Comparison of Autonomic J-Wave Modulation in Patients With Idiopathic Ventricular Fibrillation and Control Subjects

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Background: Although J-waves are seen in both patients with idiopathic ventricular fibrillation (IVF) and the general population, their genesis remains unclear. To assess the relationship between J-waves and autonomic tone we investigated the circadian variation of J-waves in individuals with and without IVF.

Methods and Results: In study 1, we obtained resting 12-lead ECG and Holter ECG recordings in 258 individuals undergoing screening for heart disease. In 60 of these subjects (23.3%), we detected J-waves on Holter ECGs; 40 of them (66.7%) had shown no J-waves on 12-lead ECGs. In study 2, we measured the J-wave amplitude, heart rate (HR), and HR variability [high frequency (HF) and the ratio of low- to high-frequency (LF/HF)] on Holter ECGs recorded in 5 patients with IVF and 20 control subjects who had manifested J-waves. The J-wave amplitude increased at night and decreased during the day in both groups; it was significantly higher in the IVF patients (P<0.0001). In both groups, the J-wave amplitude showed a significant negative correlation with HR and LF/HF and a significant positive correlation with HF. The slope of the J/HR and J/(LF/HF) relationship was significantly steeper in the IVF patients.

Conclusions: The J-wave amplitude was more significantly influenced by the autonomic balance in IVF patients than in the controls. Autonomic J-wave modulation may yield important information on the genesis of J-waves. (Circ J 2013; 77: 330–337)

Key Words: Autonomic tone; Circadian variation; Heart rate variability; Idiopathic ventricular fibrillation; J-wave

The detection of a J-wave, characterized by a notching or slurring at the terminal part of the QRS complex on standard 12-lead ECGs, has been considered an innocuous finding. Epidemiologic studies have detected this variant in 5–24% of the general population.1–4 However, case reports and case-control studies published over the past decade have documented that the presence of this pattern, especially in the inferior or lateral leads, is associated with vulnerability to ventricular fibrillation (VF).1,2,5–14 Although observations based on clinical and experimental studies suggested defects in delayed depolarization or early repolarization,5,15–20 the electrophysiological mechanisms underlying the manifestation of J-waves remain unclear.

J-waves exhibited diurnal variability or bradycardia-dependent augmentation characteristics in patients with idiopathic VF (IVF),5,6,12,21 suggesting an association between autonomic nervous activity and the occurrence of VF. Although J-waves are not uncommon in the general population, circadian variations in their amplitude and their relationship with heart rate (HR) or autonomic nervous activity has not been fully investigated in healthy subjects. We posited that the incidence of J-waves may be higher if assessed by 24-h ECG than by resting 12-lead ECG because of their bradycardia-dependent augmentation or night ascendancy.

The purpose of this study was to assess the relationship between J-waves and autonomic tone. We determined the circadian variation of J-waves and investigated the relationship between J-wave amplitude and HR variability (HRV) using 24-h Holter ECGs and compared them between individuals with and without IVF.
Methods

Our investigation involved 2 study populations and protocols. In study 1 we compared the incidence of J-waves on 24-h Holter and 12-lead resting ECGs in 258 individuals undergoing screening for heart disease. In study 2 we used 24-h Holter ECG recordings to compare circadian variations in the J-waves and to assess the relationship between the J-wave amplitude and HRV in study subjects with (group 1, n=5) and without IVF (group 2, n=20).

Study Population

Study 1 We enrolled 258 consecutive subjects who underwent screening between January and August 2010 for cardiovascular disease. We recorded both their resting 12-lead and 24-h Holter ECGs. This study did not include individuals with atrial fibrillation, atrial flutter, bundle branch block (BBB), or artificial pacemakers.

