

Paced P-wave duration as a significant predictor for atrial high-rate episodes in patients with cardiac implantable electronic devices

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Abstract

Introduction: Atrial pacing can unmask or aggravate a preexisting interatrial block (IAB). Our study aimed to determine whether atrial pacing is associated with the development of atrial high-rate episodes (AHRE) during follow-up. **Methods and Results:** Patients with dual-chamber cardiac implantable electronic devices (CIED), no previous documented atrial fibrillation, and with a 6-month minimum follow-up were included. In all patients, sinus and paced P-wave duration was measured. AHRE was defined as an episode of atrial rate ≥ 225 bpm with a minimum duration of 5 min, excluding those documented during the first three months after implantation. Two hundred twenty patients were included (75 ± 10 years, 61% male). After a mean follow-up of 59 ± 25 months, 46% of patients presented AHRE. Mean paced P-wave duration was significantly longer than the sinus P-wave duration (154 ± 27 vs 115 ± 18 ms; $p < 0.001$). Sinus and paced P-waves were significantly longer in those who developed AHRE (sinus: 119 ± 20 vs 112 ± 16 ; $p = 0.006$; paced: 161 ± 29 vs 148 ± 23 ; $p < 0.001$). A paced P-wave ≥ 160 ms was the best predictor of AHRE, especially those lasting > 24 h (OR 4.2 (95% CI) [1.6-11.4]; $p = 0.004$). **Conclusion:** Atrial pacing significantly prolongs P-wave duration and is associated with further development of AHRE. A paced P-wave ≥ 160 ms is a strong predictor of AHRE and should be taken into consideration as a new definition of IAB in the presence of atrial pacing.

Paced P-wave duration as a significant predictor for atrial high-rate episodes in patients with cardiac implantable electronic devices

Short Title: Paced-P wave duration and atrial high-rate episodes

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Methods and Results: Patients with dual-chamber cardiac implantable electronic devices (CIED), no previous documented atrial fibrillation, and with a 6-month minimum follow-up were included. In all patients, sinus and paced P-wave duration was measured. AHRE was defined as an episode of atrial rate ≥ 225 bpm with a minimum duration of 5 min, excluding those documented during the first three months after implantation. Two hundred twenty patients were included (75 $\pm$ 10 years, 61% male). After a mean follow-up of 59 $\pm$ 25 months, 46% of patients presented AHRE. Mean paced P-wave duration was significantly longer than the sinus P-wave duration (154 $\pm$ 27 vs 115 $\pm$ 18 ms; $p < 0.001$). Sinus and paced P-waves were significantly longer in those who developed AHRE (sinus: 119 $\pm$ 20 vs 112 $\pm$ 16; $p = 0.006$; paced: 161 $\pm$ 29 vs 148 $\pm$ 23; $p < 0.001$). A paced P-wave ≥ 160 ms was the best predictor of AHRE, especially those lasting >24 h (OR 4.2 (95% CI) [1.6-11.4]; $p = 0.004$).

Conclusion: Atrial pacing significantly prolongs P-wave duration and is associated with further development of AHRE. A paced P-wave ≥ 160 ms is a strong predictor of AHRE and should be taken into consideration as a new definition of IAB in the presence of atrial pacing.

KEYWORDS

Interatrial block; cardiac implantable electronic devices, P-wave duration; atrial high-rate episodes

INTRODUCTION

Interatrial blocks (IAB) were initially described as partial, when the P-wave duration was ≥ 120 ms and advanced when the P-wave duration was ≥ 120 ms and presented a biphasic morphology in the inferior leads

(II, III, aVF) ¹. These general concepts were then summarized in a consensus document ², and several studies have since demonstrated the relation between IAB and new or recurrent episodes of atrial fibrillation (AF)^{3, 4}, stroke recurrence ⁵, and progression from persistent to permanent AF ⁶.

IAB is also a relatively frequent common finding in patients referred for cardiac implantable electronic device (CIED) implantation, especially those with sick sinus syndrome, perhaps reflecting the existence of extensive atrial cardiomyopathy ⁷. Some authors have demonstrated the relationship between a pre-existing IAB and the development of new atrial high-rate episodes (AHRE) during routine CIED interrogations ⁸⁻¹⁰. On the other hand, atrial stimulation may also aggravate or even unmask an IAB, especially in patients with preexisting atrial cardiomyopathy, further evidencing the conduction delay within the atria and hence the duration of the P-wave ^{11, 12}. This is particularly frequent when the atrial lead is positioned in the right atrial appendage (considered the “preferred placement location”). In such cases, the traditional definition of IAB may not apply, because the duration of the paced P-wave may be unusually long and with different morphology patterns. Our study aimed to evaluate whether both sinus and paced P-wave duration before and after implantation of a CIED could predict future development of AHRE and to define the best paced P-wave duration cut-off to predict new AHRE episodes.

