28 (23%)	ns
COPD	14 (18%)	25 (20%)	ns
Hypertension	64 (83%)	91 (74%)	ns
Ejection fraction (%)	52.16 (± 10.36)	48.40 (± 13.79)	ns
QRS duration (ms)	93.76 (± 18.80)	95.31 (± 22.79)	ns
Heart failure medication			
Beta-blockers	59 (± 50.1)	67 (± 47.5)	ns
ACE-I	34 (± 48.4)	41 (± 49.6)	ns
ARB	38 (± 49)	16 (± 36.8)	ns
Loop diuretic	41 (± 50.1)	38 (± 49.0)	ns
Aldosterone antagonist	28 (± 45.5)	10 (± 29.6)	ns

at the time of their upgrade. The patient with the RVS lead had a baseline LVEF of 30% and the one with the RVA lead had a baseline LVEF of 20%. Time from implantation to upgrade was 4 and 10 years, respectively.

4.2. CT Chest Analysis

Out of the 77 RVS patients, 21 underwent chest CT following PPM implantation. In 16/21 (76%) of the cases, the RVS lead position was confirmed. Two of the leads appeared to be in the RVA and 3 were on the RV free wall.

4.3. Mortality and Heart Failure Hospitalization

Out of the 200 patients, 72 (36%) died over the course of the study. Among these patients, 48 (67%) had apical leads. Mortality rate with RVA-pacing was significantly lower than that with RVS-pacing (P = 0.0001, Figure 2). The mean survival from AVN ablation to death was 6.32 ± 4.294 years for RVA pacing and 3.00 ± 2.546 years for RVS pacing. In addition, the median time to death was 5.711 years in the RVA group and 2.900 years in the RVS group.

Log rank analysis (Mantel-Cox) revealed a significant difference between the RVA and RVS groups in favor of RVA pacing (chi-square = 62.897, P = 0.0001). The HR for the site of the RV lead was 3.512 (P = 0.0001).

The Kaplan-Meier survival curve across the course of the study has been depicted in Figure 2a. According to Figure 2b, the cumulative survival in the RVA group exceeded that in the RVS group (P = 0.0001). With age and total follow-up time factored in, the significance between the two groups persisted (P = 0.03). As previously mentioned, the only co-morbidity that significantly increased the probability of death was malignancy. With malignancy excluded, the survival difference between the RVA and RVS groups persisted (log-rank analysis, P = 0.009). The major cause of mortality was pneumonia in the RVA group and heart failure in the RVS group (Figure 3). The difference in cause of mortality across the two pacing sites did not reach statistical significance.

Totally, 20 patients in the RVA group (17 ± 38.2%) compared to 11 patients in the RVS group (12 ± 32.9%) had at least one admission with heart failure as the primary diagnosis (P = 0.380). The Kaplan-Meier representation

