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Relationship between right ventricular pacing and non-sustained ventricular arrhythmias in patients with dual-chamber pacemaker and normal range left ventricular ejection fraction

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Abstract

Background: Right ventricular pacing (RVP) increases heart failure, AF, and death rates in pacemaker patients and ventricular arrhythmias (VAs) in defibrillator patients. However, the impact of RVP on VAs burden and its clinical significance in pacemaker patients with normal range LVEF of > 50–55% remains unknown. We sought to evaluate the relationship of RVP and VAs and its clinical impact in a pacemaker patient population.

Methods: Records of 105 patients who underwent *de novo* dual-chamber pacemaker implant or a generator change (Medtronic™ or Boston Scientific™) for AV block and sinus node disease at a tertiary care center between September 1, 2015, and September 1, 2016, were retrospectively reviewed.

Results: Data from 105 patients (51% females, mean age 76 ± 1 years, mean LVEF 61 ± 0.7%) without history of VAs (98.2%) were reviewed over 1044 ± 23 days. Dependent patients (100% RVP) exhibited the lowest VAs burden when compared to < 100% RVP (isolated PVCs, PVC runs of < 4 beats, and NSVT; $p \leq 0.001$). Patients with < 1% RVP also exhibited low VA burden with intermediate RVP (1–99.9%) being most arrhythmogenic for PVC runs ($p = 0.04$) and for isolated PVCs ($p = 0.006$). Antiarrhythmics/beta and calcium channel blockers use and stress tests performed to evaluate VAs which were positive requiring intervention did not differ significantly. Burden of > 1/h of PVC runs and increasing PVC runs/h were significantly associated with hospitalization ($p = 0.04$) and all-cause mortality ($p = 0.03$), respectively.

Conclusions: In pacemaker patients with normal range LVEF (> 50–55%), 100% RVP is associated with the lowest burden of NSVT. Furthermore, patients with < 1% RVP also exhibit low VA burden; however, intermittent RVP seems to significantly correlate with non-sustained VAs.

Keywords: Right ventricular pacing, Non-sustained ventricular arrhythmias, Dual-chamber pacemaker, Premature ventricular complex

Background

Cardiac pacing is the established treatment for patients with symptomatic atrioventricular block (AV block) and sinoatrial nodal disease (SAND). Large pacemaker trials have reported a strong association between long-term

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right ventricular pacing (RVP) and deterioration of left ventricular function, pacing-induced cardiomyopathy (PICM), increased risk of heart failure (HF), atrial fibrillation (AF), and death in patients with both normal and reduced left ventricular ejection fractions (LVEF) [1–3]. RVP also increases the risk of ventricular arrhythmias (VAs) in patients with reduced LVEF and implantable cardioverter defibrillators (ICDs), yet this risk is not clearly defined in patients without an increased susceptibility for VAs who have a normal range LVEF of > 50–55% [4–7]. In a patient population with normal LVEF of > 50–55% and no apparent arrhythmogenic substrate, the impact of RVP on the incidence of nuisance non-sustained ventricular arrhythmias (NNVAs) such as isolated premature ventricular contraction (PVCs), PVC runs of 2–4 beats (PVC runs), and non-sustained ventricular tachycardia of > 4 beats but lasting < 30 s (NSVT) remains unknown. NNVAs are common in patients with in situ pacemakers; anecdotally, there seems to be a relationship between RVP and these NNVAs.

We hypothesized that in a pacemaker patient population, an increase in RVP increases incidence of NNVAs without adversely affecting clinical outcomes as noted from our anecdotal experience.

Methods

Study population and inclusion and exclusion criteria

Electronic medical and pacemaker interrogation records of consecutive patients who met all of the following inclusion criteria were retrospectively reviewed for the study:

1. Age > 18 years.
2. Baseline LVEF of > 50–55%.
3. New permanent dual-chamber pacemaker (PPM) implant or a generator change of an existing dual-chamber pacemaker.
4. Pacemaker manufacturer, Medtronic™ or Boston Scientific™ only.
5. Diagnosis of AV block or SAND for PPM implant.
6. Pacemaker implants performed only at a tertiary care medical center (Riverside Methodist Hospital, Columbus, Ohio, USA).
7. Procedure performed between September 1, 2015, and September 1, 2016.

Study exclusion criteria included:

1. Single-chamber pacemaker implants or generator change.
2. Post-procedure follow-up of < 12 months.
3. Pacemaker manufacturer, Abbott™ and Biotronik™.

The pacemaker interrogation data were reviewed separately by two electrophysiologists.