METHODS

Patients in sinus rhythm with no previous paroxysmal or persistent AF and with dual-chamber pacemakers (PMs), implantable cardioverter-defibrillators (ICDs), and devices for cardiac resynchronization therapy (CRT) capable of atrial activity monitoring were included in the study. Standard rate-adaptive chamber devices were used (Abbott, St Paul, MN, USA; Medtronic, Inc., Minneapolis, MN, USA). All atrial leads were bipolar and actively placed in the high right atrium (right atrial appendage), and ventricular leads were bipolar and passively placed at the right ventricular apex. By unit protocols, we set out to avoid right ventricular pacing in all dual-chamber PMs by prolonging the AV interval and/or using other dedicated algorithms when deemed necessary. ICDs were set to backup pacing mode (VDI 40 bpm) maintaining atrial sensing. Cardiac resynchronization therapy was programmed with an adequate AV interval to achieve [?]95% of biventricular pacing. Patients with sinus node dysfunction and clinical symptoms due to bradycardia were programmed in AAI/DDDR mode with a minimum frequency of 60 bpm, also using available algorithms to prevent ventricular pacing.

The following clinical and demographic data were obtained for each patient: sex, age, indication for CIED implantation, presence of cardiovascular risk factors (diabetes mellitus [DM], hypertension, and smoking), CHA₂DS₂-VASc score, presence of chronic obstructive pulmonary disease (COPD), and drugs used. A baseline echocardiographic study, including left ventricular ejection fraction (LVEF), was performed in all patients. Left atrium (LA) size (mm) measurements were obtained in four-chamber view.

All devices were first interrogated 3 months after CIED implantation and every 6 months thereafter. All scheduled PM check-ups were reviewed. Pacemaker atrial stimulation/sense parameters, atrial lead impedance, percentages of atrial and ventricular pacing, AHRE, automatic mode switch episodes, and noise episodes were recorded. AHRE was defined as an episode of atrial rate [?]225 bpm with a minimum duration of 5 min, and the duration of the episodes was divided into four groups (5 min-1 h; 1-12 h; 12-24 h; >24 h).

2.1 P-wave measurements

The surface 12-lead ECG (TraceMasterVue(r), Philips) obtained just before and immediately after implantation (filtered at 0.05-150 Hz, 10 mm/mV, 25 mm/s) were analyzed, and the sinus and paced P-waves at 60 bpm were measured with digital calipers with quadruple magnification (Figure 1). Sinus P-wave onset was defined as the point of initial upward or downward deflection from the baseline and the offset as the return of the waveform to the initial baseline. Paced P-wave onset was defined as the point of the stimulus artifact visualization. Some examples are represented in Figure 2. IAB in the sinus P-wave was defined as partial when the P-wave duration was [?]120 ms, and advanced when the duration was [?]120 ms and presented a biphasic pattern in the inferior leads. All measurements were performed by two expert cardiologists blinded to baseline patient characteristics. The study protocol was approved by the ethics committee of our

institution and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2 Statistical analysis

Normality distribution of quantitative variables was confirmed with the Kolmogorov-Smirnov test. Quantitative variables following a normal distribution are expressed as mean values $\pm$ standard deviation. Qualitative variables are expressed using frequencies and percentages. For independent variables that followed a normal distribution, we used the Student *t-test*. Qualitative variables were compared using the chi-square and McNemar tests. Only *p* values < 0.05 were considered statistically significant. Multivariate analysis with logistic regression (backward stepwise) was used to determine whether the association between sinus and paced P-wave duration and AHRE was influenced by the baseline group characteristics (confounding factors). The covariates included were left atrial diameter (SI) and CHA₂DS₂-VASc score. The magnitude of the effects was expressed in odds ratio (OR) and 95% confidence interval (95% CI). Data were collected in Excel and imported into IBM SPSS (Armonk, New York) (version 25.0 for Windows) for statistical analysis.

