# Heterogeneous response of J-wave syndromes to beta-adrenergic stimulation

Laurent Roten, MD, Nicolas Derval, MD, Frédéric Sacher, MD, Patrizio Pascale, MD, Daniel Scherr, MD, Yuki Komatsu, MD, Khaled Ramoul, MD, Matthew Daly, MD, Arnaud Denis, MD, Ashok J. Shah, MD, Mélèze Hocini, MD, Pierre Jaïs, MD, Michel Haïssaguerre, MD

*From the Hôpital Cardiologique du Haut-Lévêque, Université Victor Segalen Bordeaux II, Bordeaux, France.*

**BACKGROUND** Inferolateral early repolarization (ER) and Brugada syndrome manifest with J waves. Isoproterenol suppresses recurrent ventricular arrhythmias while reducing J waves in both disorders.

**OBJECTIVE** To characterize the effect of isoproterenol on J waves.

**METHODS** We analyzed the impact of isoproterenol on J waves in 20 patients with Brugada-type electrocardiogram (Br group) and 38 patients with ER (ER group).

**RESULTS** In the ER group, J waves were present in inferior leads in 32 patients (84%) and in lateral leads in 23 patients (61%). Isoproterenol increased the heart rate by 75 beats/min in the ER group and by 71 beats/min in the Br group ($P = .20$). The incidences of persistent (≤0.05-mV decrease), decreased, and normalized J waves (residual J wave ≤0.05 mV) were 20%, 80%, and 0% for Br group patients and 29%, 8%, and 63% for ER group patients, respectively ($P < .001$). Within the ER group, inferior J waves persisted in 34% of the cases, decreased in 9%, and normalized in 56% whereas lateral J waves always normalized ($P < .001$). Baseline QRS width was broader in ER group patients with persistent J waves (90 ms vs 80 ms; $P = .003$) and was unchanged with isoproterenol (90 ms; $P = .19$), whereas it decreased in the remaining patients (75 ms; $P < .001$).

**CONCLUSIONS** J-wave syndromes have distinct regional sensitivity to beta-adrenergic stimulation. J waves may persist in a subset of patients with right precordial and inferior J waves but never in lateral location. This heterogeneous response to isoproterenol may indicate distinctive mechanisms for Brugada and ER patterns, including depolarization abnormalities or ion channel sensitivity.

**KEYWORDS** Early repolarization; Brugada syndrome; J wave; Beta-adrenergic stimulation; Isoproterenol; Signal-averaged ECG; QRS duration

**ABBREVIATIONS** **ECG** = electrocardiogram; **ER** = inferolateral early repolarization; **SAECG** = signal-averaged electrocardiogram

(Heart Rhythm 2012;9:1970–1976) 

## Introduction

Inferolateral early repolarization (ER) has a prevalence of up to 5% in the general population and is frequently present in young athletes.[1] An association between inferolateral ER and idiopathic ventricular fibrillation has been well established by different groups.[1–6] So far, the exact pathophysiologic mechanism responsible for J-wave formation in inferolateral ER has not been clarified. Furthermore, no genetic or pharmacological test is currently available that allows to distinguish benign from malignant ER variants.[7,8] Pharmacologic challenge can help understand pathophysiologic mechanisms underlying different disorders and reveal important differences. Both inferolateral ER and Brugada syndrome manifest with prominent J waves and share important clinical characteristics.[7] Beta-adrenergic stimulation is effective in suppressing recurrent ventricular arrhythmias while reducing J-wave amplitudes in both disorders.[9–14] To date, no study has specifically characterized the effect of isoproterenol on J waves in inferolateral ER and Brugada-type electrocardiogram (ECG).

## Methods

Isoproterenol challenge is routinely performed at our institution as part of a clinical evaluation protocol in patients with corresponding symptoms and ECG patterns known to be associated with increased risk for malignant arrhythmias. From this database, we included all patients with either inferolateral ER (ER group) or Brugada-type ECG (Br group) at the beginning of isoproterenol challenge and analyzed ECSs at baseline and at maximal heart rate. For the diagnosis of inferolateral ER, an ECG with an elevation of the QRS-ST junction (J point) by ≥0.1 mV above the baseline level in ≥2 contiguous leads, either as QRS slurring (a smooth transition from the QRS segment to the ST segment) or notching (a positive J deflection inscribed on the S wave) in the inferior leads (II, III, and aVF), lateral leads (I, aVL, and $V_4$–$V_6$), or both, had to be present (J wave). Brugada-type ECG was defined as reported in the

**Address for reprint requests and correspondence:** Dr Laurent Roten, MD, Service de Rythmologie et Stimulation Cardiaque, Hôpital Cardiologique du Haut-Lévêque, Université Victor Segalen Bordeaux II, Avenue de Magellan, 33604 Bordeaux-Pessac, France. E-mail address: laurent.roten@insel.ch.

