Effects of calcium antagonists on the electrical alternans of the ST segment and on associated mechanical alternans during acute coronary occlusion in dogs

HISAKUNI HASHIMOTO, PH.D., KUNIFUMI SUZUKI, M.D., SHINYA MIYAKE, M.D., and MITSUYOSHI NAKASHIMA, M.D., PH.D.

ABSTRACT Effects of calcium antagonists on the ST alternans and associated mechanical alternans during acute coronary occlusion were examined in anesthetized dogs. The heart rate was fixed by atrial pacing. The intravenous administration of 0.2 mg/kg verapamil attenuated the ST alternans as did 0.5 mg/kg diltiazem. Although these drugs significantly attenuated TQ depression during occlusion, the attenuation was observed after a longer period of occlusion and when the degree of TQ depression was comparable to that during the control occlusion. Nifedipine, 0.03 mg/kg, slightly attenuated the ST alternans, but 0.5 mg/kg dipyridamole had no effect. These results support the idea that slow inward currents are involved in the ST alternans. On the other hand, the mechanical alternans was attenuated in six of 11 dogs. It is probable that factors other than the electrical alternans may also contribute to the mechanical alternans.


ALTERNANS of the ST segment of the electrocardiogram (ST alternans, STA) has been frequently observed in experimental animals and cases of STA also have been observed in patients with ischemic heart disease. Because STA is frequently followed by ventricular arrhythmia, many authors have suggested a causal relationship between the two phenomena. Although several authors have theorized about the mechanisms of the alternans of the repolarization phase, the mechanisms of STA have not yet been fully clarified. We have previously demonstrated that STA corresponded to the alternation of phase 2 of a membrane action potential. Hirata et al. have shown that the alternation of the repolarization phase induced by hypoxia or a low pH was attenuated by a calcium antagonist. The mechanical alternans has also been frequently observed in experimental animals and in patients, but the mechanism of this phenomenon has not yet been clarified either. Although many authors have reported the beneficial effects of the calcium antagonists on ischemic myocardium, effects of these drugs on the electrical and the mechanical alternans during left anterior descending coronary artery (LAD) occlusion have not been examined. Thus, the purpose of our study was to examine the effects of calcium antagonists on STA and associated mechanical alternans during acute coronary occlusion in dogs.

Methods

Twenty-seven mongrel dogs weighing 6.5 to 12.0 kg were anesthetized with 30 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. Standard lead II of the electrocardiogram, an epicardial unipolar electrogram (EPEG), amount of isometric myocardial contraction (contractile force) in the ischemic area, and left ventricular pressure (LVP) were recorded. For measuring LVP a catheter was placed in the left ventricle through the femoral artery. The contractile force was measured by a strain-gauge arch with adjustable feet (HDIT, Nihon Kohden). The myocardial segment between the two feet of the strain-gauge arch was stretched to about 20% of its diastolic length. The EPEG from the ischemic area was recorded by a tungsten wire with a diameter of 0.2 mm. The electrode for EPEG and the strain-gauge arch were set at the same area in order to examine the relationship between the electrical and the mechanical alternans. The indifferent electrode for EPEG was connected with Wilson’s central terminal. The lead II, EPEG, contractile force, and LVP were amplified by a polygraph (RM-85M, Nihon Kohden) and recorded on a mimeograph (800-6 Nihon Kohden). To produce transient ischemia, the LAD was occluded below its first diagonal branch for 3 to 10 min. The time interval between successive occlusions was at least 15 min.
Before the administration of a drug, coronary occlusion was induced at least twice and the STA during occlusion was recorded. After making sure that the time course and the degree of STA during two successive occlusions were not very different, drug was administered intravenously through the femoral vein. After the administration of drug the LAD was occluded twice. The first occlusion took place 5 min after drug and the second 1 1/2 hr later. Five to seven occlusions were usually induced in each series of experiments.

