Effects of a Typical $I_{Kr}$ Channel Blocker Sematilide on the Relationship Between Ventricular Repolarization, Refractoriness and Onset of Torsades de Pointes

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ABSTRACT—The effects of a typical $I_{Kr}$ channel blocker sematilide on the relationship between ventricular repolarization, refractoriness and onset of torsades de pointes (TdP) were studied using the canine isolated, blood-perfused ventricular septum preparation with monophasic action potential (MAP) recording. Intracoronary infusion of sematilide (10 – 100 $\mu$g/min) prolonged the repolarization phase and effective refractory period, the extent of which was greater in the former than in the latter, resulting in prolongation of terminal repolarization process. Prolonging the basic pacing cycle length from 400 to 600 ms and/or increasing the drug doses enhanced each of these actions. Reverse use-dependence was obvious in the drug-induced prolongation of MAP duration, but it was less clear in the effective refractory period. More importantly, during sematilide infusion, in preparations paced at longer basic cycle length of 600 – 2000 ms, TdP-like polymorphic ventricular tachycardia was repeatedly induced by an extra-stimulus applied on the terminal repolarization phase, which indicates the appearance of electrically vulnerable period. Prolonging the basic pacing cycle length and/or increasing the drug doses prolonged this electrically vulnerable period in parallel with the terminal repolarization phase. These results suggest that prolongation of the terminal repolarization process by sematilide would enhance the chance of conduction slowing at less complete repolarization levels, which may be associated with a high incidence of TdP induction.

Keywords: Repolarization, Sematilide, Torsades de pointes, Monophasic action potential, $I_{Kr}$ channel

For drugs that prolong action potential duration by blocking the rapid component of the delayed-rectifier potassium current ($I_{Kr}$), torsades de pointes (TdP) is a common proarrhythmic syndrome, occurring most often with underlying bradyarrhythmias and hypokalemia (1, 2). It seems to be most likely that the first beat of TdP is due to early afterdepolarization-induced triggered activity (3). Meanwhile, the genesis of subsequent beats during an episode of TdP is likely to be due to spiral re-entry, which is caused by the inhomogeneity of refractoriness and repolarization in the heart (4). Interventricular as well as transmural dispersion is a good parameter to estimate this inhomogeneity (3, 5), but the spatial proarrhythmic substrates should locate in more adjoining sites involved in the perpetuation of the arrhythmias.

To begin to analyze such local proarrhythmic substrates, in the present study we examined the effects of a typical $I_{Kr}$ channel blocker, sematilide (6 – 10), on the relationship between the time course of repolarization and its re-excitability at the same site. For this purpose, we used the canine isolated, blood-perfused ventricular septum preparation (11 – 14) together with a monophasic action potential (MAP) recording/pacing combination catheter to simultaneously examine the MAP duration and effective refractory period (ERP) at the same site over a wide range of the heart rate (15 – 19). The blood-donor dog was anesthetized with halothane inhalation, since halothane, but not pentobarbital, has been reported to accentuate the cardiac electrophysiological effects of an $I_{Kr}$ blocker (5).

MATERIALS AND METHODS

All experiments were performed in accordance with Guidelines for Animal Experiments of Yamanashi Medical University. Experiments were carried out using the canine isolated ventricular septum preparation cross-circulated with heparinized arterial blood of the blood-donor dog (11 – 14). Animals were obtained through the Animal Laboratory for Research of Yamanashi Medical University.
The canine isolated, blood-perfused heart preparation

The ventricular septum preparation: The preparation was obtained from a beagle dog (CSK Research Park, Nagano) of either sex, ages of 7 to 12 months, weighing approximately 10 kg. The dog was anesthetized with thiopental sodium (30 mg/kg, i.v.), given heparin calcium (500 U/kg, i.v.), and exsanguinated. The heart was excised and plunged into cold Tyrode’s solution kept at about 4°C. The preparation consisted of the anterior papillary muscle of the right ventricle and the whole ventricular septum. The anterior septal artery, a large and sole nutrient artery of this preparation, was directly cannulated. The silver-silver chloride recording electrodes were attached onto the septum of the right ventricle close to the base of the papillary muscle to monitor the local electrograms. The preparation was sutured onto an acrylic plate in a size of 30 × 75 mm to reduce motion artifact derived from the ventricular contraction.

