Effect of Calcium Antagonists on the Electrical Alternans of the ST Segment during Acute Coronary Occlusion in Dogs

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SUMMARY

Effects of calcium antagonists on the ST alternans during acute coronary occlusion were examined in dogs. The intravenous administration of verapamil at doses of 0.1 mg/Kg and 0.2 mg/Kg prominently attenuated the degree of ST alternans. Diltiazem at dose of 0.2 mg/Kg also attenuated the degree of alternans. Dipyridamole at dose of 0.5 mg/Kg did not significantly attenuate the degree of alternans. Verapamil significantly inhibited the ST-segment elevation. After verapamil, ST alternans did not occur even after a longer period of occlusion when changes in QRS complex and the ST-segment elevation were remarkable. It is possible that verapamil inhibits ST alternans by both the protecting effect against ischemic injury and a direct effect on the electrical activity of the myocardial cell membrane.

Additional Indexing Words:

ST alternans ST-segment elevation Verapamil Diltiazem dipyridamole

ALTERNANS of the ST-segment (ST alternans) in the electrocardiogram has been frequently observed in experimental animals.[1)-5)] Although clinical cases of the alternans of the QRS complex and the T wave have been reported by many authors, ST alternans is a rare phenomenon.[6)-12)] Recently clinical cases of ST alternans have been reported by several authors in patients with Prinzmetal's variant angina[13),14)] and in a patient with myocardial infarction.[5)] In both of experimental animals and clinical cases, the electrical alternans is followed by ventricular arrhythmias,[3),13),14)] and a causal relationship between two phenomena has been suggested.[3),4),13)-15)] Mechanisms of ST alternans, however, have not been clarified yet. Lu et al[16)] and others[17)] using the microelectrode technique in vitro have suggested that electrical alternans is related to alternation in rate and extent of transport of ions across the myocardial cell membrane. We have previously demon-

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strated that ST alternans corresponded to the alternation in the phase 2 of the membrane action potential in canine myocardium in situ.[5] The purpose of the present study is to examine the effects of calcium antagonists on ST alternans during acute coronary occlusion in dogs.

Methods

Twenty-nine mongrel dogs weighing 6.5 to 25.0 Kg were anesthetized with 35 mg/Kg of intravenous sodium pentobarbital. Under artificial respiration, a left lateral thoracotomy was performed through the fifth left intercostal space and the heart was cradled in the opened pericardium. The parameters recorded were the standard lead II of the electrocardiogram (L-II), epicardial electrogram (EPeg), and left ventricular pressure (LVP). For measuring LVP, a catheter was placed in the left ventricle through the femoral artery. The epicardial electrogram from the ischemic area was recorded by a tungsten wire with a diameter of 0.2 mm. The L-II, the EPeg of ischemic region, and LVP were amplified by a polygraph (RH-85M, Nihon Kohden) and recorded on a mingograph (800-6 Nihon Kohden). To produce transient ischemia, the left anterior descending coronary artery (LAD) was occluded below its first diagonal branch together with veins for 3 to 10 min. The time interval between successive occlusions was at least 10 min. Before the administration of a drug, the coronary occlusion was performed at least twice and ST alternans during the occlusions was recorded. After making sure that the time course and the degree of alternans during two successive occlusions (control-1 and -2) were not so much different, a drug was administered intravenously through the femoral vein. After the administration of a drug, the coronary artery was occluded twice, the first occlusion was 3 to 5 min after the administration and the second was 1 hour later.

Because the degree of alternans was not constant during an occlusion, the degree was measured 3 times at 30 sec intervals after T_1, T_2, and T_3 sec of the onset of an occlusion. T_1, T_2, and T_3 were fixed through 1 series of the experiment in each dog, and were determined to correspond to 30, 60, and 90 sec after the appearance of the alternans in the control occlusion. For instance, when ST-alternans appeared at 2 min after the onset of the control occlusion in a dog, the degree of alternans was measured at 2.5, 3, and 3.5 min after the onset of every occlusion in the dog. The degrees of alternans at 3 points during an occlusion after a drug were compared with those at the corresponding time during the last control occlusion (control-2). The degree of alternans was represented in terms of the difference in the ST-segment elevation of 2 adjacent potentials in the EPeg. The epicardial ST-segment elevation was measured 100 msec after the onset of the QRS complex, because alternans was usually most remarkable at this point and this point corresponded approximately to phase 2 of a membrane action potential.[18]

In order to determine the effect of drug on the ST-segment elevation, the ST-segment elevation was measured just before the appearance of alternans in control occlusion, and after drug it was measured at the same time after the onset of the occlusion as in control.

