Vagal activity modulates spontaneous augmentation of J-wave elevation in patients with idiopathic ventricular fibrillation

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BACKGROUND: Although J-wave elevation in the inferolateral leads could be related to idiopathic ventricular fibrillation (IVF), little is known about the pathophysiologic characteristics of J-wave elevation in patients with IVF.

OBJECTIVE: This study aimed to determine the relationship between augmentation of J-wave elevation and changes in RR interval or autonomic nervous activities in patients with IVF.

METHODS: Eight patients with IVF and 22 controls with J-wave elevation ($\geq$0.1 mV) in lead V5 were studied. The J-wave amplitude was automatically measured in lead CM5 of a digital Holter electrocardiogram, and the J–RR relationship was determined. Based on the analysis of heart rate variability, the relationship between the J-wave amplitude and the natural logarithm of high-frequency (HF) components (J–ln HF relationship) or the ratio of low frequency (LF) components to HF components (J–LF/HF relationship) was also determined.

RESULTS: The J–RR slope (mm/s) was greater in patients with IVF than in controls (3.5 $\pm$ 0.7 vs 2.4 $\pm$ 0.8; $P < .01$), as was J-wave amplitude (mm) at an RR interval of 1.2 seconds (2.8 $\pm$ 0.9 vs 2.0 $\pm$ 0.6; $P < .05$). The J-wave amplitude was correlated positively with ln HF and negatively with LF/HF, and the slopes of both J–ln HF and J–LF/HF regression lines were greater in patients with IVF than in controls. During an entire 24-hour period, there was no difference between the 2 groups in either HF or LF/HF. Nine of the total 11 episodes (82%) of spontaneous ventricular fibrillation occurred between 18:00 and 6:00.

CONCLUSIONS: In patients with IVF as compared with control subjects, J-wave elevation was more strongly augmented during bradycardia and was associated with an increase in vagal activity. This could be related to the occurrence of ventricular fibrillation predominantly at night in patients with IVF.

KEYWORDS Early repolarization; J wave; RR interval; Holter ECG; Ventricular fibrillation

ABBREVIATIONS ECG = electrocardiogram; **HF** = high frequency; **IVF** = idiopathic ventricular fibrillation; **LF** = low frequency; **ln HF** = natural logarithm of high-frequency components; $\mathbf{J_{(0.6)}}$, $\mathbf{J_{(1.0)}}$, $\mathbf{J_{(1.2)}}$ = the calculated J-wave amplitude at RR intervals of 0.6, 1.0, and 1.2 seconds from the J–RR regression line; **VF** = ventricular fibrillation

Introduction

Recently, several studies have reported that J-point and ST-segment elevation in the inferior or lateral chest leads is associated with arrhythmic sudden death due to ventricular fibrillation (VF) in patients without apparent organic heart diseases, that is, idiopathic VF (IVF).[1–12] Moreover, J-wave elevation, that is, the early repolarization pattern, in the lateral or inferior leads is usually considered benign because it is often observed in healthy young individuals.[1,2,13–17] Although its prevalence has been estimated to be between 1% and 9% in healthy adults,[1,2,6,13,15,17] there are as yet no criteria to identify high-risk patients within the broad population of healthy individuals with this specific electrocardiogram (ECG) pattern.

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One experimental study has revealed that the presence of a transient outward current (I_{to})-mediated prominent action potential notch in the epicardium, but not in the endocardium, provides a voltage gradient that manifests as J waves.[9,16,18] However, the exact mechanisms responsible for J-wave elevation and the pathogenesis of VF are still under investigation. In Brugada syndrome, unlike other cardiovascular diseases, VF and sudden death mainly occur in the resting state, predominantly during sleep.[19–21] The typical ECG changes in Brugada syndrome are variable over time and are modulated by exercise or pharmacological interventions that interact with autonomic nervous activities.[7,8,22] We have reported an augmentation of ST elevation through vagal activity[19] and bradycardia-dependent augmentation of ST elevation[23] in patients with Brugada syndrome. The nighttime onset of VF episodes may be related to enhanced ST elevation during bradycardia at night.[7,19,23,24] This could be due to a slow recovery from the inactivation of prominent I_{to}.[18,24] Recently, Kawata et al[25]

1547-5271/$ -see front matter © 2012 Heart Rhythm Society. All rights reserved. doi:10.1016/j.hrthm.2011.09.055

have reported differences between Brugada syndrome and early repolarization in inferolateral leads. However, previous studies have suggested a similar bradycardia-dependent augmentation of J-wave elevation in patients with IVF who did not have Brugada-type ST elevation.[3,11,20] The present study was therefore designed to determine whether rate-dependent changes in J-wave elevation could be different between patients with IVF and control subjects and whether augmentation of J-wave elevation could be related to increased vagal tone.