Study 2 This study comprised of 2 groups manifesting J-waves. Group 1 consisted of 5 IVF patients from among 23 patients with a diagnosis of IVF who were admitted to Oita University Hospital between 2005 and 2011. VF was defined as a polymorphic ventricular tachyarrhythmia with a rate exceeding 260 beats/min and hemodynamic collapse requiring electrical defibrillation. IVF was diagnosed by echocardiography, exercise testing, coronary angiography with acetylcholine, cardiac scintigraphy, and helical computed tomography. In all IVF patients, the heart was structurally normal. Based on consensus criteria,12,23 14 had a diagnosis of Brugada syndrome. In the other 9 patients we evaluated baseline resting 12-lead ECGs and 24-h Holter ECGs for the presence of J-waves. From among these 9, we enrolled 5 patients with IVF who manifested J-waves (4 men, 1 woman, mean age 43.6±7.0 years). None of the 5 patients had a Brugada-type ECG (either coved or saddle-back type), QT interval prolongation, or BBB. In the IVF patients, VF events occurred during sleep, after the ingestion of meals or alcohol, at rest, in the recovery phase after walking in the early morning, and at work.

Group 2 comprised 20 individuals who had no organic heart diseases and whose 24-h Holter ECGs obtained at screening (study 1) had shown J-waves (15 men, 5 women; mean age 46.8±4.8 years). They were age- and sex-comparable with the 5 IVF patients in group 1 and had no evidence of cardiovascular disease on standard 12-lead and Holter ECGs, chest X-rays, and echocardiograms, and they were not taking medications known to affect ECG readings or the autonomic nervous system. The study protocols were approved by the university’s review board.

J-Wave Definition and Measurement

On standard 12-lead ECGs, we defined J-waves as either notching (positive deflection) or slurring (smooth transition from the QRS to the ST segment) with an amplitude ≥0.1 mV on the terminal QRS portion in at least 2 of the inferior leads (II, III, aVF) or the left lateral leads (I, aVL, and V5+6). With the subject resting supine, we recorded standard 12-lead surface digital ECGs using Cardiofax (Nihon Kohden, Tokyo, Japan) with a 100-Hz low-pass filter.

Holter ECGs (MARS, GE Healthcare, Milwaukee, WI, USA) were recorded for 24 h in the course of normal daily activities. The setting for high- and low-pass filters was 0.4 and 40 Hz, respectively. The precordial electrodes for 2 leads were located at the right manubrial border of the sternum (positive) and the 4th intercostal space at the left margin of the sternum (positive, CM2), and at the left manubrial border of the sternum (negative) and the 5th rib at the left axillary line (positive, CM5). We chose CM5 because none of the study subjects had a J-wave in lead CM2. Using amplified waveforms (400%), we manually measured the J-wave amplitude from the baseline level in lead CM5 for 5 consecutive beats every 20 min. Averaged values were recorded as the hourly data. We selected only data in which HR, the baseline, and the configuration of QRS waves were stable for at least 5 min, as this suggests the absence of abrupt changes in posture or autonomic activity. In the 24-h Holter ECG recordings, we measured the amplitude of all QRS notches or slurrings even if they were less than 0.1 mV because we were interested in the circadian variation of J-waves. In QRS slurring, we included only beats for which the transition point could be clearly determined. When the J-waves were observed for at least 1 h through the 24 h, it was defined as J-wave positive. The J-waves were observed for 19.6±2.3 h (13–24 h) in group 1 and 17.0±1.4 h (3–24 h) in group 2. Measurement of the J-wave amplitude was performed by 2 experienced cardiologists blinded to other information and their findings were averaged. Interobserver reliability was assessed by linear regression analysis using 60 randomly selected beats. The correlation coefficient was 0.94 (P<0.0001).

HRV Analysis

The power spectrum of the RR intervals was computed by a fast Fourier transform and expressed as the square root of the areas under the power spectrum. We calculated the power of the low- and the high-frequency components (LF: 0.04–0.15 Hz; HF: 0.15–0.40 Hz) for every minute of every hour over a 24-h period and analyzed the mean hourly values. HRV measures were transformed by a common logarithm because their distributions were skewed. The mean hourly value of HR was also calculated. All parameters recorded from 10:00 to 19:00
hours and from 22:00 to 06:00 hours were used as the diurnal and nocturnal values, respectively.

