

Tachycardia-Induced J-Wave Changes in Patients With and Without Idiopathic Ventricular Fibrillation

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Background—To know the underlying mechanisms of J waves, the response to atrial pacing was studied in patients with idiopathic ventricular fibrillation (IVF) and patients with non-IVF.

Methods and Results—In 8 patients with IVF, the J-wave amplitude was measured before, during, and after atrial pacing. All patients had episodes of ventricular fibrillation without structural heart disease. The responses of J waves were compared with those of the 17 non-IVF control subjects who revealed J waves but no history of cardiac arrest and underwent electrophysiological study. The IVF patients were younger than the non-IVF patients (28 ± 10 versus 52 ± 14 years, respectively; $P=0.002$) and had larger J waves with more extensive distribution. J waves decreased from 0.35 ± 0.26 to 0.22 ± 0.23 mV ($P=0.025$) when the RR intervals were shortened from 782 ± 88 to 573 ± 162 ms ($P=0.001$). A decrease (≥ 0.05 mV) in the J-wave amplitude was observed in 6 of the 8 patients. In addition, 1 patient showed a distinct reduction of J waves in the unipolar epicardial leads. In contrast, J waves were augmented in the 17 non-IVF subjects from 0.27 ± 0.09 to 0.38 ± 0.10 mV ($P<0.001$): augmented in 9 and unchanged in the 8 subjects. The different response patterns of J waves to rapid pacing suggest different mechanisms: early repolarization in IVF patients and conduction delay in non-IVF patients.

Conclusions—The response to atrial pacing was different between the IVF and non-IVF patients, which suggests the presence of different mechanisms for the genesis of J waves. (*Circ Arrhythm Electrophysiol.* 2017;10:e005214. DOI: 10.1161/CIRCEP.117.005214.)

Key Words: electrocardiogram ■ ion channels ■ sudden death ■ ventricular fibrillation

The early repolarization pattern (ERP) is defined as notches or slurs in the terminal portion of the QRS complex with an associated elevation of the ST segment^{1,2} and has been considered to be a benign electrocardiographic finding.^{3,4} Meanwhile, notching or slurring of the terminal portion of the QRS complex has been shown to be a clue for sudden cardiac death from ventricular fibrillation (VF) from idiopathic causes (also known as idiopathic VF [IVF]).⁵⁻⁷ Notching and slurring are now referred to as J waves, which are categorized as either J-wave syndrome or early repolarization syndrome.⁸⁻¹⁰

J waves have been reproduced in animal experiments, and their dynamicity has been studied both experimentally¹¹⁻¹³ and clinically.¹¹⁻¹³ A pause-dependent augmentation of the J-wave amplitude is one of the striking features of J waves in IVF

patients.^{5,11-14} and mechanistically, J waves are related to transient outward currents (*I_{to}*), which are augmented at slower rates.¹¹⁻¹³ Because J waves are augmented at a slower rate, it is natural to expect that J waves are attenuated at higher rates, although this has rarely been confirmed in the literature.¹¹⁻¹³

On the basis of the gap in earlier reports,^{11,15} we hereby present the results of atrial pacing in IVF patients to show the tachycardia-dependent attenuation of J waves. The results from IVF patients were compared with those from non-IVF subjects.

Methods

IVF Patients

Among 48 patients diagnosed with J-wave-associated IVF, J waves were studied in 8 patients during atrial pacing. In 1 patient,

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WHAT IS KNOWN

- The notches or slurs in the terminal portion of the QRS complex, now referred to as J waves, have been shown to be associated with sudden cardiac death from VF.
- A pause-dependent augmentation of the J-wave amplitude is one of the striking features of patients with J-wave syndrome.

WHAT THE STUDY ADDS

- In patients with IVF, J waves decreased when the RR intervals were shortened by atrial pacing.
- In contrast, J waves were augmented during atrial pacing in the control subjects, which suggests the presence of different mechanisms for the genesis of J waves.

a pause-dependent augmentation was analyzed in earlier study.¹² As the entry criteria, all patients were admitted after experiencing cardiac arrest because of out-of-hospital VF and being resuscitated by emergency medical personnel. All of them showed normal findings in complete blood counts, blood chemistry panels, and serological tests after admission and echocardiography, and cardiac catheterization excluded structural heart diseases. A provocation test using acetylcholine or ergonovine maleate was negative for coronary spasms. Coexistence of Brugada syndrome was studied by Pilsicainide, a class Ic antiarrhythmic drug. All patients underwent atrial pacing during electrophysiological study (EPS) or at bedside to control VF. The atrial pacing was performed at steady rate at ≥ 1 paced cycle lengths. None was on any medication.