The blood-donor dog: HBD™ dogs (Kitayama Labes, Yoshiki Farm, Gifu), cross-bred of the beagle, Labrador and American hound, of either sex, weighing 17 – 20 kg, were used for the blood-donor dog. The dog was anesthetized with thiopental sodium (30 mg/kg, i.v.). After intubation with auffed endotracheal tube, 1% halothane vaporized with 100% oxygen was inhaled via a volume-limited ventilator (SN-480-3; Shinano, Tokyo). Tidal volume and respiratory rate were set at 20 ml/kg and 15 strokes/min, respectively. Before the start of cross-circulation, heparin calcium (500 IU/kg, i.v.) was given, and an additional dose of 200 U/kg was intravenously supplemented every hour. The ECG lead II and systemic blood pressure were continuously monitored with a polygraph system (RM-6000; Nihon Kohden, Tokyo).

Cross-circulation: Each preparation was placed in a double-wall glass jacket maintained at 38°C by circulating warm water, and perfused with arterial blood from the carotid artery of the donor dog. The perfusion pressure was kept at 120 mmHg with a peristaltic pump (7553-00; Cole-Parmer, Chicago, IL, USA) and a Starling’s pneumatic resistance placed parallel to the perfusion circuit. The coronary blood flow through the nutrient artery was continuously monitored with an electromagnetic flowmeter (MVF3200, Nihon Kohden). Venous blood from the preparation and excess blood passing through the pneumatic resistance were collected in a blood reservoir and returned to the jugular vein of the donor dog. It has been shown that these preparations usually maintain physiological responses to the multiple neurotransmitters and typical sodium and calcium channel blockers for >12 h (11 – 14).

Parameters measured: A MAP recording/pacing combination catheter (Model 1675P; EP Technologies, Sunnyvale, CA, USA) was attached onto the septum of right ventricle close to the base of the papillary muscle to obtain MAP signals. In the previous studies (13, 14), we found stable MAP can be recorded for >1 h with sufficient amplitude at this position. The signals were amplified through a DC preamplifier (Model 300, EP Technologies). The preparation was electrically driven using a cardiac stimulator (SEC-3102, Nihon Kohden) via the pacing electrodes of the combination catheter. The stimulation pulses were rectangular in shape, 1 – 2 V (about twice the threshold voltage) and of 1 ms duration. The duration of the MAP signal was measured as an interval, along a line horizontal to the diastolic baseline, from the MAP upstroke to the desired repolarization level. The interval (ms) at 90% repolarization was defined as MAP duration (= MAP₉₀). The MAP₉₀ was recorded at pacing cycle lengths of 400, 500, 600, 1000, 1500 and 2000 ms and analyzed using a recently developed fully automatic program for real time MAP analysis (MP/MAP ver 1.0; Physio-Tech, Tokyo). The measurement of MAP was the mean of three recordings of consecutive complexes.

The ERP at the same site was also assessed using a programmed electrical stimulation. The protocol consisted of eight beats of basal stimuli at pacing cycle lengths of 400, 500, 600, 1000, 1500 and 2000 ms followed by extrastimulus of various coupling intervals. Starting in late diastole, the coupling interval was shortened in 5 – 10-ms decrements until refractoriness occurred. The terminal repolarization period of the action potential (TRP) was defined as the difference between the ERP and MAP₉₀ at the same site.

