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Relation Between Repolarization and Refractoriness in the Human Ventricle: Cycle Length Dependence and Effect of Procainamide

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The cycle length dependence of the action potential duration and the effective refractory period of the right ventricular endocardium were investigated in 24 patients undergoing electrophysiologic studies for suspected ventricular tachycardia. The action potential duration at 90% repolarization and the effective refractory period at twice diastolic threshold strength were measured at the same catheter site at steady state cycle lengths of 350 to 600 ms. Both measurements decreased linearly with decreasing cycle length, maintaining a parallel relation. When the relation between action potential duration and effective refractory period was expressed as the effective refractory period-action potential duration difference, nearly constant values (range −12 to −15 ms) were obtained at all cycle lengths.

To determine whether sodium channel blocking drugs influence the effective refractory period-action potential duration relation in humans, measurements of these two variables were obtained in 15 patients before and during the infusion of procainamide. Procainamide prolonged the action potential duration at each cycle length by a near constant amount over baseline values ($p < 0.001$). Procainamide also increased the effective refractory period at each cycle length but with a greater incremental increase at the shorter cycle lengths. The rate-dependent increase in the effective refractory period-action potential duration difference became significant at cycle lengths ≤400 ms; at these high rates, the effective refractory period-action potential duration difference became positive (1.6 ms, $p < 0.01$ compared with baseline).

Thus, in the human ventricle, the action potential duration and the effective refractory period have a close relation that remains fixed over a wide range of cycle lengths. The cycle length-dependent increase in the effective refractory period relative to action potential duration induced by procainamide is consistent with use dependency of sodium channel blocking drugs observed in vitro and may be a useful marker for measuring antiarrhythmic drug activity in vivo.

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In vitro studies (1,2) have demonstrated that both the action potential duration and the effective refractory period decrease when the cycle length is shortened. Clinical electrophysiologic studies (3) have confirmed the cycle length dependence of the effective refractory period in human myocardium and studies (4,5) using monophasic action potential catheters have confirmed a similar rate response of the human action potential duration. Although these data suggest a close relation between repolarization and excitability in the human heart in vivo, one previous clinical study (6) reported only poor correlation between right ventricular action potential duration and effective refractory period measurements. However, in that clinical study, action potential duration and effective refractory period were measured at disparate right ventricular endocardial sites and lack of a close correlation between the two variables may have been due to site-specific variability of either action potential duration or effective refractory period (7,8). A direct in vivo comparison of human action potential duration and effective refractory period, both measured at the same endocardial site, has not yet been reported.

The purpose of the present clinical study was twofold. First, having developed a technique to measure both the action potential duration and the effective refractory period at the same endocardial site in the human heart (9), we wished to determine the relation of the action potential duration and the effective refractory period in human ventricular myocardium and the cycle length dependence of this relation. Second, we wanted to determine the effect of a sodium channel blocking agent, procainamide, on this relation and specifically on the cycle length dependence of this effect. Our interest in the cycle length-dependent effects of procainamide on the action potential duration-effective refractory period relation was fostered by previous reports (10–12) that sodium channel blocking agents alter myocardial excitability properties in a rate- (or use-) dependent fashion.

Methods

Study patients (Table 1). The study was performed in 24

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Table 1. Clinical Characteristics of 24 Patients

Pt No.	Age (yr)/ Gender	Heart Disease	Ejection Fraction (%)	Plasma Procainamide Level (μg/ml)
1	52/M	CM	<35	11
2	65/M	CAD	>35	6.5
3	58/M	CAD	<35	10
4	58/M	CAD	<35	8.9
5	51/M	CAD	>35	6.1
6	67/M	CAD	>35	5.1
7	43/M	CM	<35	5.9
8	75/M	CAD	>35	5.7
9	49/M	CM	<35	8.3
10	65/F	CAD	>35	5.8
11	49/M	CM	<35	5.7
12	77/M	HTN	>35	NA
13	68/M	CAD	>35	NA
14	29/M	CM	<35	5
15	72/M	CAD	>35	6.6
16	38/M	CM	<35	
17	58/F	CAD	>35	
18	59/M	CAD	NA	
19	70/M	NL	>35	
20	66/M	CAD	>35	
21	53/M	CAD	<35	
22	68/M	CM	<35	
23	59/M	CAD	NA	
24	74/M	CAD	NA	