Non-IVF Patients

As a control group, the response of J waves to atrial pacing was also studied in 17 consecutive male subjects who presented with J waves among 220 patients who had undergone EPS in the preceding 2 years: 8 patients were common to the previous study, and 9 patients were new.¹⁶

The entry criteria were identical to those for the IVF patients, and none of the patients in the control group had a past history and a family history of sudden cardiac death or cardiac arrest. All patients denied having a history of structural heart disease, and they lacked the signs and symptoms of these disorders on physical examination, ECG and echocardiography. Neither a coronary angiography nor a provocation test was attempted to exclude coronary spasm, and none of the control group patients had a clinical history or ECG that was suggestive of the presence of ischemic heart disease. None was on any medication at the time of EPS.

Data Analysis

All patients received transvenous pacing at the right atrium during EPS or at bedside to control episodes of VF. In 2 IVF patients, epicardial electrograms were recorded from the surface of the left ventricle during EPS. The right femoral vein was cannulated with a multipolar catheter (8 pole electrode catheter; Inter Nova Co, Osaka, Japan) that was introduced into the left lateral (marginal) coronary vein, the anterior interventricular vein via coronary sinus ostium.

The baseline clinical features, including RR intervals, PR intervals, QT intervals, and QT corrected using Bazett formula (QTc), were measured on the ECG that was recorded at the time of admission. The J waves were analyzed at baseline and again during atrial pacing at the shortest paced cycles attempted in the leads that would reveal the maximum amplitude after $\times 5$ -fold so that the changes in the J-wave amplitude could be determined. The J waves were also read in the first nonpaced beat after cessation of pacing. Two cardiologists

read the ECGs, and the cardiologists mutually discussed the results to reach a consensus when there was disagreement.

The J-wave dynamicity, clinical features, and ECG parameters of the IVF patients were compared with the non-IVF control group.

Definitions

The term J wave is used here interchangeably with ERP. J waves were diagnosed as (1) a notching or slurring of the terminal portion of the QRS complex; (2) an amplitude >0.1 mV above the isoelectric line; and (3) a presence in at least 2 contiguous leads. J waves were considered to be augmented if there was an increase in amplitude of ≥ 0.05 mV, unchanged for either an increase or a decrease of <0.05 mV, and attenuated if there was a decrease of ≥ 0.05 mV. The localization of J waves was classified according to the leads showing J waves: inferior (II, III, and aVF), high lateral (I or aVL), or left precordial (in V_4 through V_6). The morphology of the ST segment after the J waves was classified as previously described,^{16,17} and the T-wave amplitude in leads II and V_5 (ie, the T/R ratio) was defined as previously reported.¹⁸

Statistical Analysis

Continuous data are presented as the means \pm SD, and categorical variables are expressed as absolute numbers or percentages. Statistical comparisons were made using Wilcoxon tests (rank-sum test or signed rank test) for continuous variables, and Fisher exact tests for categorical variables. For the comparisons of RR interval and J-wave amplitude within IVF or non-IVF patients, we fit a model using a generalized estimating equation. The model was built using all 3 time points (baseline, during pacing, and post-pacing) for each patient. Initial testing was performed for comparing the 3 time points simultaneously. If the test was significant, then pairwise comparisons was conducted using Dunnett pairwise multiple comparison *t* test. JMP software (Statistical Discovery Software, version 5.0.1J; SAS Institute, Cary, NC) or SPSS Statistics (Version 24; IBM) was used to perform the statistical analysis. A *P* value <0.05 was considered to be statistically significant. The study was performed after obtaining written informed consent from all participants. The study was approved by Institutional Review Board of Tachikawa Medical Center.

Results

Clinical Features

Of the 8 patients who had prehospital episodes of VF, 7 experienced the episode at night (0:00–6:00) and 1 in the early morning (approximately at 8:00; Table 1). VF occurred as an electrical storm (≥ 3 separate episodes of VF within 24 hours) in 7 patients. One patient showed spontaneously occurring coved ST elevation during hospitalization and was diagnosed as J-wave-associated IVF combined with Brugada syndrome. The main clinical features of IVF patients are shown in Tables 1 and 2. The mean age was 28 ± 10 years, and all the patients were male.