Study variables reviewed

Clinical variables reviewed from the electronic medical and pacemaker interrogation records are shown in Table 1.

Statistical analysis

For continuous variables, mean and standard error of mean were computed, and for categorical variables, proportion and frequency count were calculated. Group comparisons of categorical variables were made using Fisher's exact or chi-square test and of continuous variables using Student's *t* test (for normally distributed variables) and nonparametric *t* test or Mann–Whitney U test (for variables not distributed normally). Multiple continuous independent variables were compared using ANOVA, and multiple categorical independent variables were compared using chi-square test. Paired continuous variables pre- and post-intervention were compared with either paired *t* test or Wilcoxon signed-rank test for normally or not normally distributed data, respectively.

The Pearson correlation coefficient was used for normally distributed continuous variables, and Spearman's Rho correlation coefficient was used for continuous variables not normally distributed to measure the strength of a linear association between two variables. A value of *r* − 1.0 to − 0.5 or 1.0 to 0.5 was considered strong correlation; − 0.5 to − 0.3 or 0.3 to 0.5 was moderate correlation; − 0.3 to − 0.1 or 0.1 to 0.3 was weak correlation, and − 0.1 to 0.1 was none or very weak correlation. A Phi correlation coefficient was used to measure the association between two dichotomous variables. A continuous variable was compared with a dichotomous variable using logistic regression analysis. A statistical test was considered significant if the *p* value was < 0.05.

Multiple logistic regression was utilized to evaluate the effect of multiple baseline parameters including RVP% on outcomes such as NSVT occurrence.

We used SAS statistical software v9.4 for statistical analysis of the data.

Results

Of the 170 patients initially identified, 65 (38.2%) patients with < 12 months of follow-up were excluded from analysis. Data from 105 patients (51% female) with a mean age of 76 ± 1 years and mean pre-procedure LVEF of 61 ± 0.7% were reviewed over a period of 1044 ± 23 days. There was no history of VAs (consecutive PVCs ≥ 4 beats) in majority (98.2%) of the patients based on extensive electronic medical record review. Baseline characteristics of the patients subdivided into

Table 1 Clinical study variables

Category	Data points
Demographics	1. Date of birth 2. Age at time of pacemaker (PPM) implant/generator change 3. Gender (male/female)
Baseline medical History	1. Left ventricle ejection fraction (LVEF) prior to implant (%) 2. Hypertension (HTN) 3. Diabetes mellitus (DM) 4. History of trans-catheter aortic valve replacement 5. Coronary artery disease (CAD) 6. History of cardiac surgery
Baseline medications	1. Medications including antiarrhythmics use (angiotensin-converting enzyme (ACE) inhibitor; angiotensin receptor blocker (ARB); beta-blocker; calcium channel blocker; amiodarone, dofetilide, dronedarone, flecainide, propafenone, sotalol)
Baseline data at the start of monitoring period	1. Date of PPM implant or generator change 2. Indication for PPM (atrioventricular conduction block [AVB], or sinoatrial nodal disease [SAND] [16]) 3. Device manufacturer (Medtronic™ and Boston Scientific™) 4. Mode of pacing (dual paced, dual sensed, dual inhibited/triggered [DDD], managed ventricular pacing, or other) 5. Minimum pacing rate (*n*/min) 6. Maximum tracking rate (*n*/min) 7. Rate response (yes/no)
Arrhythmia burden and RVP% during monitoring period	1. Date of start of monitoring period 2. Date of end of monitoring period a. Total number of days included in analysis period 3. Number of non-sustained ventricular tachycardia (NSVT) (> 4 beats but lasting < 30 s) episodes during monitoring period (VT detection programmed ≥ 150 and ≥ 160 beats per minute for Medtronic™ and Boston Scientific™, respectively) 4. NSVT (> 4 beats but lasting < 30 s) burden (#/100 days) 5. Number of premature ventricular contraction (PVC) runs of 2–4 beats during monitoring period (#/h) 6. Isolated PVC burden (#/h) 7. Atrial fibrillation (AF) burden (%; cumulative total time spent in atrial high rate episodes/total time of monitoring * 100) 8. Average percentage of right ventricular (RV) pacing over monitoring period (%; cumulative total time of RVP/total time of monitoring*100)
Clinical Outcomes	1. LVEF after PPM implant a. Measured by echocardiography, or imaging stress test b. Time from PPM implant to LVEF determination (days) c. LVEF (%) 2. Stress test after PPM implant a. Type of stress test b. Stress test positive for ischemia or infarction (yes/no) c. Time from PPM implant to stress test 3. Device upgrade (none, implantable cardioverter defibrillator [ICD], biventricular PPM [Bi-VPPM], biventricular ICD [Bi-VICD]) a. Date of upgrade b. Time from PPM implant to upgrade 4. New medications initiation including antiarrhythmics use (angiotensin-converting enzyme (ACE) inhibitor; angiotensin receptor blocker (ARB); beta-blocker; calcium channel blocker; amiodarone, dofetilide, dronedarone, flecainide, propafenone, sotalol) 5. Hospitalization related to cardiac condition a. Date of hospitalization b. Indication for hospitalization 6. Death a. Date of death b. Cause of death if known