CAD = coronary artery disease with remote myocardial infarction; CM = cardiomyopathy; F = female; HTN = left ventricular dysfunction due to long-standing hypertension; M = male; NA = not available; NL = no apparent heart disease; Pt = patient.

patients (22 men and 2 women) aged 38 to 77 years (mean 60 ± 3) undergoing electrophysiologic study for suspected ventricular tachyarrhythmias. Informed consent for the study protocol was obtained in compliance with the Stanford University Human Subjects Committee guidelines. The underlying heart disease was coronary artery disease with prior myocardial infarction (15 patients), idiopathic dilated cardiomyopathy (7 patients) and left ventricular dysfunction due to longstanding hypertension (1 patient). One patient had no apparent heart disease. Left ventricular ejection fraction was >35% in 11 patients and <35% in 10 patients (three ejection fraction measurements were unavailable).

Electrophysiologic study. Baseline electrophysiologic study was performed after all antiarrhythmic drugs had been discontinued for ≥5 half-lives and patients had given written informed consent. Standard endocardial electrodes were positioned in the right atrium, the His position and right ventricular apex in the usual manner. A monophasic action potential contact electrode catheter (9,13) was positioned in the right ventricular outflow tract. Pacing was performed at twice diastolic threshold and 2-ms pulse width at various cycle lengths between 350 and 600 ms in 50-ms increments. At each cycle length, continuous pacing was performed for ≥1 min to assure steady state. All intracardiac electrograms and surface electrocardiograms were recorded on a multichannel recorder at paper speeds of 100 to 250 mm/s.

Action potential duration and effective refractory period determinations. Simultaneous determinations and analysis of action potential duration and effective refractory period have been described previously (9,14). Briefly, determination of these variables was performed during continuous pacing from the right ventricular apex or outflow tract by a catheter that allowed pacing and monophasic action potential recordings from nearly identical sites (9). Extrastimuli were delivered after every 12th regular stimulus. By applying the extrastimulus through the monophasic action potential catheter, we eliminated the influence of conduction delay between the pacing site and a separate monophasic action potential recording site. Extrastimuli were delivered at coupling intervals of 5-ms decrements until refractoriness occurred. The interval between the upstroke of the depolarization of the monophasic action potential signal to the deflection from the longest extrastimulus that failed to capture was recorded as the effective refractory period for that paced cycle length (9). Action potential duration was measured as the interval between the monophasic action potential upstroke and the downstroke of repolarization at the 90% repolarization level (14). By measuring both action potential duration and effective refractory period at the same electrode site, the influence of intersite variability previously reported for both intervals (3,8) was avoided.

Effect of procainamide on effective refractory period and action potential duration. To assess the effect of procainamide on these two variables, measurements were obtained at baseline study and immediately after the completion of intravenous administration of the drug in 15 patients. Intravenous procainamide was given at a standard dose of 10 mg/kg body weight infused over 20 min, followed by a 3 mg/min continuous infusion. Plasma concentration of the drug obtained on termination of the study ranged from 5 to 11 μg/ml (mean 5.5 ± 3.3). Procainamide levels in two patients were unavailable.

Data evaluation and statistical analysis. Action potential duration was measured at the level of 90% repolarization and averaged from three consecutive ventricular paced complexes preceding the extrastimulus. The effective refractory period was defined as the average of at least two determinations. Data are presented as mean values ± SEM. Linear regression analysis using a 95% confidence interval was applied to cycle length versus action potential duration and effective refractory period in the drug-free state.

