Novel predictor for new-onset atrial high-rate episode in patients with dual-chamber implantable cardiac devices

Ryo Nishinarita[1], Shinichi Niwano[2], Jun Oikawa[1], Daiki Saito[1], Tetsuro Sato[1], Gen Matsuura[1], Yuki Arakawa[1], Shuhei Kobayashi[1], Yuki Shirakawa[1], Ai Horiguchi[1], Hironori Nakamura[1], Naruya Ishizue[1], Jun Kishihara[1], Hidehira Fukaya[1], and Junya Ako[2]

[1]Kitasato University School of Medicine
[2]Kitasato University

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Abstract

Introduction The incidence of new-onset atrial high-rate episode (AHRE) is higher among patients with cardiac implantable electronic devices (CIEDs) than in the general population. We sought to elucidate the clinical factors including P-wave dispersion (PWD) in sinus rhythm associated with AHRE in CIED patients. Methods and results One hundred one patients with newly implanted CIEDs from 2010 to 2014 at our institute were included. PWD was measured at the time of device implantation via a body-surface electrocardiogram. AHRE was defined as any episode of sustained atrial tachyarrhythmia (>170 bpm) recorded in the device's memory. Patients were divided into an AHRE group (n=34) and non-AHRE group (n=67) in accordance with the presence or absence of AHRE within one year of device implantation and compared. The mean age was 75 ± 11 years old. A greater incidence of sick sinus syndrome (p=0.05) and longer PWD (62.6 ± 13.1 vs. 38.2 ± 13.9 ms; p<0.0001) were apparent in the AHRE group. Multivariate analysis revealed that PWD was an independent predicting factor for new-onset AHRE (odds ratio: 1.11; 95% confidence interval: 1.06–1.17; p<0.0001). In the logistic regression analysis, the receiver-operating characteristic curve (area under the curve: 0.90; p<0.001) suggested the best cutoff value for PWD was 48 mm, achieving a sensitivity of 73.8% and specificity of 77.9%. Conclusion PWD is a simple but feasible predictor for new-onset AHRE in patients with cardiac implantable electronic devices.

Original Article

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Ryo Nishinarita, MD, PhD[1,2]; Shinichi Niwano, MD, PhD[2]; Jun Oikawa, MD, PhD[2]; Daiki. Saito, MD[2]; Tetsuro Sato, MD[2]; Gen Matsuura, MD[2]; Yuki Arakawa, MD[2]; Shuhei Kobayashi, MD[2]; Yuki Shirakawa, MD[2]; Ai Horiguchi, MD, PhD[2,3]; Hironori Nakamura, MD, PhD[2,4]; Naruya Ishizue, MD, PhD[2]; Jun Kishihara, MD, PhD[2]; Hidehira Fukaya, MD, PhD[2]; and Junya Ako, MD, PhD[2]

[1]Department of Cardiovascular Medicine, Nerima Hikarigaoka Hospital, Nerima, Japan

[2]Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Japan

[3]Department of Cardiovascular Medicine, Odawara Municipal Hospital, Odawara, Japan

[4]Department of Cardiovascular Medicine, Sagamihara Kyodo Hospital, Sagamihara, Japan

Corresponding author:

Ryo Nishinarita, MD, PhD

Department of Cardiovascular Medicine, Kitasato University School of Medicine

1-15-1 Kitasato, Minami-ku, Sagamihara, 252-0374, Japan

E-mail address: nishinari.0924@gmail.com

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Abstract

Introduction

The incidence of new-onset atrial high-rate episode (AHRE) is higher among patients with cardiac implantable electronic devices (CIEDs) than in the general population. We sought to elucidate the clinical factors including P-wave dispersion (PWD) in sinus rhythm associated with AHRE in CIED patients.