The 17 non-IVF patients underwent atrial pacing, and their mean age was 52 ± 14 years (Table 2). EPS was performed for benign cardiac arrhythmias: paroxysmal atrial fibrillation, atrial flutter, supraventricular tachycardia, or sinoatrial or atrioventricular block. Neither ventricular tachycardia nor VF was inducible during the study.

J Waves

In the 8 patients with IVF, the mean J-wave amplitude was 0.35 ± 0.26 mV, and they were localized to either the inferior and left precordial ($n=5$) or in the inferior and left precordial and high lateral leads ($n=3$; Table 2). Horizontal/downward ST-segment

Table 1. Clinical Features of the IVF Patients Who Underwent Rapid Atrial Pacing

Case	Age/ Sex	Diagnosis	Time of VF Onset	ES	Location of J Waves	J-Wave Aug.
1	13/M	IVF	0:00–6:00	+	I, aVL, II, III, aVF, V ₃ through V ₆	+
2	28/M	IVF	0:00–6:00	+	II, III, aVF, V ₃ through V ₆	+
3	18/M	IVF	0:00–8:00	+	II, III, aVF, V ₄ through V ₆	+
4	38/M	IVF	0:00–6:00	+	II, III, aVF, V ₄ through V ₆	–
5	29/M	IVF	5:00–8:00	+	I, aVL, II, III, aVF, V ₃ through V ₆	+
6	21/M	IVF	0:00–6:00	+	II, III, aVF, V ₄ through V ₆	+
7	42/M	IVF+BS	0:00–6:00	+	II, III, aVF, V ₄ through V ₆	+
8	37/M	IVF	0:00–6:00	–	I, aVL, II, III, aVF, V ₅ through V ₆	–

Aug. indicates augmentation during bradycardia; BS, Brugada syndrome; ES, electric storms; IVF, idiopathic ventricular fibrillation; and VF, ventricular fibrillation.

morphology was observed in 4 patients, and the amplitude of the T wave or T/R ratio was not depressed in all except 1 patient who showed inverted T waves in leads II and V₅ (case 1 in Table 1). One IVF patient showed distinct notching in the epicardial unipolar leads, which was considered to represent J waves.

In the 17 non-IVF patients (Table 2), the mean J-wave amplitude was 0.27±0.09 mV, which was consistent with that of the IVF patients ($P=0.748$). J waves were confined to the inferior leads in 15 patients and the inferior and left precordial leads in 2 patients. Horizontal/downward ST-segment morphology was found in 8 patients, and none of the patients satisfied the criteria for abnormal T waves or T/R ratios.

J-Wave Dynamicity

In the IVF patients, the mean RR interval was 782±88 ms at baseline and decreased to 573±162 ms by pacing the right atrium ($P=0.001$). During pacing, all patients had 1:1 atrio-ventricular conduction with normal QRS complexes. The J-wave amplitude diminished from 0.35±0.26 mV at baseline to 0.22±0.23 mV during pacing ($P=0.025$). A reduction in J-wave amplitude (≥ 0.05 mV) was evident on standard 12-lead ECGs of 6 patients (Figures 1A and 2).

Two of 8 patients showed no changes in the J-wave amplitude on a standard 12-lead ECG. They had J waves that were smaller in amplitude but were nonsignificant compared with the other 6 patients: 0.13 versus 0.43±0.26 mV, respectively ($P=0.064$). One of the patients underwent EPS, which allows electrograms to be obtained from the epicardial surface. This patient showed a distinct attenuation in the notching of the unipolar epicardial electrograms during atrial pacing (Figure 3). EPS was not performed in the other patient. The first beat occurred with prolonged RR intervals in 5 patients with larger but not significant J waves of 0.41±0.17 mV ($P=0.379$ versus baseline).

Table 2. Comparisons of the Characteristics Between the 2 Patient Groups With Different J-Wave Dynamicity

	IVF Patients (n=8)	Non-IVF (n=17)	P Value
Age, y	28±10	52±14	0.002
RR interval, ms	782±88	861±162	0.726
PR interval, ms	188±30	172±15	0.169
QRS width, ms	97±15	96±7	0.618
QT interval, ms	365±22	373±25	0.444
QTc interval, ms ^{1/2}	391±11	404±93	0.382
Basal J waves, mV	0.35±0.26	0.27±0.09	0.748
Location, n			
Inf.	0	15	<0.001
Inf.+LP	5	2	
Inf.+LP+HL	3	0	
H/D ST segment, n (%)	4	8	
Abn. T wave/T/R ratio, n (%)	1	0	

Abn. indicates abnormal; D, descending; H, horizontal; HL, high lateral leads; Inf., inferior leads; IVF, idiopathic ventricular fibrillation; and LP, left lateral precordial leads.

