Effects of Lidocaine, Disopyramide and Verapamil on the In Vivo Triggered Ventricular Arrhythmia in Digitalized Canine Heart

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Abstract—Triggered activity due to delayed afterdepolarization has been postulated to be one of the generation mechanisms of some arrhythmias, especially that due to digitalis toxicity. The present experiment demonstrates an in vivo canine model of ventricular arrhythmias that were triggered by ventricular stimulation during administration of low doses of ouabain. Ventricular ectopic beats could be induced by stimulation before the occurrence of spontaneous ventricular arrhythmia, and the coupling interval of the first ectopic beat was shortened as the stimulation rate increased. Verapamil (0.2 mg/kg, i.v.) was ineffective in suppressing the occurrence of the triggered ventricular ectopic beats, but lidocaine (1 and 3 mg/kg, i.v.) and disopyramide (0.3 and 1 mg/kg, i.v.) were effective in suppressing these digitalis-induced triggered ventricular ectopic beats in a dose-dependent fashion.

Triggered activity is recognized as one of the generation mechanisms of arrhythmias aggravated by an increased rate of beating (1–4). This type of arrhythmia is induced by rapid stimulation or premature extrastimulation and thought to be generated by action potentials produced by delayed afterdepolarization reaching the threshold for excitation (1–4). In isolated multicellular cardiac tissues or in isolated myocytes, maneuvers to raise the intracellular Ca^{++} concentration, such as treatment with digitalis (5) or a Na^+ -free (6) or K^+ -free (7) extracellular environment, cause an oscillatory release of Ca^{++} from the sarcoplasmic reticulum and induce transient depolarization either due to activation of non-selective cation channels in the sarcolemma or due to activation of the Na-Ca exchange current (8–10). Moreover, it has been demonstrated that such afterdepolarizations and resulting triggered activity were suppressed by both Ca channel blockers and Na channel blockers (11–13). However, these phenomena have only been demonstrated to occur in isolated cardiac preparations; and due to the difficulties in recording such small depolarizations by the extracellular recording technique in *in situ* hearts, there have been only few

demonstrations of triggered activity due to delayed afterdepolarization in intact, in vivo heart in experimental animals (14) and nothing in man. Therefore, it is still uncertain whether the well-known digitalis arrhythmia is caused by such delayed afterdepolarizations, i.e., whether the same type of in vitro triggered activity can be produced in the intact heart.

The purpose of the present experiment was to produce a stable in vivo canine model of arrhythmias triggered by ventricular stimulation during administration of low doses of ouabain and to examine whether these triggered ventricular ectopic beats have the same characteristics predicted by the triggered activity demonstrated in vitro. Also in the present experiment, we used this new type of arrhythmia model to assess the effects of typical antiarrhythmic drugs, verapamil (class 4 antiarrhythmic drug), lidocaine (class 1b) and disopyramide (class 1a).

Materials and Methods

A total of twenty mongrel dogs, weighing 9–15 kg, were anesthetized with pentobarbital sodium (30 mg/kg) and ventilated with room air using a constant-volume ventilator (20

ml/kg, 15 strokes/min). Catheters were placed in the femoral vein for infusion of drugs and in the femoral artery for recording the blood pressure. Bilateral vagotomy was carried out at the midcervical level. After left thoracotomy, the pericardium was opened and the heart was placed in a pericardial cradle. Bipolar stimulating electrodes were sutured on the epicardium of the left ventricle. Other bipolar electrodes were sutured on the left atrial appendage for recording atrial electrograms. Lead II ECG, the atrial electrogram, and the blood pressure were continuously recorded. Pulses of ventricular stimulation were of suprathreshold voltage and 3 msec duration obtained using a programmed stimulator (Dia Medical DPS-910). Initially, 30–40 μ g/kg ouabain was injected intravenously, followed by an additional 10 μ g/kg every 20 min, if necessary, until ventricular ectopic beats were consistently induced soon after the end of a train of ventricular stimulation.