1547-5271/$ -see front matter  http://dx.doi.org/10.1016/j.hrthm.2012.08.003

second consensus conference.[15] All patients with Brugada-type ECG included in the study had documented spontaneous or sodium channel blocker-induced Brugada type 1 ECG. Patients with structural heart disease, QRS width ≥110 ms (in the ER group), and with complete left bundle branch block during isoproterenol challenge were excluded.

### Isoproterenol challenge

The protocol for isoproterenol challenge at our institution is as follows: Patients are fasting, supine, with monitoring of blood pressure, oxygen saturation, and heart rhythm. Cardiopulmonary resuscitation equipment is available in the room during the test. From beginning until 10 minutes after the cessation of isoproterenol infusion, a 12-lead ECG is continuously recorded at a paper speed of 25 mm/s (10 mm/mV) by using standard equipment (Marquette MAC 5500; General Electrics, Waukesha, WI). For pharmacologic challenge, 0.20 mg of isoproterenol chlorhydrate (isuprel) is injected into 250 mL of glucose 5%. The glucose/isoproterenol mixture is then pressurized and infused intravenously through an 18-gauge needle, aiming at injecting the whole bag within 3 minutes to achieve a maximal beta-adrenergic stimulation (see Supplemental Figure). In case of atrial or ventricular arrhythmia, blood pressure drop, or patient discomfort, the infusion is stopped and isoproterenol effect antagonized by propranolol as necessary.

### ECG analysis

ECGs at baseline and at maximal heart rate during pharmacologic challenge were digitized and analyzed with a digital caliper (Iconico; screen caliper version 4.0; www.iconico.com). Heart rate, PR interval, QRS width in leads $V_3$/$V_4$ (without J wave), and QT interval were measured. The Bazett formula was used to correct the QT interval for heart rate. At baseline, inferior (II, III, aVF) and lateral (I, aVL, $V_4$–$V_6$) leads in the ER group and right precordial leads ($V_1$–$V_3$) in the Br group were analyzed for the presence of a J wave. Highest J-wave amplitude at baseline was measured in inferior and/or lateral leads in the ER group and right precordial leads in the Br group. At maximum heart rate, J-wave amplitude was again measured in the same lead as measured at baseline. When the terminal QRS was slurred, J-wave amplitude was measured at the point where slurring started to separate from the descending limb of the R wave. J-wave amplitude in notched QRS was measured at the top of the notch. Behavior of J waves during isoproterenol challenge in all inferior and/or all lateral leads for the ER group and all right precordial leads for the Br group was independently assessed by 2 electrophysiologists and described qualitatively as follows: 1. Persistent: J-wave amplitudes decreased by no more than 0.05 mV in at least 1 affected lead; 2. Normalized: no residual J wave with amplitude larger than 0.05 mV in any affected lead; 3. Decreased: all remaining cases. In case of disagreement, a consensus was formed. Examiners were blinded with regard to symptomatic vs asymptomatic cases of inferolateral ER.

### Signal-averaged ECG

Signal-averaged ECG (SAECG) was performed by using standard equipment (Marquette MAC 5500; General Electrics, Waukesha, WI). The following normal values for SAECG parameters were assumed: filtered QRS duration <114 ms; low-amplitude signal duration below 40 $\mu$V <38 ms; and root mean square voltage in the last 40 ms of the QRS >20 $\mu$V. SAECG was considered positive for late potentials if at least 2 of the 3 parameters were abnormal.[16]

### Statistical analysis

Categorical variables are expressed as numbers and percentages and continuous variables as mean ± standard deviation or median and quartiles. Categorical variables were compared with the $\chi^2$ test or Fisher's exact test and continuous variables with the unpaired $t$ test, Mann-Whitney test, or Wilcoxon test as appropriate. A 2-sided $P$ value of <.05 was considered statistically significant. All analyses were performed by using SPSS 17.0 (SPSS, Inc, Chicago, IL).

