

Ajmaline attenuates electrocardiogram characteristics of inferolateral early repolarization

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BACKGROUND J waves are the hallmark of both inferolateral early repolarization (ER) and Brugada syndrome. While ajmaline, a class 1a antiarrhythmic drug, accentuates the J wave in Brugada syndrome, its effect on ER is unreported.

OBJECTIVE To describe the effect of ajmaline on the electrocardiogram in ER.

METHODS We analyzed electrocardiograms before and after the administration of intravenous ajmaline (1 mg/kg) in 31 patients with ER, 21 patients with Brugada type 1 electrocardiogram (Br), and 22 controls. ER was defined as J-point elevation of ≥ 1 mm with QRS slurring or notching in ≥ 2 inferolateral leads (I, aVL, II, III, aVF, V4–V6).

RESULTS Ajmaline decreased mean J-wave amplitude in the ER group from 0.2 ± 0.15 mV at baseline to 0.08 ± 0.09 mV ($P < .001$). The QRS width prolonged significantly in all 3 groups, but the prolongation was significantly less in the ER group (+21 ms) than in the Br group (+36 ms; $P < .001$) or controls (+28 ms;

$P = .010$). Decrease in mean inferolateral R-wave amplitude was similar in all the groups (ER group -0.14 mV; Br group -0.11 mV; controls -0.13 mV; $P = \text{ns}$), but mean inferolateral S-wave amplitude increased significantly less in the ER group (ER group $+0.14$ mV; Br group $+16$ mV; controls $+0.20$ mV; $P < .001$).

CONCLUSIONS: Ajmaline significantly decreases the J-wave amplitude in ER and prolongs the QRS width significantly less than in patients with Br. This indicates a different pathogenesis for both disorders. The altered terminal QRS vector probably is responsible for the decrease in the J-wave amplitude in ER, although a specific effect of ajmaline on J waves cannot be excluded.

KEYWORDS Early repolarization; Brugada syndrome; J wave; Ajmaline; Antiarrhythmic drugs; Electrocardiogram

ABBREVIATIONS Br = Brugada type 1 electrocardiogram; ER = early repolarization

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Introduction

In 2008, different groups reported an association between inferolateral early repolarization (ER) and unexplained sudden cardiac death.^{1–3} Since then inferolateral ER has been identified as a marker of arrhythmic risk in the general population as well as in those with cardiovascular disease.^{4–6} Risk assessment remains problematic, since the prevalence of inferolateral ER in the general population is as high as 5%, and most individuals with this electrocardiogram pattern have a benign prognosis.⁴

Brugada syndrome shares some important clinical and electrocardiogram characteristics with inferolateral ER, and some investigators have claimed that they are related disorders.⁷ Pharmacologic challenge with class 1 antiarrhythmic drugs in Brugada syndrome accentuates its electrocardiogram characteristics and can help in both diagnosis and risk stratification.⁸

To date, no test has proved useful for risk stratification in patients with inferolateral ER. So far, the effect of pharmacologic challenge with any class 1 antiarrhythmic drug in inferolateral ER has not been described in detail. Case reports reporting both increasing and decreasing manifestation of inferolateral ER after pharmacologic challenge with class 1 antiarrhythmic drugs have been published.^{2,9–12} The aim of the present study was to describe the effect of ajmaline, a class 1a antiarrhythmic drug, on inferolateral ER as compared with Brugada type 1 electrocardiograms (Br) and controls.

Methods

We analyzed electrocardiograms before and at the end of the ajmaline challenge in patients with inferolateral ER (ER group), in patients with Br after the ajmaline challenge (Br group), and in controls. Patients were identified retrospectively by searching a listing of patients in whom the ajmaline challenge had been performed at our institution. For the diagnosis of inferolateral ER, an electrocardiogram with an elevation of the QRS–ST junction (J point) by ≥ 1 mV above baseline in ≥ 2 contiguous leads, either as QRS slur-

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ring (a smooth transition from the QRS segment to the ST segment) or as QRS notching (a positive J deflection inscribed on the S wave) in the inferior leads (II, III, and aVF), lateral leads (I, aVL, and V4–V6), or both had to be present (J wave). Patients meeting this electrocardiogram definition were included regardless of a history of arrhythmic events. Brugada type 1 electrocardiogram was defined as reported in the second consensus conference.⁸ For controls, patients without inferolateral ER and without Br after ajmaline challenge were selected. Patients with structural heart disease were excluded.

Pharmacologic challenge

Intravenous ajmaline was infused at a dose of 1 mg/kg over 5 minutes. We recorded continuous 12-lead electrocardiogram tracings at a paper speed of 25 mm/s during and for 15 minutes after infusion, using standard equipment (Marquette MAC 5500, General Electrics, Waukesha, WI, US). All patients received the full body weight-adjusted dose of ajmaline without complications.

