The Effect of Verapamil on Halothane-Epinephrine or Digitalis-induced Ventricular Dysrhythmias in Dogs

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The effect of verapamil on ventricular dysrhythmias was evaluated using two canine models. In one model, ventricular dysrhythmias were induced by 1% halothane-epinephrine (1.5 ~ 3.0 μg/kg/min.) in 20 dogs (Group I). In the other model, ventricular dysrhythmias were induced by digoxin (0.1 ~ 0.2 mg/kg) in 27 dogs (Group II). Verapamil (0.2 ~ 0.5 mg/kg) was given to treat these ventricular dysrhythmias. When verapamil was ineffective, lidocaine (1 ~ 2 mg/kg) was given following the administration of verapamil. In 7 dogs of group II, lidocaine alone was given. Verapamil was effective in 16 animals of group I, and in 10 animals of group II. Lidocaine was ineffective in the remaining 4 of group I, whereas effective in the remaining 17, including those given lidocaine alone of group II. From these findings, it was inferred that Ca^{2+} dependent abnormal automaticity and/or re-entry may be more closely related to the genesis of halothane-epinephrine-induced ventricular dysrhythmias refractory to lidocaine, whereas triggered activity may be more closely related to that of digitalis-induced ventricular dysrhythmias. In conclusion, verapamil was more effective against halothane-epinephrine-induced ventricular dysrhythmias than against digitalis-induced ventricular dysrhythmias.
(Key words: verapamil, ventricular dysrhythmias, Ca^{2+} dependent abnormal automaticity, triggered activity, re-entry)

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For more than a decade, verapamil, a Ca-entry blocker, has been well recognized to be effective against many atrial dysrhythmias, especially supraventricular tachycardias (SVT). Singh B.N., et al. stated that verapamil is not usually effective treatment for ventricular dysrhythmias, but may be of value in selected cases[1]. Brichard G., et al. concluded that verapamil may be used safely for the control of supraventricular and ventricular dysrhythmias in lightly anesthetized patients, but its use is contraindicated in patients with atrioventricular block of any grade and in undigitalized patients with heart failure[2]. At the present time, however, the efficacy of verapamil in the treatment of ventricular dysrhythmias has not been established. Even in cases in which verapamil is effective against ventricular dysrhythmias, the precise mechanism remains unknown. This study was performed to examine the effect of verapamil on ventricular dysrhythmias, which were induced by halothane-epinephrine or digitalis. And the mechanisms of antidysrhythmic effect of ver-

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apamil on each ventricular dysrhythmia were speculated.

Methods

Forty-seven mongrel dogs of either sex, weighing 15.0 ~ 23.0 kg, were studied. Anesthesia was induced with intravenous pentobarbital (30 mg/kg). The trachea was intubated orally with a cuffed endotracheal tube without the use of muscle relaxants. Ventilation was controlled with a volume-limited animal ventilator (Acoma Animal Respirator) to maintain a pH of 7.31–7.57, a Pa_{CO_2} of 30.6–41.7 mmHg, and a Pa_{O_2} of 108–365 mmHg. 100% oxygen was delivered to a halothane vaporizer (Acoma Co., Tokyo) in the inspiratory limb of the nonrebreathing circuit. A circulating water blanket was used to maintain pharyngeal temperature between 35.2 and 37.4°C. Heart rate and rhythm from lead II of the electrocardiogram (ECG) was continuously recorded. Catheters were placed in the femoral arteries for arterial pressure monitoring and arterial blood sampling and in the femoral vein for intravenous fluid and drug administration. The chest was opened through the left fourth intercostal space and a micromanometer tipped catheter (Miller Instruments, Inc.) was placed in the left ventricular cavity from the apex for the measurement of left ventricular pressure (LVP), left ventricular end-diastolic pressure (LVEDP), and first derivative of left ventricular pressure with time (dP/dt). Forty-seven dogs were divided randomly into two groups.