Experimental protocol

Once the preparation was stabilized, the basal control assessment was performed. Then, sematilide at a low dose of 10 µg/min was infused for 10 min into the nutrient artery using an infusion pump (STC-521; Terumo, Tokyo). The MAP₉₀ and ERP at each basic pacing cycle length were assessed for 5 – 10 min after the start of the infusion, since in the preliminary experiments, we found the responses by sematilide became constant 3 min after the start of drug infusion. After the assessment of the low dose, sematilide at a middle dose of 30 µg/min was additionally infused for 10 min, and the parameters were assessed in the same manner. After the assessment of the middle dose, sematilide at a high dose of 100 µg/min was additionally infused for 10 min, and the parameters were assessed in the same manner.

Drugs

Sematilide (N-[2(diethylamino)ethyl]-4-[(methylsulfonyl)amino]-benzamide hydrochloride; MW = 349.88) was provided by Nippon Roussel (Tokyo), and it was dissolved in saline in concentrations of 0.1, 0.3 and 1 mg/ml for the respective doses of the drug infusion (100 µl/min). We have confirmed that infusion of ≤300 µl/min of solvent sa-
line into the nutrient artery does not affect the electrophysiological parameters of the same preparations as those used in this study (11–14, 20). The other drugs were purchased: thiopental sodium (Tanabe, Osaka), halothane (Takeda, Osaka) and heparin calcium (Mitsui, Tokyo).

Statistical analyses

The data are presented as the mean ± S.E.M. The statistical significance within a parameter was evaluated by one-way repeated-measures analysis of variance (ANOVA). When a P value was <0.05 by ANOVA, the drug was judged as having affected the parameter. In this case, the statistical significance between the paired data within a parameter was determined by Contrasts for mean values comparison. A P value <0.05 was considered significant.

RESULTS

The basal coronary blood flow through the nutrient artery of the preparation was 5.8 ± 1.0 ml/min (n = 6). Since four preparations out of six showed relatively faster spontaneous depolarization rate of >60 beats/min, MAP$_{90}$ and ERP at basic pacing cycle lengths of 1000, 1500 and 2000 ms were assessed in only two preparations that showed slower spontaneous rate of <30 beats/min. Meanwhile, those of 400, 500 and 600 ms were examined in all six preparations.

Effects of sematilide at shorter pacing cycle lengths of 400 – 600 ms

**MAP duration:** The basal control MAP$_{90}$ values at the pacing cycle lengths of 400, 500 and 600 ms were 297 ± 4, 312 ± 4 and 324 ± 9 ms, respectively (n = 6). Typical tracings of MAPs at the basic pacing cycle lengths of 400 and 600 ms during the assessment of ERP at the pre-drug control and during 30 μg/min of sematilide infusion are depicted in Fig. 1. The effects of sematilide on MAP$_{90}$ values at these shorter pacing cycle lengths of 400 – 600 ms are summarized in Fig. 2A. Infusion of sematilide prolonged MAP$_{90}$ values in a dose-related manner at each

![Fig. 1. Original tracings of monophasic action potential (MAP) and local electrogram before (control) and during the infusion of sematilide at basic pacing cycle lengths of 400 and 600 ms. The stimulation protocol consists of eight beats of basal stimuli (S$_{1}$) followed by an extra-stimulus (S$_{2}$). The S$_{i}$ just before S$_{2}$ indicates the 8th basal stimulus. Sematilide lengthened MAP duration with beat-by-beat instability. The prolongation was likely to be associated with triangulation (slowing of phase 3 repolarization). MAP$_{90}$: monophasic action potential duration at 90% repolarization level, ERP: effective refractory period, and TRP: terminal repolarization period.](image-url)
pacing cycle length compared with the respective pre-drug control values (closed symbols). In addition, MAP$_{90}$ values were prolonged by increasing the pacing cycle length before as well as during the infusion of each dose of sematilide (asterisks). The effect of sematilide on the rate-dependency of action potential duration was assessed by comparing the slopes of linear regression fits of MAP$_{90}$ versus pacing cycle length. The regression slopes were $0.133 \pm 0.043$, $0.155 \pm 0.038$, $0.220 \pm 0.088$ and $0.285 \pm 0.087$ at pre-drug control and during the infusion of 10, 30 and 100 $\mu$g/min of sematilide, respectively. Sematilide increased the slope in a dose-related manner, and significant increase was detected during the infusion of 100 $\mu$g /min of sematilide. In addition, beat-by-beat MAP variability (instability) was observed in each preparation during the high dose of sematilide infusion. This instability was prominent when the preparation was paced at cycle length of 400 ms, as shown in Fig. 1.