RESULTS

Between July 2014 and December 2017, we included 220 patients (61% male, age 75 $\pm$ 10 years) with a CIED implanted in our center (Fundacion Jimenez Diaz, Madrid, Spain; dual-chamber PM 96%, ICD 2%, and CRT 4%). The reasons for implantation were sinus node disease (30%), advanced AV block (52%), and different types of conduction disorders symptomatic with syncope (18%). Patients were divided into two groups depending on the presence of AHRE during device interrogation. Clinical characteristics of the patients included in both groups can be seen in Table 1.

After a mean follow-up of 59 $\pm$ 25 months, 46% of the patients presented AHRE on device interrogation. Half of the episodes had a duration of between 1 h and 12 h (50%) and 21% of them were > 24 h. The age of the patients with AHRE was significantly higher (77 $\pm$ 8 vs 74 $\pm$ 10 years; *p* = 0.028). There were also significant differences in the CHA₂DS₂-VASc scale (3.7 $\pm$ 1.5 vs 3.3 $\pm$ 1.5; *p* = 0.02) and the SI diameter of the LA (53 $\pm$ 7 vs. 49 $\pm$ 6 mm; *p* = 0.017).

3.1 Sinus and paced P-wave duration analysis

The distribution of sinus P-wave duration was as follows: < 120 ms (64%), 120-139 ms (26%), and ≥ 140 ms (10%); and for paced P-wave, < 120 ms (11%), 120-159 ms (49%), and ≥ 160 ms (40%). Table 1 reflects sinus and paced P-wave duration (ms) according to the presence of AHRE. Mean paced P-wave was significantly longer than sinus P-wave (154 $\pm$ 27 vs 115 $\pm$ 18 ms; *p* < 0.001), both in patients with AHRE (161 $\pm$ 29 ms vs 119 $\pm$ 20 ms; *p* < 0.001) and without AHRE (148 $\pm$ 23 ms vs 112 $\pm$ 16 ms; *p* < 0.001). IAB was present in 36% of the patients in sinus rhythm (31% partial, 5% advanced) and 89% during atrial stimulation (*p* = 0.011). IAB in sinus rhythm was present in 43% of the patients with AHRE and 30% of the patients without AHRE (*p* = 0.039) and 14% and 86%, respectively, during atrial stimulation (*p* = 0.034).

ROC curves showed the following values for area under the curve (AUC): sinus P-wave: 0.594 $\pm$ 0.038 (*p* = 0.016) and paced P-wave: 0.635 $\pm$ 0.038 (*p* < 0.001) (Figure 2). No significant difference between sinus and paced P-wave duration for AHRE development was found, although paced P-wave showed a better performance.

In a subgroup analysis dividing the population according to paced P-wave duration (Table 3), a paced P-wave ≥ 160 ms showed the strongest association with AHRE development, especially for those lasting > 24 h (OR 4.2; 95% CI [1.6-11.4] *p* < 0.004)

Table 4 shows the results of a univariate analysis in which several cut-off points in sinus/paced P-waves and clinical factors were included. Among the statistically significant predictors for AHRE, a paced P-wave ≥ 160 ms, a CHA₂DS₂-VASc score ≥ 4 , and a LA SI dimension ≥ 55 mm were included in a multivariable model which yielded the following 3 independent predictors augmenting AHRE: paced P-wave ≥ 160 ms (OR: 1.84; 95% CI [1.03-3.28]; *p* = 0.038), CHA₂DS₂-VASc score ≥ 4 (OR: 2.01; 95% CI [1.13-3.55]; *p* = 0.016), LA dimension ≥ 55 (OR 2.69; 95% CI [1.48-4.90]; *p* = 0.001).

DISCUSSION

We have found that patients with CIED using right atrial stimulation in conventional atrium lead location presented significant prolongation of the P-wave duration and a higher prevalence of IAB. Furthermore, our results show that a longer P-wave duration and a higher presence of IAB are significantly related to the development of AHRE during long-term follow-up. A paced P-wave duration ≥ 160 ms had the highest predictive value for AHRE of any duration, especially for those lasting >24 h. Only patients without prior known AF were included, since a history of this entity is considered an independent risk factor for the development of AHRE.