Group I

Twenty dogs were studied. The halothane vaporizer was adjusted to maintain an end-tidal halothane concentration at 1% measured by an anesthetic agent monitoring device (Datex). After stabilization on halothane, epinephrine (1.5–3.0 μg/kg/min.) was given continuously by a constant infusin pump (TFV-1100 Nihon Khoden Co. Ltd., Tokyo). If ventricular dysrhythmias were not induced by halothane-epinephrine alone, $CaCl_2$ (1–2 mg/kg/min.) was supplemented intravenously in 4 of 20 dogs.

When ventricular dysrhythmias were induced and continued, verapamil (0.2 mg/kg) was given intravenously as a single bolus. At the same time, arterial blood was sampled and gas tensions, pH, serum Na^+, and K^+ concentrations were measured. If hypercarbia, hypocarbia or hypoxia was present, it was corrected by adjusting alveolar ventilation. If base deficit was greater 3–4 meq/l, it was corrected with sodium bicarbonate. No abnormalities in serum Na^+ and K^+ concentrations were observed in any dog, therefore, arterial blood gas tensions and serum electrolyte balance were within normal limits at the time when verapamil was given.

During and following the administration of verapamil, the epinephrine infusion was continued at the same rate as ventricular dysrhythmias developed. When verapamil was not effective in controlling ventricular dysrhythmias, lidocaine (1–2 mg/kg) was given intravenously as a single bolus. The dose of lidocaine was dtermined by assessing the hemodynamic consequences of epinephrine administration.

Group II

Twenty-seven dogs paralyzed with pancuronium were studied. After stabilization on mechanical ventilation with 100% oxygen, digoxin (0.1–0.2 mg/kg) was given intravenously as a bolus. When ventricular dysrhythmias were induced and continued, verapamil (0.2–0.5 mg/kg) was given intravenously in 20 of 27 dogs. The dose of verapamil was determined by assessing the hemodynamic consequences of digoxin administration. When verapamil was not effective against ventricular dysrhythmias, lidocaine (1–2 mg/kg) was given intravenously as a single bolus. In the remaining 7 dogs, a single intravenous bolus of lidocaine (1–2 mg/kg) alone was given to examine its efficacy against this type of ventricular dysrhythmia. If ventricular dysrhythmias were not induced by digoxin alone, $CaCl_2$ (15 mg/kg) was supplemented intravenously as a bolus in 3 of 20 dogs and in 1 of 7 dogs, respectively. Arterial blood was sampled and gas tensions, pH, serum Na^+, and K^+ concentrations were measured as described

Table 1. Effect of verapamil on halothane-epinephrine or digitalis-induced ventricular dysrhythmias

	No. of dogs	No. (%) of effectiveness	95% confidence limits for the probability of effectiveness
Group I (halothane-epinephrine)	20	16 (80%)*	58 ~ 93%
Group II (digitalis)	20	10 (50%)	29 ~ 71%

*$P<0.05$ versus Group II

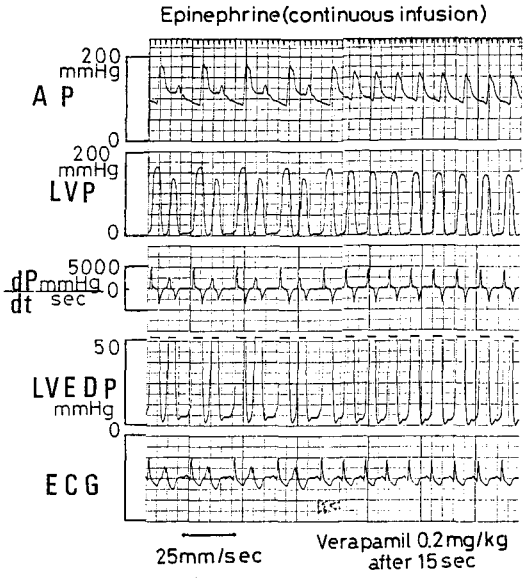

Fig. 1. Verapamil (0.2 mg/kg) converted halothane-epinephrine-induced premature ventricular beats to a sustained sinus rhythm after about 15 seconds in spite of continuous 1% halothane-epinephrine (2.2 μg/kg/min.) challenge (bottom record). AP = arterial pressure; LVP = left ventricular pressure; dP/dt = first derivative of LVP with time; LVEDP = left ventricular end-diastolic pressure; ECG = electrocardiogram (lead II)