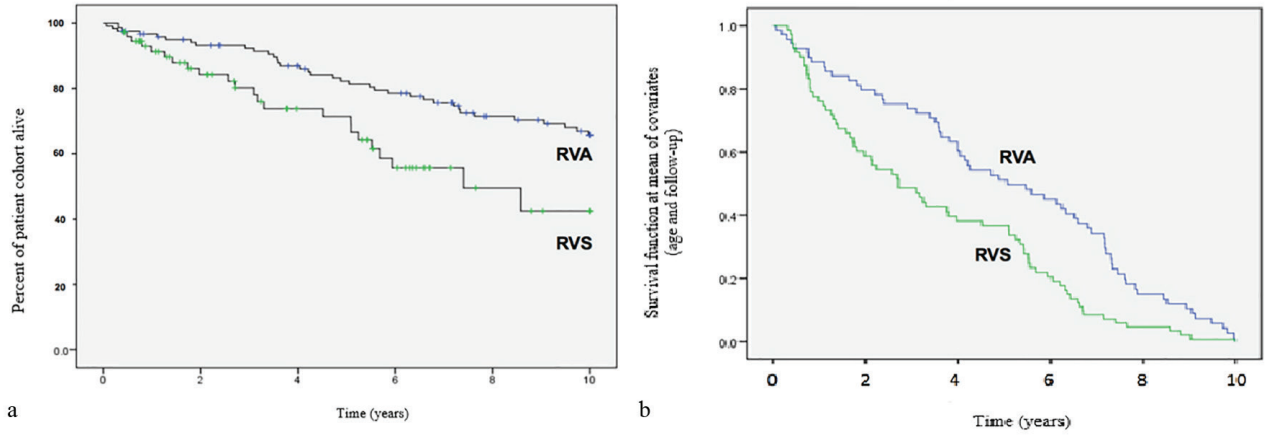
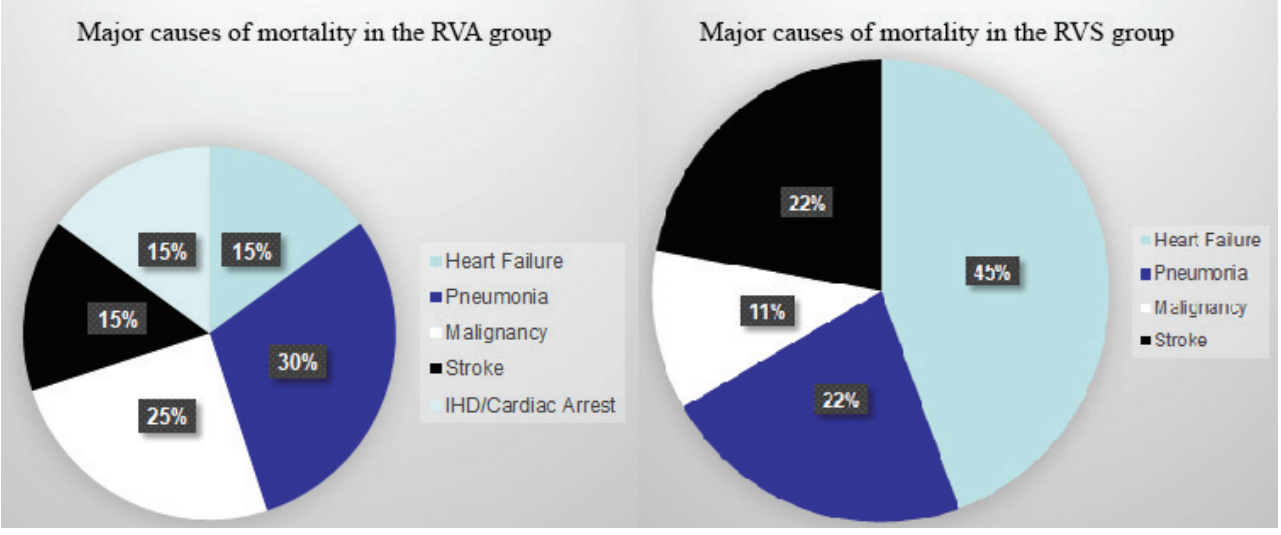


Figure 2. a, Kaplan-Meier Estimates of Event-Free Survival. Survival Rates Were Significantly Higher with RVA Pacing Compared to RVS Pacing (P < 0.001); b, Cox Proportional Survival Model with Age and Total Follow-up of the Patients Factored in (P < 0.001)

Figure 3. Causes of Mortality



There were no significant differences between RVA and RVS pacing regarding the causes of mortality

for freedom from heart failure admission over the course of the study has been depicted in Figure 4. Accordingly, the difference between the two groups was not statistically significant.

Among the dead patients, 31.25% had a primary cause of death as 'heart failure' or 'arrhythmia'. There were no significant differences between the two lead sites regarding arrhythmic death.

4.4. Background Variables and Congestive Heart Failure (CHF)

Following pacemaker implantation, 31 patients developed new CHF requiring hospital admission. The Kaplan-Meier representation of time to heart failure admission has been presented in Figure 4. Accordingly, there were no significant differences between the two groups concerning the rates of heart failure admission. Background variables of the patients who developed CHF compared to those who did not develop CHF have been listed in Table 2. The results indicated no significant relationships between the pacing site and development of heart failure. However, baseline EF was lower in the patients who developed CHF compared to those who did not (40.94 ± 15.85% vs. 51.98 ± 9.64%, P = 0.006). Indeed, the paced QRS interval in the first 40 months following pacemaker implantation was longer in the patients with CHF than in those without CHF (156.8 ± 11.6 ms vs. 144.6 ± 22.7 ms; P = 0.041). Moreover, the incidence of CHF was significantly higher in the patients with a prior diagnosis of Ischemic Heart Disease (IHD) than those without IHD (64% vs. 14.8%, P = 0.0001). The incidence of CHF was also significantly higher in the patients with a prior diagnosis of reduced LVEF (defined as at least moderate LV impairment, EF < 45%) compared to those who were not admitted with CHF (79% vs. 14.8%, P = 0.0001).