The development of AHRE is relatively common among patients with CIED^{13, 14}. In the recently published IMPACT study, AHRE episodes of >6 min to <6 h were the most prevalent among all duration categories, and age, history of AF, and hypertension were the most important risk factors¹⁴. Although they have been related to the development of clinical AF, their clinical implications are not yet sufficiently clarified¹⁵. Even so, finding prognostic markers for the development of AHRE and therefore of possible clinical AF is currently an important goal due to the possible therapeutic implications, especially as concerns anticoagulation¹⁶.

Our group previously analyzed 380 patients who had undergone CIED implantation, showing that IAB is a significant predictor of AHRE, both in subjects with and without a previous history of AF⁸. Tekkesin et al included 367 patients with CIED with no previous history of AF, and 32% of them had IAB (29% partial and 3% complete)¹⁰. This proportion was also higher in patients who developed AHRE during follow-up (12). In the present study, this proportion was similar: 36% of the patients had IAB, and its presence was significantly higher in patients with AHRE than without it (43% vs 30%; $p = 0.039$). Ariyaratnam et al found a higher IAB prevalence in patients with previous embolic stroke than in patients with a non-embolic stroke (61% vs. 41%; $p < 0.05$)⁵. Some other studies also support the same relation between the presence of advanced IAB and the development of AF and ischemic stroke¹⁷. Tse et al. carried out a meta-analysis of 16 studies with 18204 patients in which they found that IAB, especially advanced IAB, was a significant predictor of de novo and recurrent AF¹⁸. In the study by Lehtonen et al with 5667 patients, AF, male sex, hypertension, age, and obesity were identified as clinically significant factors that prolonged the duration of the P-wave¹⁹. The REGICOR registry showed a higher IAB prevalence in patients with AF vs. without AF (63% partial and 11% advanced vs 46% partial and 9% advanced; $p = 0.0006$)³.

However, there are almost no studies analyzing the paced P-wave, the incidence of IAB, and the development of AHRE. Only Kristensen et al.²⁰ conducted a study with 109 patients who had undergone CIED implantation due to sinus node disease or brady-tachy syndrome, in which the duration and dispersion of the sinus and paced P-waves were measured, analyzing their relationship with AHRE and AF during follow-up. Although the paced P-wave was wider than the sinus P-wave during high atrial pacing (155 $\pm$ 27 ms vs 117 $\pm$ 26 ms), there was no significant difference in the paced P-wave duration between patients with and without AHRE, and it was not a significant predictor of AHRE/AF. Only a previous diagnosis of brady-tachy syndrome was a significant predictor. These findings differ from ours since we demonstrated that the paced P-wave duration or the presence of IAB during atrial pacing are significant predictors of AHRE during follow-up. In addition, as in the study by Kristensen et al, we found that with atrial stimulation the duration of the P-wave increases by 39 $\pm$ 29 ms on average and, consequently, the proportion of patients with IAB (89% with stimulation vs. 36% without stimulation).

All traditional works define the presence of IAB by taking a P-wave duration ≥ 120 ms, though this value may not be appropriate if atrial stimulation alone increases the duration of the P-wave and generates a greater degree of IAB or develops a previously nonexistent IAB. Perhaps values greater than 120 ms should be considered to define IAB in the presence of atrial stimulation, making them better predictors of AHRE. That is why we have carried out a predictive analysis of AHRE as a function of the width of the paced P-wave, finding that a greater width increases the risk of presenting AHRE of longer duration. A paced P-wave ≥ 160 ms has the best prognostic value for any duration of AHRE episodes, but especially for those lasting >24 h, which are perhaps those with the most important clinical implications.

We found that in addition to paced P-wave duration, the presence of left atrial enlargement and a CHA₂DS₂-VASc scale [?]4 are significant independent predictors of AHRE development in the general population with CIED. Atrial enlargement by itself is associated with IAB ^{2, 21, 22}. All these findings may have an important clinical impact since some studies have shown that a higher percentage of atrial pacing is associated with an increased risk of AHRE ²³. This could also explain why the vast majority of studies on the prevention of AHRE/AF with different lead atrial placements have failed ²⁴. Whether atrial stimulation itself could be also pro-arrhythmic, especially in patients with previous IAB, is subject to debate, and better control of the paced P-wave duration during implantation and follow-up of patients with CIED would be necessary to avoid future episodes of AHRE.

Limitations

Our study was an observational single-center study and this did not include a large number of patients. We have not included patients with previous known AF. We defined AHRE as atrial rates faster than 225 bpm and longer than 5 minutes. Other definitions of AHRE, in terms of atrial rate and duration, are available in the literature, and results may vary depending on the definition used.