Electrocardiogram analysis

In each patient, the electrocardiograms just before and after the ajmaline challenge were analyzed manually. In all electrocardiograms, the heart rate, PR interval, QRS width (without J wave), QT interval, precordial R/S transition, and amplitudes of R and S waves (and Q and R' waves for lead aVR) were measured. The Bazett formula was used to correct the QT interval for the heart rate. Precordial R/S transition was defined as the first precordial lead with R wave taller than S wave. Two electrophysiologists independently analyzed the inferolateral leads I, aVL, II, III, aVF, V4, V5, and V6 of the ER group for the presence of a J wave, and if present measured the amplitude of the J wave to an accuracy of 0.5 mV. 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. In case of disagreement on the presence of a J wave in any lead, or >0.5 mV difference in measured J-wave amplitude, a third electrophysiologist was asked and a consensus formed. Examiners were blinded with regard to symptomatic versus asymptomatic cases of ER.

Statistical analysis

Categorical variables are expressed as numbers and percentages, and continuous variables are expressed as mean ± 1 standard deviation. Categorical variables were compared with the χ^2 test and the Fisher exact test and continuous variables with the Wilcoxon test and the Mann–Whitney test, as appropriate. A P value of <.05 was considered statistically significant. All analyses were performed by using SPSS 17.0 (SPSS, Inc, Chicago, IL).

Results

Study population

The characteristics of the 31 ER group patients, 21 Br group patients, and 22 controls are summarized in Table 1. There were more women in the control group, and Br group patients had more frequently experienced syncope. The reasons for the ajmaline challenge in patients with ER were idiopathic ventricular fibrillation in 3 patients, syncope in 16, ventricular extrasystole in 3, positive family history of sudden cardiac death in 5, and palpitations in 1 patient. Three patients were asymptomatic. ER affected the lateral leads in 5 patients (16%), the inferior leads in 13 patients (42%), and both in another 13 patients (42%).

Effect of ajmaline on J wave in the ER group

In the ER group, a J wave at the beginning of the ajmaline challenge was observed in 130 of the 248 inferolateral leads examined (52%). Figure 1 shows the prevalence of J waves for each analyzed lead. Overall, mean J-wave amplitude decreased significantly by –0.12 mV from 0.2 ± 0.15 mV at baseline to 0.08 ± 0.09 mV after the ajmaline challenge (P < .001). Considering only leads with J waves at the beginning of the

Table 1 Patient characteristics of the ER group, the Br group, and controls

	ER group (n = 31)	Br group (n = 21)	P value*	Controls (n = 22)	P value†
Age (y)‡	38.0 ± 13.5	44 ± 10.2	.10	38.6 ± 14.2	.92
Male	28 (90%)	15 (71%)	.13	14 (64%)	.036
Weight (kg)‡	71 ± 11	76 ± 16	.46	69 ± 12	.47
Left ventricular ejection fraction (%)‡	65 ± 0	65 ± 0	1.0	65 ± 2	.42
Idiopathic ventricular fibrillation	3 (10%)	0	.26	3 (14%)	.68
Syncope (including idiopathic ventricular fibrillation)	19 (61%)	3 (14%)	.001	12 (55%)	.62
Positive family history for sudden cardiac arrest	6 (19%)	9 (43%)	.066	5 (23%)	1.0

Unless otherwise specified, numbers in parentheses are percentages.

Br = Brugada type 1 electrocardiogram; ER = early repolarization.

*For comparison of ER group vs Br group.

†For comparison of ER group vs controls.

‡Mean ± 1 standard deviation.