Methods and results

One hundred one patients with newly implanted CIEDs from 2010 to 2014 at our institute were included. PWD was measured at the time of device implantation via a body-surface electrocardiogram. AHRE was defined as any episode of sustained atrial tachyarrhythmia (>170 bpm) recorded in the device's memory. Patients were divided into an AHRE group (n=34) and non-AHRE group (n=67) in accordance with the presence or absence of AHRE within one year of device implantation and compared. The mean age was 75 ± 11 years old. A greater incidence of sick sinus syndrome (p =0.05) and longer PWD (62.6 ± 13.1 vs. 38.2 ± 13.9 ms;p <0.0001) were apparent in the AHRE group. Multivariate analysis revealed that PWD was an independent predicting factor for new-onset AHRE (odds ratio: 1.11; 95% confidence interval: 1.06–1.17;p <0.0001). In the logistic regression analysis, the receiver-operating characteristic curve (area under the curve: 0.90;p <0.001) suggested the best cutoff value for PWD was 48 mm, achieving a sensitivity of 73.8% and specificity of 77.9%.

Conclusion

PWD is a simple but feasible predictor for new-onset AHRE in patients with cardiac implantable electronic devices.

Keywords: atrial fibrillation; atrial high-rate episode; cardiac implantable electronic device; P-wave dispersion

Abbreviations: AF, atrial fibrillation; CIEDs, cardiac implantable electronic devices; SSS, sick sinus syndrome; LAVI, left-atrial volume index; ROC, receiver-operating characteristic; HR, hazard ratio; CI, confidence interval

Short title: Predictor of new-onset atrial high-rate episode

Introduction

Atrial fibrillation (AF), the most frequently encountered clinical cardiac arrhythmia, is associated with increased mortality and morbidity rates, largely due to thromboembolic complications and heart failure. Clinically detecting AF in the early phase is significantly important for avoiding such events but it is not always easy to do so, particularly in cases of asymptomatic AF. Although repeated electrocardiogram (ECG) recording or 24-hour ambulatory ECG monitoring are considered useful in detecting AF in the early phase, their sensitivities as such detection tools are totally limited.[1] Recently, continuous rhythm monitoring with cardiac implantable electronic devices (CIEDs) has been used to diagnose brief episodes of arrhythmia including paroxysmal AF, which are recorded as atrial high-rate episodes (AHREs), particularly in the absence of clinical evidence of AF.[1] By using this approach, new-onset atrial tachyarrhythmia/AF can be diagnosed earlier in patients with CIEDs in comparison with in those without CIEDs.

Previous reports have demonstrated that a prior history of heart failure, the presence of sick sinus syndrome (SSS), and the existence of a large left-atrial volume index (LAVI) were independent predictors for new-onset

AHRE in patients with CIEDs.[2] Furthermore, new-onset AHRE in patients with CIED has been linked to increased risks of stroke, systemic embolism, and worsening heart failure.[3–5] As such, predicting new-onset AHRE following CIED implantation in patients without a history of AF is key to obtaining good patient outcomes.

P-wave dispersion (PWD), a well-known ECG parameter and predictor of AF, is defined as the difference between the maximum and the minimum P-wave durations detected on the body-surface 12-lead ECG.[6,7]Previous studies have suggested that longer PWD may be associated with AF occurrence following cardiac surgery, AF recurrence after conversion, and the appearance of the first AF episode or/and paroxysmal AF.[7–10] Furthermore, it was reported that PWD could be a sensitive and specific ECG marker for the risk of AF occurrence with a cutoff value of 40 ms for the identification of patients with a history of paroxysmal AF.[6] However, the connection between PWD and new-onset AHRE in patients with CIED remains largely unexamined. In the present study, we therefore sought to elucidate clinical factors including PWD that are associated with silent AHRE in CIED patient population.

Methods

Study population

The institutional review boards at the Kitasato University school of medicine approved retrospective review of these data. The study population consisted of 258 consecutive patients newly implanted with CIEDs between January 2010 and December 2014 at our institute. For the study purpose of monitoring for AHREs, patients without atrial leads were excluded. The CIEDs used in this study consisted of permanent DDD pacemakers for SSS or atrioventricular block. Patients with implantable cardioverter-defibrillators and cardiac resynchronization therapy devices were excluded because such patients are believed to be at higher risk for cardiac events. Each device was implanted in accordance with the class I to IIa indications of the current American Heart Association/JCS guidelines.[11,12] Patients with idiopathic cardiomyopathy, end-stage renal disease (with hemodialysis), previously documented AF and/or without 12-lead ECG recordings made just prior to DDD pacemaker implantation were also excluded. The absence of AF history was confirmed by repeated body-surface ECG and/or Holter ECG. Finally, a total of 101 patients were included in the study analysis (Figure 1).