**Statistical Analysis**

Data are presented as the mean±SE. Two-way analysis of variance (ANOVA) followed by the Bonferroni post hoc test and the paired and unpaired t-test were used to evaluate differences between groups. The relationship between the J-wave amplitude and HR or HRV was assessed by linear regression analysis using hourly data obtained in individual subjects. A P value <0.05 was considered statistically significant.

**Results**

**Study 1: Incidence of J-Waves on 24-h Holter ECGs**

We detected J-waves in 60 of the 258 individuals undergoing screening for cardiovascular disease (23.3%); none of the others (n=198) manifested J-waves on 24-h Holter ECG recordings. Table compares the characteristics of subjects with and without J-waves on Holter ECGs. Although more men than women tended to manifest J-waves (P=0.07), age, underlying cardiac diseases, and complicated arrhythmias were not significantly different between subjects with and without J-waves.

Figure 1 shows the relationship between the incidence of J-waves on Holter and 12-lead ECGs. Of 60 individuals with J-waves on Holter ECGs, 20 (33.3%) had J-waves on 12-lead ECGs: 10 (16.7%) in the inferior leads only, 6 (10.0%) in the lateral leads only, and 4 (6.7%) in both leads. The other 40 subjects (66.7%) had no J-waves on 12-lead ECGs. Among 198 study subjects without J-waves on Holter ECGs, 176 (88.9%) had no J-waves on 12-lead ECGs. The other 22 (11.1%) manifested J-waves on 12-lead ECGs: 21 (10.6%) in the inferior leads only and 1 (0.5%) in the lateral leads only.

![Figure 1. Relationship of the incidence of J-waves on Holter and 12-lead ECGs.](image)

Among the 198 individuals with no J-waves on Holter ECGs, 22 (11.1%) had J-waves on 12-lead ECGs: 21 (10.6%) in the inferior leads only and 1 (0.5%) in the lateral leads only.

**Study 2**

Representative examples of 12-lead- and Holter ECGs obtained in the 5 patients with IVF (group 1) and the 20 individuals from study 1 who manifested J-waves (group 2) are shown in Figure 2 and Figure 3, respectively. Figure 2 shows ECG recordings from a 43-year-old man with IVF (group 1) who experienced sudden syncope at night. His 12-lead ECG showed J-waves in the inferior and lateral leads. Although there were prominent J-waves on his Holter ECG during the day, the J-wave amplitude was higher at night than in the daytime. During hospitalization, he experienced another episode of VF at night. The monitor ECG before VF onset showed prominent J-waves (Figure 2C).

Figure 3 presents ECG recordings of a 28-year-old man in group 2. His 12-lead ECG showed J-waves in the inferior leads; on the Holter ECG we observed prominent J-waves at night, but not in the daytime.

**Circadian Variations in the J-Wave Amplitude**

We evaluated the circadian variations in the J-wave amplitude, HR, and HRV for each individual and used averaged results as group data. The J-wave amplitude increased at night and decreased during the day in both groups (Figure 4). However, the J-wave amplitude was significantly higher in group 1 than group 2 (P<0.0001). HR and the LF/HF ratio increased during the day and decreased at night, and LF exhibited an inverse pattern in both groups.

When we compared the diurnal and nocturnal values of the J-wave amplitude, HR, and HRV we found that the J-wave amplitude was significantly higher in the 5 IVF patients both during the day (P<0.05) and at night (P<0.0001), irrespective of small differences in the HF, LF/HF, and HR of individuals with and without IVF (Figure 5).
Autonomic J-Wave Modulation

Relationship of J-Wave Amplitude With HR and HRV
The correlation between J-wave amplitude and HR or HRV was evaluated in each individual using hourly data. The J-wave amplitude showed a significant negative correlation with HR in all IVF patients and in 17 of 20 control subjects (85%) and with the LF/HF ratio in all IVF patients and 14 control subjects (70%). The J-wave amplitude showed a significant positive correlation with HF in all IVF patients and in 14 control subjects (70%). We obtained the slopes and intercepts of these regression lines for each individual who showed a significant correlation, and then compared the 2 groups. Figure 6 shows the individual regression lines (black lines) and the average regression lines (red and blue lines) obtained by the mean values of the slopes and intercepts for each group.