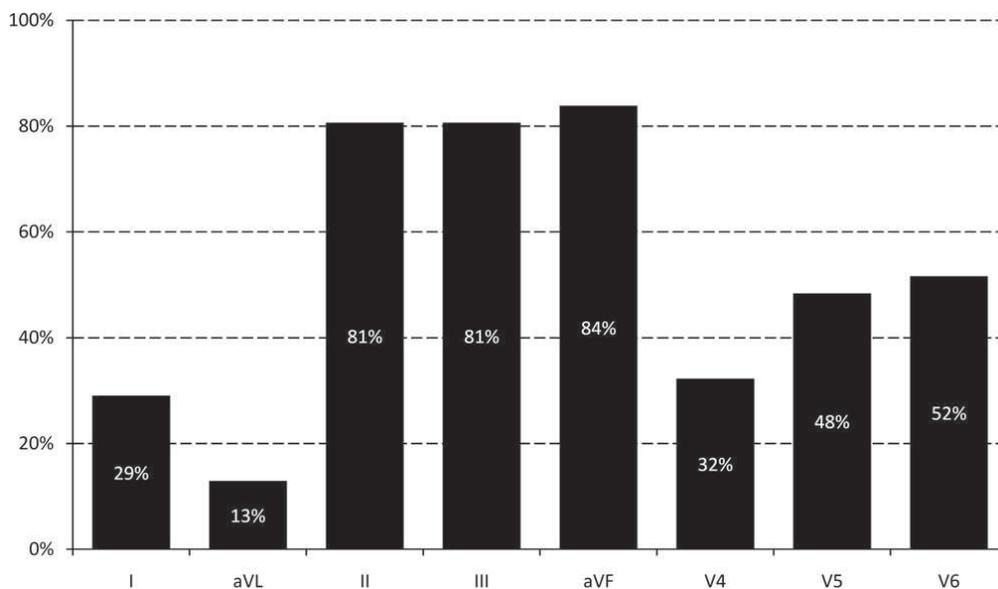


Figure 1 Bar graphs showing the prevalence of J waves at the beginning of the ajmaline challenge for the respective leads in patients with inferolateral early repolarization.

ajmaline challenge, the rate of complete disappearance of J waves varied according to regions: 28% in the inferior leads (II, III, and aVF), 46% in the high lateral leads (I and aVL), and 63% in the lateral leads (V4–V6; $P = .001$; Figure 2). Figure 3 shows the mean J-wave amplitude before and after the ajmaline challenge for every lead. Except for lead aVL, where a J wave was present in only 4 patients, the mean J-wave amplitude decreased significantly in every lead. In the 3 patients with idiopathic ventricular fibrillation and in patients with syncope, the J-wave amplitude decreased similarly as in asymptomatic patients ($P = ns$). Figure 4 shows the electrocardiogram of 3 patients before and after the ajmaline challenge.

Effects of ajmaline on the QRS complex in the ER group

Figure 3 shows the mean R- and S-wave amplitudes before and after the ajmaline challenge in patients with ER. Except for leads III, aVL, and V3, the ajmaline challenge resulted in a significant reduction in the mean R-wave amplitude in every lead. The mean S-wave amplitude increased significantly in all leads except for leads aVL and V2. The rate of a new S wave after pharmacologic challenge was 16% in lead I, 46% in II, 14% in III, 43% in aVR (R' wave instead of S wave), 5% in aVL, 24% in aVF, 0% in V1 and V2, 3% in V3, 24% in V4, and 32% in both V5 and V6.

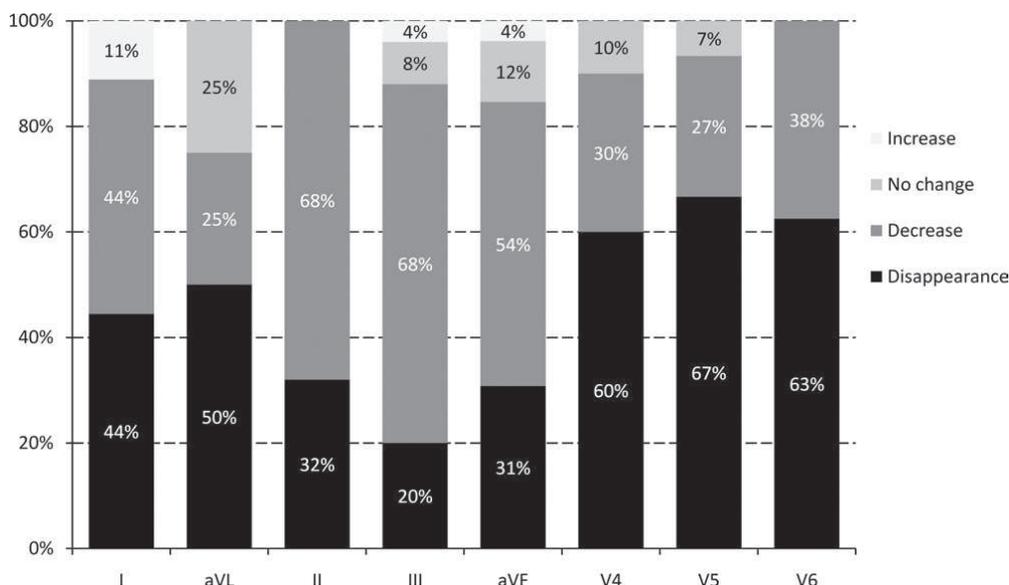


Figure 2 Bar graphs showing the behavior of the J waves during the ajmaline challenge for the respective leads in patients with inferolateral early repolarization.

