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EFFECTS OF CALCIUM ANTAGONISTS ON THE ALTERNATION OF THE ST-T COMPLEX AND ASSOCIATED CONDUCTION ABNORMALITIES DURING CORONARY OCCLUSION IN DOGS

HISAKUNI HASHIMOTO & MITSUYOSHI NAKASHIMA

Department of Pharmacology, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu, Shizuoka, Japan 431–31

1 The effects of Ca^{2+}-antagonists on the relationships between alternate changes in the ST-T complex in the epicardial electrogram, ST-T alternans, and associated excitation-conduction abnormalities during coronary occlusion were examined in anaesthetized dogs.

2 Epicardial unipolar electrograms, bipolar electrograms (BPEG) and monophasic action potentials (MAP) were recorded with unipolar, composite and suction electrodes, respectively.

3 ST-T alternans was associated with serious conduction delay. During the period of ST-T alternans, the amplitude of MAP changed alternately and the negative deflection of the ST-T complex was associated with a larger MAP. A depression of the TQ level and decrease in the resting potential of MAP were marked.

4 Verapamil (0.2 mg/kg) and diltiazem (0.5 mg/kg) inhibited ST-T alternans, conduction abnormalities, TQ depression and changes in MAP. However, after these drugs, the TQ depression and the decrease in the resting potential were evident after a longer period of occlusion at a time when ST-T alternans, conduction abnormalities and alternate changes in MAP were still inhibited. Dipyridamole (0.5 mg/kg) had no effect on either ST-T alternans or the conduction abnormalities.

5 Verapamil and diltiazem inhibited ST-T alternans and the associated excitation and conduction abnormalities. The effects of these two drugs cannot be explained on the basis of attenuation of the decrease in the resting potential.

Introduction

Alternation of the deflection of the ST-T complex (ST-T alternans) in the electrocardiogram has been frequently observed in experimental animals (Hellerstein & Liebow, 1950; Goselle, Crampton & Case, 1966; Downar, Janse & Durrer, 1977a, b; Kléber, Janse, van Capelle & Durrer, 1978; Nakashima, Hashimoto, Kanamaru, Nagaya, Hashizume & Oishi, 1978). Recently clinical cases of ST-T alternans have also been reported in patients with Prinzmetal's variant angina (Kleinfeld & Rozanski, 1977) and in patients with myocardial infarction (Nakashima *et al.*, 1978). In both experimental animals and in man, the electrical alternans is frequently followed by ventricular arrhythmias (Kleinfeld & Rozanski, 1977; Downar *et al.*, 1977a b; Kléber *et al.*, 1978; Janse, van Capelle, Morinsk, Kléber, Wilms-Schopman, Cardinal, D'Alnoncourt & Durrer, 1980). Kléber *et al.* (1978) and Janse *et al.* (1980) have proposed a causal relationship between the electrical alternans and ventricular arrhythmias during acute ischaemia. In the present study, the relationship between ST-T alternans and conduction abnormalities was examined during coronary occlusion in dogs, and the effects of Ca^{2+}-antagonists on these electrical abnormalities were tested. Ca^{2+}-antagonists have been shown to inhibit the alternans of the repolarization phase *in situ* (Hashimoto, Suzuki, Miyake & Nakashima, 1981) and in the isolated ventricle (Hirata, Toyama & Yamada, 1980).

Methods

Fifty-one mongrel dogs weighing 5.0 to 14.2 kg were anaesthetized with pentobarbitone (35 mg/kg by intravenous injection) and artificial respiration commenced. 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 electrocardiogram (L-II), epicardial unipolar electrocardiogram (EPEG) and epicardial bipolar electrocardiogram (BPEG) and blood pressure from the femoral artery. EPEG was recorded by a tungsten wire with a diameter of 0.2 mm. BPEG was recorded by a com-

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posite electrode. This electrode was made of two parallel enamel-coated copper wires (0.1 mm diameter) attached to an acrylic plate (20 mm × 5 mm). Each enamel coated wire was about 1.5 cm in length, and the enamel coating was scraped off at three points. The acrylic plate was sutured to the surface of the anticipated ischaemic zone so that the exposed points of the wires touched the epicardial surface. The electrode for EPEG was placed at the same site as the composite electrode. The BPEG was amplified with a filter frequency of 40 to 300 Hz. The EPEG was amplified with d.c. amplifiers (KM-85M, Nihon Kohden). All parameters were recorded on an ink-writing oscillograph (800-6, Nihon Kohden).