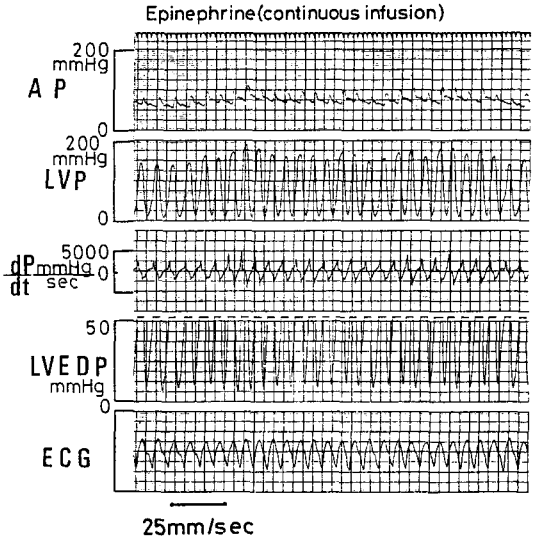

Fig. 2. Halothane-epinephrine-induced ventricular tachycardias (VT) is shown (bottom record). Abbreviations are the same as in figure 1.

in Group I. When ventricular dysrhythmias were induced, the blood level of digoxin was measured by flourescence polarization immunoassay (FPIA) method.

Statistical analysis of data

The 95% confidence limits for a binominal proportion was used to estimate the probability of effectiveness. χ^2 analysis was performed to compare proportions of effectiveness between the two groups. $P<0.05$ was regarded as statistically significant.

Results

Group I

In 16 (80%) of 20 dogs, verapamil (0.2 mg/kg) converted halothane-epinephrine-induced ventricular dysrhythmias to a sustained sinus rhythm, which was maintained in spite of continued halothane-epinephrine challenge (table 1). Typical examples are shown in figures 1, 2 and 3. Verapamil was not effective against ventricular dysrhythmias in the remaining 4 of Group I. Furthermore, lidocaine was also ineffective against halothane-epinephrine-induced ventricular dysrhythmias which were refractory

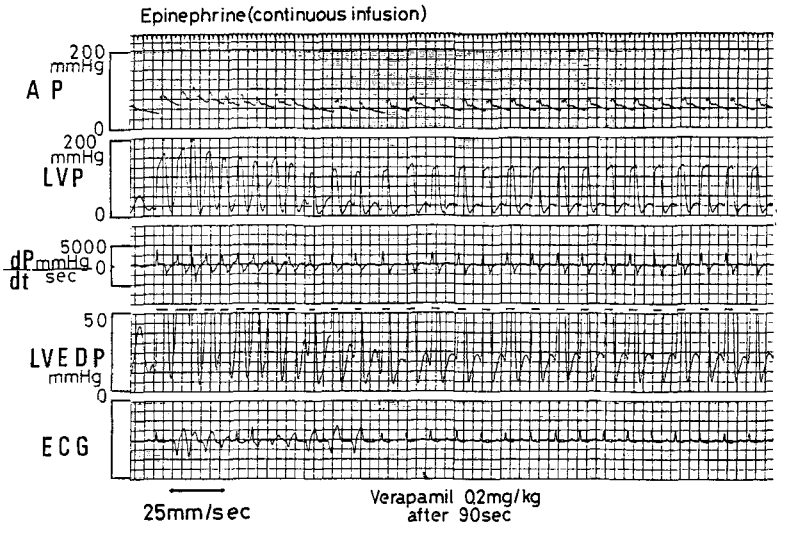

Fig. 3. Verapamil (0.2 mg/kg) converted VT in figure 2 to a sustained sinus rhythm via ventricular dysrhythmias after about 90 seconds in spite of continuous 1% halothane-epine-phrine (2.5 μg/kg/min.) challenge (bottom record). Abbreviations are the same as in figure 1.