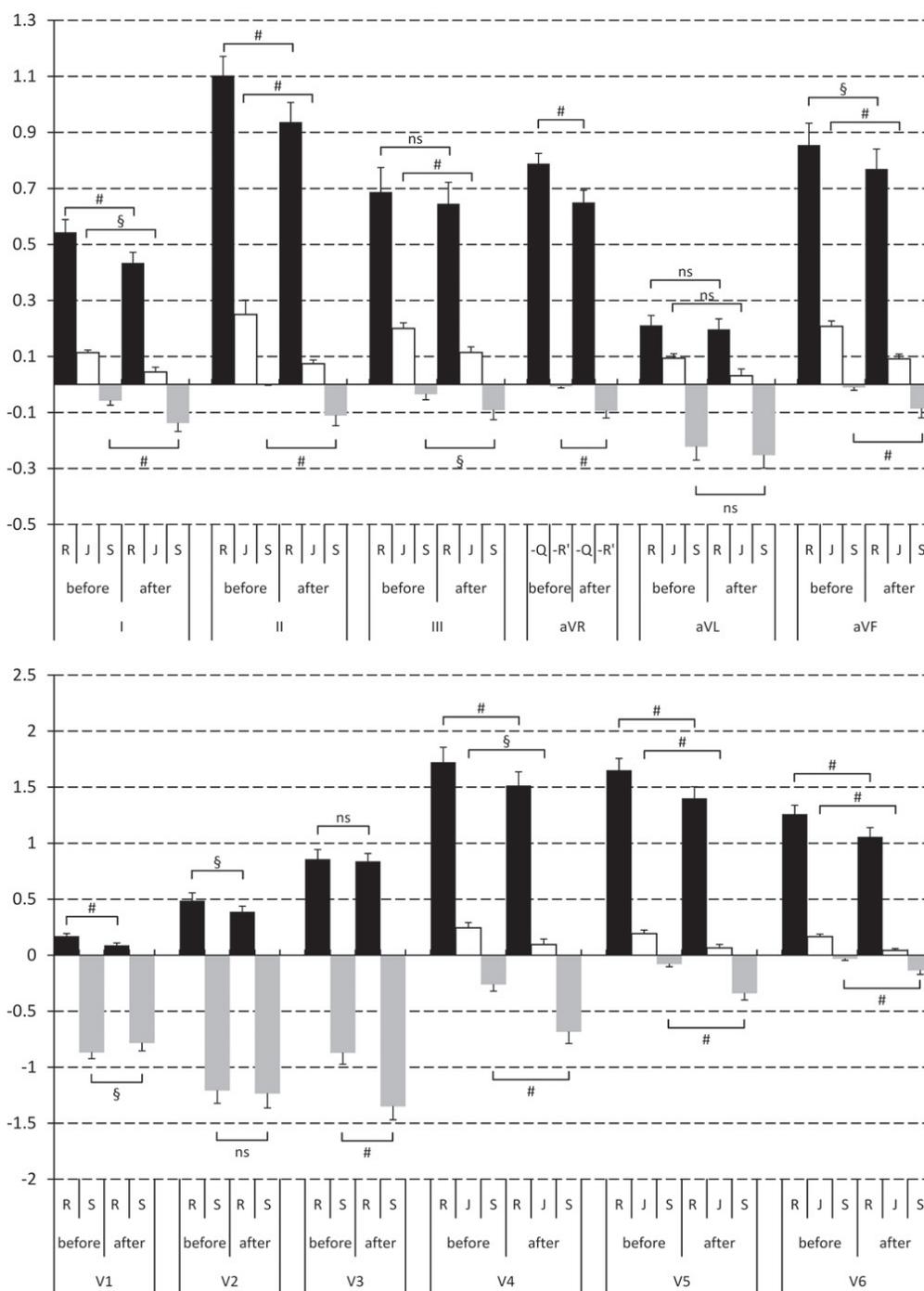


Figure 3 Bar graphs representing mean and 1 standard error of mean. Shown are R-wave amplitude (black bars), J-wave amplitude (white bars), and S-wave amplitude (gray bars) in millivolts for the respective leads at baseline and at the end of the ajmaline challenge in patients with inferolateral early repolarization. For lead aVR, reversed Q- and R'-wave amplitudes are shown instead. #*P* ≤ .001; §*P* ≤ .05; ns = *P* > .05.

Ajmaline challenge in the ER group versus the BR group and controls

In all the 3 groups, the ajmaline challenge significantly increased the heart rate, PR interval, corrected QT interval, and QRS width compared with baseline (Table 2). Prolongation of the QRS width was significantly less in the ER group (+21 ms) than in both the Br group (+36 ms; *P* < .001) and controls (+28 ms; *P* = .010). Compared with the ER group, decrease in the mean R-wave amplitude was similar in the Br group and controls, both when considering all 12 leads (−0.12, −0.9, and

−0.11 mV, respectively) and when considering the inferolateral leads (−0.14, −0.11 and −0.13, respectively). Increase in the mean S-wave amplitude in all 12 leads was similar in the ER group and the Br group (+0.14 and +0.11 mV, respectively), but compared with the ER group the mean S-wave amplitude increased significantly more in controls (+0.17 mV; *P* < .001). Considering only inferolateral leads, the mean S-wave amplitude increased significantly more both in the Br group and in controls (+0.16 and +0.20 mV, respectively) than in the ER group (+0.14 mV; *P* < .001 for both comparisons; Table 2).