1. Effect of rapid ventricular stimulation

Seven mongrel dogs were used. When ventricular ectopic beats were shown to be consistently induced soon after the end of a train of 10 ventricular stimuli at a cycle length of 273 msec, about 30 beats/min over the spontaneous heart rate, the effects of various patterns of stimulation were examined. The common patterns employed for all animals were as follows: 10 and 30 stimuli at a cycle length of 273 msec followed by a 3 sec pause, and 10 and 30 stimuli at a cycle length of 240 and 200 msec followed by a 3 sec pause. The total heart beats, regardless of sinus or ventricular origin, and the number of ventricular beats during the 3 sec pause were counted, and the coupling interval was measured as the time from the last driven beat of a train to the onset of the first ventricular beat. Statistical evaluation of the data was performed using a paired *t*-test.

2. Effects of drugs

Thirteen mongrel dogs were used. For induction of stable ectopic beats, the cycle length of the stimulation was set at 277 msec or 300 msec, and the number of stimuli was set at 15. After confirming the repeated induction of stable ventricular ectopic beats during the 3 sec pause between trains of stimuli, the effects of intravenous verapamil (up to 0.2

mg/kg), lidocaine (1 and 3 mg/kg) and disopyramide (0.3 and 1 mg/kg) were examined for 10 min. In most of the animals, two drugs were tested in two concentrations with sufficient intervals (about 30 min) between drug administrations. The total heart beats and the number of ventricular ectopic beats for the 3 sec pause were counted. The number of cases in which ventricular ectopic beats were induced during the pause were also examined and expressed as "inducibility" in Figs. 3–5. Data were analyzed using a paired *t*-test.

Results

1. Effect of rapid ventricular stimulation

No ventricular ectopic beats were induced by rapid ventricular stimulation in dogs used in the present study (Fig. 1A). Administration of ouabain in low doses (30–60 μ g/kg) manifested ventricular ectopic beats triggered by ventricular stimulation at a rate of about 30 beats/min over the spontaneous heart rate (Fig. 1B). These arrhythmias, hereafter referred to as triggered ventricular ectopic beats, were induced at total ouabain doses of between 30–60 μ g/kg, which were less than those reported to induce spontaneous ventricular arrhythmias (70–90 μ g/kg). During this period, no spontaneous ventricular arrhythmia was observed in the absence of ventricular stimulation. The inducibility of ventricular ectopic beats for the 3 sec pause was examined by changing the stimulation patterns. The inducibility or the number of ventricular ectopic beats during the 3 sec pause was not changed either by shortening the cycle length or increasing the number of the continuous stimuli, as shown in Table 1. The number of driven beats was not exactly the same as the number of stimuli, especially when a longer cycle length of over 300 msec was used. This was because the average spontaneous sinus rate in the present experiment was about 188 beats/min (cycle length of 320 msec), and the first couple of ventricular stimuli very often fell in the refractory period. A faster driving rate at 300 beats/min (cycle length of 200 msec) or 250 beats/min (cycle length of 240 msec) could drive the ventricle better than the slower ones. A higher stimulation rate of more than 300

Fig. 1. Ventricular tachycardia induced by ouabain and rapid ventricular stimulation and effects of verapamil and lidocaine. A) Ventricular ectopic beat was not induced by 15 continuous ventricular stimuli (marked by dark dots) before injection of ouabain (control). B) Ventricular tachycardia was triggered soon after stopping continuous ventricular stimulation after injection of ouabain at 50 $\mu\text{g/kg}$. C) Verapamil was ineffective in suppressing ventricular ectopic beats triggered by continuous ventricular stimulation after 45 sec. D) Ventricular tachycardia was triggered soon after stopping continuous ventricular stimulation again by further addition of ouabain (10 $\mu\text{g/kg}$). E) Lidocaine was effective in suppressing ventricular ectopic beats triggered by continuous ventricular stimulation after 60 sec.

Table 1. Effects of the cycle length and the number of stimuli on the triggered ventricular ectopic beats

Cycle length (msec)	Number of stimuli	Number of driven beats	Total number of beats during pause (/3 sec)	Number of ectopic beats (/3 sec)
200	10	10	8.6 $\pm$ 1.0	2.7 $\pm$ 1.9
	30	30	8.9 $\pm$ 1.3	3.2 $\pm$ 2.3
273	10	8–10	8.6 $\pm$ 1.0	3.0 $\pm$ 2.0
	30	28–30	8.9 $\pm$ 1.3	3.3 $\pm$ 1.2

n=7. There were no statistically significant changes between these values.