The effect of drugs on alternans was examined under atrial pacing as well as

sinus rhythm. The atrial pacing was performed at a frequency slightly above the sinus rhythm.

The drugs examined were verapamil (Eisai Co, Ltd) at doses of 0.1 mg/Kg and 0.2 mg/Kg, diltiazem (Tanabe Co, Ltd) at a dose of 0.2 mg/Kg, and dipyridamole (Yamanouchi Co, Ltd) at a dose of 0.5 mg/Kg.

All data were expressed as means±standard errors, and Student's paired *t*-test was used for statistical analysis.

Results

1. Changes in L-II, EPeg, and LVP during the control LAD occlusion

Fig. 1 shows one of typical recordings. The L-II showed a slight widening of the QRS complex and the ST-segment elevation. In the EPeg, the ST-segment was gradually elevated and the negative T wave was reversed to positive. The height and the width of the QRS complex usually increased. One to 3 min after the onset of the occlusion, the ST alternans appeared and its degree gradually increased until 30 to 60 sec after its appearance (B). Thereafter, the degree of alternans fluctuated slightly (C). The alternans did not disappear before the release of the occlusion in all cases. ST alternans was observed in 26 of 29 dogs. No alternative change was observed in L-II and LVP in most cases (B and C). Ventricular premature beats were observed during the period of electrical alternans in some cases.

2. Effects of verapamil on ST alternans

A typical effect of 0.2 mg/Kg of verapamil is shown in Fig. 2. ST alternans was observed 2 to 3 min after the onset of the control-2 occlusion (A2–4). Five min after 0.2 mg/Kg of verapamil, the heart rate slightly

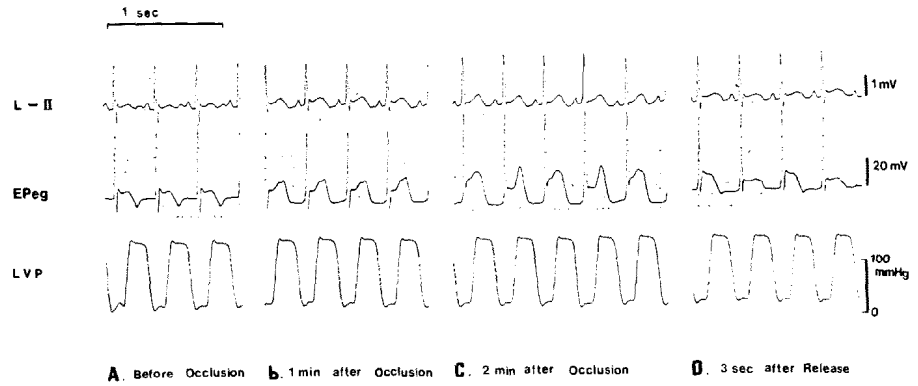

Fig. 1. Changes in L-II, EPeg, and left ventricular pressure (LVP) during a control coronary occlusion. Typical electrical alternans was observed 2 min after the onset of the occlusion (C). No alternative change was observed in L-II and LVP (B, C).