Data collection and AHRE detection

All patients underwent baseline clinical history-taking, 12-lead ECG recording, chest X-ray imaging, transthoracic echocardiography, and blood sampling as basic examinations prior to DDD pacemaker implantation. All of the CIEDs implanted had the capacity to record AHREs; 32 devices were manufactured by St. Jude Medical (Saint Paul, MN, USA), 25 devices were manufactured by Medtronic (Minneapolis, MN, USA), 18 devices were manufactured by Biotronik (Berlin, Germany), 15 devices were manufactured by Ela Medical (Montrouge, France), and 11 devices were manufactured by Boston Scientific (Marlborough, MA, USA). All patients were assessed at six-month intervals after the initial device check performed one week postimplantation. Clinical data including the presence of AHREs during the preceding six-month period were collected at each follow-up visit via device interrogation. An AHRE was defined as any episode of sustained atrial tachyarrhythmia (>5 min and >170 bpm) detected through the atrial lead (Figure 2).[13] The atrial sensing threshold was set at 0.5 mV. To detect the existence of AHRE, a cutoff of five minutes or greater was employed in this study for the exclusion of over-diagnosis of various atrial signals such as far-field oversensing and/or sinus tachycardia.[13] Other atrial noises were excluded by checking the intracardiac ECGs stored in the pacemakers as much as possible.[3] We classified the study population as patients with and without new-onset AHRE during the initial one year after CIED implantation.

Analysis of the P-wave

In all patients, the body-surface 12-lead ECG was recorded at a paper speed of 25 mm/s with a calibration of 1 mV = 10 mm and analyzed thoroughly for the calculation of the maximum P-wave amplitude, minimum P-wave amplitude, maximum P-wave duration, minimum P-wave duration, and PWD. For P-wave analysis,

the most recent ECG recording of sinus rhythm recorded just prior to CIED implantation was used (Figure 2). P-wave duration and PWD were manually measured in all leads with an ECG magnifier being used to mark the P-wave onset and offset, respectively. The P-wave duration was defined as the time measured from the onset to the end of the P-wave deflection. The onset of the P-wave was considered to be the junction between the isoelectric line and the first visible upward or downward slope of the trace, while the return of the trace to its isoelectric line was considered to be the end of the P-wave. When a P-wave exhibited a biphasic form, the latter negative phase was also included in the P-wave duration (Figure 3A). The P-wave amplitude was measured as the height of the peak of positive deflection or the depth of the bottom of negative deflection from the isoelectrical line of the onset point.[14–17] In the case of a biphasic P-wave, the P-wave amplitude was measured as the difference between the positive peak and negative bottom of the recording (Figure 3A). For P-wave analysis, durations and amplitudes of P-waves in leads II and V1 and the maximum P-wave duration in all 12 leads were used as the parameters of interest. Furthermore, PWD was calculated as the difference between the maximum and minimum P-wave durations in milliseconds within the same 12-channel ECG (Figure 3B).[8,18]

Statistical analysis

Data were analyzed using the JMP software (SAS Institute, Cary, NC, USA). Continuous variables were compared using the independent t-test or the Mann–Whitney U test, while categorical data were analyzed using the chi-squared test. A binary logistic regression approach was adopted to evaluate the independent predictive factors and to create an odds risk of the occurrence of AHRE. A receiver-operating characteristic (ROC) curve was used to analyze the diagnostic accuracy, sensibility, specificity, and predictive value of PWD for new-onset AHRE. For all comparisons, p <0.05 was considered to be statistically significant.

Results

Comparison of basic characteristics

Among the 101 patients, 34 exhibited AHREs during the initial one year after CIED implantation and were subsequently allocated to the AHRE group, while the remaining 67 patients were allocated to the non-AHRE group. Table 1 summarizes the basic clinical characteristics of the included patients before CIED implantation. Statistical differences were analyzed between the AHRE and non-AHRE groups. Although the subpopulation of SSS patients was larger in the AHRE group than in the non-AHRE group (p =0.05), the other parameters did not present any statistical differences.

