Significance of Ventricular Arrhythmia Based on Stored Electrogram Analysis in a Pacemaker Population

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Summary

The incidence of ventricular arrhythmia in patients with an implanted pacemaker is not yet known. The aim of this study was to analyze non-sustained ventricular tachycardia (NSVT) episodes based on stored electrograms (EGM) and determine the occurrence rate and risk factors for NSVT in a pacemaker population.

This study included 302 consecutive patients with a dual-chamber pacemaker. A total of 1024 EGMs stored in pacemakers as ventricular high-rate episodes were analyzed. The definition of NSVT was ≥ 5 consecutive ventricular beats at ≥ 150 bpm lasting < 30 seconds.

In baseline, most patients (94.8%) had ≥ 60% left ventricular ejection fraction. Of 1024 EGMs, 420 (41.0%) showed appropriate NSVT episodes, as well as premature atrial contractions, atrial tachyarrhythmia, or atrial fibrillation with a rapid ventricular response, whereas other EGMs did not show an actual ventricular arrhythmia. On EGM analysis, during a mean follow-up period of 46.1 months, NSVT occurred one or more times in 82 patients (33.1%). On multivariate analysis, ≥ 50% right ventricular pacing was an independent risk factor for NSVT (odds ratios, 4.519; P < 0.001), but NSVT was not associated with increased all-cause mortality.

Moreover, in the pacemaker population, ≥ 50% right ventricular pacing is an independent risk factor for NSVT; however, NSVT was not associated with increased all-cause mortality because of the preserved left ventricular function.

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Key words: Non-sustained ventricular tachycardia, Right ventricular pacing, Outcomes

Over the last 50 years, approaches and developments for cardiac implantable electronic device have continued. Current implanted pacemakers have the capacity to record multiple types of atrial and ventricular arrhythmia, including non-sustained ventricular tachycardia (NSVT), which has been shown to be the most common event observed on routine pacemaker follow-up.13 The incidence and significance of NSVT have been reported in the implantable cardioverter defibrillator (ICD) population with low left ventricular ejection fraction (LVEF) or coronary artery disease (CAD).23 However, the incidence and clinical impact of ventricular arrhythmia in patients with an implanted pacemaker are not yet known. The aim of this study was to analyze NSVT episodes based on stored electrograms (EGM) and determine the occurrence rate and risk factors for NSVT in a pacemaker population.

Methods

This study included 302 consecutive patients who had undergone implantation of a dual-chamber pacemaker at Yokohama City University Hospital between 2011 and 2017. All patients had a class I or II indication for pacemaker implantation according to guidelines of the Japanese Circulation Society.6 Patients with NSVT detected by resting electrocardiograms (ECGs) or 24-hour Holter ECG recordings, continuous atrial fibrillation, or a history of AV node ablation were excluded. Therefore, a total of 248 patients were retrospectively analyzed in the present study.

Baseline patient characteristics, including physical examination findings, underlying disease, and 12-lead ECG, were collected just before implantation of the pacemaker. Settings of the pacemaker, such as lower rate, were decided by each physician. The patients were followed at 1 month after implantation of the pacing system and every 5 months thereafter during the study. At each follow-up, the stored data on the pacemaker memory were retrieved, and a total of 1024 EGMs related to ventricular high-rate episodes were collected. The detected and stored criteria of the ventricular high-rate episodes were nominal settings in all pacemakers. Each waveform of these stored EGMs

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VENTRICULAR ARRHYTHMIA IN A PACEMAKER POPULATION

Figure 1. Electrogram of appropriate NSVT episode consisting of 13 ventricular beats with atrioventricular dissociation. Atrial and ventricular electrograms are shown in the upper tracing and atrial and ventricular markers in the lower tracing.

was carefully analyzed. In this study, NSVT was defined as ≥ 5 consecutive ventricular beats at ≥ 150/minutes lasting < 30 seconds. This threshold was chosen to balance the default settings for NSVT detection of each manufacturer. The definition of the patients with NSVT was those with one or more past histories of NSVT after implantation.