Groups A, B, and C in correlation with high RVP of 100%, low RVP of ≤ 1%, and intermediate RVP of > 1 and < 100%, respectively, are detailed in Table 2. RVP% is percentage of the total cumulative time spent in right ventricular pacing during the monitoring period noted on pacemaker interrogation data. It was calculated as an average for the entire period of monitoring. It was 100, 0.2 ± 0.03, and 55.8 ± 5.2 for Groups A, B, and C, respectively.

There were no significant differences in majority of the baseline characteristics with notable exceptions. Group A had patients in whom pacemaker was implanted for AV block with DDD pacemaker programming being most common. This group had high RV pacing burden as expected (100%). Group B consisted of a relatively younger and predominantly female (72%) population. Managed ventricular pacing (MVP™) pacemaker programming was most common in this group giving rise to

Table 2 Comparison of baseline characteristics in patients with high RVP, low RVP, and intermediate RVP

Patient characteristics	Group A; 100% RV pacing ($n=16$)	Group B; ≤ 1% RV pacing ($n=29$)	Group C; > 1–< 100% RV pacing ($n=60$)	*p* value
Age (years)	75 ± 3.5	68 ± 1.8	80 ± 1.2	< 0.0001
Gender (female)	50%	72%	42%	0.02
Hypertension	81%	72%	90%	ns
Diabetes mellitus	25%	17%	27%	ns
Coronary artery disease	44%	41%	53%	ns
Trans-aortic valve replacement	25%	3%	12%	ns
Cardiac bypass/valve surgery	31%	17%	23%	ns
Baseline LVEF%	60 ± 1.4	62 ± 1.3	57 ± 1	0.005
Beta-blocker use	19%	38%	50%	ns
Calcium channel blocker use	6%	7%	7%	ns
Antiarrhythmic medication use	0%	7%	18%	ns
De novo pacemaker implant	56%	48%	48%	ns
Indication for pacemaker	94% (AVB)	7% (AVB)	53% (AVB)	< 0.0001
	6% (SSS)	93% (SSS)	47% (SSS)	
Duration of analysis (days)	1029 ± 67	1076 ± 38	1033 ± 32	ns
Pacemaker company	50% (MDT) 50% (BS)	69% (MDT) 31% (BS)	65% (MDT) 35% (BS)	ns
Programmed mode of pacing	100% (DDD)	31% (DDD)	62% (DDD)	< 0.0001
	0% (MVP)	69% (MVP)	23% (MVP)	
	0% (VVI and DDI)	0% (VVI and DDI)	15% (VVI and DDI)	
Minimum pacing rate (*n*/min)	61 ± 1	59 ± 1	60 ± 0.5	ns
Maximum tracking rate (*n*/min)	127 ± 2.4	128.4 ± 1.2	126 ± 1.2	ns
Rate response present	50%	76%	70%	ns

LVEF, left ventricular ejection fraction; AVB, atrioventricular block; SSS, sick sinus syndrome; MDT, Medtronic; BS, Boston scientific; DDD, dual paced, dual sensed, dual inhibited/triggered; MVP, managed ventricular pacing; RV, right ventricular; ns, not significant. ANOVA for continuous variables; chi-square test for categorical variables

a very low RV pacing burden (0.2 ± 0.03%). Group C had the oldest population with lowest LVEF although still in normal range (> 50–55%). LVEF was modestly but significantly higher in Group B (62 ± 1.3%), followed by Group A (60 ± 1.4% and then Group C (57 ± 1%).

We then compared patients who underwent generator change *versus* new pacemaker implant to rule out significant differences which would preclude combining these groups for data analyses. We found no significant difference between the two groups with respect to gender distribution, age, baseline LVEF, cardiac surgery, HTN, DM, use of beta-blockers, calcium channel blockers, and AADs. We also did not find any difference in AF, NNVAs (isolated PVCs, PVC runs, and NSVT), and RVP burdens. However, more patients had CAD and history of TAVR in the new pacemaker implant group. The two groups were deemed reasonably similar such that the data were combined to produce the following analyses.