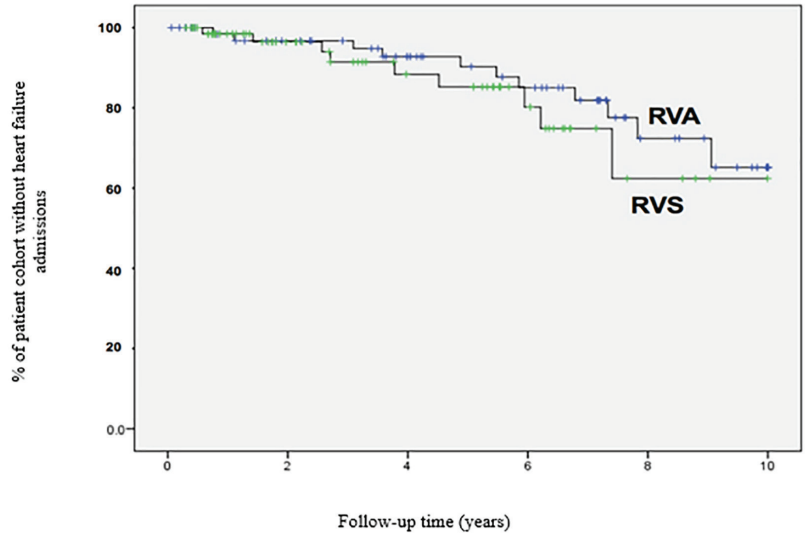


Figure 4. Event-Free Survival Curve Estimates Revealed No Significant Differences between RVA and RVS Pacing Regarding the Rates of Heart Failure Admission

Table 2. Baseline Characteristics of Patients with and without Heart Failure Admission

	Characteristics of Patients with at Least One Heart Failure Admission	Characteristics of Patients with No Heart Failure Admissions	P value
N	31	169	
Age (mean ± SD)	75.76	73.56	ns
Gender			
Male	23 (62%)	96 (49%)	0.145
Female	14 (38%)	101 (51%)	
Pacing site			
RVA	20 (62%)	108 (49%)	0.922
RVS	11 (26%)	61 (36%)	0.395
Baseline ejection fraction	40.94 (± 15.85)	51.98 (± 9.64)	0.006
Cardiac disease			
Ischemic heart disease	24 (64%)	29 (14.8%)	0.0001
Left ventricular ejection fraction < 40%	29 (79%)	55 (28%)	0.0001
Valvular heart disease	16 (63%)	72 (36.6%)	0.651
Heart failure medications at implant, n (%)			
B-blocker	24 (64%)	118 (60%)	0.712
Angiotensin–converting enzyme inhibitor	17 (45%)	74 (37.5%)	0.712
Angiotensin II receptor blocker	17 (45%)	37 (19%)	0.443
Loop diuretic	17 (45%)	71 (36%)	0.465
Aldosterone antagonist	7 (18%)	28 (14%)	0.420
QRS duration before implantation (mean ± SD)	91 (± 16.8)	99.16 (± 25.7)	0.732
QRS duration 0-40 months following AVNA (mean ± SD)	156.8 (± 11.6)	144.6 (± 22.7)	0.041
QRS duration 40 - 80 months following AVNA (mean ± SD)	159 (± 13.3)	163 (± 49.6)	1.00
QRS duration 80-120 months following AVNA (mean ± SD)	164 (± 12.6)	142 (± 22.9)	0.229

4.5. Change in Ejection Fraction over Time

There was no diminution in EF with either pacing modality over the course of the study (Figure 5). The echocardiographic data revealed a baseline and follow-up EF of respectively 48.4 ± 13.8% and 53.1 ± 8.5% for RVA-pacing and 52.0 ± 10.6% and 55.2 ± 11.3% for RVS-pacing (P = 0.480).