Because the degree of STA was not constant during occlusion, the degree was measured three times at 30 sec intervals (T1, T2, and T3) after the start of the occlusion. During occlusion 5 min after drug, the degree of STA was also measured at T4 (2 min after T3). T1, T2, and T3 were fixed for one series of experiments in each dog, and were determined to correspond to 30, 60, and 90 sec after the appearance of the STA in the control occlusion. For instance, when STA appeared at 2 min after the start of the control occlusion, T1, T2, T3, and T4 were determined to be 2.5, 3, 3.5, and 5.5 min after the start of the occlusion. The degree of STA at three times during occlusion after a drug were compared with those at corresponding times during the last control occlusion. The degree of STA was represented in terms of the difference in the ST segment elevation of two adjacent potentials on the EPeG. The epicardial ST segment elevation was measured 100 msec after the onset of the QRS complex since the degree of alternation was usually most remarkable at this point and because this point corresponds (approximately) to phase 2 of a membrane action potential. In addition to the degree of STA, the degree of the depression of the TQ segment during the occlusion was measured at T1 to T4. The degree of the alternation in the contractile force (mechanical alternans) was measured at a time when the mechanical alternans was most remarkable and the time for the measurement during the occlusion was not fixed. The degree of the mechanical alternans was represented in terms of the difference in the contractile force of two adjacent beats divided by the contractile force before the occlusion.

The drugs tested were verapamil (Eisai Co. Ltd.) at a dose of 0.2 mg/kg, diltiazem (Tanabe Co. Ltd.) at a dose of 0.5 mg/kg, nifedipine (Bayer Co. Ltd.) at a dose of 0.03 mg/kg, and dipyridamole (Tanabe Co. Ltd.) at a dose of 0.5 mg/kg.

All data were expressed as mean ± SE, and Student’s paired t test was used for statistical analysis.

Results

Changes in lead II, EPeG, contractile force, and LVP during the control occlusion. Figure 1 shows typical recordings. Changes in lead II were usually negligible. On the EPeG the TQ depression and ST segment elevation were observed at 1.75 min after the start of the occlusion, while STA was negligible. At 2.5 min slight STA appeared. As ischemia progressed, the degree of STA increased. The typical STA was observed at 3 to 4.5 min after the start of the occlusion and it did not disappear before the release of the occlusion in any dog. STA was observed in 25 of 27 dogs and in some, ventricular premature beats occurred during the period of STA. The contractile force of the ischemic area rapidly decreased after the start of the occlusion. The mechanical alternans appeared 1 to 3 min after the start of the occlusion. However, the time course of the electrical and the mechanical alternans was different. As shown in figure 1, a slight mechanical alternans appeared at 1.75 min after the start of the occlusion (when no STA was observed). At 2.5 min a typical STA appeared, while the mechanical alternans was slight. At 3.5 and 4.25 min the degree of STA increased, but the degree of mechanical alternans did not change substantially. The difference between the electrical and the mechanical alternans is more clear in figure 2, in which the change in the relationship between the two is shown after successive occlusions in the same animal. Figure 2, A illustrates that a higher ST segment was accompanied by a larger contractile force and the reverse can be observed in figure 2, B. LVP slightly decreased after the LAD occlusion, but the alternation in LVP was negligible.

FIGURE 1. The time course of the electrical and the mechanical alternans during the control LAD occlusion. The slight alternation of the contractile force, mechanical alternans, appeared at 1.75 min after the start of occlusion when the electrical alternans was negligible. At 2.5 min the mechanical alternans was obvious, whereas the electrical alternans was slight. At 3.5 and 4.25 min, both type of alternans were clearly observed.
Effects of verapamil and diltiazem on STA. A typical
effect of 0.2 mg/kg verapamil is shown in figure 3. The
STA was observed 1.75 to 3 min after the start of the
control occlusion. Five minutes after verapamil, lead
II and E Peg before the occlusion did not change. Three
minutes after the start of the occlusion, STA was mar-
kedly attenuated, as were the changes in the QRS com-
plex and TQ depression. Five minutes after the start of
the occlusion, the changes in the QRS complex and TQ
depression were comparable to those in control, while
the STA was feeble. The effects of verapamil in six
animals are shown in figure 4. Verapamil markedly
attenuated the degree of STA even after a longer period
of occlusion, but 1 1/2 hr after the administration of
the drug this effect was lost. The TQ depression was also
attenuated by verapamil at T1 and T2, while the TQ
depression at T4 was comparable to that at control. The
effect of the drug on the TQ depression was not ob-

FIGURE 2. The change in the relationship be-
tween the electrical and the mechanical alternans
during two successive LAD occlusions. The higher
ST segment was accompanied by a larger contractile
force in A, but the reverse occurred in B.