NSVT in dependent patients with 100% RVP burden

Among the NNVAs, NSVT is clinically the most relevant arrhythmia. Although its occurrence is infrequent, it obligates the clinical electrophysiologist to pursue further evaluation. Using univariate analysis, we found that dependent patients with 100% RVP when compared to < 100% RVP exhibited the lowest burden of NSVT/100 days (0.05 ± 0.02 vs 0.5 ± 0.2; $p=0.01$) (Fig. 1). In fact, patients with 100% RVP also displayed significantly less NSVT/100 days when compared to patients with minimal RVP of < 1%.

Furthermore, using a multiple logistic regression model with 0.077 NSVT/100 days as the median value, we found no other baseline co-variables (as noted in Table 2) except for RVP% to significantly influence the occurrence of NSVT. We found that for every 20% reduction in RVP there was a 1.3 increased odds of having high burden of NSVT/100 days (high burden defined as > 0.077).

Intermittent RVP and NNVAs in pacemaker patients

Dependent patients with 100% RVP also exhibited the lowest burden for other varieties of NNVAs such as isolated PVCs/h (3 ± 0.8 vs 32.4 ± 7.7; $p<0.001$) and PVC runs/h (0.03 ± 0.01 vs 2.6 ± 0.9; $p<0.01$), when compared to < 100% RVP (Fig. 2). Very low RVP burden (< 1%) also correlated with low NNVAs with intermittent RVP

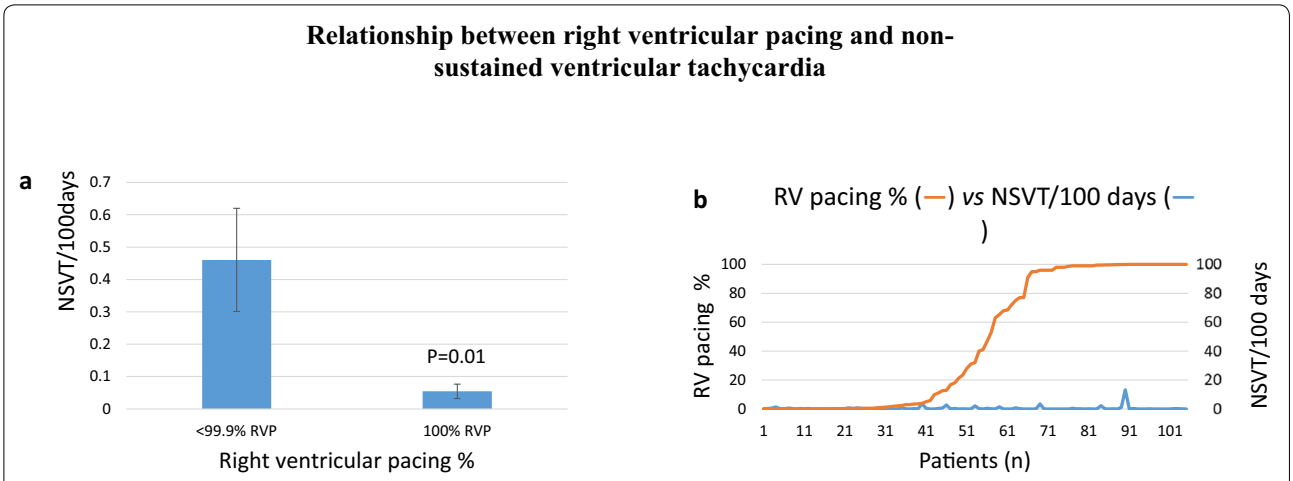

Fig. 1 Relationship between right ventricular pacing and non-sustained ventricular tachycardia. **a** Bar graph depicting the relationship between right ventricular pacing (RVP)% (*x* axis) and non-sustained ventricular tachycardia episodes (NSVT)/100 days (*y*-axis). Note that patients with 100% RVP had significantly less NSVT burden than patients with < 99.9% RVP. **b** Line graph depicting the relationship between NSVT episodes/100 days (blue line; *y*-axis on the right) and RVP% (orange line; *y*-axis on the left) for all the studied patients (*x*-axis) aligned from left to right in increasing order of RVP%. Note the increase in NSVT burden (blue line) from left to right as RVP% (orange line) increases, till it reaches 100% RVP when the NSVT burden is dramatically reduced

burden being most arrhythmogenic for isolated PVCs/h and PVC runs/h (Fig. 2).