The other 17 non-IVF patients underwent atrial pacing during EPS (Figures 1B and 2). The J-wave amplitude increased from 0.27±0.09 mV at baseline to 0.38±0.10 mV during atrial pacing in all ($P<0.001$); augmented in 9 and unchanged in 8 patients. The RR interval shortened from 861±162 to 445±29 ms during pacing ($P<0.001$). The J-wave amplitude was 0.27±0.09 mV in the first beat after pacing occurred at 1009±193 ms ($P=0.786$ versus baseline), but no bradycardia-dependent augmentation was observed.

Comparisons Between IVF and Non-IVF Groups

The mean age was higher in the IVF patients who showed attenuation of the J waves during pacing compared with the non-IVF subjects: 28±10 versus 52±14 years ($P=0.002$). ECG parameters were not different between the 2 groups (Table 2). Although the amplitude and morphology of the basal J waves was similar, the distribution was more extensive in the IVF patients ($P<0.001$).

Discussion

Atrial pacing induced an attenuation of J waves on standard 12-lead ECGs of 6 of 8 IVF patients. Another patient showed an attenuation of J waves in the epicardial electrograms obtained during EPS. The remaining patient did not have an attenuation of the J waves on a standard 12-lead ECG, and this patient's epicardial electrograms were not studied. In total, J waves were found to be attenuated in 7 of 8 IVF patients. Alternately, atrial pacing induced augmentation in 9 of 17 non-IVF patients with baseline J waves. Our findings suggest that the different rate dependence of J-wave amplitude may be because of different mechanisms underlying the genesis of the J waves: *Ito*-mediated differences in transmural