The Hotelling T-squared test (15), a multiple variate analysis, was used to compare the effects of procainamide on action potential duration and effective refractory period as compared with baseline at each cycle length. A repeated measures analysis of variance with the Greenhouse-Geisser correction (16) for intrasubject correlations was used to compare the difference between effective refractory period-action potential duration difference obtained with procainamide versus that obtained at baseline as a function of cycle length. The cycle length of 600 ms was omitted from the statistical analysis of this comparison because data from

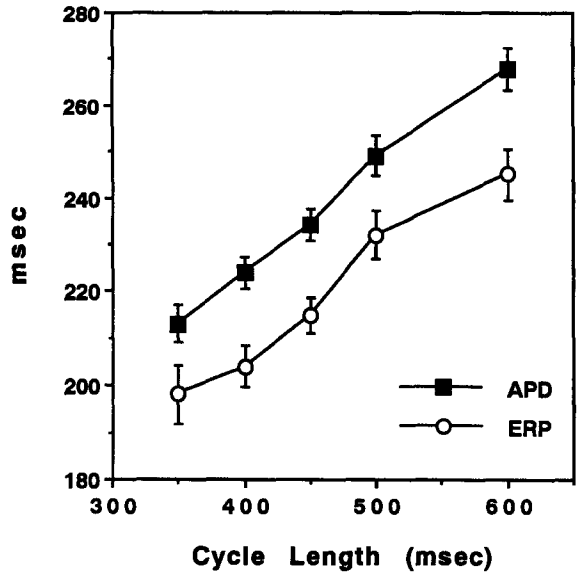


Figure 1. Relation between action potential duration (APD) and effective refractory period (ERP) with varying cycle length. Note the parallel linear shortening of the action potential duration and the effective refractory period with shorter cycle lengths.

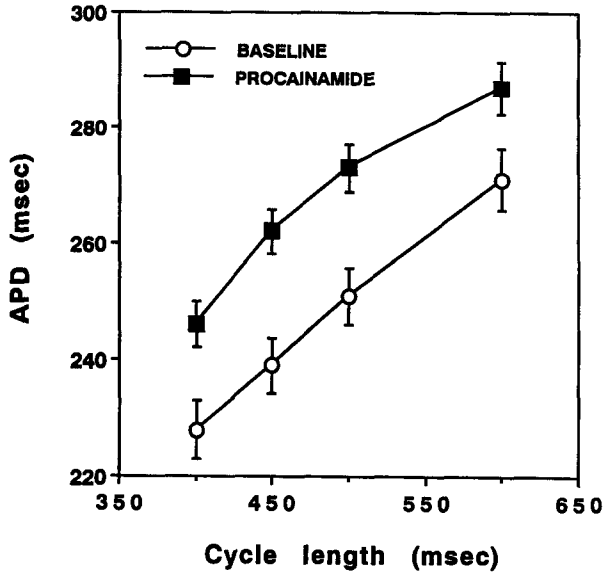


Figure 2. Effect of procainamide on action potential duration (APD) with varying cycle lengths.

three patients from the procainamide group and six patients from the baseline group were not obtained because the cycle length in these patients was <600 ms.

Results

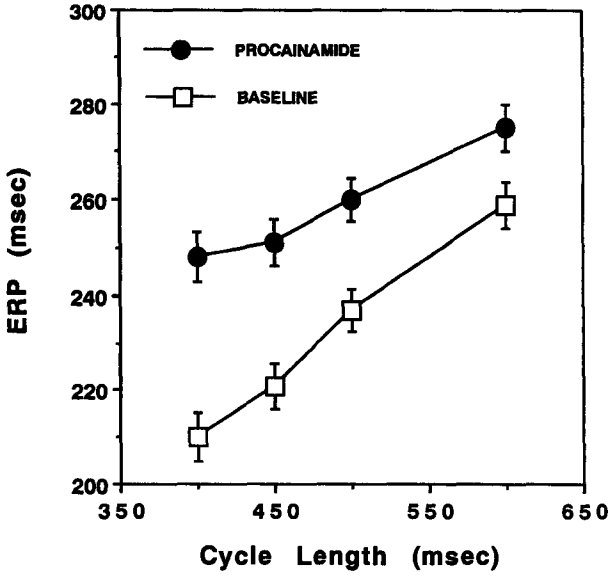
Stability and quality of monophasic action potential recordings. Once a firm contact between the tip of the monophasic action potential catheter and the endocardial surface of the right ventricular outflow tract was established, the quality of the monophasic action potential recording remained satisfactory throughout the study (which usually took 30 to 40 min to complete). The amplitude of the monophasic action potential recording did decrease by approximately 10% to 30%; however, its shape and duration were stable at each paced cycle length. The diastolic pacing threshold of the electrodes remained stable and was always <0.3 mA at current pulse width of 2 ms. After ≥1 min of pacing to assure steady state at each particular cycle length, the action potential duration was constant (variability <5% among three consecutive measurements).