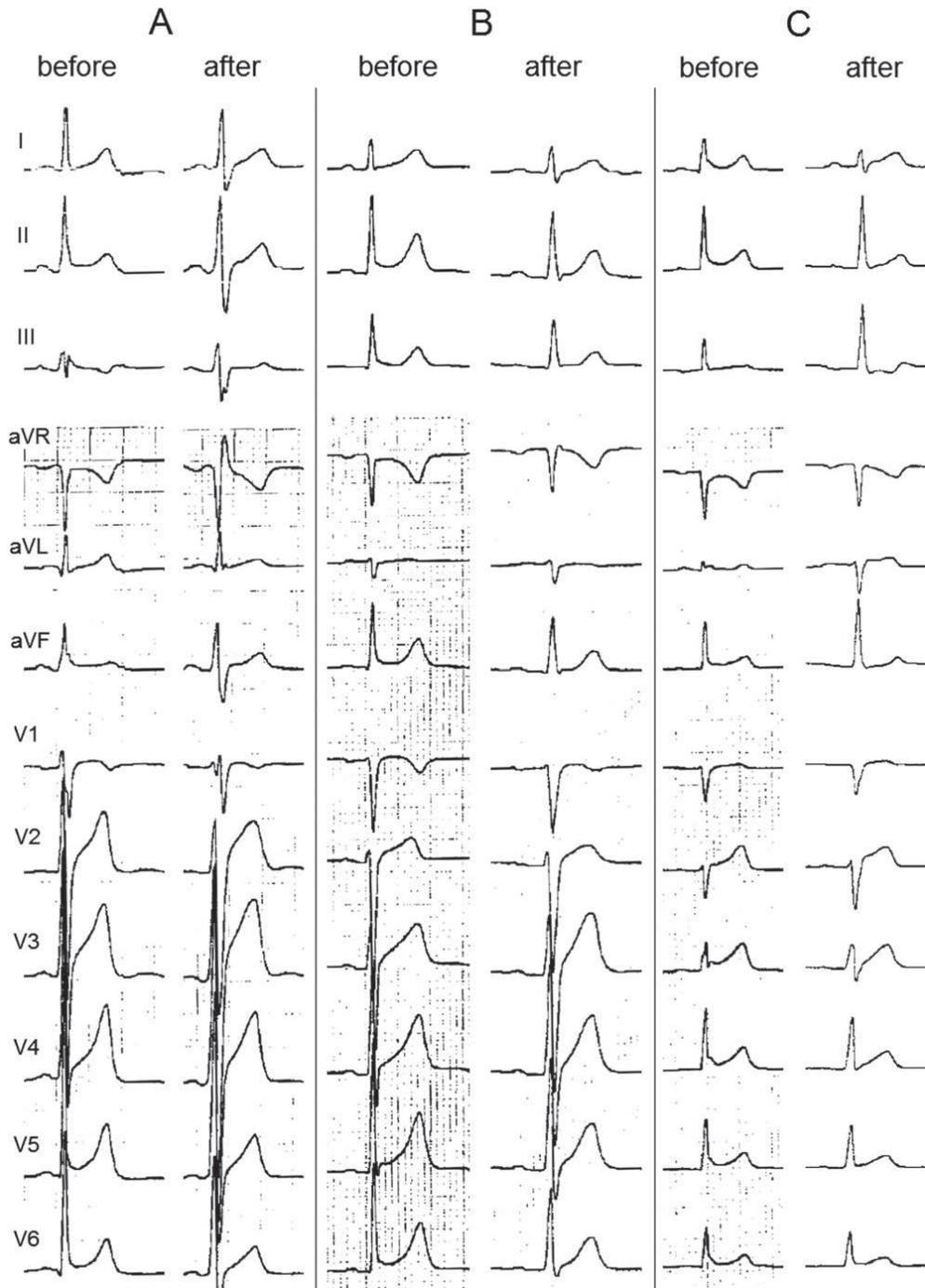


Figure 4 Example electrocardiograms of 3 patients with inferolateral early repolarization (A, B, and C) before and after the ajmaline challenge.

Figure 5 shows the mean differences between the R- and S-wave amplitudes in each lead before and after the ajmaline challenge for the ER group and controls. The mean R-wave amplitude decreased similarly in all leads in both the ER group and controls. However, ajmaline increased the mean S-wave amplitude significantly more in controls than in the ER group in leads I, II, aVR (R' instead of S wave), aVF, and V6.