## Results

### Study population

A total of 38 patients with inferolateral ER (ER group) and 20 patients with Brugada-type ECG (Br group) were included. Patient characteristics are given in Table 1. Br group patients were older and a history of syncope that was less prevalent than in ER group patients. The reason to perform pharmacological testing in ER group patients was idiopathic ventricular fibrillation in 3 patients (8%), syncope in 18 (47%; 1 of these patients also had a positive family history for sudden cardiac arrest), positive family history in 7 (18%), palpitations and/or premature ventricular contractions in 5 (13%), and other reasons in 6 (16%). In the ER group, J waves were present in inferior leads in 32 patients (84%, inferior ER group) and in lateral leads in 23 patients (61%, lateral ER group). In 15 Br group patients (75%), a spontaneous Brugada type 1 ECG had been observed at least once, whereas in the other 5 Br group patients, Brugada type 1 ECG had been documented only after ajmaline challenge. Genetic testing had been performed in 15 Br

**Table 1** Patient characteristics for the ER group and the Br group

| | ER group (n = 38) | Br group (n = 20) | P |
|---|---|---|---|
| Age (y) | 34.6 ± 12.9 | 42.9 ± 7.7 | .004 |
| Sex: Man | 34 (90%) | 18 (90%) | 1.0 |
| Idiopathic VF | 3 (8%) | 1 (5%) | 1.0 |
| Syncope or idiopathic VF | 21 (55%) | 3 (15%) | .005 |
| Positive family history for SCA | 8 (21%) | 1 (5%) | .143 |
| Positive SAECG | 10 of 26 (39%) | 5 of 7 (71%) | .20 |

Shown are means ± standard deviation or numbers with percentages in parentheses.

Br = Brugada-type ECG; ECG = electrocardiogram; ER = early repolarization; SAECG = signal-averaged electrocardiogram; SCA = sudden cardiac arrest; VF = ventricular fibrillation.

**Table 2** Baseline ECG parameters and ECG changes with isoproterenol infusion for the ER group and the Br group

| | ER group | Br group | *P* |
|---|---|---|---|
| Heart rate (beats/min) | | | |
| Baseline | 68 (60; 79) | 71 (62; 82) | .52 |
| ΔBaseline, isoproterenol | +75 (+62; +86) | +71 (+58; +79) | .20 |
| PR (ms) | | | |
| Baseline | 160 (140; 183) | 180 (167; 189) | .026 |
| ΔBaseline, isoproterenol | −52 (−71; −27) | −54 (−67; −45) | .50 |
| QRS (ms) | | | |
| Baseline | 83 (75; 90) | 90 (85; 95) | .002 |
| ΔBaseline, isoproterenol | −5 (−5; 0) | −5 (−5; 0) | .45 |
| QT (ms) | | | |
| Baseline | 363 (340; 383) | 364 (344; 387) | .87 |
| ΔBaseline, isoproterenol | −75 (−97; −52) | −75 (−92; −38) | .60 |
| Corrected QT interval (ms) | | | |
| Baseline | 388 (371; 413) | 400 (382; 410) | .40 |
| ΔBaseline, isoproterenol | +52 (+29; +81) | +54 (+35; +65) | .72 |

Shown are medians with lower and upper quartiles in parentheses.

Br = Brugada-type ECG; ECG = electrocardiogram; ER = early repolarization; ΔBaseline, isoproterenol = difference baseline to maximal heart rate during isoproterenol challenge.

group patients (75%) with positive results in 2. In the Br group, Brugada type 1 ECG was present at the beginning of isoproterenol challenge in 6 patients (30%), type 2 in 9 (45%), and type 3 in 5 (25%). Two patients in the Br group (10%) also had inferolateral ER in inferior leads. At baseline, patients in the Br group had a significantly longer median PR interval and broader median QRS width than did patients in the ER group (Table 2).

## Impact of isoproterenol challenge on ECG and adverse events

With isoproterenol challenge, median heart rate increased from 68 to 147 beats/min in the ER group and from 71 to 139 beats/min in the Br group. Median change in heart rate, PR interval, QRS width, QT interval, and corrected QT interval are given in Table 2 and were not different in the ER group vs the Br group. One patient in the ER group developed right ventricular outflow tract tachycardia during maximal isoproterenol infusion that stopped after the termination of isoproterenol challenge. Junctional ectopic tachycardia was observed in 3 ER group patients (8%) and 1 Br group patient (5%). No other adverse events were observed, and pharmacologic challenge was completed according to the protocol in all patients.

## Effect of isoproterenol challenge on J waves

Figure 1 shows in detail the behavior of J waves for Br group and ER group patients and within the ER group for inferior and lateral J waves. The rates of persistent, decreased, and normalized J waves were significantly different for both comparisons ($P < .001$ for both). Of the 11 patients with persistent J waves in the ER group, 2 patients had J waves at baseline in both inferior and lateral leads (the lateral J waves normalized during isoproterenol infusion) and the remaining patients exclusively in the inferior leads. An increasing J-wave amplitude was observed in 2 cases with inferior ER (by +0.1 mV in both) but not in any Br group or lateral ER group patient. In the 2 Br group patients with inferior ER, these J waves decreased in one and normalized in the other.