Methods

Patients with IVF

The study enrolled 8 consecutive male patients with IVF (mean age 33 ± 17 years) who were admitted to our hospital because of documented episodes of VF between December 2006 and July 2009 and who had J-wave elevation ≥0.1 mV in at least 2 leads within either the inferior or lateral chest leads. Notched-type J-wave elevation in the V5 lead was required for inclusion because of the analysis of Holter ECG by using the CM5 lead. The review board of our institution approved the study protocol, and written informed consent was obtained from all patients before participation. No patients showed Brugada-type ST changes in V1–V3 leads of ECG, in either the normal intercostal space or the upper intercostal space, either at baseline or after intravenous administration of pilsicainide (1.0 mg/kg). In all patients, physical examination, chest X-ray, echocardiography, exercise test, and thallium or ^{99m}Tc-tetrofosmin myocardial single-photon emission computed tomography failed to disclose apparent evidence of organic heart diseases. Patients with long QT syndrome, catecholaminergic arrhythmias, or electrolyte abnormality and patients taking any drugs were excluded from the study.

Control subjects

For control subjects, patients who had health care examinations (including 12-lead ECG and chest X-ray) at our hospital between July 2008 and December 2009 were recruited. Subjects with abnormal 12-lead ECG (ie, wide QRS complex, ST-segment elevation, T-wave inversion, and QT-interval prolongation) or abnormal chest X-ray films were excluded, leaving a total of 2464 control subjects (1202 men and 1262 women; mean age 38 ± 14 years). Among these, 85 male and 37 female subjects exhibited notched-type or slurred-type J-wave elevation ≥0.1 mV in at least 2 of either inferior or lateral leads. Hence, the prevalence of early repolarization in our control subjects was 122 of 2464 (4.95%). Among these, 30 consecutive male subjects with notched-type J-wave elevation (≥0.1 mV) in lead V5 who were matched for age to patients with IVF were selected for the analysis of Holter ECG by using the CM5 lead. Written informed consent was obtained from 22 of these 30 subjects before participation; these 22 subjects served as controls in the following analysis.

Analysis of Holter ECG recordings

Augmentation of J-wave elevation in patients with IVF was estimated with a 2-channel 24-hour digital Holter ECG with CM5 and NASA leads recorded out of hospital between 3 and 11 (6.5 ± 2.7) weeks after VF episodes. All control subjects also underwent ambulatory Holter ECG out of hospital. All ECG recordings were analyzed for morphology; any extrasystole mistakes were amended, and R-wave trigger was corrected. The CM5 lead of the digital Holter ECG was analyzed by using a Holter ECG analyzing system (SCM 6000, Fukuda Denshi, Tokyo, Japan). Beat-to-beat J-wave amplitude was automatically measured from the isoelectric line to the peak of the notched-type J wave. The accuracy of automatic measurement of J-wave amplitude for every beat was confirmed manually on the monitor screen of SCM 6000 by 2 experienced investigators who were blind to the clinical information of patients. Any difference in the determination was resolved by a third observer's opinion. To exclude the postural shift of ECG, changes in J-wave amplitude should be gradual on the J-amplitude trendgrams and not coincident with abrupt changes in QRS amplitude or the RR interval. If unavoidable momentary ECG drift due to respiration or slight postural change was recorded, this part of the recording was excluded from the analysis. After the automatic measurement of J-wave amplitude on each beat, a mean J-wave amplitude was calculated during each 15-second period of the 24-hour recording and plotted against the corresponding mean RR intervals. For the analysis of J-wave and RR (J–RR) relationship, linear regression analysis was used. The J-wave amplitude was calculated from the J–RR regression line at RR intervals of 0.6, 1.0, and 1.2 seconds ($J_{(0.6)}$, $J_{(1.0)}$, and $J_{(1.2)}$).

Consecutive RR intervals comprising only normal sinus rhythm were analyzed every 5 minutes during the 24-hour recording by using software for RR spectral analysis (HPS-RRLOP(I), Fukuda Denshi, Tokyo, Japan). With the maximum entropy method using the Akaike algorithm, power spectra were quantified by measuring the area in high frequency (HF, 0.15–0.4 Hz) and in low frequency (LF, 0.04–0.15 Hz), and the ratio of LF components to HF components (LF/HF) was determined. Because of the skewness of the data, the natural logarithm of HF value (ln HF) was analyzed. Mean J-wave amplitude was calculated for each 5-minute period during the 24-hour recording and plotted against the corresponding ln HF or LF/HF. The relationship between the J-wave amplitude and ln HF or the ratio of LF components to HF components (LF/HF) was analyzed through linear regression analysis.

Statistical analysis

The values are presented as mean ± standard deviation. The dependence of J-wave amplitudes on RR intervals, ln HF, and LF/HF was analyzed by linear regression by using the 24-hour recording ($J = A \times RR + B$, where A is the slope and B is the intercept). The unpaired t test was used to compare the mean value between IVF and control groups. Serial changes in the variables of heart rate variability over