The slope of the J-wave amplitude/HR relationship was significantly steeper ($-0.010\pm0.004$ vs. $-0.003\pm0.001$, $P<0.005$) and the intercept was significantly greater ($0.848\pm0.259$ vs. $0.318\pm0.046$, $P<0.005$) in group 1 than in group 2. The slope of the J-wave amplitude/(LF/HF) relationship was significantly steeper ($-0.207\pm0.049$ vs. $-0.068\pm0.027$, $P<0.05$) and the intercept was significantly greater ($0.296\pm0.084$ vs. $0.139\pm0.028$, $P<0.05$) in group 1 than in group 2. The slope ($0.140\pm0.037$ vs. $0.097\pm0.024$, $P=0.40$) and the intercept ($-0.088\pm0.075$ vs. $-0.092\pm0.046$, $P=0.97$) of the J-wave amplitude/HF relationship were not significantly different between the 2 groups.

Discussion
Incidence of J-Waves on Holter ECGs
To our knowledge, this is the first study to compare the incidence of J-waves on 24-h Holter and resting 12-lead ECG recordings. The incidence was significantly higher on Holter than on 12-lead ECGs (23.2% vs. 16.7%, $P<0.0001$). Interestingly, there was a significant difference in the presence of J-waves on the 2 types of ECG; 66.7% of the subjects with J-waves on Holter ECGs had no J-waves on the 12-lead ECGs recorded during the day. This suggests that the presence of J-waves should be determined not only on 12-lead but also on 24-h Holter ECGs because of their circadian variation and night-time ascendency.

According to earlier reports, 5–24% of the general population manifests J-waves on 12-lead ECGs.\textsuperscript{1–4} Their prevalence...
Figure 3. ECG recordings of a 28-year-old male subject without idiopathic ventricular fibrillation (VF). The 12-lead ECG shows J-waves in the inferior leads (II, III, aVF) (A). The Holter ECG (CMS) shows J-waves at night but not in the daytime (B).

Figure 4. Circadian variations in the J-wave amplitude. The J-wave amplitude increased at night and decreased during the day in subjects with (group 1) and without (group 2) idiopathic ventricular fibrillation (IVF). The amplitude was significantly higher in patients with IVF (P<0.0001). Data are the mean±SE.
Autonomic J-Wave Modulation

is age- (predominant in young adults), sex- (predominant in males), and race-dependent and is affected by the criteria set for J-wave detection. In addition, the ECG filter setting is an important factor for explaining the observed variations in the prevalence of J-waves, because the use of low-pass filters with a low cutoff attenuates or eliminates J-waves. On Holter ECGs, the cutoff setting for low-pass filters is usually lower than for standard 12-lead ECGs to account for the higher noise and electromyogram levels during the pursuit of daily activities. We used 100-Hz and 40-Hz low-pass filters in the 12-lead and Holter ECGs, respectively, and consequently, on the Holter ECG recordings J-waves may have been attenuated or eliminated. This may partly explain why 11.1% of our study subjects without J-waves on Holter ECGs manifested J-waves on the 12-lead ECGs. Nonetheless, our finding that 66.7% of individuals with J-waves on Holter ECGs had no J-waves on 12-lead ECGs supports our contention that the occurrence of J-waves is increased at night.

On the 12-lead ECGs, all J-waves appeared in the inferior or lateral leads. As the Holter CM5 lead resembles leads II and V5 and reflects both inferior and lateral leads, we think that our selection of CM5 was suitable for the assessment of J-waves.

