Correlation Between the Effective Refractory Period and Activation-Recovery Interval Calculated From the Intracardiac Unipolar Electrogram of Humans With and Without dl-Sotalol Treatment

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In experimental studies and/or human body surface mapping, the activation–recovery interval (ARI) is used as a parameter to estimate local repolarization. However, it has not been clarified whether the ARI calculated from the intracardiac unipolar electrogram of humans reasonably represents the local effective refractory period (ERP). Measurement of ARIs at multiple ventricular sites can be helpful in assessing the dispersion of ventricular refractoriness of humans, so we examined the relationship between ERP and ARI in the control state and under treatment with dl-sotalol during clinical electrophysiology studies (EPS). Of 19 patients, an EPS was performed in the control state in 12 and during treatment with dl-sotalol in the other 7. Quadrupolar electrode catheters with an interelectrode distance of 5 mm were placed at the right atrium and in the right ventricle. Using atrial pacing, the heart rate was increased incrementally by 10 beats/min, and ERP and ARI were measured for each pacing rate. The ERP at the right ventricle was measured by single extrastimulation between the first and third distal electrodes of the catheter in the right ventricle, and the ARI was calculated from the second distal unipolar electrode of the same catheter as the interval between the minimum derivative of the intrinsic deflection and the maximum derivative of the T wave. In all patients, the unipolar electrogram was stable during the entire EPS, and 83 data points in the control group and 50 in the dl-sotalol group were analyzed. At each pacing rate, the beat-to-beat difference of ARI was less than 10 ms. As the atrial pacing rate increased, the ERP and ARI were progressively shortened, and linear regression analysis revealed an excellent correlation between ERP and ARI. At the same pacing rate, the ERP and ARI in the dl-sotalol group were longer than those in the control group, but no difference was observed in the slope (close to 1.0) and in the intercept of the regression lines between ERP and ARI. In the human ventricle, the ARI calculated from the intracardiac unipolar electrogram represents the local ERP both in the control state and under treatment with dl-sotalol. The ARI can be used as a parameter of local refractoriness and used to study the distribution of refractoriness in the human ventricle. (Jpn Circ J 2001; 65: 702–706)

Key Words: Activation–recovery interval; dl-sotalol; Effective refractory period; Ventricular tachyarrhythmia

Methods

Subjects

Nineteen patients were enrolled and of these, an EPS was performed without any medication, except for diuretics.
and angiotensin converting enzyme inhibitors, in 12 patients (control group; 8 males, 4 females; age range, 12–74 years) and in 7 patients under treatment with dl-sotalol (dl-sotalol group; 5 males, 2 females; age range, 21–60 years). The results of hematological and serological examinations were normal, and no electrolyte abnormalities were observed. The 12-lead electrocardiogram (ECG) at rest showed normal sinus rhythm, and bundle branch blocks or fascicular blocks were not observed in any patient. Patients with congenital or acquired long QT syndrome were excluded.

In the control group, the heart rate and QT(QTc) interval were 69±9 beats/min and 400±26 (430±48) ms, respectively. The indication for an EPS was supraventricular tachycardia in 3, ventricular tachyarrhythmia in 6 and unexplained syncope in the remaining 3 patients. Conventional cardiac examination demonstrated that 4 patients had an old myocardial infarction associated with left-sided coronary artery occlusion, 2 patients had cardiomyopathy, and the one remaining patient had mild mitral and aortic valve regurgitation. No underlying heart disease was detected in the other 5 patients.

In the treatment group, dl-sotalol was being used to treat ventricular tachyarrhythmia in all patients, and the EPS was performed to evaluate drug efficacy. dl-Sotalol was started at a dose of 80 mg/day and increased by 40 mg/day weekly under the monitoring of blood pressure, heart rate and ECG. At the time of the EPS, dl-sotalol was being prescribed at 160 mg/day in 3 patients, 200 mg/day in 1 patient and 240 mg/day in the other 3 patients. The mean duration of treatment before the EPS was 25.8±7.6 days (18–37 days). After treatment with dl-sotalol, the heart rate decreased from 71±17 to 56±6 beats/min and the QT(QTc) interval was prolonged from 410±30 (441±28) to 467±43 (457±49) ms, respectively. Three patients had cardiomyopathy, 1 had an old myocardial infarction, and 1 was post-operative after correction of tetralogy of Fallot. No underlying heart disease was observed in the remaining 2 patients.