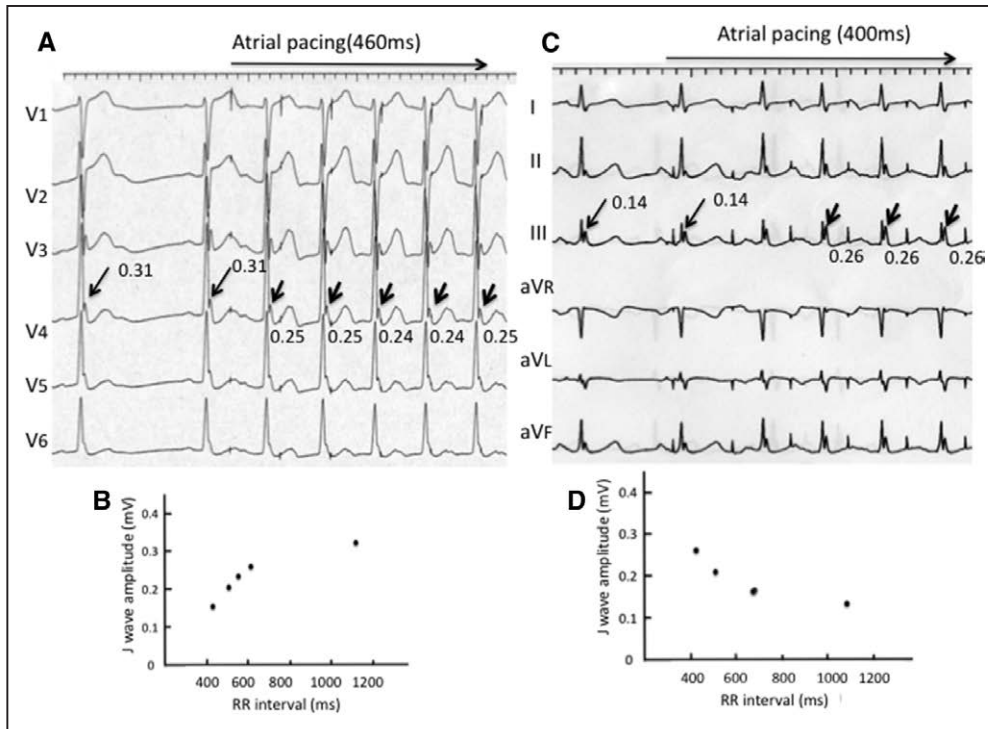


Figure 1. J-wave changes during atrial pacing. **A**, A 28-year-old male with idiopathic ventricular fibrillation (IVF; case 2). The patient had no evidence of structural heart disease, and atrial pacing was performed for the control of ventricular fibrillation (VF). J waves were present in the inferior leads (II, III, aVF) and the V₃ through V₆ precordial leads, with the highest amplitude in lead V₄ (long arrows). An attenuation of the J-wave amplitude is evident during atrial pacing in V₃ through V₆ (thick arrows) and in the inferior leads (not shown). **B**, The relation between the RR intervals and the J-wave amplitude during pacing. **C**, A non-IVF patient who underwent electrophysiological study for atrial flutter. J waves were observed in the inferior leads (II, III, aVF; long arrow), which were augmented during atrial pacing at paced cycle lengths of 600–450 ms (thick arrows). **D**, The relation between the RR intervals and the J-wave amplitude during pacing.

repolarization—in the IVF patients versus delayed conduction in the non-IVF subjects.

J-Wave Dynamicity in IVF Patients

Of the ECG findings of ERP, notching or slurring of the terminal portion of the QRS complex in association with IVF^{5–8,14} has received attention and has been categorized as J-wave syndrome.^{8,9} One of most striking features of J waves in IVF is the rate dependency: a bradycardia-dependent augmentation of J waves.^{5–8,12,14} In our earlier study, bradycardia-dependent augmentation of J waves was confirmed in IVF patients when the RR intervals suddenly prolonged because of sporadic sinoatrial or atrioventricular block or because of ectopic premature contractions.¹¹ Because of this J-wave behavior, it is natural to expect that J waves in IVF are attenuated at a higher rate; however, this has rarely been shown in the literature. Thus far, the pacing-induced attenuation of J waves has only been demonstrated by Shinohara et al¹³ and Nakagawa et al.¹⁹

This study confirmed that J waves in IVF patients are attenuated at a higher rate. Together with bradycardia-dependent augmentation, the J waves of IVF patients are characterized by an inverse relationship between the J-wave amplitude and the heart rate. For such a rate-dependent alteration of J waves, transient outward current (*I_{to}*)-mediated early repolarization suggested the underlying mechanism because this phenomenon is known to be augmented at slower rate.¹⁰

However, bradycardia-dependent augmentation was observed in 15 (55.6%) of the 27 IVF patients with J

waves and was not observed in the remaining patients in response to a slowing of the heart rate.¹¹ The patients without demonstrable pause-dependent augmentation had smaller J waves at baseline compared with those with J-wave augmentation: 0.173 ± 0.086 versus 0.391 ± 0.126 mV, respectively. In this study, 2 patients without attenuation had smaller J waves than the other patients, although the difference was not significant: 0.13 versus 0.43 ± 0.26 mV, respectively ($P=0.064$).

It is noteworthy that a distinct change was observed in the notching of the unipolar epicardial leads of the left ventricle in a patient who showed no rate-dependent change of J waves on the surface ECG (Figure 3). The notching of the unipolar epicardial leads was considered to represent J waves because it occurred exactly at the same time as the J waves on the surface ECG. In an IVF patient, Nakagawa et al¹⁹ demonstrated concordance between J waves on the surface ECG and the notching of unipolar leads on the epicardial surface. Recordings of epicardial electrograms may more easily demonstrate the rate-dependent alteration of J waves to characterize this electrophysiological feature.

J-Wave Dynamicity in the Non-IVF Patients

There are individuals who showed slurring or notching at the terminal end of the QRS in a general population that was considered to have an ERP.^{16–18,20} The subjects with J waves in our control group showed different responses of the J waves to changes in the heart rate compared with the IVF patients. In our previous study,¹⁵ the J-wave amplitude is augmented when