beats/min could not drive the heart. In contrast to the inducibility, the coupling interval was significantly shortened after rapid stimulation. This is shown as the shorter coupling interval at the cycle length of 200 msec as compared to the coupling interval at

240 or 273 msec (Fig. 2). This relationship was not influenced by the number of stimuli in a train used in the present study. The coupling interval at the cycle length of 200 msec was significantly shorter than that of 273 msec when the number of driven beats

Fig. 2. Effect of rapid ventricular stimulation. The coupling interval of the first ventricular ectopic beat at the cycle length of 200 msec was significantly shorter than that of 273 msec. The statistical significance was $P < 0.05$ for the drive number of 10, and $P < 0.01$ for the drive number of 30.

was 10 or 30. Thus in the following studies, the drive number was set at 15.

2. Effects of drugs

1) **Verapamil:** An intravenous dose of 0.2 mg/kg verapamil markedly decreased the mean blood pressure from 149 ± 33 mmHg to 99 ± 21 mmHg within 30 sec. This dose of verapamil, which was nearly the maximum dose producing recoverable hypotension, was ineffective in suppressing the occurrence of triggered ventricular ectopic beats, but it suppressed the maintenance of ventricular tachycardia, resulting in reduction of total ventricular ectopic beats for a 3 sec pause, as shown in Fig. 1C. This is also shown in Fig. 3 where the number of ventricular ectopic beats as well as the total beats for the 3 sec pause decreased significantly for up to 10 min. The inducibility was not changed for up to 10 min as shown in the upper column of the figure.

2) **Lidocaine:** An intravenous dose of 3 mg/kg lidocaine, which did not produce marked changes in the mean blood pressure, was effective in suppressing triggered ventricular ectopic beats as shown in Fig. 1E.

This effect was not prominent when a lower dose of 1 mg/kg lidocaine was used. As shown on the left in Fig. 4, the number of ventricular beats or the total beats for the 3-sec pause was not decreased significantly by

Fig. 3. Summary of the effects of verapamil. The number of ventricular beats as well as the total beats for the 3 sec pause decreased for up to 9 min. The inducibility, number of cases in which triggered ventricular beats were induced after the end of the train of ventricular stimulation, were not decreased.

a dose of 1 mg/kg. On the other hand, as shown on the right in Fig. 4, when a dose of lidocaine was increased to 3 mg/kg, the number of ventricular beats as well as the total heart rate for the 3 sec pause decreased significantly for up to 10 min from that of the control period. The inducibility dramatically decreased in the case of 3 mg/kg lidocaine. This demonstrates that lidocaine had a dose-dependent effect in suppressing these ventricular arrhythmias.

3) **Disopyramide:** An intravenous dose of 0.3 mg/kg or 1 mg/kg disopyramide did not produce marked changes in the total heart beats of the 3-sec pause as well as in the mean blood pressure, but suppressed the occurrence of ectopic beats. A dose of 1 mg/kg disopyramide was more effective than a dose of 0.3 mg/kg in suppressing triggered ventricular beats induced after the end of the train of ventricular stimulation.

As shown on the left in Fig. 5, when a dose of 0.3 mg/kg disopyramide was used, the number of ventricular beats for the 3-sec

Fig. 4. Summary of the effects of lidocaine. The number of ventricular beats as well as the total beats for the 3 sec pause decreased significantly for up to 10 min dose-dependently as compared to those at the control period. The inducibility also decreased.

Fig. 5. Summary of the effects of disopyramide. The number of ventricular beats for the 3 sec pause decreased dose-dependently. The inducibility also decreased.

pause decreased only slightly, and the inducibility did not decrease for up to 10 min. However, when a dose of 1 mg/kg disopyramide was used, the number of ventricular

beats for the 3-sec pause as well as the inducibility decreased significantly for up to 10 min as shown on the right in Fig. 5. Thus, disopyramide also suppressed these arrhyth-

mias in a dose-dependent fashion.