**ERP:** The basal control ERP values at the pacing cycle lengths of 400, 500 and 600 ms were 274 $\pm$ 7, 282 $\pm$ 7 and 292 $\pm$ 7 ms, respectively (n = 6). The effects of sematilide on ERP values at these shorter basic pacing cycle lengths are summarized in Fig. 2A. Infusion of sematilide prolonged ERP values in a dose-related manner at each basic pacing cycle length (closed symbols). In addition, ERP values were prolonged by increasing the basic pacing cycle length before as well as during the infusion of each dose of sematilide (asterisks). The effect of sematilide on rate-dependency of ERP was assessed by comparing the slopes of linear regression fits of ERP versus pacing cycle length. The regression slopes were $0.079 \pm 0.026$, $0.083 \pm 0.025$, $0.113 \pm 0.025$ and $0.138 \pm 0.033$ in the control period and during the infusion of 10, 30 and 100 $\mu$g/min of sematilide, respectively. Sematilide tended to increase the slope, but this change did not achieve a statistical significance.

**TRP:** The basal control TRP values at shorter pacing cycle lengths of 400, 500 and 600 ms were 23 $\pm$ 9, 30 $\pm$ 9 and 32 $\pm$ 9 ms, respectively (n = 6). The effects of sema-

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![Fig. 2. Summary of the effects of sematilide on MAP$_{90}$, ERP and TRP at basic pacing cycle lengths of 400, 500 and 600 ms.](image)

The data are presented as mean $\pm$ S.E.M. (n = 6). Closed symbols represent significant difference from respective pre-drug control values by P$<0.05$. Asterisks indicate statistically significant difference of the values among different basic pacing cycle lengths of 400, 500 and 600 ms by P$<0.05$. MAP$_{90}$: monophasic action potential duration at 90% repolarization level, ERP: effective refractory period, and TRP: terminal repolarization period.
tilide on TRP values at these shorter pacing cycle lengths are summarized in Fig. 2B. Infusion of sematilide prolonged TRP values in a dose-related manner at basic pacing cycle lengths of 500 and 600 ms (closed symbols), while no significant change was detected in those at 400 ms. In addition, TRP values were prolonged by increasing the basic pacing cycle length before and during the infusion of a high dose of sematilide (asterisks). A similar trend was observed during the infusion of low and middle doses of sematilide, but this change did not achieve statistical significance. The effect of sematilide on rate-dependency of TRP was assessed by comparing the slopes of linear regression fits of TRP versus pacing cycle length. The regression slopes were $0.046 \pm 0.014$, $0.072 \pm 0.053$, $0.108 \pm 0.079$ and $0.156 \pm 0.057$ in the control period and during the infusion of 10, 30 and 100 $\mu$g/min of sematilide, respectively. Sematilide tended to increase the slope, but this change did not achieve statistical significance.

$ERP/\text{MAP}_{90}$: $ERP/\text{MAP}_{90}$ was also calculated (data not shown in the figure). The basal control $ERP/\text{MAP}_{90}$ values at shorter pacing cycle lengths of 400, 500 and 600 ms were $0.924 \pm 0.028$, $0.905 \pm 0.029$ and $0.903 \pm 0.027$, respectively ($n = 6$). The effects of sematilide on $ERP/\text{MAP}_{90}$ values were essentially the same as those on TRP; namely, infusion of sematilide decreased $ERP/\text{MAP}_{90}$ values. Significant changes were detected for the same data points as those of TRP.