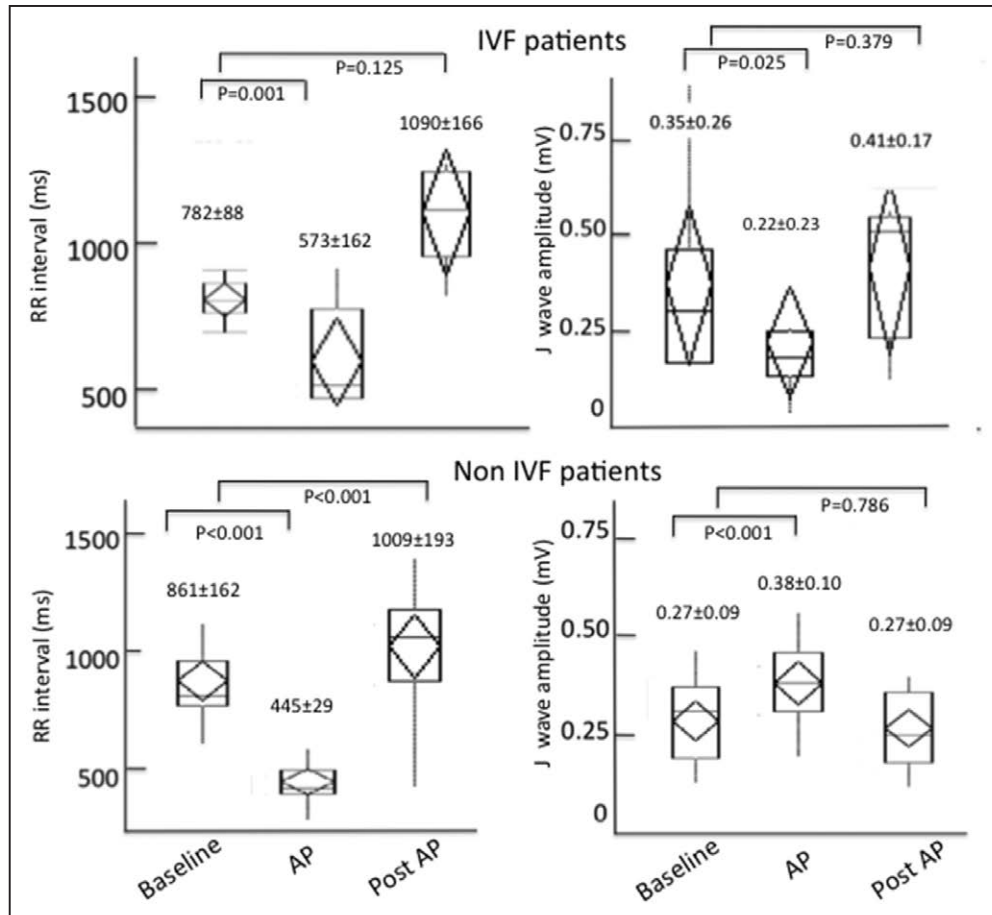


Figure 2. Changes of RR intervals and J-wave amplitude by atrial pacing (AP). Significant attenuation and augmentation are evident during AP in idiopathic ventricular fibrillation (IVF) and non-IVF group, respectively. J wave in the beat next to the last pacing was augmented in the IVF group but nonsignificantly. Post-pacing J waves were available in 5 patients. *P* values are those for vs baseline. post-AP indicates the RR intervals immediately after cessation of atrial pacing.

the RR intervals are shortened, which occurred in 10 of 23 patients with the conduction of premature atrial contractions or during atrial stimulation but was unchanged in 13 of 23 subjects. The findings are consistent with those of this study. A pause-dependent attenuation of the J-wave amplitude was not clear, but a positive correlation of the J-wave amplitude with increasing heart rate was suggested (Figures 1 and 2). The most likely mechanism for the tachycardia-dependent augmentation of J waves would be conduction delay.¹⁵

It is well known that activation delay occurs at longer coupling intervals during premature stimulation of the heart after a healed myocardial infarction.²¹ Discontinuity in the myocardial bundle or nonuniform anisotropy from fibrosis would be responsible for such conduction delay. Furthermore, this activation delay may also occur in hearts without these structural changes. We observed an early onset of activation delay in patients with Brugada syndrome: patients without structural changes, when the heart was stimulated at increasingly shorter coupling intervals. A delay occurred at longer coupling intervals of premature stimulation compared with a control.²² The detailed mechanism for a delay occurring at longer coupling intervals in hearts without organic heart disease is not apparent, but it may be because of undefined electric instability.

Clinical Implications

This study shows that similar ECG findings of J waves (or ERP) can be caused by multiple mechanisms. A pause-dependent augmentation is the hallmark of J waves in IVF patients, and such J waves represent current (*I_{to}*)-mediated early repolarization.¹⁰ Such J waves have been shown to be associated with a poorer prognosis in patients with VF or sudden cardiac death. Drugs such as isoproterenol, quinidine, and bepridil have been shown to suppress J waves and, possibly, VF recurrence in IVF patients.^{23–25}

On the other hand, J waves in the non-IVF subjects showed a direct relationship to heart rate and might be explained by a conduction delay. Some J waves (or ERP) observed among individuals in the general population may be associated with poorer prognosis.^{16,17,20} In most cases, J waves are found in subjects with no history of VF or cardiac arrest, which suggests relatively good long-term outcomes, but a study exploring this concept should be conducted in a larger number of subjects.