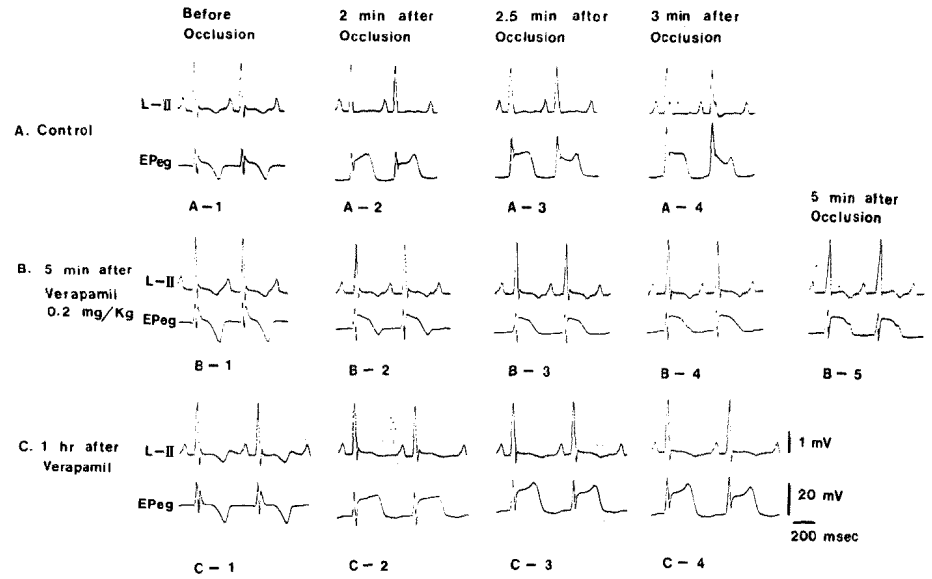

Fig. 2. Effect of 0.2 mg/Kg of verapamil on ST alternans. Five min after verapamil, the alternans was not observed (B2–4), even though the period of the occlusion was longer than that in control (B5). One hour after verapamil, the alternans was observed again (C2–4).

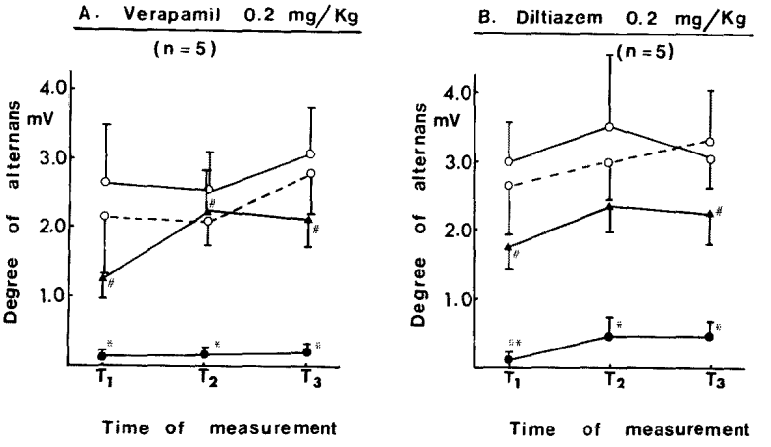

Fig. 3. Effects of verapamil and diltiazem on the degree of ST alternans. A, Effect of 0.2 mg/Kg of verapamil. B, Effect of 0.2 mg/Kg of diltiazem. See Methods for detailed description of degree of alternans and time of measurement. ○·····○=control-1; ○——○=control-2; ●——●=5 min after a drug; ▲——▲=1 hr after a drug. *$p<0.05$, **$p<0.01$ vs. control-2. #$p<0.05$, vs. 5 min after a drug.

decreased, but the L-II and the EPeg before the occlusion did not change. Two to 3 min after the onset of the occlusion, the changes in QRS complex and the ST-segment elevation in EPeg were attenuated, and ST alternans was remarkably inhibited (B2–4). Five min after the onset of the occlusion, ST alternans was still feeble (B5). One hour after verapamil, ST alternans was clearly observed again (C2–4).

The effect of 0.2 mg/Kg of verapamil on the degree of alternans in 5 animals is shown in Fig. 3A. The degrees of alternans in control-1 and control-2 occlusions were not significantly different. Five min after verapamil, the degrees of alternans were significantly less than those in control-2 occlusion. The heart rate was lowered from 146.2 ± 7.5 beats/min in control-2 occlusion to 138.0 ± 7.5 beats/min 5 min after verapamil ($p<0.05$). One hour after verapamil, the inhibitory effect of verapamil disappeared.

3. Effect of diltiazem on ST alternans

Fig. 4 shows a typical effect of 0.2 mg/Kg of diltiazem on ST alternans. Diltiazem inhibited the occurrence of ST alternans (B2–5). The heart rate was lowered by diltiazem. ST alternans did not occur even after a longer period of the occlusion (B5). One hour after diltiazem, ST alternans was observed again (C2–4). Fig. 3B shows the effect of 0.2 mg/Kg of diltiazem on the degree of alternans in 5 animals. Diltiazem significantly attenuated