4.6. Change in QRS Interval

The pre-PPM QRS interval was 93 ± 19 ms in the RVS-pacing group and 95 ± 23 ms in the RVA-pacing group (P = 0.359). There were no significant differences between RVS-pacing and RVA-pacing with regard to QRS interval throughout the course of the study.

4.7. Inter-Ventricular Dyssynchrony

The mean difference between Doppler acquisition of aortic and pulmonic outflow velocities was as follows: 48 ± 46.67 ms in the RVA group and 28.8 ± 22.2 ms in the RVS group. The differences between the groups did not reach statistical significance (P = 0.288).

4.8. Intra-Ventricular Dyssynchrony

The mean time interval between the maximal inward movements of the basal septal and posterior walls was 165 ± 88 ms in the RVA-pacing group and 177 ± 76 ms in the RVS-pacing group. However, the difference did not reach statistical significance (P = 0.405).

4.9. Pacing Threshold, R-Wave Sensing, and Lead Impedance (Figures 6a and 6b)

The RV lead threshold was significantly higher in RVA-pacing compared to RVS-pacing at 6 years following implantation (0.88 ± 0.73 V vs. 0.73 ± 0.19 V, P = 0.001).

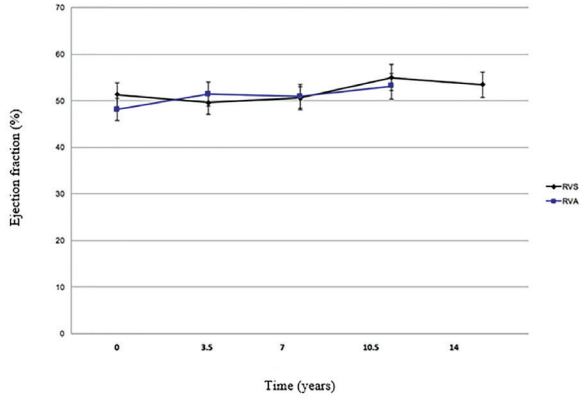


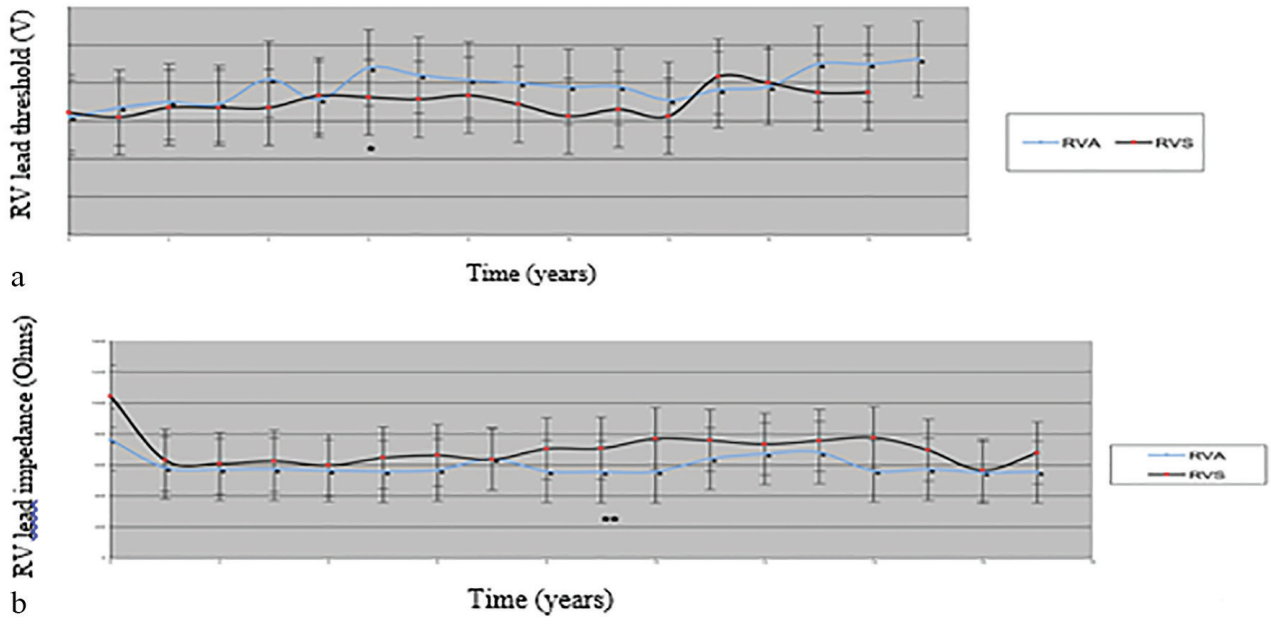
Figure 5. Trend in Ejection Time for the two Pacemaker Sites over the Course of the Study