To produce transient ischaemia, the left anterior descending coronary artery (LAD) was occluded, together with the adjacent veins, below its first diagonal branch for 3 to 10 min. The time interval between successive occlusions was at least 10 min. Before drug administration, coronary occlusion was performed at least twice and it was determined that the time course and the degree of alternans and conduction abnormalities were similar in the two successive occlusions (control-1 and control-2). Drugs were administered via the femoral vein. Occlusion was again performed 5 min and 1.5 h after drug administration.

The degree of alternans and of conduction abnormalities were measured at 30 s intervals (T_1, T_2 and T_3) after the start of occlusion and also 2 min after T_3 (= T_4). T_1, T_2 and T_3 were timed to correspond to 30, 60 and 90 s after the appearance of ST-T alternans in the control occlusion. For instance, when ST-T alternans appeared at 2 min after the start of the control occlusion, T_1, T_2, T_3 and T_4 were determined at 2.5, 3, 3.5 and 5.5 min after the start of each occlusion.

The degree of ST-T alternans was represented in terms of the difference in the ST-segment elevation of two adjacent potentials in the EPEG, as shown in Figure 1. The epicardial ST-segment elevation was measured 180 ms after the onset of the QRS complex, because the alternate change was most marked at this time. The magnitude of TQ segment depression in the EPEG during an occlusion was also determined by measuring the displacement of the TQ segment level at T_1, T_2, T_3 and T_4. The delayed conductions were reflected as delayed deflections in BPEG as previously reported (El-Sherif & Lazzara, 1979) (lower tracings in Figure 1). ST-T alternans was associated with the alternate changes in the

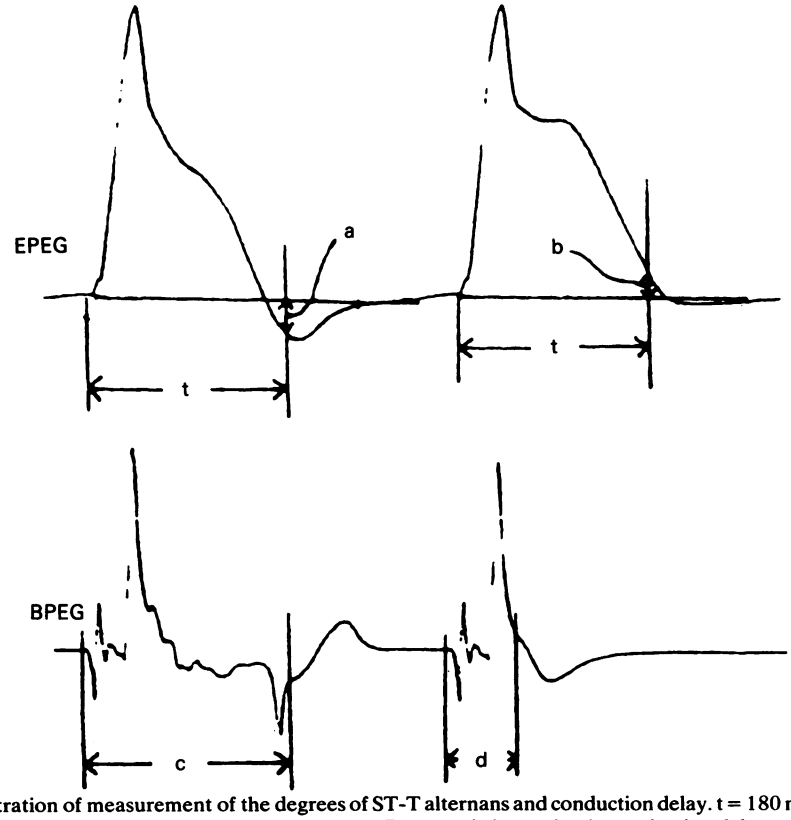

Figure 1 Illustration of measurement of the degrees of ST-T alternans and conduction delay. t = 180 ms. Degree of alternans = a + b mV. Maximal conduction delay = c ms. Degree of alternation in conduction delay = c − d ms.