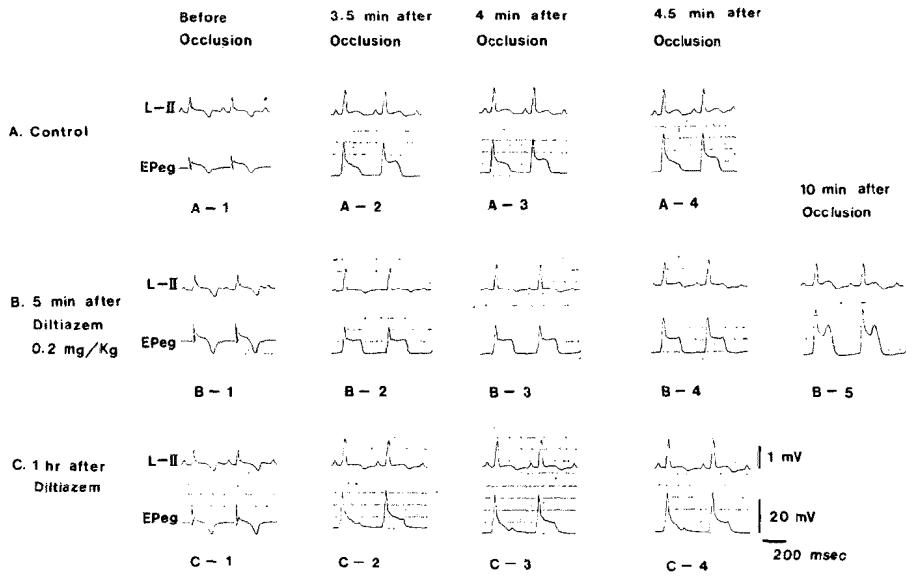

Fig. 4. Effect of 0.2 mg/Kg of diltiazem on ST alternans. Five min after diltiazem, the alternans was not observed (B2–4), even after the longer period of the occlusion (B5). One hour after diltiazem, the alternans was observed again (C2–4).

the degree of alternans. The heart rate was lowered from 164.0±4.6 beats/min in control-2 occlusion to 149.8±5.2 beats/min 5 min after diltiazem ($p<0.05$). One hour after diltiazem, the effect of drug completely disappeared.

4. Effect of verapamil on ST alternans during atrial pacing

As mentioned above, verapamil has a negative chronotropic effect. Therefore, we tested the effect of verapamil on the degree of alternans under a heart rate fixed by atrial pacing. The typical tracings are shown in Fig. 5. In control occlusion, typical ST alternans was observed 4 to 5 min after the onset of the occlusion (A2–4). The increase in the height of R wave and widening of QRS complex in both L-II and EPeg were also remarkable. Five min after 0.1 mg/Kg of verapamil, ST alternans was not observed (B2–4). The changes in QRS complex and the ST-segment elevation were less than those in control. Ten min after the onset of the occlusion, the changes in QRS complex and the ST-segment elevation were remarkable, while ST alternans did not occur (B5). One hour after verapamil, the effects of the drug disappeared (C2–4).

Fig. 6 shows the effect of 0.1 mg/Kg of verapamil in 6 animals during atrial pacing. The rate of pacing was 165.7±4.0 beats/min. Five min after verapamil, both the degree of alternans and the ST-segment elevation were significantly attenuated. One hour after verapamil, the effects of the drug