During isoproterenol challenge, mean maximal J-wave amplitude decreased from 0.23 to 0.11 mV for inferior J waves, from 0.23 to 0 mV for lateral J waves, and from 0.27 to 0.16 mV for right precordial J waves, respectively. Mean percentage decrease of J-wave amplitude was significantly larger in lateral (−100%) than in both inferior (−55%; $P < .001$) and right precordial J waves (−46%; $P < .001$), whereas it did not differ between inferior and right precordial J waves ($P = .48$).

In the ER group, symptomatic patients (syncope or idiopathic ventricular fibrillation) did not differ from asymptomatic patients with regard to persistent J waves during

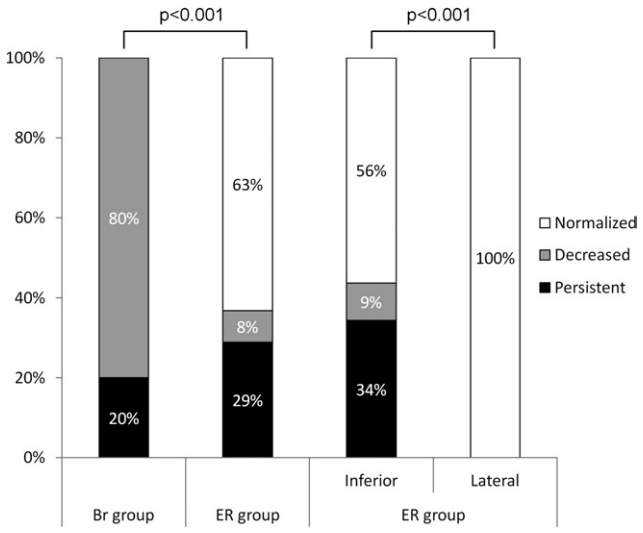


**Figure 1** Bar graph showing rates of normalized, decreased, and persistent J waves during isoproterenol challenge for the Br group, the ER group, and within the ER group for the inferior and lateral ER groups. Br = Brugada-type ECG; ECG = electrocardiogram; ER = early repolarization.