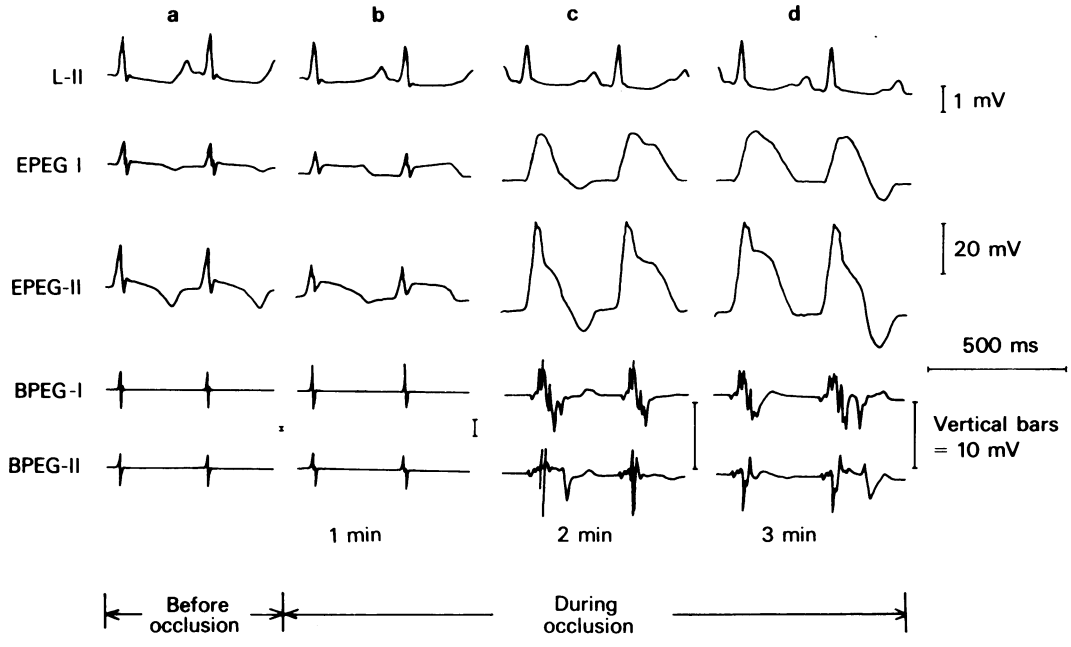

Figure 2 Changes in EPEG and BPEG during control occlusion. One min after the start of occlusion, ST alternans appeared, while conduction delay was negligible (b). After 2 min, ST-T alternans appeared, and conduction delay and its alternate change are observed (c). Three min after the onset of occlusion, these changes are more marked (d). The more negative deflection of the ST-T complex is accompanied by considerable conduction delay.

delayed deflection in BPEG. Thus, the degree of conduction abnormalities was represented in terms of the maximal conduction delay and its alternate change. The conduction delay was represented as the time from the onset of an initial deflection to a final rapid deflection ((c) and (d) in Figure 1). Because the conduction delay changed alternately, the longer delay (Figure 1c) was regarded as 'the maximal conduction delay'. The degree of the alternation of the conduction delay was represented in terms of the time difference in the conduction delay in the adjacent beats ((c) minus (d) in Figure 1).

In five dogs, effects of a drug on changes in the monophasic action potential (MAP) were also investigated. These were recorded from the ischaemic epicardial surface using a suction electrode with a diameter of 0.5 mm and were amplified with a d.c. amplifier. The reduction of the amplitude of MAP and the change in the resting potential were measured. EPEG was recorded simultaneously from an area which was less than 2 mm from the suction electrode.

The blood pressure was measured before each occlusion. After a drug, heart rate was maintained at pre-drug level by atrial pacing.

The drugs examined 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 and dipyridamole (Yamanouchi Co. Ltd) at a dose of 0.5 mg/kg. The doses of the Ca^{2+}-antagonists were chosen, because a previous study showed that verapamil 0.1 and 0.2 mg/kg and diltiazem 0.2 and 0.5 mg/kg inhibited the alternation of repolarization phase during coronary occlusion (Hashimoto *et al.*, 1981). All data are expressed as the means ± s.e. and Student's paired *t* test was used for statistical analysis.