Baseline action potential duration and effective refractory period. Figure 1 demonstrates the relation between cycle length and action potential duration and effective refractory period, respectively, in the 24 patients in the drug-free state. The data at a 350-ms cycle length represent only nine patients as a result of intolerance to such rapid pacing in the others. The data at a 600-ms cycle length represent only 17 patients because the other 7 patients had a sinus cycle length <600 ms.

Both the action potential duration and the effective refractory period shortened linearly with a shorter cycle length, maintaining a parallel relation. Linear regression of the lines utilizing a 95% confidence interval yielded a linear regression equation of $y = 0.22x + 135$ with a correlation coefficient of 0.995 for the action potential duration and $y = 0.20x + 127$ with a correlation coefficient of 0.972 for the effective refractory period. The action potential duration was always greater than the effective refractory period at each cycle length, with a mean difference of 18.8 ± 1.4 ms.

Effect of procainamide. Figures 2 to 4 demonstrate the effects of procainamide on action potential duration, effective refractory period and effective refractory period-action potential duration difference over several cycle lengths. Procainamide significantly prolonged action potential dura-

Figure 3. Effect of procainamide on the effective refractory period (ERP) with varying cycle lengths.



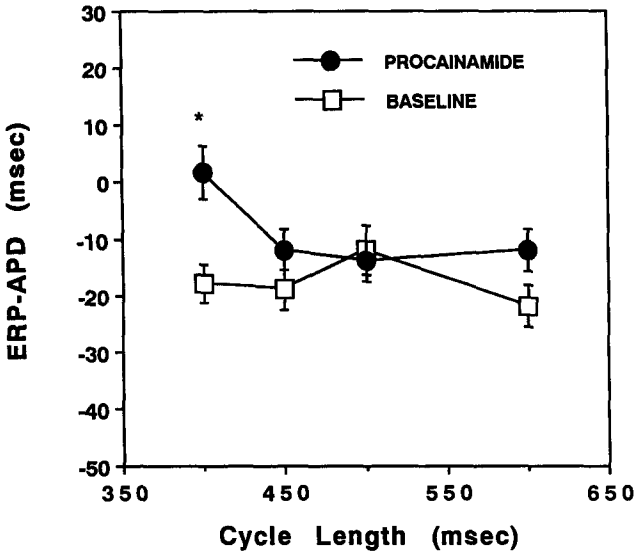


Figure 4. Effect of procainamide on the effective refractory period-action potential duration difference (ERP-APD) with varying cycle lengths. *$p < 0.01$.

tion at each cycle length by a near constant amount compared with baseline values (mean 19.9 ± 1.2 ms) (Fig. 2). The effective refractory period was increased by procainamide by an amount similar to that of action potential duration at cycle lengths of 600 to 450 ms, but more than action potential duration at cycle lengths 400 and 350 ms (mean 30 + 5 at cycle length of 600 ms; mean 37.6 + 6.1 at a cycle length of 400 ms) (Fig. 3). The greater increase in the effective refractory period relative to the action potential duration at shorter cycle lengths is reflected by a reduction in the effective refractory period-action potential duration difference (Fig. 4). The effective refractory period-action potential duration difference produced by procainamide at cycle lengths of 600 to 450 ms is approximately −13 ms, which is the same as the baseline difference. However, at a cycle length ≤400 ms, the effective refractory period-action potential duration difference becomes positive ($p < 0.01$).