Precordial R/S transition had rotated clockwise by ≥ 1 lead in 39% of the patients in the ER group, 38% of the patients in the Br group, and 41% of controls.

Discussion

The main findings of the present study are as follows: (1) Ajmaline challenge significantly decreases the J-wave amplitude and can normalize inferolateral ER. (2) Ajmaline prolongs the QRS width significantly less in inferolateral ER patients than in controls or in patients with Br. (3) In all the 3 groups, the mean inferolateral R-wave amplitude decreases significantly with ajmaline, but without differences among groups. (4) Ajmaline significantly increases the mean inferolateral S-wave amplitude in all the groups, but this effect is significantly less pronounced in inferolateral ER.

Table 2 Change in electrocardiogram parameters after the ajmaline challenge (end) compared with baseline (start) in the ER group, the Br group, and controls

	ER group		Br group		P value*	Controls		P value*
	Start	End	Start	End		Start	End	
Heart rate (min ⁻¹)	68 ± 10	76 ± 9	74 ± 14	81 ± 13	.44	74 ± 14	81 ± 13	.15
PR interval (ms)	173 ± 35	215 ± 51	171 ± 22	213 ± 28	.47	178 ± 31	227 ± 43	.21
Corrected QT interval (ms)	386 ± 21	419 ± 22	401 ± 30	451 ± 36	.021	398 ± 26	436 ± 28	.37
QRS width (ms)	81 ± 6	102 ± 12	85 ± 9	121 ± 14	<.001	85 ± 9	113 ± 13	.010
Mean R-wave amplitude (all leads) (mV)	0.86 ± 0.64	0.74 ± 0.58	0.68 ± 0.52	0.59 ± 0.48	.24	0.71 ± 0.49	0.60 ± 0.43	.27
Mean S-wave amplitude (all leads) (mV)	0.31 ± 0.50	0.44 ± 0.58	0.28 ± 0.34	0.39 ± 0.36	.33	0.34 ± 0.42	0.51 ± 0.49	<.001
Mean R-wave amplitude (ER leads) (mV)	1.0 ± 0.68	0.87 ± 0.61	0.79 ± 0.55	0.68 ± 0.51	.44	0.82 ± 0.52	0.69 ± 0.45	.92
Mean S-wave amplitude (ER leads) (mV)	0.09 ± 0.19	0.23 ± 0.34	0.15 ± 0.21	0.31 ± 0.29	<.001	0.17 ± 0.24	0.38 ± 0.34	<.001
R/S transition	3.4 ± 0.7	3.9 ± 0.8	3.5 ± 0.8	4.1 ± 1.1	.92	3.9 ± 0.4	4.4 ± 0.7	.85

Mean ± 1 standard deviation are shown. ER leads: inferolateral leads (I, aVL, II, III, aVF, and V4–V6).

Br = Brugada type 1 electrocardiogram; ER = early repolarization.

*For comparison with the ER group.

Pharmacologic challenge with class I antiarrhythmic drugs has profound effects on the electrocardiogram. It is well known to increase the PR interval, QRS width, corrected QT interval, and heart rate and to help in diagnosing suspected cases of Brugada syndrome.^{13,14} Less known are specific effects of class I drugs on the J-wave amplitude and on the QRS complex (reflected by changes in R/S-wave amplitudes).

Effect of ajmaline on J wave

Several mechanisms can possibly explain the observed decrease in the J-wave amplitude. First, the ajmaline challenge not only broadens the QRS complex but also alters the terminal QRS vector, reflected by the newly appearing S waves or the increase in S-wave amplitudes. Except for lead aVL, we observed a significant increase in the S-wave amplitude in all inferolateral leads with the ajmaline challenge. Overall, the S-wave amplitude increased from 0.09 to 0.23 mV in inferolateral leads. These S waves represent an opposing force to the J waves and depending on their amplitude and duration can either decrease or completely hide the J waves. This hypothesis is supported by the finding that after the ajmaline challenge the increase in the S-wave amplitude in inferolateral leads was significantly less in patients with inferolateral ER compared with controls, while the decrease in the R-wave amplitude was similar in both groups. Because of conduction slowing at peak ajmaline dose, reflected by QRS broadening, the terminal ventricular activation is further delayed, that is, the S waves will even more superimpose the J waves.