Results

Changes in EPEG and BPEG during control occlusion

Typical changes in EPEG and BPEG are shown in Figure 2. EPEG-I and EPEG-II were recorded from the same area as BPEG-I and BPEG-II, respectively. In EPEG, the ST-segment was gradually elevated during occlusion. This is partially due to the depression of the TQ level. One min after the start of the occlusion, an alternate change in the ST-segment (ST alternans) appeared (b), while no remarkable change was observed in BPEG except a slight widening of the deflection. ST alternans was followed by an alternate change in the ST-T complex (ST-T alternans) (c). In this period, the depression of the TQ level was more pronounced, and an increase in the height of R wave

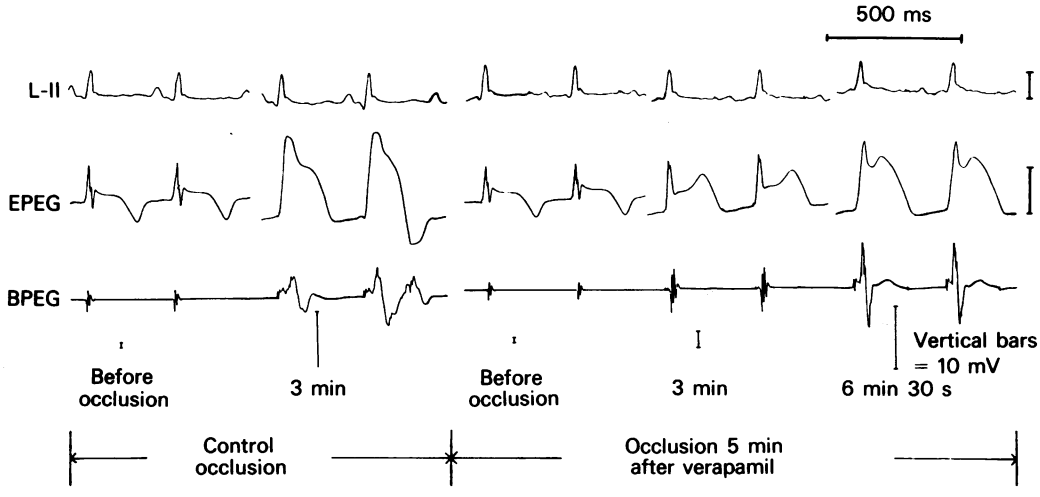

Figure 3 Effects of verapamil on ST-T alternans and conduction abnormalities. Verapamil attenuated ST-T alternans and the conduction delay.

was remarkable. In BPEG, the delayed deflection which reflects conduction delay was prominent, and alternate changes in the delayed deflection appeared (c). As ischaemia progressed, ST-T alternans became more marked and the conduction delay increased. The alternate change in the conduction delay was clearly observed (c). The negative deflection in the ST-T complex was associated with a longer conduction delay. EPEG and BPEG in the non-ischaemic area did not change during occlusion.

Effects of verapamil on ST-T alternans and associated conduction abnormalities

A typical trace is shown in Figure 3. In the control occlusion, ST-T alternans and conduction delay were prominent at 3 min after the start of occlusion. Verapamil at a dose of 0.2 mg/kg inhibited ST-T alternans, the changes in the QRS complex, the TQ depression and the conduction abnormalities. At 6.5 min after the onset of occlusion, changes in the ST-T complex and TQ depression were pronounced, and either ST-T alternans or the conduction abnormalities did not occur. Verapamil did not produce any change in EPEG and BPEG of the non-ischaemic area.

Figure 4 shows the effects of verapamil in nine dogs. The degree of ST-T alternans, TQ depression and the maximal conduction delay were not significantly different between the two control occlusions. The degree of ST-T alternans was significantly attenuated by verapamil (a). TQ depression was also attenuated at T_1, T_2 and T_3 (b). However, TQ depression at T_4 was not significantly different from that in control occlusions. The maximal conduction delay and alternate changes in conduction delay were reduced by verapamil (c, d). The effects of verapamil on ST-T alternans, TQ depression and conduction delay were no longer observed 1.5 h after the drug. The blood pressure was not significantly affected by verapamil.

Effects of verapamil on the change in monophasic action potentials during LAD occlusion

A typical trace is shown in Figure 5. As ischaemia progressed, the resting potential and the MAP amplitude decreased. One min after the start of occlusion, ST alternans appeared and was associated with an alternate change in the repolarization phase of MAP. During the period of ST-T alternans, the amplitude of MAP changed alternately, and the negative deflection of the ST-T complex was associated with a larger amplitude of MAP. Pronounced ST-T alternans was accompanied by 2:1 block. The difference in time between the Q wave in L-II and the depolarization phase of MAP increased; in other words, the initiation of the depolarization was delayed. After 0.2 mg/kg of verapamil, the decrease in both the resting potential and the amplitude of MAP was attenuated, alternate changes in the amplitude of MAP were not observed. At 6 min after the onset of occlusion, the resting potential and amplitude of MAP further decreased, but no alternate change was observed. In addition, the delay in the initiation of depolarization was slight.