CONCLUSION

Left atrial enlargement and a sinus P-wave duration [?] 140 ms are strong AHRE predictors. Atrial pacing significantly prolongs P-wave duration and is associated with further development of AHRE. A paced P-wave [?]160 ms is also a predictor of AHRE and should be considered as a new definition of IAB in the presence of atrial pacing.

Conflict of interest: None

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TABLES

Table 1. Demographic and clinical characteristics of patients with and without AHRE during follow-up of the overall population. P-wave duration analysis in sinus rhythm and during atrial pacing (ms)

N
Age
Gender (male)
Hypertension
Diabetes mellitus
Smoker (former/present)
CHA ₂ DS ₂ -VASc
Previous cardiomyopathy
LVEF (%)
LA (mm)
ACEi/ARB
BB
Aspirin
Sinus P-wave (ms)
Paced P-wave (ms)
IAB (sinus)
IAB (paced)
Note: Values are mean ± SD or n (%) Abbreviations: AHRE: atrial high-rate episodes; LVEF: left ventricular ejection fraction

Table 2: Subgroup analysis according to AHRE development, AHRE duration, and paced P-wave duration groups.

	AHRE (duration)	AHRE (duration)	AHRE (duration)	AHRE (duration)
Paced P-wave	5min-1h 16 (16)	1h-12h 51 (50)	12h-24h 13 (13)	>24h 21 (21)
<120 ms 23 (11)	0.4 [0.1-1] p = 0.049	0.3 [0.1-0.9] p = 0.04	-	-
120-159 ms 108 (49)	0.7 [0.4-1.1] p = 0.139	0.6 [0.3-1.0] p = 0.072	0.6 [0.3-1.3] p = 0.194	0.4 [0.1-1] p = 0.065
[?]160 ms 89 (40)	2.1 [1.3-3.8] p = 0.006	2.5 [1.4-4.4] p < 0.001	2.8 [1.3-5.9] p = 0.008	4.2 [1.6-11.4] p = 0.004
Note: Values are n (%)	Note: Values are n (%)	Note: Values are n (%)	Note: Values are n (%)	Note: Values are n (%)
Abbreviations:	Abbreviations:	Abbreviations:	Abbreviations:	Abbreviations:
AHRE: atrial high-rate episodes	AHRE: atrial high-rate episodes	AHRE: atrial high-rate episodes	AHRE: atrial high-rate episodes	AHRE: atrial high-rate episodes

Table 3: Univariate analysis. Sinus and paced P-wave duration; AHRE development

	OR
Sinus P-wave [?] 120 ms	1.70
Sinus P-wave [?] 140 ms	3.8
Paced P-wave [?] 120 ms	2.6
Paced P-wave [?] 160 ms	2.17
CHA ₂ DS ₂ -VASc [?] 4	2.3
LA (SI) [?] 55 mm	2.8
Age [?] 80 years	1.9
Abbreviations: AHRE: atrial high-rate episodes; LA: left atrium (superior-inferior) Abbreviations: AHRE: atrial high-rate	