Limitations

The study treated only a small number of patients. The age of IVF and non-IVF subjects was different, and the results need to be confirmed in a study with a larger number of patients of the same age. However, including the previous

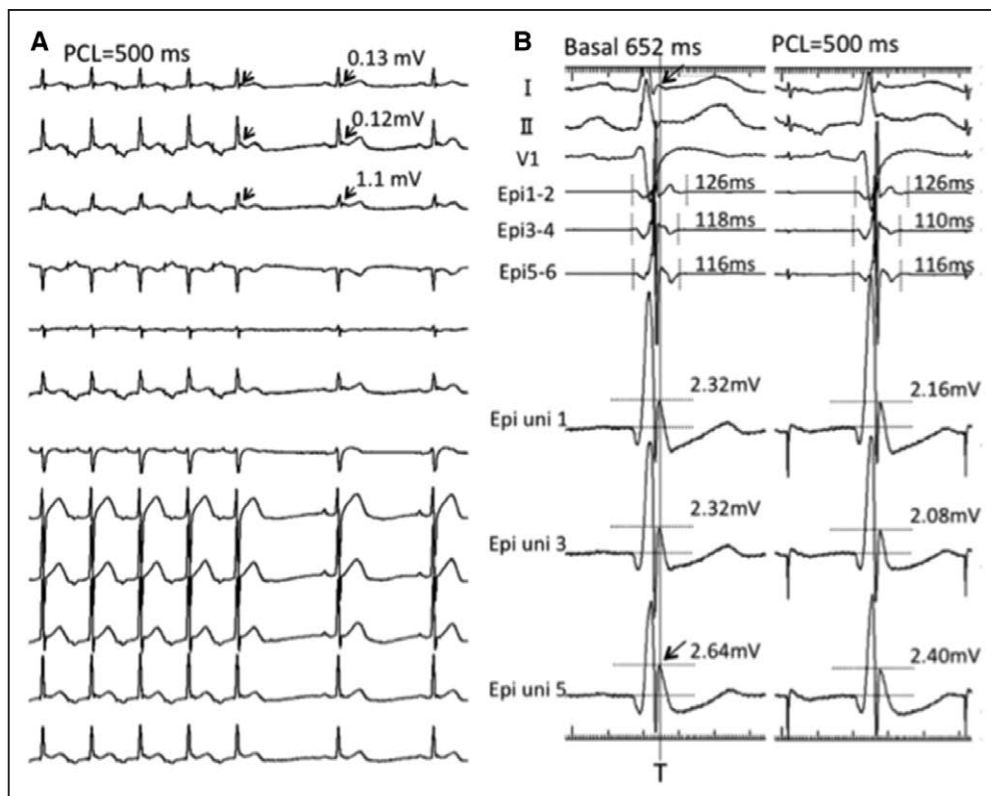


Figure 3. Rapid atrial pacing during an electrophysiological study. A 37-year-old male (case 7) who had received an implantable cardioverter-defibrillator (ICD) was admitted for the recurrence of ventricular fibrillation (VF). J waves (0.11–0.13 mV) were observed on the surface ECG. During atrial pacing at cycle lengths of 600–460 ms, no attenuation of the J waves was observed (A), but J waves in the unipolar leads showed a distinct decrease in amplitude (B). T, timeline for the peak of J waves in lead II, which was identical to the peaks of the notching on the epicardial leads.

study,^{11,15} it is likely that there are different mechanisms of J-wave genesis. There are subjects in whom we are unable to determine the response of J waves to heart rate on the surface ECG. If we record electrograms from the epicardial surface of the left ventricle, we may be able to demonstrate the rate dependency of J waves more efficiently (Figure 3).

Conclusions

J waves were attenuated and augmented during atrial pacing in IVF patients and in non-IVF patients, respectively. The likely mechanism would be a repolarization abnormality in IVF patients and a depolarization abnormality in non-IVF patients. We may be able to differentiate the underlying mechanisms from the rate-dependent changes of J waves.

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Disclosures

None.

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