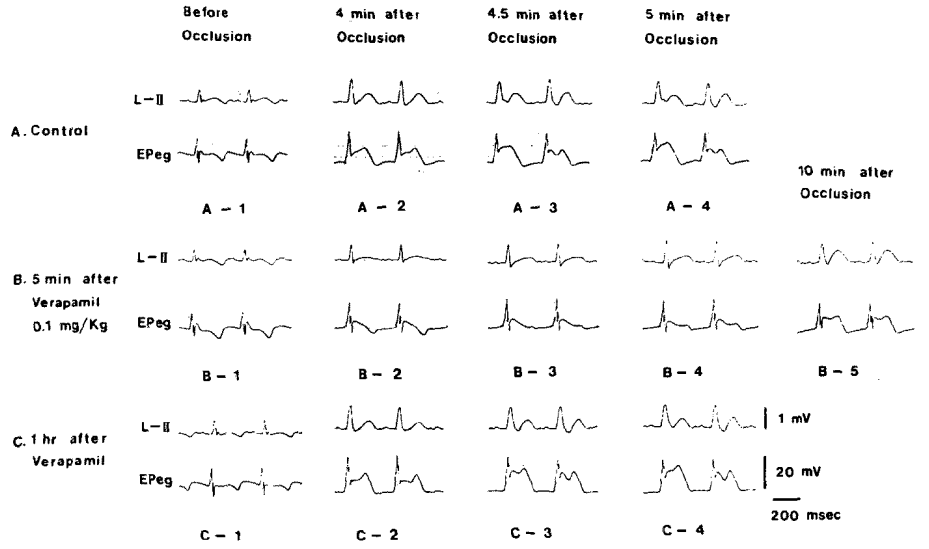

Fig. 5. Effect of 0.1 mg/Kg of verapamil on ST alternans under a heart rate fixed by left atrial pacing. Five min after verapamil, alternans was remarkably inhibited (B2–4), even though the changes in QRS complex and the ST-segment elevation were remarkable after a longer periold of the occlusion (B5). One hour after verapamil, alternans was observed again (C2–4).

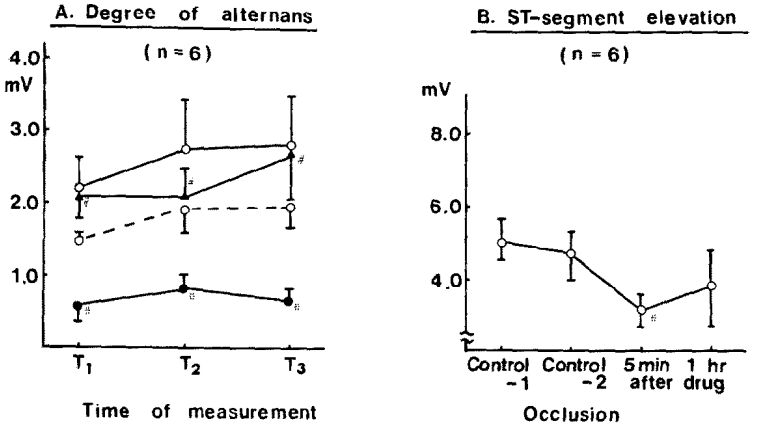

Fig. 6. Effects of 0.1 mg/Kg of verapamil on ST alternans and the ST-segment elevation under atrial pacing. See Methods for detailed description of degree of alternans and time of measurement. ○- - -○=control-1; ○——○=control-2; ●——●=5 min after verapamil; ▲——▲=1 hr after verapamil. *$p<0.05$ vs. control-2. #$p<0.05$ vs. 5 min after verapamil.

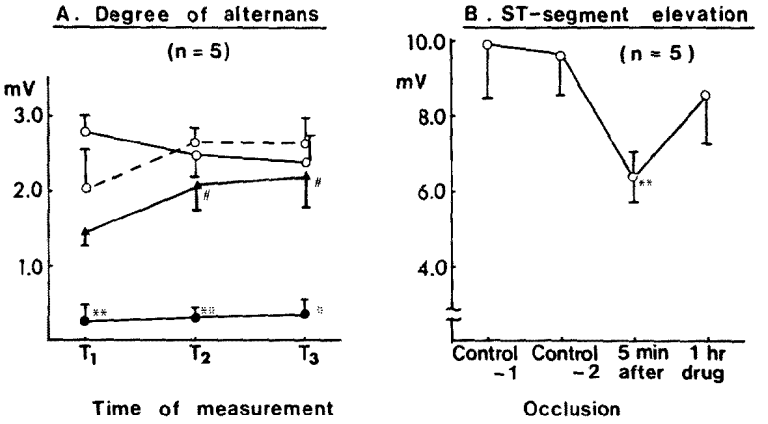

Fig. 7. Effects of 0.2 mg/Kg of verapamil on ST alternans and the ST-segment elevation under atrial pacing. See Methods for detailed description of degree of alternans and time of measurement. ○- - -○=control-1; ○——○=control-2; ●——●=5 min after verapamil; ▲——▲=1 hr after verapamil. *$p<0.05$, ** $p<0.01$ vs control-2. #$p<0.05$ vs. 5 min after verapamil.

were not observed. The effect of 0.2 mg/Kg of verapamil in 5 animals is shown in Fig. 7. The rate of atrial pacing was 167.4±4.3 beats/min in this group. The effects of 0.2 mg/Kg were more prominent than those of 0.1 mg/Kg.