Second, the heart rate increased by a mean of 8 beats per minute during the ajmaline challenge. The heart rate

increase by adrenergic stimulation can reduce the J-wave amplitude in both inferolateral ER and Brugada syndrome.⁷ Nevertheless, it is unlikely that this effect plays a major role in reducing the J-wave amplitude, because the heart rate increase was only small, and in Brugada syndrome there is a clear accentuation of the J wave with the ajmaline challenge despite a well-described increase in the heart rate.^{13,14}

Third, a specific effect of ajmaline on the ionic currents responsible for the generation of the J wave might also play a role. To date, the exact pathophysiological mechanism responsible for the development of inferolateral J waves is a matter of debate. The hypothesis is that an outward shift in repolarizing current due to a decrease in sodium- or calcium-channel currents or an increase in I_{to}, I_{K-ATP}, I_{K-ACh}, or other outward currents can give rise to a J wave both in Brugada syndrome and in inferolateral ER.⁷ Ajmaline is a potent inhibitor of the sodium-channel current I_{Na}, which is responsible for its prolonging effect on the PR interval and the QRS width. Ajmaline also inhibits the transient outward current I_{to} and accelerates its decay. A Brugada-type electrocardiogram can be unmasked in affected individuals by the ajmaline challenge because it reduces net inward currents, that is, greater effect on I_{Na} than on I_{to}.¹⁴ In our study, we did not observe an accentuation of the electrocardiogram phenotype of inferolateral ER with the ajmaline challenge.

Effect of ajmaline on the QRS complex

Electrophysiological studies have suggested delayed depolarization in the right ventricular outflow tract being responsible

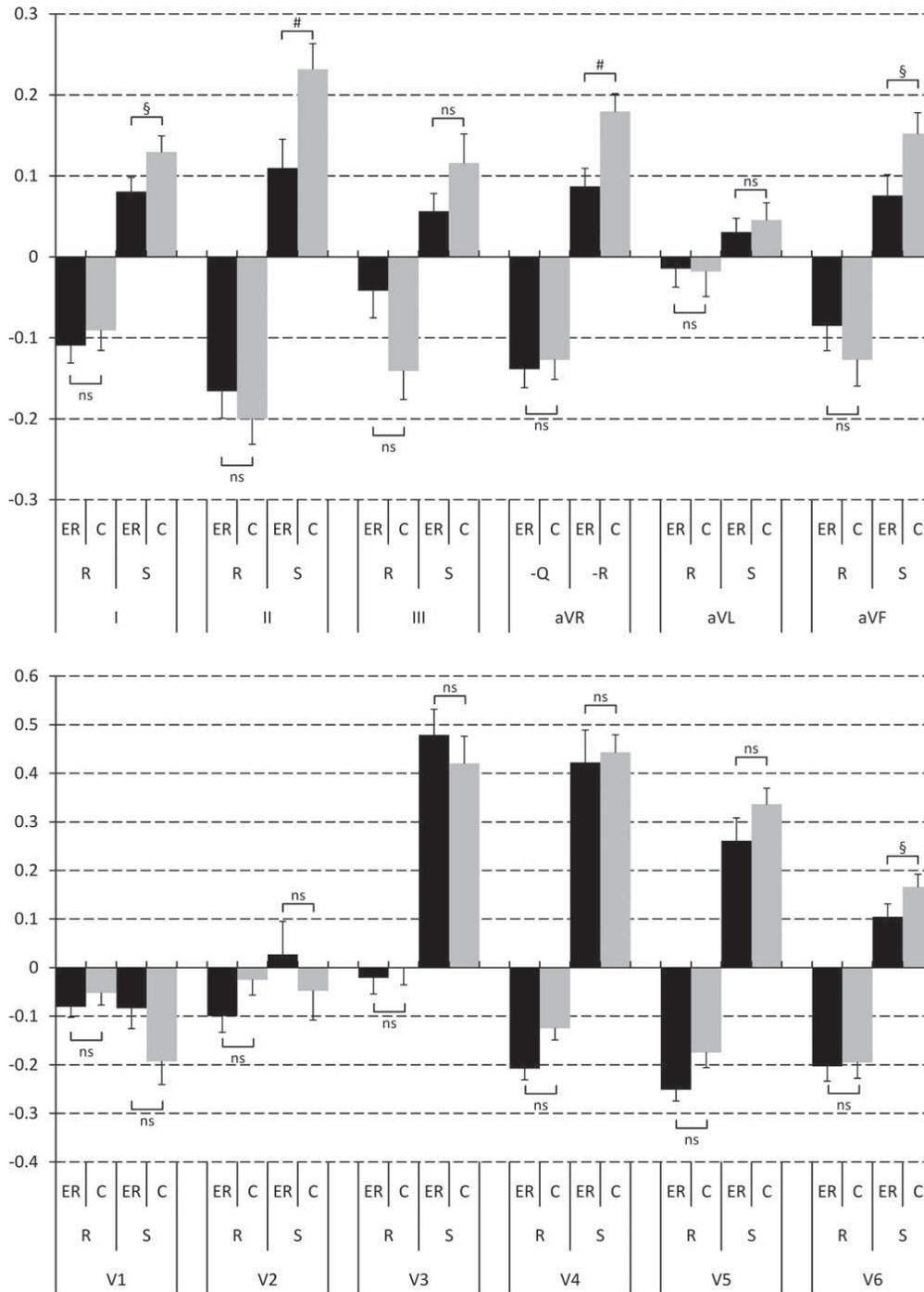


Figure 5 Bar graphs representing mean and 1 standard error of mean. Shown are differences of R-wave amplitude and S-wave amplitude in millivolts for the respective leads after the ajmaline challenge compared with baseline for the inferolateral ER group (ER; black bars) and controls (C; gray bars). For lead aVR, reversed Q- and R'-wave amplitudes are shown instead. ER = early repolarization. #*P* ≤ .001; §*P* ≤ .05; ns = *P* > .05.