FIGURE TITLES AND LEGENDS

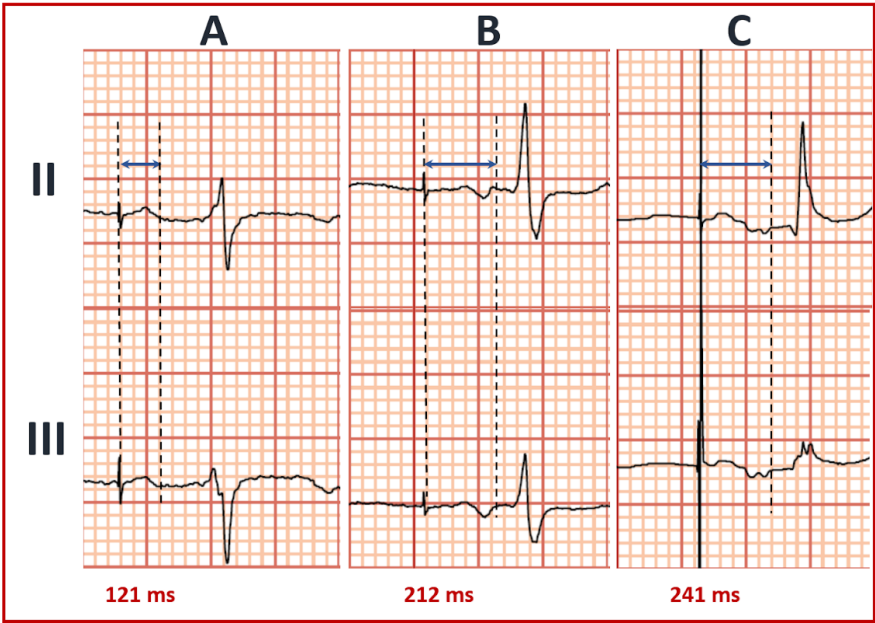


Figure 1. (A, B, C) ECG examples of paced P-wave analysis. From top to bottom, ECG leads II and III. Dotted lines (black) and arrows (red) indicates onset and offset of paced P-wave. (see text for explanation)

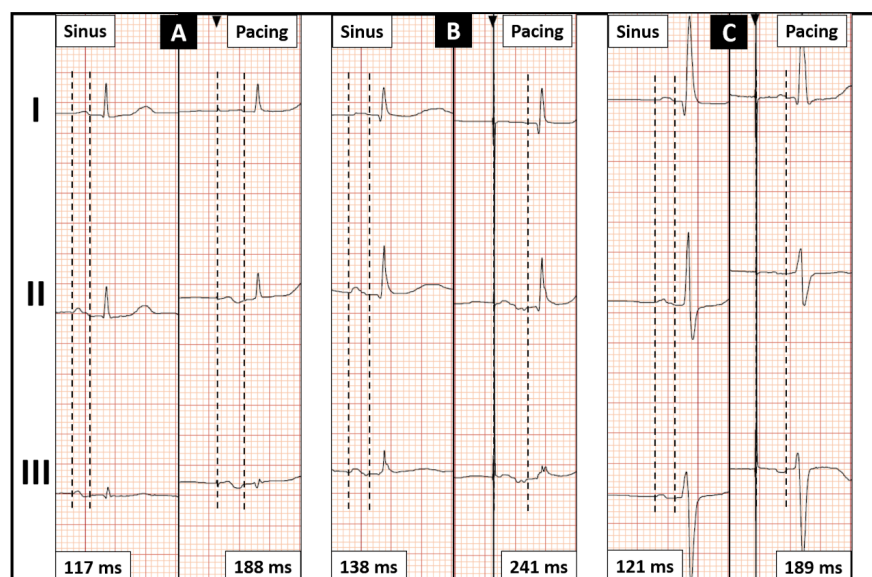


Figure 2. (A, B, C) ECG examples of sinus and paced P-wave duration. From top to bottom, ECG leads I, II, and III. In each example, sinus P-wave (left) duration (ms) and paced P-wave (right) duration (ms). Example A: Bipolar atrial pacing. Examples B and C: unipolar atrial pacing (note stimulus artifact; black arrow).

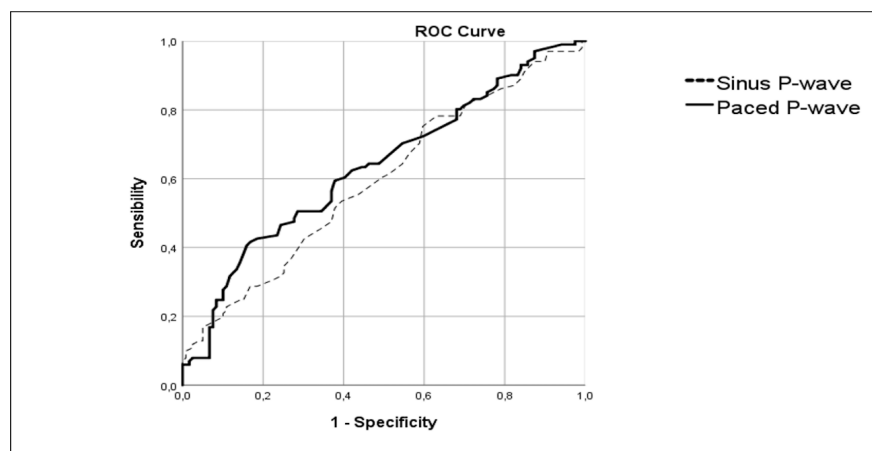


Figure 3. Receiver operating curve analysis for sinus/paced P-wave duration and AHRE episodes.