As expected, more than one variety of NNVAs were noted in a given patient. There was a moderately strong positive relationship between occurrence of PVC runs/h and isolated PVCs/h ($r = 0.56$; $p < 0.001$). Furthermore, there was also a moderately positive relationship between occurrence of PVC runs/h and NSVT/100 days ($r = 0.42$; $p < 0.001$). However, no such relationship existed between isolated PVCs/h and NSVT/100 days ($p = 0.2$) suggesting a continued spectrum of increasing intensity of NNVAs in our patient cohort.

Association of RVP burden and AF occurrence and impact on LVEF

In Groups A, B, and C with high RVP of 100%, low RVP of ≤ 1%, and intermediate RVP of > 1 and < 100%, the baseline prevalence of paroxysmal atrial fibrillation was 0%, 18.3%, and 6.8%, respectively. During the monitoring period, we observed an increase in PAF to 6.25%, 55%, and 13.8% in the respective groups. We observed an increase in AF burden (percentage of the total cumulative time spent in atrial high rates on pacemaker interrogations) with an increase in RVP%. Specifically, there was a precipitous and significant increase in AF prevalence in patients with RV pacing over 5% in our patient cohort (Fig. 3). AF burden continued to be high in patients who were dependent unlike for NNVAs.

We observed a post-procedure reduction in LVEF in 33% of patients over a mean period of 495 ± 34 days (60.7 ± 1.3% vs 49.7 ± 1.7%; $p < 0.001$). Furthermore, the mean RVP% was modestly higher in patients who exhibited reduction in LVEF (70.7 ± 8.8% vs 47.7 ± 6.7%; $p = 0.04$). However, there was no significant difference in NSVT burden between patients with unchanged and reduced LVEF. None of the patients in our cohort underwent upgrade to a biventricular device (PM or ICD) during the period of analysis.

Stress test yield in pacemaker patients with NNVAs

A total of 18 patients (~ 17%) underwent stress testing (1 dobutamine stress echocardiography, 3 treadmill exercise stress tests with ECG, 2 regadenoson positron emission tomography with rubidium, and 12 regadenoson single-photon emission computed tomography with Technetium 99) over a period of 493 ± 82 days after pacemaker implant/generator change on the managing physician's discretion, largely, to evaluate higher burden of NSVT in this subset of patients. Average episodes of NSVT/100 days were higher in the patients who underwent stress testing when compared to the rest of the cohort (1.07 ± 0.8 vs 0.27 ± 0.06). Majority (10 patients) of them were from Group C, followed by Group B (7 patients), and only 1 patient from Group A. Among them, only 5 patients had a positive stress test (3 from Group C, 1 each from Group A and B) and only 2 underwent coronary intervention (1 each from Group B and C). The other 3 patients had mild perfusion defects managed with medical therapy.