**Electrophysiologic Study**

The EPS was performed in the non-sedated and post-absorptive state. Informed consent was obtained after explanation of the procedure, results and possible complications. Three 6Fr quadripolar electrode catheters with interelectrode distances of 5 mm (Josephson Electrode Catheter, Bard Electrophysiology) were positioned at the right atrium, the His-electrogram recording site and the right ventricle. Then, single premature ventricular stimulation that was triggered by the local electrogram was applied between the first and third distal electrodes of the catheter placed in the right ventricle. The coupling interval of premature stimulation was progressively shortened in steps of 2 ms and the longest coupling interval that failed to provoke the propagated response on 2 successive attempts was defined as the ERP. To obtain a steady state, each premature stimulation was applied after a 20 s interval.

According to previous reports, the ARI is defined as the interval between the time of minimum derivative of the intrinsic deflection and the maximum derivative of the T wave of the unipolar electrogram. For the analysis of the ARI, analog data of the intracardiac electrogram were digitized at a sampling rate of 1,000 samples per second (MacLab System). The digitized signals were then stored on the hard disk of a personal computer. The ARI was measured in each atrial pacing rate and averaged ARI values were calculated from 3 consecutive beats prior to the last extrastimulation. The relationship between the ERP and the ARI was examined by linear regression analysis.

**Statistical Analysis**

Statistical analysis between the 2 groups was performed using the Student’s t-test and Fisher’s exact probability test. Correlation between the ERP and the ARI was assessed by linear regression analysis with comparison of the 2 regression parameters of slope and intercept, and these were compared between the control and dl-sotalol groups. Data are expressed as mean±SD value, except for those shown in the Figures, which are expressed as mean±SEM values. Significance was defined as p<0.05.

**Results**

**Measurement of ERP and ARI**

At the time of the EPS, the basic heart rate in the control group was faster than that in the dl-sotalol group (69±9 vs 58±8 beats/min, p<0.05). Attrioventricular conduction showed Wenckebach conduction at the atrial pacing rate of 154±17 beats/min in the control group and the same was shown at the slower pacing rate of 133±18 beats/min in the dl-sotalol group (p<0.05). In the control group, 5–9 data points were obtained from each patient by increasing the atrial pacing rate, and a total of 83 data points were analyzed (Fig 1). On the other hand, 50 data points (4–10 points from each patient) were obtained in the dl-sotalol group (Fig 2).

In all patients, stable unipolar electrograms were recorded during the entire study protocol. At the same atrial pacing rate, the ARI calculated from each beat was quite similar and the difference was always less than 10 ms (Figs 1, 2). As the atrial pacing rate increased, the ARI shortened in concordance with the shortening of ERP. At the same pacing rate (ranging from 70 to 140 beats/min), the ERP and ARI of the control group were significantly shorter than the EPS. To control the heart rate, fixed pacing was applied from the right atrium starting at the rate that was 10 beats/min higher than that of sinus rhythm. Rapid pacing was then increased incrementally by 10 beats/min until atrioventricular conduction showed the Wenckebach phenomenon. Each pacing was continued for more than 60 s before measuring the ERP and ARI. During the measurement of the ERP, the unipolar electrogram was continuously recorded from the second distal electrode of the catheter placed in the right ventricle. Then, single premature ventricular stimulation that was triggered by the local electrogram was applied between the first and third distal electrodes of the same catheter. The coupling interval of premature stimulation was progressively shortened in steps of 2 ms and the longest coupling interval that failed to provoke the propagated response on 2 successive attempts was defined as the ERP. To obtain a steady state, each premature stimulation was applied after a 20 s interval.

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those of the dl-sotalol group (Fig 3). Statistical comparison could not be attempted beyond the pacing range because the basic heart rate of the control group was usually more than 60 beats/min and the atrioventricular conduction of the dl-sotalol group sometimes showed the Wenckebach phenomenon at the pacing rate of more than 150 beats/min.