Discussion

This study characterizes the cycle length relation of the action potential duration and the effective refractory period in the human right ventricle measured simultaneously and at the same endocardial site. In the drug-free state, both action potential duration and effective refractory period shortened linearly as heart rate increased, maintaining a parallel relation. These observations are in agreement with previous in vitro and in vivo animal studies (17–19) that also showed a close correspondence between rate-dependent changes in action potential duration and effective refractory period. An earlier clinical study (3) investigating the relation of the effective refractory period and the QT interval, which is thought to reflect the sum of the action potential durations of all ventricular muscle cells, reported that these two measurements decreased as the cycle length decreased. A more recent human study (5) demonstrated a progressive decrease in action potential duration, with an increase in ventricular pacing rate. However, this study did not directly compare the effects of varying cycle length on action potential duration and effective refractory period.

Importance of single-site measurement of action potential duration and effective refractory period. Olsson et al. (6) measured both of these variables in the human right ventricle and found a poor correlation. However, they measured the two variables at different sites and at different times. Substantial variation of action potential duration and effective refractory period occurs in measurements taken at different sites in the ventricle (7,8). This observation emphasizes the need to analyze the relation of action potential duration and effective refractory period at the same ventricular site. In the present study, measurements of both variables were obtained at the same time and at the same ventricular site, thus eliminating errors caused by spatial nonuniformity of electrophysiologic properties.

The data in the present study were obtained from patients undergoing electrophysiologic evaluation for suspected ventricular tachycardia and most of these patients had documented heart disease. However, in the majority of these patients there was little reason to assume significant disease involvement of the right ventricle, from which recordings were obtained. Also, linear regression analysis of the cycle length dependence of action potential duration yielded values nearly identical to those obtained in an earlier action potential duration investigation (4) in patients without overt myocardial disease and the parallel changes in effective refractory period are consistent with normal myocardium.

Possible mechanisms for drug-induced changes in the cycle length dependence of action potential duration and effective refractory period. The progressive shortening of the action potential duration with increasing heart rates has been explained by alterations in intracellular and extracellular ion concentrations. As the heart rate increases, there is an accumulation of extracellular potassium ions and intracellular calcium ions that hastens repolarization (20,21). Furthermore, fast heart rates shorten diastole and impede the complete recovery of inward currents that compose the action potential duration (4,21).

In the present study, procainamide significantly increased the effective refractory period at each cycle length, with greater relative increases at the shorter cycle lengths. This finding is consistent with observations in isolated cardiac tissue (10–12) and in in vivo canine hearts (19,22,23), which demonstrated a rate-dependent increase in refractoriness relative to repolarization by class I antiarrhythmic drugs. Because an increase in refractoriness relative to repolarization reflects voltage-independent but time-dependent suppression of excitability, the cycle length dependence of the increase in the effective refractory period-action potential duration difference may be an index for the drug's rate-dependence of sodium channel blockade (19,22,23). In these

experimental studies, the effective refractory period-action potential duration difference after the administration of class Ia antiarrhythmic drugs did not begin to increase compared with baseline until the preparation was paced at a cycle length of ≤400 ms and did not become significant until the cycle length was ≥300 ms. This may explain why there was only a small incremental increase in the effective refractory period-action potential duration difference after procainamide at cycle length 400 ms and why a recent study (5) did not find any cycle length dependence of the effect of quinidine on human ventricular effective refractory period. Pacing at a cycle length 400 ms may be at the threshold for demonstrating rate-dependent effects of class IA antiarrhythmic drugs on human effective refractory period in vivo. Other antiarrhythmic drugs with slower rate-dependence characteristics (such as class IC drugs or drug combinations) may be better candidates for demonstrating significant effective refractory period increases relative to action potential duration at clinically tolerated pacing rates.

Conclusions. The present study demonstrates a striking correlation between the action potential duration and the effective refractory period at a given endocardial site in the human right ventricle and confirms previous in vitro findings of a close relation between membrane repolarization and the recurrence of excitability. Because this relation is constant within narrow limits, provided that action potential duration and effective refractory period measurements are made at the same site, it may serve as a basis for detecting abnormalities in excitatory membrane properties caused by antiarrhythmic drugs or myocardial disease.

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