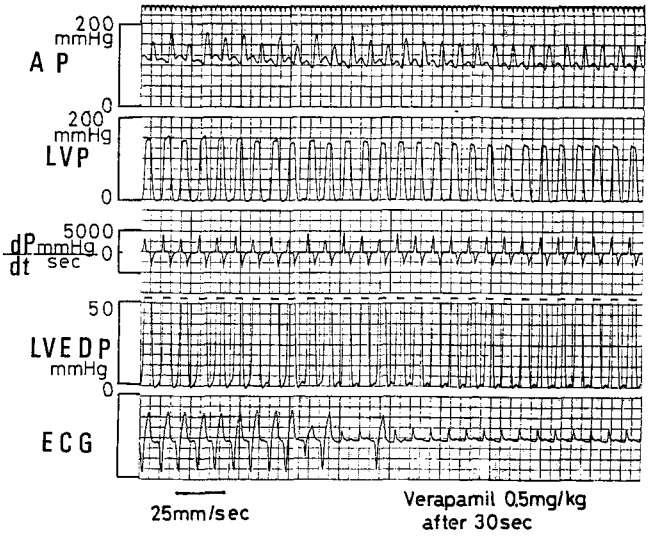

Fig. 4. Verapamil (0.5 mg/kg) converted digitalis induced VT to a sustained sinus rhythm after about 30 seconds (bottom record). The Digoxin level was 114 ng/ml. Abbreviations are the same as in figure 1.

to verapamil.

Group II

In 10 (50%) of 20 dogs, verapamil (0.2–0.5 mg/kg) converted digoxin-induced ventricular dysrhythmias to a sustained sinus rhythm (table 1). A typical example is shown in figure 4. Verapamil was not effective against ventricular dysrhythmias in the remaining 10 of Group II. However, lidocaine (1–2 mg/kg) was effective against digoxin induced ventricular dysrhythmias which were refractory to verapamil, in contrast to halothane-epinephrine-induced ventricular dysrhythmias. In all 7 dogs that did not receive administration of verapamil, lidocaine was effective against digoxin-induced ventricular dysrhythmias.

Discussion

Under physiologic conditions, in atrial, ventricular or Purkinje fibers, the fast depolarization phase (phase 0) depends mainly on a large influx of Na^+, and the plateau of the action potential (phase 2) on an influx of Ca^{2+} respectively. In the sinus node and A-V node, Ca^{2+} instead of Na^+ plays a vital role in the formation of phase 0[3]. Under abnormal conditions

such as ischemia, hypoxia, or exposure to catecholamines, depolarization of phase 0 of atrial and ventricular cells may also depend primarily on Ca^{2+} movement as seen in the sinus node[4]. Thus, abnormal conditions may alter the ionic mechanisms underlying action potential generation in atrial, ventricular, or Purkinje fibers so that they also show slow response activity. These conditions may convert fast fibers to slow fibers[5]. Therefore, the mechanism of halothane-epinephrine-induced ventricular tachydysrhythmias can not be explained by solely the enhancement of abnormal automaticity of which action potential depends on slow response.

Slow response action potentials conduct at extremely low velocities and is prone to block in a unidirectional manner[4]. The electrophysiologic properties of the slow fibers may provide a requirement to develop tachydysrhythmias as seen in the fast fibers through the re-entrant mechanism, because the basic requirements for re-entry of excitation are threefold: 1) an area of unidirectional block, 2) a circumscribed pathway over which the impulse travels, and 3) sufficiently slowed conduction for the transit time in the pathway to be greater than the effective refractory period of fibers proximal to the site of unidirectional block[6]. Re-entrant excitation may also appear when slow conduction is produced throughout a network of Purkinje fibers exposed to high K^+ and epinephrine[7,8].