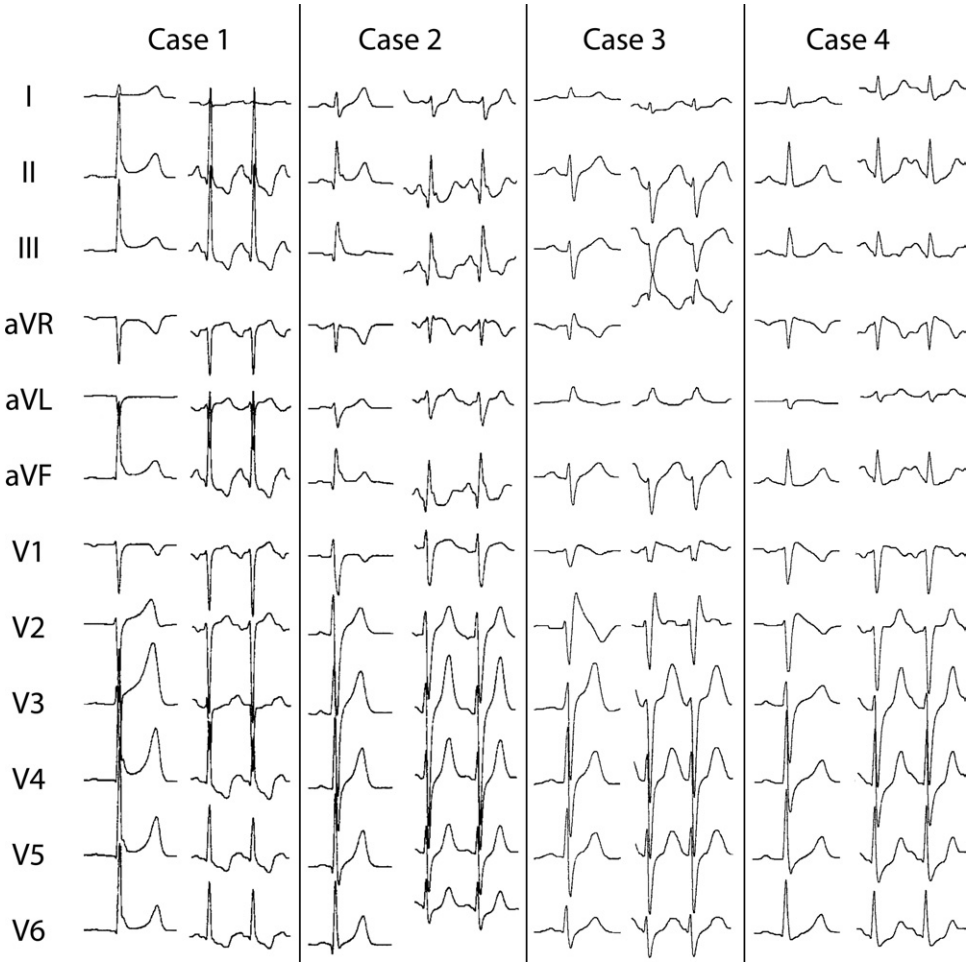


**Figure 2** Four examples of 12-lead ECGs at baseline (left tracing for each case) and at maximal heart rate during isoproterenol challenge (right tracings for each case). Case 1: inferolateral ER with normalized J waves during isoproterenol challenge. Case 2: inferior ER with persistent J waves during isoproterenol challenge. Case 3: Brugada type 1 ECG with persistent J waves in leads $V_1$ and $V_2$ during isoproterenol challenge. Case 4: Brugada type 1 ECG with normalized J wave in lead $V_2$ and decreased J wave in lead $V_1$ during isoproterenol challenge. ECG = electrocardiogram; ER = early repolarization.

isoproterenol challenge ($P = .49$) or mean decrease in inferior J-wave amplitude ($P = .46$). Figure 2 shows some examples of J-wave behavior during isoproterenol challenge for ER group and Br group patients.

### QRS width and SAECG in ER group patients with persistent J waves

Persistent J waves during isoproterenol challenge were observed in 11 ER group patients (29%; Figure 1). Median QRS width at baseline was significantly broader in these 11 patients (90 ms [quartiles 85 ms; 95 ms]) than in the remaining 27 ER group patients (80 ms [quartiles 75 ms; 85 ms]; $P = .003$; Figure 3). In the 11 patients with persistent J waves, median QRS width did not change during beta-adrenergic stimulation (90 ms [quartiles 80 ms; 95 ms]; $P = .19$; Figure 3), whereas in the remaining patients, the median QRS width decreased significantly (75 ms [quartiles 75 ms; 80 ms]; $P < .001$; Figure 3). Heart rate increase was not different in ER group patients with persistent J waves (+76 beats/min [quartiles +63 beats/min; +85 beats/min]) compared with the remaining patients (+73 beats/min [quartiles +56 beats/min; +85 beats/min]; $P = .47$).

An SAECG was available for analysis in 26 ER group patients: in 7 patients with persistent J waves and in 19 patients with decreased or normalized J waves (Table 3). SAECG was positive for late potentials in more than half of the patients with persistent J waves and in one third of the remaining patients, but this difference was not significant (Table 3).

## Discussion

This study demonstrates important differences of J-wave behavior during beta-adrenergic stimulation: right precordial and inferior J waves may persist in a subset of patients, whereas lateral J waves always normalize. The reason for this distinctive regional sensitivity of J waves remains speculative.

The pathophysiologic mechanism responsible for the development of J waves in these disorders is still controversial. For Brugada-type ECG, both a depolarization disorder hypothesis and a repolarization disorder hypothesis are debated.[17] However, inferolateral ER is mainly considered to be a disorder of repolarization.[2,17] The different regional behavior of J waves during beta-adrenergic stimulation

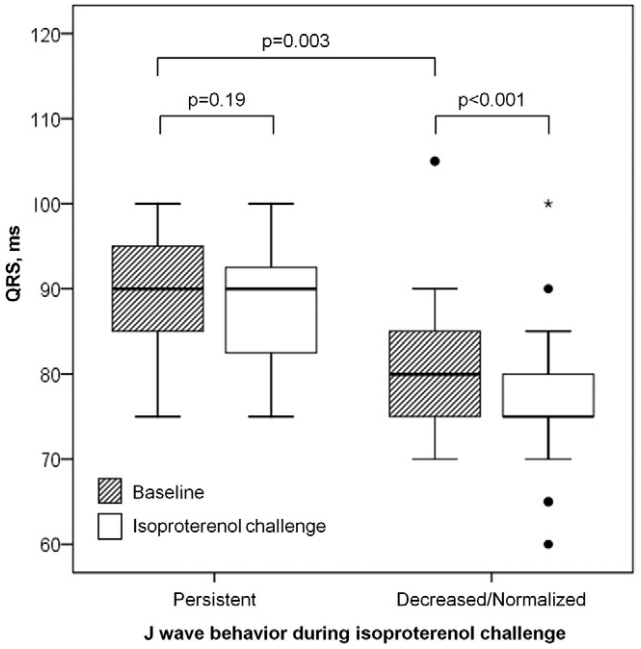


**Figure 3** Boxplots showing median QRS width at baseline and at maximal heart rate during isoproterenol challenge for patients with persistent J waves (n = 11) and for patients with decreased or normalized J waves (n = 27).

might be the consequence of a different pathophysiology and may serve as a test to investigate different mechanisms demonstrated in experimental conditions.