for the Brugada-type electrocardiogram.^{15,16} This delayed depolarization probably is caused by structural abnormalities located in the right ventricular outflow tract.¹⁷ A recent study showed that conduction disturbances because of current-to-load mismatch, as can be expected in the case of structural abnormalities, can cause a Brugada-type electrocardiogram in a porcine model.¹⁸ Therefore, an alternate hypothesis to Brugada syndrome pathogenesis is a conduction disorder, reflected by excessive QRS width prolongation after the ajmaline challenge. Contrary to Brugada syndrome, electrophysiological

studies were unable to demonstrate delayed depolarization in hearts affected by inferolateral ER, and late potentials were only infrequently found by signal-averaged electrocardiograms in these patients.¹ In the present study, the QRS width prolonged significantly less after the ajmaline challenge in inferolateral ER compared with Brugada-type electrocardiogram and even controls. This intriguing finding could therefore reinforce the hypothesis of inferolateral ER being a disorder of repolarization and have a different pathogenesis as compared with Brugada syndrome.

After the ajmaline challenge, Batchvarov et al¹⁹ observed a type 1 Brugada pattern in ≥ 1 peripheral lead in 6 of 143 patients, 3 of which were tested positive and 2 borderline for Brugada syndrome. Interestingly, a type 1 Brugada pattern in peripheral leads was mostly seen in lead aVR, where during the ajmaline challenge a R' wave develops in many patients, and in lead III, where the S-wave amplitude increases considerably less during the ajmaline challenge than in the other peripheral leads. Therefore, the formation of a type 1 Brugada pattern in most peripheral leads as well as in leads V4 to V6 might have been prevented by increasing S-wave amplitudes induced by the ajmaline challenge. Nevertheless, in our patient population of inferolateral ER we did not observe development of a type 1 Brugada electrocardiogram in any peripheral lead with the ajmaline challenge.

Effect of other class 1 antiarrhythmic drugs on ER

The effect of ajmaline on inferolateral ER might differ from the effect of other antiarrhythmic drugs. Ajmaline is more effective than flecainide in unmasking a Brugada-type electrocardiogram in affected individuals, probably because it is a less potent inhibitor of I_{to} than is flecainide.¹⁴ Nam et al² reported no provocation of inferolateral ER with flecainide, but they did not state whether J waves were attenuated by flecainide. Some case reports describe no change or augmentation of J waves after pharmacologic challenge with procainamide.^{9–11} Disopyramide has been reported to reduce J waves in 2 case reports.^{11,12} Finally, quinidine was the most successful antiarrhythmic drug in eliminating ventricular fibrillation in patients with inferolateral ER, whereas mexiletin was not and class 1c antiarrhythmic drugs were only partially successful.²⁰ Quinidine can also normalize the electrocardiogram in inferolateral ER. Therefore, there is a wide variability in the effect of different class 1 antiarrhythmic drugs on inferolateral ER. Unfortunately, pharmacologic challenge so far has not been helpful in further risk stratification of patients with inferolateral ER. And unlike in Brugada syndrome, ajmaline attenuates rather than accentuates the electrocardiogram characteristics of inferolateral ER in the vast majority of patients.

Limitations

This is a retrospective study without follow-up. Only a limited number of patients in the inferolateral ER group had an arrhythmic event and patients with both malignant and probably benign forms of inferolateral ER were included. The results might be different if only malignant forms of inferolateral ER would be included in the study. The effect of other class 1 antiarrhythmic drugs such as flecainide, disopyramide, or procainamide might differ from the effect of ajmaline in patients with inferolateral ER; therefore, these findings cannot be generalized to other class 1 antiarrhythmic drugs.

Conclusions

Ajmaline significantly decreases the J-wave amplitude in inferolateral ER and prolongs the QRS width significantly

less than in patients with Br or controls. This indicates a different pathogenesis for both disorders. The altered terminal QRS vector probably is responsible for the decrease in the J-wave amplitude after the ajmaline challenge in inferolateral ER, although a specific effect on J waves cannot be excluded. Contrary to the accentuating effect of ajmaline on the J wave in Brugada-type electrocardiogram, our data do not support a role for ajmaline in the risk stratification of patients with inferolateral ER.

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