On the other hand, it is well known that halothane depresses the SA node and slows A-V conductin and intraventricular conduction[9]. In combination with catecholamines which enhance the spontaneous firing of Purkinje fibers and cause a difference in the rate of recovery of excitability in various areas of ventricular myocardium, halothane may favor the development of re-entrant circuits[10]. As catecholamines increase the rate at which spontaneous diastolic depolarization carries membrane potential to threshold in normal atrial specialized fibers, fibers of the A-V nodes, or Purkinje fibers, catecholamines enhance spontaneous diastolic depolarization of both fast and slow fibers and thereby may initiate atrial or ventricular tachycardias[5].

If the slow response depends mainly on Ca^{2+} currents[4,11], and does not depend on the rapid increase in permeability to sodium that is characteristic of the normal action potential[11], verapamil may modify the slow response to a much greater extent than the fast response[12].

It is known as a fact that lidocaine is effective against various types of ventricular dysrhythmias, including those induced by halothane-epinephrine.

The ionic basis for Purkinje fiber automaticity has been challenged by Carmeleit and Saikawa[13]. Rather than spontaneous diastolic depolarization (phase 4) resulting from inactivation of an outward K^+ current called ik_2, it is proposed that diastolic depolarization results from activation of an inward Na^+ current referred to as iF. This is blocked by lidocaine[14]. Superfusion with lidocaine slowed the spontaneous discharge rate and reduced the amplitude of action potentials associated with normal automaticity, but had no effect on abnormal automaticity, whereas superfusion with verapamil suppressed abnormal automaticity associated with a reduced level of membrane potential, but had no effect on normal automaticity[15].

If the mechanism of halothane-epinephrine-induced obstinate ventricular dysrhythmias refractory to lidocaine is due primarily to enhancement of Ca^{2+} channel dependent abnormal automaticity or re-entry, it is reasonable that verapamil, a Ca^{2+} entry blocker, was effective and lidocaine, a Na^+ channel blocker, was not effective against ventricular dysrhythmias as seen in this study. However, the reason why verapamil as well as lidocaine was not effective against halothane-epinephrine-induced obstinate ventricular dysrhythmias in 4 (20%) of 20 dogs is unknown. Further studies will be necessary to clarify this. We also have a few experience that halothane-epinephrine-induced ventricular dysrhythmias refractory to lidocaine were successfully treated with verapamil both in dogs and in some patients.

With regard to digitalization, the resting

membrane potential is less negative than normal, the rate of spontaneous diastolic depolarization (phase 4) is increased, and there is an accompanying increase in automaticity and enhanced activity of latent pacemaker (ectopic activities)[16].

From the point of view of ion fluxes in digitalization, there are a small increase in intracellular Na^+ during phase 0, a small increase in intracellular Ca^{2+} during phase 2, and a small decrease in intracellular K^+ during phase 3 of the cardiac action potential, as a result of Na^+ – K^+ adenosine triphosphatase (ATPase) inhibition. Therefore, passive Na^+ influx during the remainder of the resting period is increased, and the rate of phase 4 depolarizaiton is increased[18].

Digitalis cardiotoxicity is probably the result of an advanced stage of Na^+ – K^+ ATPase inhibition. Excessive inhibition of Na^+ – K^+ ATPase leads to the excessive loss of intracellular K^+ with loss of membrane potential and enhanced phase 4 automaticity in Purkinje fibers[17].

Thus, if the mechanism of digitalis-induced ventricular dysrhythmias is due to enhancement of Na^+ related ectopic activity, it is reasonable that lidocaine, a Na^+ channel blocker, which can suppress spontaneous diastolic depolarization in Purkinje fibers was effective against digitalis-induced ventricular dysrhythmias.