5. Effect of dipyridamole on the degree of ST alternans

The effect of 0.5 mg/Kg of dipyridamole was examined under atrial

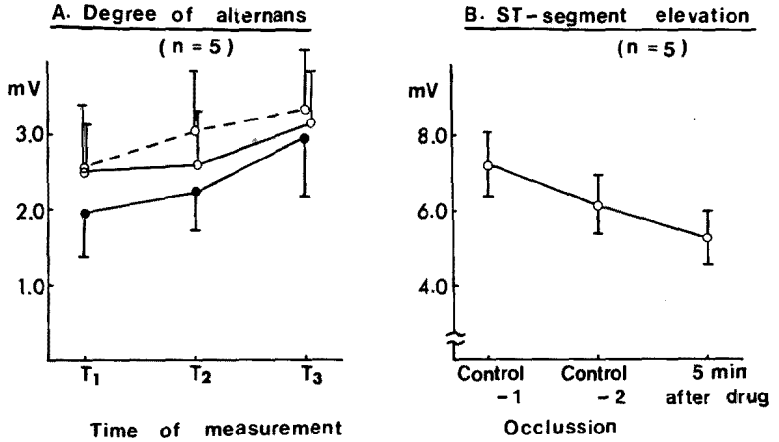

Fig. 8. Effects of 0.5 mg/Kg of dipyridamole on ST alternans and the ST-segment elevation during atrial pacing.See Methods for detailed description of degree of alternans and time of measurement. ○- - -○=control-1; ○——○=control-2; ●——●=5 min after dipyridamole.

pacing (Fig. 8). Dipyridamole slightly attenuated the degree of alternans and the ST-segment elevation, but these effects were not statistically significant.

Discussion

In 26 of 29 dogs, beat to beat alternation in the epicardial electrograms occurred during the acute myocardial ischemia produced by the occlusion of LAD. The most common alternans was that of the ST segment, as previously reported.[5] Although a number of investigators have postulated the mechanisms of electrical alternans, the precise mechanism of this phenomenon has not been clarified yet. Many investigators using microelectrode technique have demonstrated that the electrical alternation is produced in individual myocardial cells.[3)-5),16),17]

In the present study, verapamil and diltiazem prominently attenuated the degree of the alternans. Although the heart rate is lowered by verapamil and diltiazem, it is unlikely that the negative chronotropic effect of these drugs contributes to their inhibitory effects on ST alternans, because verapamil is effective during both atrial pacing and sinus rhythm. The ST-segment elevation in EPeg was attenuated by verapamil even under atrial pacing. This effect of verapamil is probably due to its protective effect against ischemic injury. Reimer et al[19] and Smith et al[20] showed that verapamil reduced the necrosis following temporary coronary occlusion in dogs, supporting this idea. Therefore, it seems that the inhibitory effect of verapamil on ST

alternans may be at least partially owing to its protective effect against ischemic injury of myocardial cells. Although calcium antagonists have a coronary vasodilating effect,[51] a potent coronary vasodilator dipyridamole attenuated neither the degree of ST alternans nor the ST-segment elevation, suggesting that the effect of calcium antagonists on ST alternans is not due to their vasodilating effects.

Previously, we have shown that ST alternans corresponded to the alternation in the phase 2 of the membrane action potential in canine myocardium in situ,[2] and suggested that slow inward currents were involved in ST alternans. In the present study, after verapamil ST alternans was not observed even after a longer period of the occlusion when changes in QRS complex and the ST-segment elevation were comparable to those in control. Therefore, it seems that the inhibitory effect of verapamil on ST alternans is not only due to the protecting effect against ischemic injury but also a direct effect on the electrical activity of cell membrane such as the inhibition of slow inward calcium currents. Several investigators[16),17),22),23] have reported the alternation of the phase 2 of a membrane action potential under various conditions in the isolated heart. Kleinfeld et al,[22] have observed the similar alternation in the left ventricle of the isolated perfused rabbit heart. Edmonds et al[23] have reported the similar alternation produced by an abrupt acceleration in driving rate in the isolated canine ventricular myocardium. Pop and Fleischmann[24] have observed the alternans of phase 2 of repolarization in human atrial monophasic action potential, and suggested the involvement of slow inward calcium currents in this alternans. Spear et al[25] have recorded slow response potentials in infarcted area of human myocardium in vitro, and indicated that the slow response potential alternatively changes in the amplitude and is inhibited by verapamil. These facts support the idea that the alternative change in slow inward calcium currents is involved in ST alternans, and that the inhibitory effect of verapamil on slow inward currents may partially contribute to the inhibition of ST alternans by verapamil. However, more direct evidences may be required.

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