This study was approved by the Yokohama City University Hospital Ethics Committee (B190300030).

Statistical analysis: Comparisons of quantitative and categorical variables between groups were performed using Pearson chi-squared test or Student’s t-test. All continuous data were expressed as mean ± standard deviation. Univariate or multivariate Cox regression models with a forward stepwise approach were run to assess crude and multivariate adjusted odds ratios (ORs), which were presented with 95% confidence intervals (CIs). For all tests, \( P < 0.05 \) was considered statistically significant. All statistical analysis was carried out using SPSS.

Results

Baseline characteristics: The mean age of the study population was 72.0 years, 55.6% of which were male. Indications in all patients for original pacemaker implantation were atrioventricular block (AVB) in 50.4%, sick sinus syndrome (SSS) in 48.8%, and others in 0.8%. The underlying diseases were hypertension in 55.2%, diabetes mellitus in 17.7%, paroxysmal atrial fibrillation in 37.1%, cerebral infarction in 6.5%, and CAD in 17.3%. The mean LVEF was 68.4 ± 9.9%, and most patients (94.8%) had ≥ 60% LVEF. The proportion of patients receiving an anti-coagulant drugs at the time of discharge after pacemaker implantation was 50.4%, which also included β-blocker in 17.7%, angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker in 35.1%, and anti-arrhythmic drug (AAD) in 13.7%. AAD, however, consisted of flecainide in 35.2%, bepridil in 26.5%, cibenzoline in 14.7%, pilsicainide in 14.7%, and others. Device manufacturers included St. Jude Medical (28.0%), Medtronic (24.0%), Boston Scientific (21.7%), SORIN (15.4%), and Biotronik (10.9%).

EGM analysis of ventricular high-rate episodes: During a mean follow-up period of 46.1 months, a total of 1024 EGMs stored on the pacemaker memory were collected as ventricular high-rate episodes. Of 1024 EGMs, 420 (41.0%) showed NSVT episodes (Figures 1, 2). The other EGMs did not show actual ventricular episodes and showed premature atrial contractions in 219 (21.4%), atrial tachycardia in 215 (21.0%), atrial fibrillation in 113 (11.0%), paroxysmal supraventricular tachycardia or atrioventricular junctional rhythm in 32 (3.1%), sinus tachycardia in 14 (1.4%), far-field atrial sensing by ventricular lead in 9 (0.9%), and electromagnetic noise in 2 (0.2%) (Figures 3, 4).

Occurrence rate and risk factors for NSVT: EGM analysis revealed that NSVT occurred one or more times in 82 patients (33.1%) during the follow-up period. All 82 patients were free of symptoms. Baseline characteristics according to NSVT are listed in Table I. In NSVT group, male gender and AVB were more prevalent. We focused on the cumulative percent of right ventricular pacing, which was calculated as the ratio of right ventricular pacing beats to the total beats during the life of the pacemaker. The mean right ventricular pacing percent in NSVT group was significantly higher than that in no NSVT group (72.0% versus 38.5%, \( P < 0.001 \)). In the present study, the cut-off value of the mean right ventricular pacing percent was defined as 50%, which was used in prior studies.\(^7\)\(^8\)

In univariate Cox regression analysis, ≥ 50% right ventricular pacing was associated with a higher risk of NSVT (odds ratio = 4.652, 95% CI 2.612-8.286, \( P < 0.001 \)). Other clinical variables, including male gender, were associated with NSVT (Table II). Multivariate Cox regression analysis controlling for age and sex revealed that ≥ 50% right ventricular pacing was an independent risk factor for NSVT (odds ratio = 4.519, 95% CI 2.480-8.237, \( P < 0.001 \)) (Table III). Furthermore, right ventricular pacing percent itself was a strong risk factor for NSVT.
Figure 2. Electrogram of appropriate NSVT episode consisting of 18 ventricular beats with atrioventricular dissociation. Atrial and ventricular electrograms are shown in the upper tracing and atrial and ventricular markers in the lower tracing.