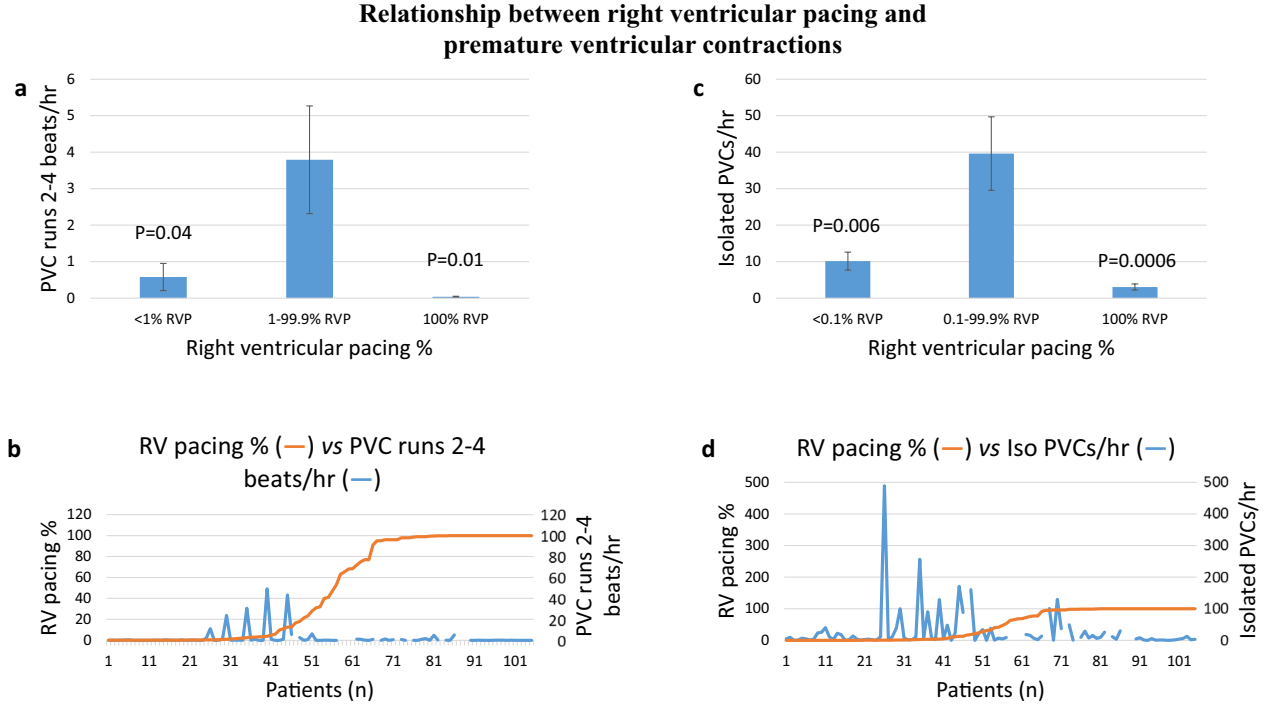

Fig. 2 Relationship between right ventricular pacing and premature ventricular contractions. **a** Bar graph depicting the relationship between right ventricular pacing (RVP)% (*x* axis) and premature ventricular contraction (PVC) runs of 2–4 beats/h (*y* axis). Note that patients with intermittent RVP (1–99.9%) had the highest burden of PVC runs which was significantly higher when compared to patients with < 1% ($p = 0.04$) and 100% RVP ($p = 0.01$). **b** Line graph depicting the relationship between PVC runs of 2–4 beats/h (blue line; *y*-axis on the right) and RVP% (orange line; *y*-axis on the left) for all the studied patients (*x*-axis) aligned from left to right in increasing order of RVP%. Note the low burden of PVC runs (blue line) with < 1% (patients 1–21 on *x*-axis) and 100% RVP (patients > 91 on *x*-axis). Intermittent RVP (1–99.9%; patients between 21 and 91 on *x*-axis) dramatically increases the burden of PVC runs (blue line). **c** Bar graph depicting the relationship between RVP% (*x*-axis) and isolated PVCs/h (*y*-axis). Note that patients with intermittent RVP (0.1–99.9%) had the highest isolated PVC burden which was significantly higher when compared to patients with < 0.1% ($p = 0.006$) and 100% RVP ($p = 0.0006$). **d** Line graph depicting the relationship between isolated PVCs/h (blue line; *y*-axis on the right) and RVP% (orange line; *y*-axis on the left) for all the studied patients (*x*-axis) aligned from left to right in increasing order of RVP%. Note the low burden of PVCs (blue line) with < 0.1% (patients 1–21 on *x*-axis) and 100% RVP (patients > 91 on *x*-axis). Intermittent RVP (0.1–99.9%; patients between 21 and 91 on *x*-axis) dramatically increases the burden of isolated PVCs

Antiarrhythmics use and NNVAs in pacemaker patients

It is well known that the use of beta-blockers, calcium channel blockers, and AADs can influence VA occurrence. Although we found no statistically significant differences with respect to the use of these medications and NNVAs in our patient cohort (Table 2), the baseline use of AADs was higher in Group C (11/60; 18%) followed by Group B (2/29; 7%) and none in Group A. Additional 5, 2, and 1 patients were started on AADs in Groups C, B, and A, respectively, during follow-up period. AADs were only used for AF treatment and not for NNVAs suppression.

Morbidity and mortality in pacemaker patients with NNVAs

Twice as many patients with a mean burden of PVC runs > 1/h were hospitalized for a cardiac indication (heart failure, acute coronary syndrome, coronary intervention, atrial arrhythmias, and cardiac valve replacement) than patients with a burden of < 1/h (47% vs 23%; $p = 0.04$). Furthermore, there was a significant relationship between increase in PVC runs/h and all-cause mortality ($p = 0.03$).