The RV lead impedance was significantly lower in RVA-pacing in comparison to RVS-pacing at 8 years (559 ± 142 ohms vs. 708 ± 174 ohms, P = 0.005) 9 years (554 ± 169 ohms vs. 771 ± 169 ohms, P = 0.006), and 10 years following implantation (556 ± 161 ohms vs. 759 ± 189 ohms, P = 0.008).

5. Discussion

RVA-pacing was superior to RVS-pacing following AVN ablation. This finding was unexpected and the reason is unclear. However, almost one quarter of the documented RVS leads were found to be in alternate sites to the RVS on CT review.

Figure 6. a, Changes in RV Lead Threshold over Time; b, Changes in RV Lead Impedance over Time



* The RVA lead threshold was significantly higher tha RVA pacing at 6 years following implant; P = 0.001
** The RVA lead impedance was significantly lower at 9 years post implant; P = 0.008

Mortality was higher in the patients with prior diagnosis of malignancy. However, no significant differences were found between the two study groups regarding the rate of malignancy. Yet, the results of log rank analysis showed that the mortality differences between RVA and RVS pacing persisted with patients with malignancy excluded. The potential hypotheses for the difference in mortality include pacemaker failure in the absence of an escape rhythm or exacerbated repolarization abnormalities secondary to an abrupt change in heart rate.

In the present study, RVS lead impedance was significantly higher than with RVA-pacing at years 9 and 10. High lead impedance could suggest an open pacing circuit suggestive of fragility of the RVS lead. Repolarization abnormalities mediated by bradycardia have been a suspected mechanism of sudden death after AV node ablation. The potential mechanisms of arrhythmogenesis are complex (9, 12). The observations in the current study do not preclude rate-dependent repolarization as a potential arrhythmogenic mechanism, exacerbated by a fragile RVS lead position.

Although many studies suggest a benefit from RVS-pacing (13), other studies have reported no significant difference (14, 15). Many non-RVA pacing studies have small sample sizes and variability of pacing percentage, making conclusions regarding 'hard' endpoints, such as mortality, a challenge. The current study included a large chronically paced patient population. Whilst many imaging and hemodynamic studies have indicated a benefit of non-RVA pacing, this does not extend to survival in patients paced at different sites. Large, long-term prospective studies have found no significant differences between the two pacing sites regarding mortality rates (14). The current study supported the finding that RVA pacing is non-inferior to RVS pacing for mortality in long-term follow-up.

The second major finding was that there was no diminution in LVEF with either pacemaker site in 10 years of follow-up. This is relevant for two reasons. Firstly, the patients were using their ventricular lead > 98% of the time following AVN ablation. If RVA pacing was associated with a deteriorating LVEF, this could be a major concern. Secondly, the extended follow-up of these patients up to and including 10 years was considerably longer than that in other studies comparing the two sites (8, 10, 16-18). The mean baseline LVEF in the current study was within normal limits across the study population. Other studies have shown that different RV pacing sites did not tend to cause such deleterious effects on EF in patients with preserved baseline systolic function (19), which is in keeping with the current study.