Figure 3. Electrogram of atrial tachycardia consisting of fast regular atrial activity with transmitted ventricular 1:1 conduction. Atrial and ventricular electrograms are shown in the upper tracing and atrial and ventricular markers in the lower tracing.

(odds ratio = 1.016 per 1% increase, $P < 0.001$). In addition, subgroup analysis was performed in the SSS patient group. SSS patients with $\geq 50\%$ right ventricular pacing had a statistically higher rate of NSVT compared with SSS patients with $< 50\%$ right ventricular pacing (65.0% versus 15.3%, $P < 0.001$).

Impact of ventricular pacing and NSVT on clinical outcomes: During the follow-up period, 35 (14.1%) of 248 patients died of any cause, including 7 (2.8%) cardiovascular deaths. In Kaplan-Meier analysis, there was no evidence for the effect of NSVT on increased all-cause mortality. Furthermore, there was no association between the fastest cycle length of NSVT and all-cause mortality.

Discussion

The major findings of the present study are that 82 (33.1%) patients had episodes of NSVT documented by stored EGM and that $\geq 50\%$ right ventricular pacing is an independent risk factor for NSVT in the pacemaker population. However, NSVT was not associated with increased all-cause mortality.

There are several studies on the burden of NSVT in a pacemaker population. The first study of NSVT, which enrolled 231 patients with a pacemaker, showed that 54 (25.7%) patients had episodes of NSVT documented by stored EGM.9) Seth, et al. suggested that 223 of 1125 patients (20%) with an implanted pacemaker had NSVT.10) In a recent prospective cohort study, among 565 patients with long-term pacemakers, NSVT was found in 125 (22.1%).11) In this study, the occurrence rate of NSVT in a pacemaker population was 33.1%, which is similar to that in previous studies.

Furthermore, in the present study, we focused on the cumulative percent of right ventricular pacing. In previous studies, frequent right ventricular pacing correlated with asynchronous ventricular contraction and an increased incidence of heart failure in the pacemaker or ICD popula-
of the indication for the pacemaker implantation.

In this study, however, NSVT was not associated with all-cause mortality. In a large cohort study including 1125 patients with a pacemaker, there were 93 deaths, with no differences in survival between the NSVT and no NSVT groups during a mean follow-up of 2.8 years.\textsuperscript{10} Gabries, et al. analyzed all 262 patients with an implanted Medtronic pacemakers and suggested that NSVT was not associated with increased mortality.\textsuperscript{17} In the US population without a pacemaker, the long-term outcome in asymptomatic subjects with no structural heart disease and frequent and complex ventricular ectopy was similar to that of the healthy US population, with no increased risk

Table I. Baseline Characteristics According to NSVT

|          | NSVT (n = 82) | No NSVT (n = 166) | P-value |
|----------|---------------|-------------------|---------|
| Age (years) | 72.1 ± 12.7   | 72.0 ± 14.1       | 0.958   |
| Male      | 60 (74%)      | 76 (46%)          | < 0.001 |
| Right ventricular pacing percent | 72.0 ± 41.8 | 38.5 ± 45.2 | < 0.001 |
| Atrialventricular block | 54 (66%) | 70 (42%) | < 0.001 |
| Hypertension | 52 (63%) | 85 (51%) | 0.069 |
| Diabetes mellitus | 16 (18%) | 28 (17%) | 0.874 |
| Atrial fibrillation | 23 (29%) | 68 (41%) | 0.073 |
| Heart failure | 5 (6%) | 8 (5%) | 0.871 |
| LVEF (%) | 66.2 ± 10.5 | 69.4 ± 9.4 | 0.099 |