## Isoproterenol effect

Isoproterenol is a potent beta-adrenergic agonist with very low affinity to alpha-adrenergic receptors. Isoproterenol has both direct and indirect effects on cardiac ion channels, mainly on the L-type calcium current ($I_{Ca-L}$) and the transient outward potassium current ($I_{to}$). The effect of beta-adrenergic stimulation on $I_{Ca-L}$ is an increase in mean channel open time and probability of channel opening, thereby augmenting $Ca^{2+}$ influx.[18] This is an important parameter for the duration of the plateau phase of the action potential and thereby determines action potential duration and refractoriness. While alpha-adrenergic stimulation is reported to have an inhibiting effect on $I_{to}$, the effect of combined alpha- and beta-adrenergic stimulation or beta-adrenergic stimulation alone on $I_{to}$, although controversial, is probably to inhibit $I_{to}$.[19] Because of slow recovery from inactivation, $I_{to}$ is rate dependent with decreasing current magnitude at higher heart rates.[20]

## Beta-adrenergic stimulation and repolarization/depolarization disorder hypothesis

In the repolarization disorder hypothesis, the formation of J waves is considered to be the result of an outward shift in repolarizing currents, either because of a decrease in sodium or calcium channel currents or an increase in $I_{to}$, $I_{K-ATP}$, $I_{K-ACh}$, or other outward currents, resulting in a transmural voltage gradient.[7]

Because beta-adrenergic stimulation decreases $I_{to}$ via an acceleration of heart rate and increases $I_{Ca-L}$, isoproterenol challenge counteracts some of the primary mechanisms thought to underlie the formation of J waves in the repolarization disorder hypothesis. Accordingly, Yan and Antzelevitch[21] were able to demonstrate normalization of ST-segment elevation on isoproterenol administration in their canine model of epi-endocardial repolarization gradient induced by the potassium channel opener pinacidil. Therefore, the normalization of J waves during beta-adrenergic stimulation is consistent with the repolarization disorder hypothesis.

Impulse conduction is slowed in regions of scars or increased fibrosis, and this effect may be amplified at faster heart rates unless conduction slowing is functional, in which case beta-adrenergic stimulation might improve conduction. J waves resulting from nonfunctional conduction slowing, that is, depolarization abnormalities, would therefore be expected to persist or even increase during an accelerated heart rate. Accordingly, persistent J waves during beta-adrenergic stimulation could be a clue to depolarization abnormalities involved in J-wave formation.

**Table 3** Signal-averaged ECG in ER group patients

| | All patients | Persistent J waves (n = 7) | Decreased/normalized J waves (n = 19) | *P* |
|---|---|---|---|---|
| SAECG | | | | |
| positive | 10 (39%) | 4 (57%) | 6 (32%) | .37 |
| fQRS | | | | |
| ms | 116 (112; 121) | 116 (105; 128) | 116 (114; 119) | .97 |
| positive | 19 (73%) | 4 (57%) | 15 (79%) | .34 |
| LAS 40 | | | | |
| ms | 36 (28; 39) | 37 (23; 43) | 34 (28; 38) | .46 |
| positive | 8 (31%) | 3 (43%) | 5 (26%) | .64 |
| RMS 40 | | | | |
| $\mu$V | 26 (18; 35) | 20 (14; 42) | 28 (22; 34) | .26 |
| positive | 8 (31%) | 4 (57%) | 4 (21%) | .15 |

Shown are numbers with percentages in parentheses or medians with lower and upper quartiles in parentheses.
fQRS = filtered QRS duration; LAS 40 = low-amplitude signal duration below 40 $\mu$V; RMS 40 = root mean square voltage in the last 40 ms of the QRS.