Discussion

The electrophysiological mechanism for generation of digitalis arrhythmia is still a matter of debate. Vassalle et al. have demonstrated that ouabain enhances automaticity by increasing the rate of slow diastolic depolarization in isolated Purkinje fibers (15). This enhanced automaticity might be the mechanism of spontaneously occurring ventricular tachycardia induced by toxic doses of ouabain. In contrast to the activity of normal and intrinsic pacemakers that show postpacing depression (16), a special type of automaticity which shows acceleration by rapid pacing rather than depression was reported to occur in isolated canine false tendons treated with acetylcholinesterase inhibitor (5, 17). This abnormal automaticity is believed to be caused by transient depolarizations (also called "oscillatory afterpotentials (OAPs)" or "delayed afterdepolarizations"), which may be responsible for triggered activity (17). The most remarkable characteristic of this abnormal automaticity is that the amplitudes of transient depolarizations were increased, and their coupling intervals were shortened as the cycle length of stimulation became shorter or the number of driven beats in a train was increased (3, 18). A very similar phenomenon of induction of ventricular ectopic beats, but under *in vivo* conditions, has been reported to occur during infusion of digitalis in the dog heart by Hagemer and Lown, which they called the repetitive ventricular response (RVR) (19). They showed that the RVR could be elicited at an early stage of digitalis toxicity, i.e., before the occurrence of spontaneous ventricular tachycardia. Although various pacing techniques were not used in differentiating the generation mechanism of the RVR *in vivo*, RVR might well be the result of triggered activity (3).

The ventricular ectopic beats shown in the present experiment were induced after a train of stimuli, so they seem to be quite similar to RVR for two reasons. Firstly, they could be triggered by ventricular stimulation before the generation of the spontaneous ventricular arrhythmia and secondly, the coupling interval of the first ectopic beat was shortened

with an increase in the stimulation rate. When the number of stimuli in a train ranged between 10 or 30, we did not see significant changes in the number of ventricular ectopic beats. It is questionable whether all the ectopic beats are generated by the delayed afterpotentials, but it was demonstrated in isolated Purkinje fibers exposed to acetylcholinesterase inhibitor that the number of ectopic beats increased as the stimulation frequencies were increased (3, 7). It is quite probable that the number of stimuli employed in the present experiments was already supramaximal, and a smaller number of stimuli should be used. However, because of frequent failure of ventricular stimulation by the first couple of stimuli, we could not examine a smaller number of stimuli, i.e., less than 10.

If the mechanism of the triggered ventricular ectopic beats is most probably due to delayed afterdepolarization, then verapamil may be effective on this special type of digitalis arrhythmia. However, we did not find any effectiveness of verapamil on this new digitalis arrhythmia model. Instead, our triggered ventricular ectopic beats were suppressed dose-dependently by lidocaine and disopyramide, Na channel blockers. Similar results of the pattern of effectiveness of antiarrhythmic drugs were obtained using our canine spontaneously occurring digitalis arrhythmia (20, 21).

Recently a new classification of class 1 antiarrhythmic drugs was introduced according to the modulated receptor hypothesis (22): drugs that rapidly bind to and dissociate from the proposed site in the Na channel were designated as fast kinetic drugs, e.g., lidocaine; and those that are slow were designated as slow kinetic drugs, e.g., disopyramide. If the triggered activity arrhythmia was much more easily produced as the stimulation interval became shorter, it may be speculated that a fast kinetic drug, lidocaine, may be more effective than a slow kinetic drug, disopyramide, as compared to the effects of these drugs on spontaneously occurring digitalis arrhythmia. We previously reported that 2 mg/kg for lidocaine and 3 mg/kg for disopyramide, respectively, were minimum effective doses on spontaneously occurring digitalis arrhythmia (20). However, in

the present experiments, 3 mg/kg lidocaine was required to suppress the triggered ventricular ectopic beats, while the lower 1 mg/kg disopyramide showed similar effectiveness to lidocaine at 3 mg/kg; namely, contrary to our expectations, disopyramide was more effective than lidocaine on this *in vivo* triggered arrhythmia. This result may be explained by the fact that the coupling interval of the triggered ventricular ectopic beats was around 400 msec as shown in Fig. 2, but the average total heart rate of the spontaneously occurring digitalis arrhythmia was around 200 beats/min, namely around 300 msec interval (20). Thus the faster spontaneously occurring digitalis arrhythmia might have been strongly suppressed by the fast kinetic drug lidocaine.

The ineffectiveness of verapamil may be due to the low doses of verapamil used *in vivo* because of the danger of unrecoverable hypotension or AV block in the present experiment. Considering the possible difference in the generation mechanism of the present triggered ventricular ectopic beats from the spontaneously occurring one, further studies are needed to solve this problem.

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