The present study results revealed no significant differences between the RVA- and RVS-paced patients regarding the QRS interval measured at different times after pacemaker implantation. However, a significantly longer QRS interval was observed in the patients who went on to develop CHF in the first 40 months following pacemaker implantation. The clinical implication of this finding was reflected in the increased rate of hospitalization due to CHF in these patients. Previous reports have suggested that prolongation of the QRS interval resulted in decreased LVEF and a higher risk of CHF (16, 17, 20). Indeed, some studies suggested that pacing from a septal stimulation site was associated with a narrower paced QRS duration than from an RVA position (10). This was not supported by the current study findings. However, the findings did support aiming for a ventricular lead site providing the smallest width QRS possible at implantation.

The baseline predictors of development of CHF were prior diagnosis of IHD and prior diagnosis of reduced LVEF, which is in line with other studies (21, 22).

In summary, the results of the present single-centered

experience supported the use of an RVA lead in patients undergoing AVN ablation in this age group. To study this in more details, large, multi-centered prospective randomized controlled trials should be performed. This would allow a more stringent assessment of true RVS lead position. In this context, baseline and paced QRS duration has to be measured at PPM implant. Additionally, an increment in QRS duration more than 50% should be avoided and, if necessary, alternative pacing sites should be assessed until this is achieved.

5.1. Study Limitations

The study has a number of limitations. Firstly, it was a retrospective analysis of the patients with an indication for an AV node ablation and the results might not be applicable to a more general population. Secondly, selection bias could be an important factor in the observed difference in outcomes between RVS and RVA pacing. Thirdly, the majority of the data regarding the cause of death was obtained from death certificates, which are considered significantly less reliable than post-mortem analyses. Finally, almost a quarter of the documented RVS leads did not appear to be actually on the septum on CT chest review.

5.2. Conclusions

RVA pacing was associated with a more favorable mortality profile compared to planned RVS pacing. However, there were no significant differences between the two groups with respect to heart failure admissions. There was no diminution in EF with either pacing site. Prior diagnosis of IHD and reduced LVEF independently predicted future admissions due to heart failure. In addition, a longer QRS duration in the first 40 months following AVN ablation predicted heart failure admission.

Acknowledgements

This work was financially supported by grant No. 91-6357 from the Research Vice-chancellor of Shiraz University of Medical Sciences, Shiraz, Iran.

Authors' Contribution

W Eysenck did the conception and design, analyzed and interpreted the data, and drafted the manuscript. N Sulke did the conception and design, interpreted the data, revised the manuscript critically for important intellectual content, and approved the final version of the manuscript submitted. A Gallagher revised the manuscript critically for important intellectual content and contributed to performing dyssynchrony echocardiograms. F Jouhra revised the manuscript critically for important intellectual content and contributed to performing dyssynchrony echocardiograms. N Patel revised the manuscript critically for important intellectual content. S Furniss revised the manuscript critically for important intellectual content and approved the final version of the manuscript submitted. R Veasey did the conception and design and revised the manuscript critically for important intellectual content.

Funding/Support

There is no funding/support.

Financial Disclosure

There is no financial disclosure.