Discussion

In our study of a cohort of 105 consecutive patients undergoing dual-chamber PPM implantation or generator change for AV block or SAND, the main findings are: (1) very high (100%) RVP burden is associated with the lowest NNVAs. It seems especially protective against the clinically most relevant NNVA: NSVT, even when compared to patients with minimal RVP of < 1% which is generally considered cardio-protective and possibly less arrhythmogenic [6]; (2) intermittent RVP burden (> 1% to < 100%) is significantly associated with NNVAs in a dual-chamber pacemaker population with normal range LVEF of > 50–55%; and (3) very low (< 1%) RVP burden is

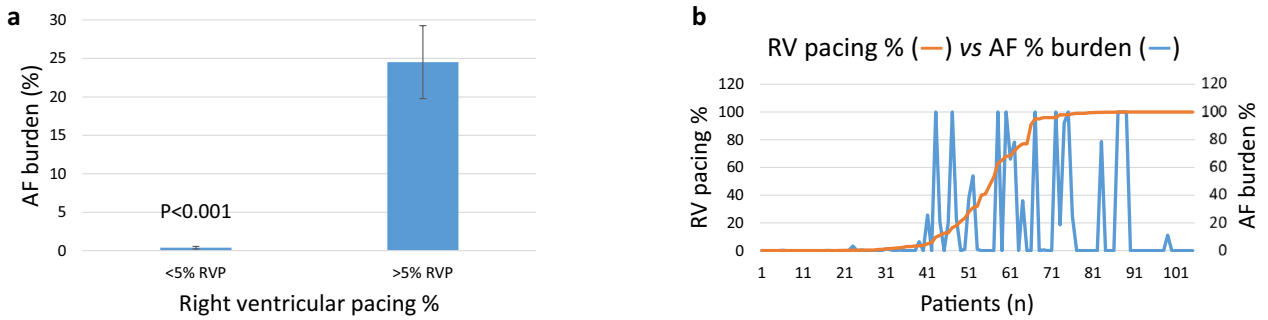

Fig. 3 Relationship between right ventricular pacing and atrial fibrillation. **a** Bar graph depicting the relationship between atrial fibrillation (AF)% burden (*y*-axis) and right ventricular pacing (RVP)% (*x*-axis). Note that patients with RVP burden of < 5% had the lowest AF burden. **b** Line graph depicting the relationship between AF% burden (blue line; *y*-axis on the right) and RVP% (orange line; *y*-axis on the left) for all the studied patients (*x*-axis) aligned from left to right in an increasing order of RVP%. Note a precipitous increase in AF burden (blue line) as RVP% increases (orange line) after patient 31 on *x*-axis. Also note that patients with high RV pacing (patient > 81 on *x*-axis) also had high AF burden as opposed to ventricular arrhythmias

also associated with lower isolated PVCs and PVC runs burden.

Prior studies have focused on ICD patient populations which have significant ventricular scar and subsequent arrhythmogenic substrate. Therefore, in ICD patients, it is well known that RVP increases incidence of VAs [6]. Nonetheless, even in this patient population, high RV pacing burden (> 98%) was associated with low VAs [6]. This intriguing observation also seems to extend to the pacemaker population as noted in our study. Although not clear, the putative mechanism is likely the pro-arrhythmic effect of competing native and paced rhythms [5]. This can be especially seen with pacing algorithms where native and paced rhythms are intricately intertwined like MVP™ in Medtronic® dual-chamber devices which are known to instigate VA [8]. The underlying mechanism seems to be the repolarization abnormality that occurs following a change in depolarization with contribution of dispersion of repolarization, evidenced by changes in T wave morphology on the ECG (T wave memory) compounded by the irregularity of the rhythm. This observation further begs the question whether RVP by itself or *intermittent* RVP instigates VAs. From the data we present here, it seems that the latter is more arrhythmogenic in causing VAs than the former.

It is well known that excessive RVP is detrimental. However, the conundrum of obligatory RVP in patients with AV block is faced by practicing electrophysiologists on an everyday basis. Increasing AF burden and worsening LVEF are undesirable but known consequences of excessive RVP [2, 9, 10] and were also observed in our patient cohort. Even RVP percentage burden as low as 20% has been associated with developing PICM in patients with previously normal EF [9]. Through electrical and mechanical dyssynchrony, RVP may negatively affect left ventricular activation, myocardial perfusion, remodeling, and cardiac hemodynamics [11]. In our study, we observed two interesting findings: (1) reduction in LVEF, noted in a subset of patients, correlated with high RVP burden but did not associate with NNVAs, suggesting an independent pro-arrhythmic effect of *intermittent* RVP; (2) high RVP (100%) seems protective against VAs but not against AF, akin to what has been noted in previous studies [2]. Long-term RVP has been reported to cause atrial electrical remodeling and increased atrial diameters associated with an increased risk of AF [12, 13].