**Effects of sematilide at longer pacing cycle lengths of 1000 – 2000 ms**

MAP duration, ERP and TRP: Typical tracings of MAPs at a basic pacing cycle length of 2000 ms during the assessment of ERP before and during 30 $\mu$g/min of sematilide infusion are depicted in Fig. 3. The summary of the results of this preparation at pacing cycle lengths of 600 – 2000 ms is shown in Fig. 4A. Infusion of sematilide prolonged the MAP$_{90}$ and ERP at these longer pacing cycle lengths ($n = 2$). Also, infusion of middle and high doses of sematilide tended to prolong TRP, but the dose-related prolongation plateaued, as shown in Fig. 4B. In addition, TRP values were not necessarily prolonged by increasing the basic pacing cycle length from 1000 ms to 2000 ms ($n = 2$).

Proarrhythmic effects: After the start of sematilide infusion, the programmed electrical stimulation was often interrupted by extra-systoles. Only at longer basic pacing cycle lengths, TdP-like polymorphic ventricular tachycardia, which was judged by irregular R waves of the local electrograms, was repeatedly initiated by the premature stimulus ($S_2$). The arrhythmia lasted for 5 – 30 s and spontaneously terminated. Typical tracings of this arrhythmia during 30 $\mu$g/min of sematilide infusion are depicted in Fig. 3, and the ranges of coupling intervals ($S_1 - S_2$) that induced this type of polymorphic ventricular arrhythmia are summarized in Fig. 4A (hatched rectangles). These results indicate that the electrically vulnerable period of the ventricular

![Control](image1)

**Control**

$S_1 - S_1 = 2000$ ms

$\uparrow \uparrow \uparrow \uparrow$

$S_1 \quad S_1 \quad S_2 \quad S_1 \quad S_2$

490 ms 480 ms 380 ms 370 ms

MAP$_{90}$ = 452 ms, ERP = 380 ms

![Sematilide (30 $\mu$g/min)](image2)

**Sematilide (30 $\mu$g/min)**

$S_1 - S_1 = 2000$ ms

$\uparrow \uparrow \uparrow \uparrow$

$S_1 \quad S_1 \quad S_2 \quad S_1 \quad S_2$

500 ms 480 ms 420 ms 380 ms

MAP$_{90}$ = 528 ms, ERP = 390 ms

Electrically Vulnerable Period = 390 – 480 ms

![Fig. 3](image3)

**Fig. 3.** Original tracings of monophasic action potential (MAP) before (control) and during the infusion of sematilide at basic pacing cycle lengths of 2000 ms. Polymorphic ventricular tachycardia along with irregular shape of MAP was induced during sematilide infusion. The $S_2$ just before $S_2$ indicates the 8th basal stimulus. MAP$_{90}$: monophasic action potential duration at 90% repolarization level, ERP: effective refractory period.
DISCUSSION

The effects of class III drugs on the relationship between ventricular repolarization, refactoriness and onset of TdP have not been studied systematically in a large in vitro heart. In this study, we used a canine isolated, blood-perfused ventricular septum preparation together with a MAP recording/pacing catheter that allows simultaneous analysis of the instantaneous relation between the local repolarization time course and the recovery of excitability (15–19). Since it has been shown that less critical mass is required to maintain ventricular fibrillation in the septal wall than in the right or left ventricular free walls (21), the currently used in vitro model can be expected to be a convenient tool to detect proarrhythmic effects of drugs.

As demonstrated in the present study, sematilide prolonged the repolarization phase and ERP, the extent of which was greater in the former than in the latter, resulting in the prolongation of the terminal repolarization process. Prolonging the basic pacing cycle length and/or increasing the drug doses enhanced each of these actions. Reverse use-dependence was obvious in the sematilide-induced prolongation of MAP$_{90}$, but it was less clear for ERP. More importantly, during sematilide infusion, in the preparations paced at longer basic cycle length of 600–2000 ms, TdP was repeatedly induced by an extra-stimulus applied on the terminal repolarization phase. This torsadogenic action of sematilide is in good accordance with previous reports in patients and an animal model (10, 22). Previous experimental and clinical studies (8, 10, 23) have shown that sematilide exerted class III action in the range of 0.35–3.5 µg/ml, while the drug concentration in this study can
be roughly estimated to be 1.7 – 17 µg/ml. Thus, the present overall electrophysiological findings would reflect those of sematilide at therapeutically relevant to moderately supra-therapeutic concentrations.