### Distinctive regional sensitivity of J waves to beta-adrenergic stimulation

In Brugada syndrome, there is accumulating evidence supporting altered depolarization and mild structural abnormalities to be part of the disorder and also responsible for the manifestation of the Brugada ECG pattern.[17,22–24] Depolarization abnormalities in the right ventricular outflow tract could therefore account for the persistent J waves during isoproterenol challenge in Br group patients. Nevertheless, there is also evidence for repolarization abnormalities to be involved in right precordial J-wave formation, and both mechanism are not mutually exclusive.[17] The fact that J waves persist during beta-adrenergic stimulation in 20% of the patients with Brugada-type ECG and decrease but never normalize in the remaining patients is compatible with a disorder involving both depolarization and repolarization.

While there is evidence that depolarization abnormalities are involved in the formation of Brugada-type ECG, there is less evidence for depolarization abnormalities in patients with inferolateral ER.[2] In this study, beta-adrenergic stimulation completely normalized all J waves in affected lateral leads of ER group patients. This is most compatible with the repolarization disorder hypothesis for lateral ER. On the other hand, J waves in affected inferior leads of ER group patients normalized in only 56% of the cases and persisted during isoproterenol challenge in 34% of the cases. Possible explanations to this different regional behavior are varying ion channel sensitivity or the involvement of depolarization abnormalities in a subset of patients with inferior J waves.

QRS width of ER group patients with persistent J waves during beta-adrenergic stimulation was slightly but significantly broader than the QRS width of the remaining patients. Furthermore, QRS width remained unchanged in patients with persistent J waves while it decreased significantly in the remaining patients. Although these are subtle differences and patient number was low in the group with persistent J waves, this may suggest that depolarization abnormalities are involved in a subset of patients with inferior ER.

Ventricular late potentials recorded by SAECG are generally thought to correspond to depolarization abnormalities, although this has been questioned by some groups.[17] The prevalence of late potentials in ER group patients was 39% in our study. Late potentials have previously been described in patients with inferolateral ER with varying prevalence among different studies depending on the definition of late potentials and equipment used.[2,5,25–27] For example, Soliman et al[27] described a prevalence of late potentials of 11% in a large group of patients with inferolateral ER out of a patient population referred for Holter ECG recording, similar to the original report by Haissaguerre et al.[2] Abe et al,[28] on the other hand, used a specific Holter ECG system in patients with idiopathic ventricular fibrillation and inferolateral ER and found late potentials in 6 of the 7 patients, most prominent during nighttime. In our study, the high prevalence of late potentials in patients with persistent J waves during isoproterenol challenge is another finding suggesting that depolarization abnormalities may play a role in the genesis of J waves in inferior leads.

Our results clearly indicate that the patient population presenting with the ECG pattern of inferolateral ER might be heterogeneous. Patients with lateral ER, which is the typical type of ER in young, athletic, and predominantly male subjects, display a uniform response to isoproterenol challenge compatible with a disorder of repolarization. In a subset of patients with inferior ER, on the other hand, J waves persist, suggesting that other mechanism may be involved in J-wave formation.

### Limitations

Patient number in this study was low, especially for those with persistent J waves during beta-adrenergic stimulation, and larger studies are needed to confirm these results. Brugada type 1 pattern was present at baseline in only 30% of the Br group patients, and results may be different if more such patients were included. There is a selection bias as most patients undergoing isoproterenol testing had symptoms compatible with an arrhythmia and results therefore cannot be generalized to the general population with J-wave syndromes. Furthermore, except for the 3 patients with idiopathic ventricular fibrillation we do not know which patients had a malignant variant of early repolarization and results of drug effect might be different if more such patients would be included. Finally, the definition employed for the qualitative analysis of J-wave behavior is arbitrary. For example, if decreasing and normalized J-wave behavior would be grouped together in Figure 1, there would be no difference any more between the Br group and the ER group.

## Conclusions

J waves respond heterogeneously to beta-adrenergic stimulation: right precordial and inferior J waves may persist in a subset of patients with J-wave syndromes, whereas lateral J waves always normalize. This distinctive regional sensitivity of J waves could indicate a different pathophysiological mechanism, and depolarization abnormalities or different regional ion channel sensitivity may be possible explanations.

## Appendix

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.hrthm.2012.08.003.

## References

1. Tikkanen JT, Anttonen O, Junttila MJ, et al. Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med 2009;361:2529–2537.
2. Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358:2016–2023.
3. Nam GB, Kim YH Antzelevitch C. Augmentation of J waves and electrical storms in patients with early repolarization. N Engl J Med 2008;358:2078–2079.