Anecdotally, cardiac electrophysiologists, when faced with NNVAs in a patient with a pacemaker, invariably end up ordering an echocardiogram to gauge LVEF, initiate beta-blockers, and sometimes proceed with stress testing if the VA burden is high. However, our data suggest that these interventions are likely futile in reducing VA burden in this cohort of patients. Specifically, we find no association between LVEF reduction or beta-blocker usage and NNVA burden in our data. The number of patients who underwent stress testing (guided by NNVA burden) in our cohort was too small (~ 17%) to make any firm conclusion. Of note, nearly all stress tests were performed in patients with < 100% RVP who tend to have high NSVT burden. However, even among them,

the positive stress test patients requiring coronary intervention were only 11% (< 2% of the total patients). This finding suggests that the yield of performing a stress test directed by NSVT burden in a pacemaker patient is minimal at best.

Although causality cannot be established, and other potential confounders may exist, a potentially troubling finding from our study is that non-sustained PVC runs of 2–4 beats, which are deemed harmless in clinical practice, are significantly associated with both hospital admissions and mortality in a pacemaker population. If future larger studies endorse this observation, then pacemaker programming/implant strategies to reduce their burden may be desirable.

To this end, minimizing unnecessary RVP in pacemaker patients (a firmly established paradigm) would be one such option. Pacing algorithms like managed ventricular pacing (MVP™; Medtronic®) and ventricular intrinsic preference (VIP™; Abbott®) and others already exist for this indication. However, it would be intriguing to conceptualize a 100% obligatory ventricular pacing algorithm to minimize NNVAs. This idea would be against the existing paradigm and would have likely been disregarded had the option of His-bundle pacing (HBP) not existed. HBP can be used to pace 100% in the ventricle potentially reducing NNVAs. Along with its reduced risk of AF in comparison with RVP [14], HBP can also reverse the LVEF reduction caused by RVP, as shown in a retrospective analysis of 60 patients with PICM [15]. Thus, HBP is proving to be a possible therapeutic option for patients with PICM.

Study limitations

Our study is a retrospective cohort study, and therefore inherent limitations include selection bias, potentially inadequate number of subjects or follow-up, and inability to rule out silent ischemia as a cause of NNVAs by performing myocardial perfusion imaging stress tests in all patients. In addition, we did not use data from patients who had undergone Saint Jude Medical® (now Abbott®) or Biotronik® pacemakers since their use is minimal at our institution. Furthermore, we specifically chose patients for the study who underwent the pacemaker procedure during the 1-year period of September 1, 2015, to September 1, 2016, because a new electronic medical record system was introduced at our institution just before the start of 2015. This made data collection convenient and gave us at least 3 years (data until September 30, 2019, were reviewed for the study) of data to review, thus improving study outcomes analyses.

It is also possible that VAs data collection by pacemakers in dependent patients (100% RVP) underestimates VAs due to inherent algorithm bias. However, this is less likely due to the following reasons: (1) no significant difference existed when we analyzed NNVAs data based on the pacemaker company (Medtronic™ or Boston Scientific™); (2) a prior study has already shown a significant reduction in *appropriate* ICD shocks in patients who exhibited > 98% RVP [6].

A significant percentage of patients in our patient cohort (Table 2) had coronary artery disease (CAD), risk factors for CAD, or had undergone cardiac bypass or value surgery. Therefore, these patients cannot be considered entirely devoid of any arrhythmogenic substrate, although their LVEF were in the normal range (> 50–55%). However, since the prevalence of these risk factors was similar in the three groups (Table 2), we think their potential confounding effect on clinically unapparent arrhythmogenic substrate should be neutralized.

Conclusion

In this retrospective cohort study of a dual-chamber pacemaker patient population with normal range LVEF of > 50–55%, 100% right ventricular pacing as observed in dependent patients seems to protect against non-sustained ventricular tachycardia of > 4 beats. Intermittent right ventricular pacing is associated with the highest incidence of non-sustained ventricular arrhythmias (isolated PVCs and PVC runs of 2–4 beats and NSVT). Lowest burden of < 1% right ventricular pacing may protect against non-sustained ventricular arrhythmias like PVCs and PVC runs of 2–4 beats but not against NSVT.

Future larger studies need to confirm these findings. Reducing unnecessary right ventricular pacing and potentially obligatory His-bundle pacing may mitigate non-sustained ventricular arrhythmias in this patient population.

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Author's contributions
NC was involved in creating concept of study. RE and NC were involved in writing draft, data collection, and analyzing data. A-KA, S-RB, E-YF, A-JN, S-DN, RE, and NC were involved in data review and writing draft. All authors read and approved the final manuscript.

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The study protocol of the current study was approved and waived for informed consent by the OhioHealth Corporation Institutional Review Board.

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