Digitalis also shortens the duration of the action potential, mostly by shortening the effective refractory period. The maximum rate at which depolarization occurs during phase 0 ($\dot{V}max$) and action potential amplitude also decrease with continued exposure to digitalis. When toxic effects have fully developed, the resting membrane potential and $\dot{V}max$ are markedly reduced, with the result that conduction velocity is reduced[18]. This combination of increased automaticity, depressed impulse conduction and shortened effective refractory period predisposes to the development of re-entrant dysrhythmias[19].

Thus, not only the efficacy of verapamil but also the mechanism of digitalis-induced ventricular dysrhythmias can be partially explained in terms of re-entry. However, verapamil was not always effective, whereas lidocaine was always effective against ventricular dysrhythmias of this sort.

Recently, oscillatory afterpotentials (OAPs) have received considerable attention in relation to the genesis of dysrhythmias, especially digitalis-induced dysrhythmias[20] and those observed in depolarized fibers[21]. OAPs can induce triggered activity when they become large enough to attain threshold. The resultant triggered activity is not the result of re-entry, but rather, abnormal pacemaker activity, resulting from a mechanism other than normal pacemaker activity[20,21]. The OAPs can also cause repetitive excitation; thus forming sustained rhythmic activity or runs of tachycardia[22].

It was previously presumed that the slow inward current might be involved in the generation of OAPs. However, it has been established that the transient inward current or oscillatory current (TI or Ios) responsible for OAPs may be distinguished from the slow inward current by its kinetic, pharmacological and ionic properties. In regard to the ionic mechanism of TI, a phasic release of Ca^{2+} from intracellular stores is the primary event which controls TI across the surface membrane, and Na ions play a major role in carrying TI, because intracellular Ca^{2+} regulates the membrane permeability to certain other ions[23]. Also amplitude of delayed afterdepolarization or OAPs induced by digitalis can be reduced by decreasing extracellular sodium concentration ($[Na^+]_0$)[24].

Thus, in regard to the ionic mechanism of OAPs and triggered activity, Na^+ may be more important than Ca^{2+}. However, Cranefield P.F., et al. observed triggered activity in canine Purkinje fibers exposed to Na^+ -free, Ca^{2+} -rich solution[25]. Verapamil, a Ca^{2+} entry blocker, has abolished OAPs or suppressed amplitude of OAPs[22], whereas lidocaine, a Na^+ channel blocker, has the possibility which decreases amplitude of OAPs and also suppresses inward Na current.

Therefore, if the mechanism of digitalis-induced ventricular dysrhythmias is due primarily to OAPs induced triggered activity, verapamil may be effective to a certain degree but less effective than lidocaine as seen in our study, though Sung R.J., et al. suggested that verapamil does not affect VT caused by re-entry and catecholamine-sensitive automaticity but is effective in suppressing VT caused by triggered activity related to delayed afterdepolarization or OAPs in man[26].

In our present study, however, verapamil was more effective against halothane-epinephrine-induced obstinate ventricular dysrhythmias, whereas less effective against digitalis-induced ventricular dysrhythmias. Even in effective cases, higher doses of verapamil were needed against digitalis-induced ventricular dysrhythmias than halothane-epinephrine-induced ventricular dysrhythmias.

Racemic verapamil used clinically does have some local anesthetic potency, a property of its (+) stereoisomer. The (−) stereoisomer blocks the slow current carried mainly by Ca^{2+} and does not have local anesthetic potency[27]. This means that verapamil can affect not only "slow", but also "fast" channels[28]. Accordingly, if the mechanism of digitalis-induced ventricular dysrhythmias is due to either re-entry or OAPs related triggered activity, or both, verapamil may be partially effective.

The results of our study led us to suggest that triggered activity re-entry may be more closely related to the genesis of digitalis-induced ventricular dysrhythmias, whereas Ca^{2+} dependent abnormal automaticity and/or re-entry may be more closely related to that of halothane-epinephrine-induced obstinate ventricular dysrhythmias refractory to lidocaine.

In conclusion, verapamil was more effective against halothane-epinephrine-induced ventricular dysrhythmias. On the other hand, lidocaine was very effective and verapamil was less effective against digitalis-induced ventricular dysrhythmias.

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