Effects on repolarization

Repolarization is controlled by the delicate balance between inward and outward currents (2). During the plateau phase, the small declining inward currents flow primarily through slowly inactivating sodium and L-type calcium channels. Meanwhile, the progressively increasing outward currents flow largely through the slow component of the delayed-rectifier potassium current (I_{Kr}) channel, and I_{Kr} is inactivated primarily at more positive potentials in the plateau (24). On the other hand, during phase 3 repolarization, open inward channels rapidly close by deactivation, but I_{Kr} and I_{K1} potassium channels open, and I_{Kr} slowly deactivates (24, 25). Sematilide has been shown to specifically inhibit I_{Kr} but hardly affect sodium or calcium channels (6, 8, 9), which can explain the present effects of sematilide on MAP duration. In addition, clinical studies have shown a relationship between increased beat-by-beat QT interval variability (instability) and increased risk for sudden cardiac death (26, 27). We also found a close relationship between sematilide-induced instability of MAP and proarrhythmia as shown in Fig. 1; however, this aspect was not studied systematically in the present study because of the limited number of preparations that can be used for its assessment.

Proarrhythmic effects

Drugs that prolong refractoriness are thought to exert antiarrhythmic effects by decreasing the likelihood of the occurrence of re-entrant arrhythmia (2). It has been reported that sematilide can effectively suppress sustained ventricular tachycardia induced by programmed electrical stimulation in dogs with previous myocardial infarction (7, 28). However, at slow heart rates, marked prolongation of action potential duration and ERP induced by the drug may increase the disparity of repolarization in different portions of the heart, which may potentiate the appearance of TdP under certain conditions (10, 22, 29). To begin to assess the local proarrhythmic substrates involved in the perpetuation of re-entry arrhythmias, we examined the drug-induced electrophysiological changes of the terminal repolarization phase of action potential. As shown in this study, induction of TdP was facilitated by sematilide in parallel with the prolongation of TRP. This result may support our recent hypothesis that prolongation of TRP by I_{Kr} channel blockers promotes the chance of conduction slowing at less complete repolarization levels, which may result in a high incidence of TdP (17 – 19, 30).

In addition, a recent paper described that triangulation of the action potential (slowing of phase 3 repolarization) is an important determinant of proarrhythmia, while squaring of the action potential (prolongation of the plateau without phase 3 prolongation) will be antiarrhythmic (24). We could not assess the shape of the action potential precisely in this study, since the amplitude of MAP as well as the plateau amplitude often alters with time by the change in the contact pressure of the MAP catheter against the ventricular wall. However, one can speculate that prolongation of phase 3 repolarization by sematilide through its selective I_{Kr} blockade may result in the triangulation of action potential, which can be another electrophysiological manifestation that reflects TRP prolongation.

Limit of study

In a previous clinical study (29), sematilide hardly affected the ventricular ERP - to - action potential duration ratio, which is different from our present results showing that the ratio was decreased by increasing the drug doses. The halothane inhalation may have enhanced the sematilide-induced prolongation of action potential duration in this study (5). Another shortcoming is that we collected data of arrhythmogenesity from only two preparations that showed slow idioventricular automaticity. Therefore, we cannot definitely predict proarrhythmic effects of the drug.

Conclusions

This study demonstrates that therapeutically relevant to moderately supra-therapeutic concentrations of sematilide induce reverse use-dependent prolongation of the MAP duration with beat-by-beat instability. Prolongation of TRP by sematilide may be closely associated with impaired impulse propagation, leading to TdP induction. In order to maximize antiarrhythmic efficacy of new agents and minimize their risk of TdP, assessment of the effect on TRP may become a useful marker of pre-clinical drug evaluation.

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