4. Rosso R, Kogan E, Belhassen B, et al. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. J Am Coll Cardiol 2008;52:1231–1238.
5. Cappato R, Furlanello F, Giovinazzo V, et al. J wave, QRS slurring, and ST elevation in athletes with cardiac arrest in the absence of heart disease: marker of risk or innocent bystander? Circ Arrhythm Electrophysiol 2010;3:305–311.
6. Patel RB, Ng J, Reddy V, et al. Early repolarization associated with ventricular arrhythmias in patients with chronic coronary artery disease. Circ Arrhythm Electrophysiol 2010;3:489–495.
7. Antzelevitch C, Yan GX. J wave syndromes. Heart Rhythm 2010;7:549–558.
8. Roten L, Derval N, Sacher F, et al. Ajmaline attenuates electrocardiogram characteristics of inferolateral early repolarization. Heart Rhythm 2012;9:232–239.
9. Haissaguerre M, Sacher F, Nogami A, et al. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization role of drug therapy. J Am Coll Cardiol 2009;53:612–619.
10. Ohgo T, Okamura H, Noda T, et al. Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation. Heart Rhythm 2007;4:695–700.
11. Watanabe A, Fukushima Kusano K, Morita H, et al. Low-dose isoproterenol for repetitive ventricular arrhythmia in patients with Brugada syndrome. Eur Heart J 2006;27:1579–1583.
12. Shimizu W, Matsuo K, Takagi M, et al. Body surface distribution and response to drugs of ST segment elevation in Brugada syndrome: clinical implication of eighty-seven-lead body surface potential mapping and its application to twelve-lead electrocardiograms. J Cardiovasc Electrophysiol 2000;11:396–404.
13. Tanaka H, Kinoshita O, Uchikawa S, et al. Successful prevention of recurrent ventricular fibrillation by intravenous isoproterenol in a patient with Brugada syndrome. Pacing Clin Electrophysiol 2001;24:1293–1294.
14. Maury P, Couderc P, Delay M, Boveda S, Brugada J. Electrical storm in Brugada syndrome successfully treated using isoprenaline. Europace 2004;6:130–133.
15. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference. Heart Rhythm 2005;2:429–440.
16. Breithardt G, Cain ME, el-Sherif N, et al. Standards for analysis of ventricular late potentials using high-resolution or signal-averaged electrocardiography: a statement by a Task Force Committee of the European Society of Cardiology, the American Heart Association, and the American College of Cardiology. Circulation 1991;83:1481–1488.
17. Wilde AA, Postema PG, Di Diego JM, et al. The pathophysiological mechanism underlying Brugada syndrome: depolarization versus repolarization. J Mol Cell Cardiol 2010;49:543–553.
18. van der Heyden MA, Wijnhoven TJ, Opthof T. Molecular aspects of adrenergic modulation of cardiac L-type $Ca^{2+}$ channels. Cardiovasc Res 2005;65:28–39.
19. van der Heyden MA, Wijnhoven TJ, Opthof T. Molecular aspects of adrenergic modulation of the transient outward current. Cardiovasc Res 2006;71:430–442.
20. Boyett MR. Effect of rate-dependent changes in the transient outward current on the action potential in sheep Purkinje fibres. J Physiol 1981;319:23–41.
21. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation 1999;100:1660–1666.
22. Nademanee K, Veerakul G, Chandanamattha P, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation 2011;123:1270–1279.
23. Postema PG, van Dessel PF, Kors JA, et al. Local depolarization abnormalities are the dominant pathophysiologic mechanism for type 1 electrocardiogram in Brugada syndrome: a study of electrocardiograms, vectorcardiograms, and body surface potential maps during ajmaline provocation. J Am Coll Cardiol 2010;55:789–797.
24. Catalano O, Antonaci S, Moro G, et al. Magnetic resonance investigations in Brugada syndrome reveal unexpectedly high rate of structural abnormalities. Eur Heart J 2009;30:2241–2248.
25. Kawata H, Noda T, Yamada Y, et al. Effect of sodium-channel blockade on early repolarization in inferior/lateral leads in patients with idiopathic ventricular fibrillation and Brugada syndrome. Heart Rhythm 2012;9:77–83.
26. Nam GB, Ko KH, Kim J, et al. Mode of onset of ventricular fibrillation in patients with early repolarization pattern vs. Brugada syndrome. Eur Heart J 2010;31:330–339.
27. Soliman EZ, Elsalam MA, Li Y. Early repolarization and markers of ventricular arrhythmogenesis in patients referred to ambulatory 24-hour ECG recording. Int J Cardiol 2012; http://dx.doi.org/10.1016/j.ijcard.2011.04.005.
28. Abe A, Ikeda T, Tsukada T, et al. Circadian variation of late potentials in idiopathic ventricular fibrillation associated with J waves: insights into alternative pathophysiology and risk stratification. Heart Rhythm 2010;7:675–682.