Circadian Variations in the J-Wave Amplitude and Relationship With Autonomic Tone

Circadian variations in the J-wave (ie, higher at night and lower during the day) were observed in study subjects with and without IVF. However, in study 2 their amplitude was significantly higher in the IVF patients especially at night; HR and HRV indices were not significantly different between groups 1 and 2. According to Tikkanen et al,13 subjects with a J-point elevation exceeding 0.2 mV in the inferior leads were at increased risk of dying from arrhythmia. Our findings are consistent with theirs, suggesting that the magnitude of the J-point amplitude may serve as a risk stratification method for individuals manifesting J-waves.

Study 2 showed that the amplitude of J-waves was positively correlated with vagal activity (HF) and negatively correlated with HR and sympathetic activity (LF/HF) in both groups. Abe et al5 reported significant circadian variations in the J-wave and a strong association between the J-wave amplitude and HRV in patients with IVF, although this was not the case in their control subjects manifesting J-waves. On the other hand, Mizumaki et al25 recently reported that J-waves were strongly associated with vagal activity in both IVF patients and control subjects; their findings are consistent with ours, suggesting that a high vagal tone might be associated with the genesis of not
only pathological but also physiological J-waves.

The slope of the J-wave amplitude/HR relationship and the J-wave amplitude/(LF/HF) relationship was significantly steeper in our subjects with than without IVF, suggesting that J-waves are more sensitively modulated by autonomic tone in IVF patients.

The relationship between J-wave amplitude and the occurrence of VF in patients with IVF has been reported; the J-wave amplitude increased just before the occurrence of VF. In our study, most of the VF episodes occurred under vagal conditions. In an IVF patient with prominent J-waves reported elsewhere by our group, the J-waves were accentuated by propranolol and verapamil and eliminated by isoproterenol, atrial pacing, disopyramide and cilostazol. We suggested that the elimination of J-waves by isoproterenol or cilostazol was attributable to an increase in the inward calcium...
current (I_{Ca}) and a decreased in the transient outward current (I_{to}) secondary to an increase in HR. The present result that J-waves were negatively correlated with HR and L/HF is consistent with the pharmacologic effects on J-waves we documented in our earlier report.

Study Limitations

First, the number of IVF patients with J-waves was small. A multicenter study is underway to examine the relevance of our results. Second, we analyzed only data from the CM5 lead on Holter ECGs because we posited that this lead reflects precordial (V5-like) and inferior leads. However, if 12-lead Holter ECG recordings were available, we could compare them more precisely with 12-lead resting ECGs. Third, because we enrolled only subjects who underwent both resting 12-lead and 24-h Holter ECG studies at the same screening examination, in each subject, except the 5 IVF patients included in study 2, ECG readings were recorded only once, whereas for the IVF patients in study 2, we recorded 12-lead and Holter ECGs several times. We used the first recordings obtained upon hospitalization of the IVF patients and we must confirm the reproducibility of our data because there are day-to-day variations in J-waves. Finally, the ECG amplitudes are influenced by posture and respiration. In our previous study, the circadian change in J-waves was evaluated on the standard 12-lead ECG recordings in an IVF patient and showed its night ascendancy, which was consistent with the present results determined by Holter ECG recordings. However, the possible role of postural and respiratory changes in the J-wave amplitude should be evaluated in the future study.

Conclusions

Holter ECGs detected a higher incidence of J-waves than 12-lead resting ECGs because of the waves’ circadian variation and night ascendancy. The J-wave amplitude was significantly higher and more closely associated with HR and HRV in sub and night ascendancy. The J-wave amplitude was significantly higher and more closely associated with HR and HRV in sub and night ascendancy. The J-wave amplitude was significantly higher and more closely associated with HR and HRV in sub and night ascendancy. The J-wave amplitude was significantly higher and more closely associated with HR and HRV in sub and night ascendancy.

Disclosures

No conflicts of interest.

References