References

1. Ozcan C, Jahangir A, Friedman PA, Patel PJ, Munger TM, Rea RF, *et al.* Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. *The New England journal of medicine*. 2001;**344**(14):1043-51.
2. de Cock CC, Giudici MC, Twisk JW. Comparison of the haemodynamic effects of right ventricular outflow-tract pacing with right ventricular apex pacing: a quantitative review. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2003;**5**(3):275-8.
3. Harris ZI, Gammage MD. Alternative right ventricular pacing sites--where are we going? *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2000;**2**(2):93-8.
4. Thambo JB, Bordachar P, Garrigue S, Lafitte S, Sanders P, Reuter S, *et al.* Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. *Circulation*. 2004;**110**(25):3766-72.
5. Victor F, Mabo P, Mansour H, Pavin D, Kabalu G, de Place C, *et al.* A randomized comparison of permanent septal versus apical right ventricular pacing: short-term results. *Journal of cardiovascular electrophysiology*. 2006;**17**(3):238-42.
6. Leclercq C, Gras D, Le Helloco A, Nicol L, Mabo P, Daubert C. Hemodynamic importance of preserving the normal sequence of ventricular activation in permanent cardiac pacing. *American heart journal*. 1995;**129**(6):1133-41.
7. Dabrowska-Kugacka A, Lewicka-Nowak E, Tybura S, Wilczek R, Staniewicz J, Zagozdzon P, *et al.* Survival analysis in patients with preserved left ventricular function and standard indications for permanent cardiac pacing randomized to right ventricular apical or septal outflow tract pacing. *Circulation journal : official journal of the Japanese Circulation Society*. 2009;**73**(10):1812-9.
8. Hillock RJ, Mond HG. Pacing the right ventricular outflow tract septum: time to embrace the future. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2012;**14**(1):28-35.
9. Molina L, Sutton R, Gandoy W, Reyes N, Lara S, Limon F, *et al.* Medium-term effects of septal and apical pacing in pacemaker-dependent patients: a double-blind prospective randomized study. *Pacing and clinical electrophysiology : PACE*. 2014;**37**(2):207-14.
10. Zou C, Song J, Li H, Huang X, Liu Y, Zhao C, *et al.* Right ventricular outflow tract septal pacing is superior to right ventricular apical pacing. *Journal of the American Heart Association*. 2015;**4**(4).
11. Muto C, Calvi V, Botto GL, Pecora D, Ciaramitaro G, Valsecchi S, *et al.* Is there a right place to pace the right ventricle? Evaluation of apical and septal positions in a pacemaker population: study protocol for a prospective intervention-control trial. *Contemporary clinical trials*. 2014;**39**(2):320-6.
12. Tan ES, Rienstra M, Wiesfeld AC, Schoonderwoerd BA, Hobbel HH, Van Gelder IC. Long-term outcome of the atrioventricular node ablation and pacemaker implantation for symptomatic refractory atrial fibrillation. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2008;**10**(4):412-8.
13. Witt CM, Lenz CJ, Shih HH, Ebrille E, Rosenbaum AN, van Zyl M, *et al.* Right ventricular pacemaker lead position is associated with differences in long-term outcomes and complications. *Journal of cardiovascular electrophysiology*. 2017;**28**(8):924-30.
14. Dabrowska-Kugacka A. [Can we predict responsiveness to fluids in spontaneously breathing healthy volunteers?]. *Kardiologia polska*. 2009;**67**(3):272-3.
15. Nikoo MH, Ghaedian MM, Kafi M, Fakhrpour A, Jorat MV, Pakfetrat M, *et al.* Effects of right ventricular septal versus apical pacing on plasma natriuretic peptide levels. *Journal of cardiovascular disease*

research. 2011;**2**(2):104-9.
16. Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. *Journal of the American College of Cardiology*. 2005;**46**(12):2183-92.
17. Sharma G, Shetkar SS, Patel CD, Singh H, Naik N, Roy A*, et al*. Paced QRS duration predicts left ventricular function in patients with permanent pacemakers - One-year follow-up study using equilibrium radionuclide angiography (ERNA). *Indian pacing and electrophysiology journal*. 2015;**15**(2):90-5.
18. Zhang HX, Qian J, Hou FQ, Liu YN, Mao JH. Comparison of right ventricular apex and right ventricular outflow tract septum pacing in the elderly with normal left ventricular ejection fraction: long-term follow-up. *Kardiologia polska*. 2012;**70**(11):1130-9.
19. Ebert M, Jander N, Minners J, Blum T, Doering M, Bollmann A*, et al.* Long-Term Impact of Right Ventricular Pacing on Left Ventricular Systolic Function in Pacemaker Recipients With Preserved Ejection Fraction: Results From a Large Single-Center Registry. *Journal of the American Heart Association*. 2016;**5**(7).
20. Morris-Thurgood JA, Frenneaux MP. Pacing in congestive heart failure. *Current controlled trials in cardiovascular medicine*. 2000;**1**(2):107-14.
21. Kobza R, Schoenenberger AW, Erne P. Effects of right ventricular pacing on left ventricular ejection fraction in a pacemaker clinic. *Acta cardiologica*. 2012;**67**(5):577-82.
22. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT*, et al.* Significance of Ischemic Heart Disease in Patients With Heart Failure and Preserved, Midrange, and Reduced Ejection Fraction: A Nationwide Cohort Study. *Circulation Heart failure*. 2017;**10**(6).