FIGURE 3. Effects of 0.2 mg/kg of verapamil on the electrical and the mechanical alternans. After verapamil, the electrical
alternans was not observed even after a longer period of occlusion, when the changes in the QRS complex and the TQ depression
were comparable to those at control. The mechanical alternans, however, was not inhibited.
Mechanical alternans were observed 1½ hr after the administration of the drug. The effects of 0.5 mg/kg diltiazem are shown in figure 5; this drug markedly attenuated STA even at T₄. One and one-half hours after dosing the effect of diltiazem also disappeared. TQ depression was also attenuated by diltiazem at T₁, T₂ and T₃, but at T₄ depression was similar to that at control.

Effects of verapamil and diltiazem on the mechanical alternans. Data from one of six dogs in which 0.2 mg/kg verapamil had an effect on the mechanical alternans is illustrated in figure 3. During the control occlusion the mechanical alternans was observed at 1.5 to 3 min. Five minutes after verapamil the contractile force decreased slightly compared with that before occlusion. Three minutes after the start of the occlusion the mechanical alternans was still observed in spite of the fact that STA was almost completely inhibited. The effects of verapamil and diltiazem on the mechanical alternans are summarized in figure 6. Verapamil attenuated the mechanical alternans in three of six dogs; in the other three, although this alternans was not attenuated, STA was inhibited. Diltiazem, 0.5 mg/kg, attenuated the mechanical alternans in two of five dogs; in the other three, it was not attenuated in spite of the fact that STA was inhibited by the drug in all dogs tested.

Effects of nifedipine and dipyridamole on STA. Nifedipine, 0.03 mg/kg, slightly attenuated STA at T₁, T₂, and T₃ (figure 7), but 0.5 mg/kg dipyridamole, a coronary vasodilator, did not.

Discussion

In 25 of 27 animals beat-to-beat alternation in the epicardial unipolar electrogram was observed during acute LAD occlusion. The most common alternans was that of the ST segment, as previously reported; the T wave alternans that has been observed during

![Figure 4](http://circ.ahajournals.org/)

**FIGURE 4.** Effects of 0.2 mg/kg verapamil on the degree of the electrical alternans and the TQ depression in six animals. ○ = control; ● = 5 min after the drug; △ = 1.5 hr after the drug. *p < .05; **p < .01 vs control.

![Figure 5](http://circ.ahajournals.org/)

**FIGURE 5.** Effects of 0.5 mg/kg of diltiazem on the degree of the electrical alternans and the TQ depression in six animals. ○ = control; ● = 5 min after the drug; △ = 1.5 hr after the drug. *p < .05; **p < .01 vs control.

![Figure 6](http://circ.ahajournals.org/)

**FIGURE 6.** Effects of 0.2 mg/kg verapamil and 0.5 mg/kg diltiazem on the mechanical alternans. On the ordinates are the degrees of mechanical alternans. The open circles represent mean ± SE.

![Figure 7](http://circ.ahajournals.org/)

**FIGURE 7.** Effects of 0.03 mg/kg of nifedipine and 0.5 mg/kg of dipyridamole on the degree of electrical alternans. ○ = control; ● = 5 min after the drug; △ = 1.5 hr after drug. Five animals received each drug. *p < .05 vs control.
abrupt increases in the heart rate of experimental animals or in clinical studies was rare. Although a number of investigators have theorized about the mechanisms of the alternans, the precise mechanism of this phenomenon has not yet been clarified. Many authors have demonstrated that the electrical alternans is produced in individual cells. We have previously shown that the STA is a correlate to the alternation in phase 2 of a membrane action potential, and that STA is not always accompanied by the alternation of the duration of the action potential. Therefore, it seems that the alternation in the calcium flow during the phase 2 may be involved in STA.