P-wave analysis

Findings of the P-wave analysis are summarized in Table 2. In the univariate analysis, the P-wave durations in leads II and V1, respectively, were longer in the AHRE group than in the non-AHRE group (118 ± 24 vs. 109 ± 22 ms; p =0.04 for lead II and 111 ± 26 vs. 95 ± 20 ms; p =0.005 for lead V1) and the maximum P-wave duration was similarly longer in the AHRE group than in the non-AHRE group (132 ± 22 vs. 117 ± 13; p =0.0009). The PWD was also longer in the AHRE group than in the non-AHRE group (63 ± 13 vs. 38 ± 14; p =0.001) (Table 2).

Association between new-onset AHRE and PWD

Logistic regression analysis revealed the existence of a correlation between PWD and new-onset AHRE with a 11% relative risk increase for each millisecond of PWD [hazard ratio (HR): 1.11; 95% confidence interval (CI): 1.06–1.17; $p < 0.0001$] (Table 3) but not so for SSS (HR: 1.6; 95% CI: 0.44–5.8; p =0.48) nor left atrium diameter (HR: 0.94; 95% CI: 0.84–1.1; p =0.26). The maximum and minimum P-wave durations were not included in this analysis because they were considered to be strong confounding factors of PWD. The cutoff points of PWD for the prediction of new-onset AHRE was determined from the ROC curve of the logistic regression analysis (Figure 4). The most powerful cutoff point was 48 ms, with a sensitivity of 0.738 and specificity of 0.779, for the PWD (area under the curve: 0.90; p <0.0001).

Discussion

In the present study, we demonstrated that the PWD as measured just before CIED implantation was associated with the appearance of new-onset AHRE in the first year after CIED implantation. Specifically, longer PWD was an independent predicting factor for the appearance of new-onset AHRE in the multivariate analysis. The cutoff value of PWD of 48 ms as determined by the ROC curve (area under the curve: 0.90) achieved considerably high sensitivity and specificity values of 73.8% and 77.9%.

In this study, we detected a considerable number of patients with new-onset AHREs in the relatively early phase after CIED implantation. In prior studies, AHRE was defined as an episode lasting at least five to six minutes with an atrial rate of greater than 170 to 190 beats/min,[1,19,20] and we employed a similar definition in this study. By using such criteria, the overdetection of AHREs due to various atrial noise signals could be avoided as much as possible. In this study, AHREs were detected in 34% of patients, which was within the reported range of incidence of such detections over a two-year observation period (i.e., 20%–60%).[21–23]

Some reports exist concerning predictors of AHREs following CIED implantation. Prior heart failure and large LAVI were reported to be major risk factors for the appearance of new-onset AHREs in CIED patients.[2] The ASSERT study and the Canadian Trial of Physiologic Pacing also demonstrated that sinus node dysfunction may be correlated with an increased risk of AHRE.[5,24] The clinical association of these diseases has been recognized for a long time, suggesting that these diseases are associated with atrial structural and electrical remodeling.[25] In this study, although SSS was more prevalent in the AHRE group than in the non-AHRE group, other parameters including prior heart failure and LAVI did not show any statistical differences between the two groups, possibly because we excluded patients with serious structural heart disease, which might cause atrial structural remodeling as the substrate for AHRE. Sinus node dysfunction creates an electrophysiological substrate that facilitates AF initiation and perpetuation.[25]Theoretically, prolonged PWD reflects the inhomogeneous propagation of atrial impulses and/or the prolongation of atrial conduction time, which may participate in the construction of the arrhythmogenic substrate of AF. Atrial conduction disturbances can also be revealed by realizing the conduction delay during sinus rhythm, which can be observed as prolongation of PWD and P-wave duration. Because such prolongation in PWD was observed even just before CIED implantation, it is suspected that atrial electrical remodeling had already progressed in at least some patients before CIED implantation in this study. Probably, such electrical changes might be a precursor for the appearance of new-onset AHRE at least in patients with CIEDs.