**Correlation Between the ERP and ARI**

In both the control and dl-sotalol groups, the ARI calculated from the second distal unipolar electrode of the
catheter placed at the right ventricle was approximate to the local ERP in the various atrial pacing rates (Figs 1, 2). Linear regression analysis revealed an excellent correlation between the ERP and the ARI in both groups (Fig 4), and there were no statistical differences in the slope and intercept of linear regression between the ERP and ARI in the 2 groups. The slope of the ERP and ARI relation was close to 1.0 in both groups (1.08 in the control group and 1.01 in the dl-sotalol group).

**Discussion**

In clinical EPS, local refractoriness is usually assessed using programmed electrical stimulation and/or recording of the monophasic action potential. However, these methods are unsuitable when evaluating the distribution of intraventricular refractoriness because programmed electrical stimulation can not measure ventricular refractoriness at multiple sites during the same beat and a stable monophasic action potential is difficult to record for relatively longer periods.

The ARI has been used as a parameter to estimate local refractoriness in experimental studies and in humans using the body surface electrocardiogram. Although the ARI is analyzable from the intracardiac unipolar electrocardiogram during a clinical EPS, the correlation between local refractoriness and the ARI obtained from the intracardiac electrogram has not been studied much in humans. Thus, we examined the relationship between the ERP and the ARI during clinical EPS to clarify whether the ARI can be used as a parameter of intracardiac refractoriness. Our results showed that the ARI measured from the unipolar intracardiac electrogram represents the local ERP at various heart rates (Figs 1, 2), which was consistent with the results of previous experimental studies. Further, the same excellent correlation was observed in patients treated with dl-sotalol, and the result showed that the ARI in the dl-sotalol group corresponded as well to the ERP as in the control group. Further, the slope and intercept of the linear regression line did not differ between the control and treatment groups (Fig 3). Although we did not measure the serum concentration of dl-sotalol, it was considered to be acting on the heart because of the slower sinus rate, longer ERP at various pacing rates (Fig 3), and the development of the Wenckebach phenomenon at slower atrial pacing compared with the control group.

**Clinical Implications**

Because the unipolar electrogram from the intracardiac electrode catheter was stable, clearly recorded during the whole protocol and the ARI obtained from the intracardiac electrogram reasonably represented the local ERP, the distribution of intraventricular refractoriness could be evaluated by the ARIs at multiple sites using multipolar electrodes catheters placed at different ventricular sites. Analysis of the intracardiac ARIs may be useful for studying the arrhythmogenic substrate of ventricular tachyarrhythmia during a clinical EPS.

**Study Limitations**

Sites showing abnormal local electrograms may be involved in the arrhythmogenic substrate of ventricular tachyarrhythmia, but in such sites the late diastolic threshold of pacing is usually high (>5 V) and is able to capture a large amount of the myocardium surrounding the unipolar electrogram recording site. Thus, as the first step, we studied the relationship between the ERP and the ARI at the sites where the local electrogram showed normal configuration and its late diastolic threshold was less than 1.5 V. Because previous experimental studies have shown that the ARIs derived from unipolar electrograms are reasonably approximate to local ERPs regardless of the T wave morphology, we consistently measured the ARI as the interval between the time of minimum derivative of the intrinsic deflection and the maximum derivative of the T wave of the unipolar electrogram, and confirmed a reasonable correlation between the ERP and the ARI in the sites showing normal bipolar electrocardiograms. However, more complicated T wave configurations (bi- and triphasic morphology or low amplitude), possibly from an area with abnormal local electrogram, may modulate the excellent relationship between the ERP and the ARI. Although we only studied the ARI in the right ventricle, there seems to be no specific reason why the ARI obtained from the left ventricle would not represent the local ERP. Further studies...
will be required in patients with congenital or acquired long QT syndrome and patients treated with other kinds of antiarrhythmic drugs.

Because we applied extrastimulation during simultaneous recording of the unipolar electrocardiogram from different electrodes (pacing using the most and third distal electrodes and recording using the unipolar electrogram of the second distal electrode), errors from some spatial difference may be involved for the ERP and the ARI. The interelectrode distance of the multipolar electrode catheter may modulate the relationship, but we used only standard catheters with an interelectrode distance of 5 mm. Finally, larger studies will provide more precise and confirming results concerning the clinical importance of measuring the ARI from the intracardiac electrograms during a clinical EPS.

Acknowledgments

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References

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