Table II. Univariate Risk Factors for NSVT

| Variables                          | Odds Ratio | 95% CI    | P-value |
|------------------------------------|------------|-----------|---------|
| ≥ 50% right ventricular pacing     | 4.652      | 2.612-8.286 | < 0.001 |
| Male                               | 3.357      | 1.876-6.010 | < 0.001 |
| Hypertension                       | 1.652      | 0.960-2.842 | 0.070 |
| Atrial fibrillation                | 0.596      | 0.338-1.052 | 0.074 |
| LVEF                               | 0.968      | 0.932-1.005 | 0.090 |
| Anti-arrhythmia agent              | 0.480      | 0.200-1.155 | 0.102 |
| Anticoagulant agent                | 0.676      | 0.374-1.221 | 0.195 |
| β-blocker                          | 0.820      | 0.404-1.668 | 0.585 |
| Heart failure                      | 1.063      | 0.512-2.204 | 0.870 |
| Age                                | 1.001      | 0.981-1.020 | 0.958 |

LVEF indicates left ventricular ejection fraction.

Table III. Multivariate Risk Factors for NSVT

| Variables                          | Odds Ratio | 95% CI    | P-value |
|------------------------------------|------------|-----------|---------|
| ≥ 50% right ventricular pacing     | 4.519      | 2.480-8.237 | < 0.001 |
| Male                               | 3.074      | 1.665-5.674 | < 0.001 |
| Age                                | 1.007      | 0.986-1.028 | 0.521 |

NSVT indicates non-sustained ventricular tachycardia; LVEF, left ventricular ejection fraction; ACE-I, angiotensin-converting enzyme inhibitor; and ARB, angiotensin receptor blocker.

To our knowledge, research focused on the right ventricular pacing percent and occurrence rate of NSVT has not yet been reported. In the present study, ≥ 50% right ventricular pacing was an independent risk factor for NSVT (OR, 4.519; P < 0.001). This cut-off value of 50% was used in prior studies.\textsuperscript{7,10,12-16} The vast majority of patients had right ventricular pacing under 10% (41.5%) or over 90% (45.1%), with the remaining patients spread fairly evenly between 10% and 90%. Therefore, in further analysis using a different pacing percent cut-off value of 40%, 70% or 90%, very similar findings were obtained. Subgroup analysis in the SSS patient group revealed that SSS patients with ≥ 50% right ventricular pacing had a statistically higher rate of NSVT compared with patients with < 50% right ventricular pacing (65.0% versus 15.3%, P < 0.001). This finding could support the idea that ventricular pacing itself was a risk factor for NSVT, independent of the indication for the pacemaker implantation.

Figure 4. Electrogram of electromagnetic noise. Atrial and ventricular electrograms are shown in the upper tracing and atrial and ventricular markers in the lower tracing.
of death.\textsuperscript{19} On the other hand, some studies suggested that NSVT may be a predictor of sudden cardiac death in patients with ischemic heart disease, hypertrophic cardiomyopathy, or dilated cardiomyopathy.\textsuperscript{19-21} However, in the present study, most patients (94.8% in this study population) had \textgreater{} 60% LVEF, and many patients (84.7% in this study population) did not have structural heart disease. Therefore, the reason for these benign outcomes in a pacemaker population was that the majority of patients had normal or near-normal left ventricular function at the time of implantation.

The present study has several limitations. One possible limitation is the retrospective analysis in a single center. Another possible limitation is that a limited number of EGMs can be stored due to the finite storage capability of the pacemaker, although all of the NSVT episodes can be counted. Further study with a larger sample size is needed to confirm the present study results.

Conclusion

Stored EGM analysis is useful to detect NSVT in patients with an implanted pacemaker. A higher percent of right ventricular pacing is an independent risk factor for NSVT in the pacemaker population. However, NSVT was not associated with all-cause mortality because of the preserved left ventricular function.

Disclosure

Conflicts of interest: None.

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