In this study, verapamil and diltiazem prominently attenuated the degree of STA. The TQ depression in EVec during the occlusion was also attenuated by these drugs. Reimer and Lowe and others have shown the protecting effects of verapamil against ischemia after temporary LAD occlusion in dogs. Weishaar et al. and others showed beneficial effects of diltiazem on acute myocardial ischemia. It therefore seems that the inhibitory effect of the calcium antagonists on STA may be at least partially due to their protective effects against ischemic injury of myocardial cells. However, STA did not occur even after a longer period of occlusion when the changes in the QRS complex and the TQ depression were comparable to those at control, suggesting that the effects of the calcium antagonists on STA were not solely due to their protective effect against ischemic injury.

Although calcium antagonists have a coronary vasodilating effect, a potent coronary vasodilator, dipyr.

idamole, did not attenuate STA, suggesting that the effects of the calcium antagonists on STA were not due to their vasodilating effects.

As mentioned above, STA is a reflection of the alternation of phase 2 of the membrane action potential. The alternation of phase 2 of the membrane action potential has been observed in the left ventricle of the isolated perfused rabbit heart during the abrupt increase in driving rate in the isolated canine ventricular myocardium, or in the cat papillary muscle. Bass has studied the electrical recovery of the membrane after an action potential. The author has suggested that the membrane action potential goes through a specific time course of recovery (electrical restitution) and that the changes in the configuration of the premature action potential are due to incomplete electrical restitution. Cinca et al. and others have studied T wave alternans and the alternans in the repolarization phase of an action potential after an abrupt increase in heart rate in situ or in the isolated heart. According to these authors, the diastolic resting period duration changes alternately during the period of the alternans, which in turn causes the alternation of the electrical restitution that results in alternation in the repolarization phase. However, in this study STA was not accompanied by the alternation of the TQ interval, which corresponds to the diastolic resting period, and the alternation in the late phase of the ST segment was almost negligible. STA in this study was not accompanied by alternation of the action potential. Thus, STA may not be due to alternation of the resting diastolic period. Nevertheless, incomplete electrical restitution may effect STA since the decrease in heart rate attenuates the degree of STA.

It has been suggested that alteration of the slow inward calcium currents is involved in the configurational changes in the action potential by incomplete electrical restitution. Inuma and Kato have found that a premature action potential that is evoked during incomplete electrical restitution is accompanied by an increased plateau duration. Hirata et al. have found that the alternation of the repolarization induced by hypoxia or low pH is attenuated by verapamil in the isolated canine ventricular myocardium. Considering these facts and our results, it is likely that the alternation of slow inward calcium currents may be involved in STA during acute LAD occlusion.

In this study STA was accompanied by mechanical alternans. However, the time course of the two alternans was different. The mechanical alternans appeared when STA was negligible. The higher ST segment was accompanied by a larger contractile force in some occlusion, but the reverse occurred in the next occlusion. Many authors have observed mechanical alternans in experimental animals and in patients. Kleinfeld et al. and others have reported that the electrical alternans is always accompanied by the mechanical one. According to Roselle et al., the electrical complex with deeper ST segment in lead II resulted in a greater systolic pressure during the period of alternans of the ST segment of lead II induced by LAD occlusion in dogs. On the other hand, D’Cruz et al. and Gilbert et al. have found mechanical alternans without any electrical alternans. Thus, as reported by Chung and others, the electrical alternans is frequently accompanied by mechanical alternans, whereas the reverse relationship is unusual. Gilbert et al. have suggested that the mechanical alternans is due to some failure in the excitation-contraction coupling rather than to membrane electrical activity. The fact that calcium antagonists did not always inhibit the mechanical alternans in spite of the remarkable inhibition of STA sug-
gests that mechanisms other than electrical alternans may also be involved in the mechanical alternans.

References
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