In a recent study, a PWD value of 40 ms was considered to be prolonged and was correlated with physiological and/or pathological dysfunction.[26] A PWD of more than 40 ms indicates the presence of heterogeneous electrical activity in different regions of the atrium that might cause atrial tachyarrhythmias. Yoshizawa et al. suggested that new-onset AF could be predicted by a PWD of more than 50 ms with a sensitivity of 69.1% and specificity of 88.2%.[8] Perzanowski et al. contended that a PWD value of 80 ms or longer was an independent predictor for AF recurrence after cardioversion.[10] Similarly, in recurrent transient ischemic attacks, high PWD values were observed, suggesting that a PWD of greater than 40 ms may be linked to an underlying silent paroxysmal AF as the possible cause of ischemic recurrence. Based on these reports, the prediction of new-onset AHRE by a PWD cutoff value of 48 mm in this study should be considered as reasonable.

In a recent review, Pérez-Riera et al. listed some possible scenarios in which the PWD may be prolonged and concluded that PWD is an important and easy-to-measure parameter that indicates a greater tendency of appearance of supraventricular arrhythmias, particularly paroxysmal AF.[26] Notably, our results in the present study match well to one of their stated possible scenarios. Of course, there should be some difference apparent between clinical AF and device-detected AHRE. However, because AHRE has been reported to be associated with increased risks of stroke, systemic embolism, and worsening heart failure, the prediction of new-onset AHRE through PWD evaluation should be useful in managing patients with CIED.[2,5,27]

Limitations

There are several limitations to this study. First, this was a single-center study and the number of analyzed patients was relatively small. Second, atrial undersensing can occur during AHREs, which can lead to either

a failure to detect an AHRE or the truncation of a single AHRE into multiple shorter episodes. Moreover, we could not analyze the duration of AHREs in detail as a device parameter in this study because its extraction from the device record was difficult. Third, there was a slight configuration difference apparent in the AHRE detection because of the different pacemaker manufacturers involved. Fourth, because the measurements of P-waves were based on morphological determinations of P-waves, some errors may have occurred. Finally, because we didn't evaluate the correlation between PWD and the future detection of AF, further prospective studies are necessary that evaluate the relationship between PWD values and clinical AF in patients with AHRE.

Conclusion

PWD was identified as an independent predictor for the appearance of new-onset AHRE in patients with CIEDs.

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No financial support from any specific company was received for this study and there is no conflict of interest to report. No specific unapproved use of any compound or product occurred.

CONFLICT OF INTEREST STATEMENT

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Figure legends

Figure 1. *Study flowchart.*

Among 258 patients with newly implanted CIEDs, 101 patients without a previous diagnosis of AF and with preceding sinus rhythm ECGs were selected. In all patients, the appearance of new-onset AHRE was evaluated in the initial one year after CIED implantation. The 101 patients were then divided into two groups in accordance with the presence or absence of AHREs.

Figure 2. *Definition.*

P-wave analysis including PWD was evaluated just prior to CIED implantation. AHRE was defined as any episodes of sustained atrial tachyarrhythmia of more than 170 bpm and longer than five minutes, with at least one detected episode occurring during the initial one year after CIED implantation.

Figure 3.

Analysis of P-wave.

P-wave duration was measured from the beginning of the P-wave deflection from the isoelectric line to the end of the deflection returning to the isoelectric line in all simultaneous 12 leads of ECG. When a P-wave exhibited a biphasic form, the latter negative phase was also included for the measurement of P-wave duration. The P-wave amplitude was measured as the height of the peak of positive deflection or the depth of the bottom of negative deflection from the isoelectric line of the onset point. In the case of a biphasic P-wave, the P-wave amplitude was measured as the difference between the positive peak and the negative bottom of the recording.

B) *Representative examples of the analysis of PWD.*

PWD was defined as the difference between the maximum and the minimum P-wave durations as detected in the body-surface 12-lead ECG. The maximum and minimum P-wave durations were calculated from the

standard ECG during sinus rhythm. PWD was derived by subtracting the minimum P-wave duration from the maximum duration in any of the 12 ECG leads.

Figure 4. *ROC analysis for determining the cutoff value of PWD.*

The best cutoff value of PWD in CIED patients with AHREs was determined to be 48 ms, achieving a sensitivity of 73.8% and specificity of 77.9% (area under the curve: 0.90; $p < 0.0001$). The arrows indicate the most powerful cutoff points for the appearance of new-onset AHRE.

Tables

Table 1

Comparison of baseline characteristics between patients with and without AHREs

Table 2

Analysis of P-waves between patients with and without AHREs

Table 3

Independent predictors for the appearance of new-onset AHRE following CIED implantation

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