Figure 6 shows the effect of verapamil on the decrease in the amplitude of MAP and in the resting potential in five dogs. In the control occlusion, the amplitude of the smaller MAP rapidly decreased

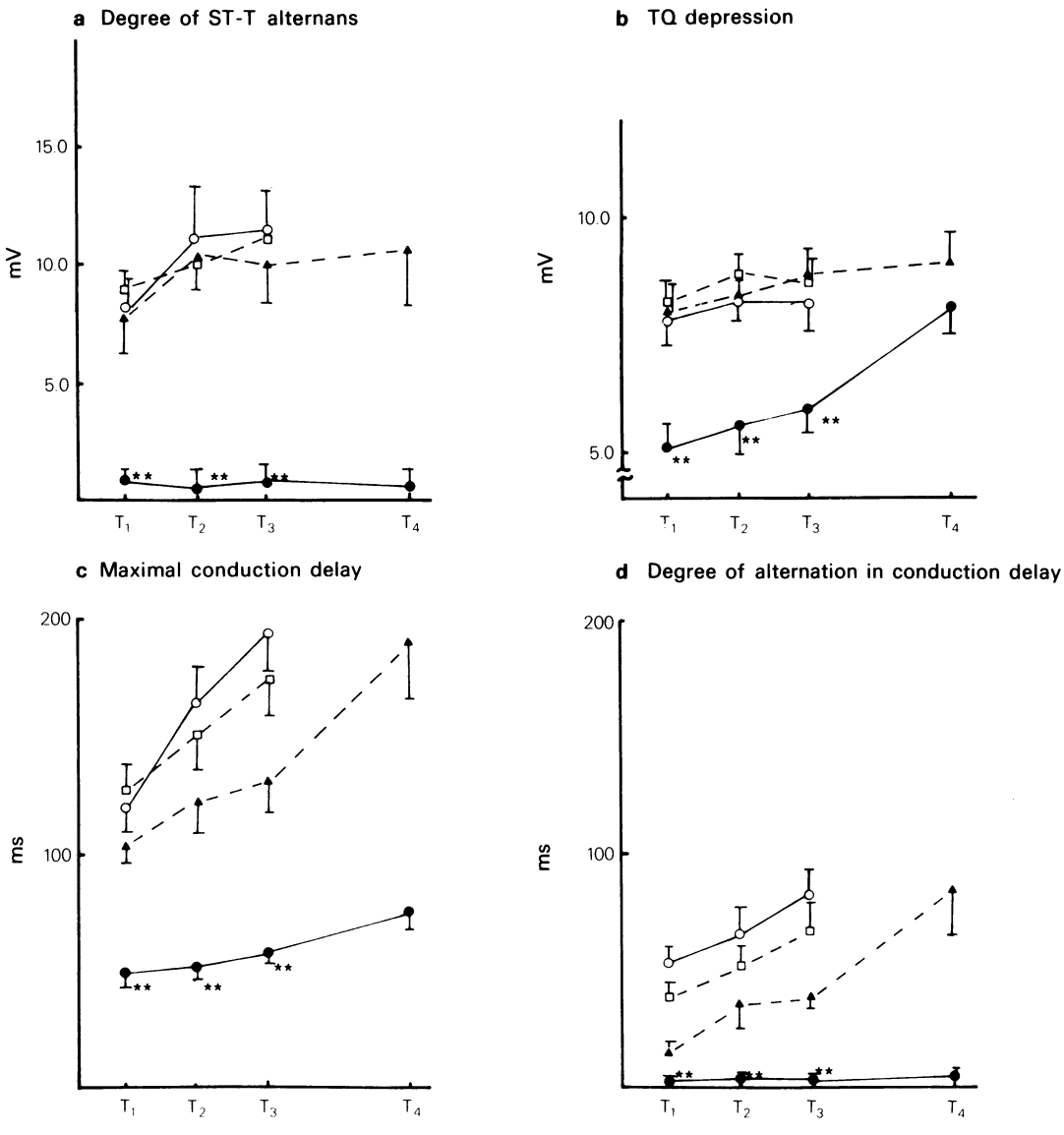

Figure 4 Effects of verapamil on the ST-T alternans, TQ depression and conduction abnormalities. (□) Control-1; (○) control-2; (●) 5 min after verapamil; (▲) 1.5 h after verapamil. Nine dogs were used. $^{**}P < 0.01$ vs Control-2.

between T_1 and T_2, while the amplitude of the larger MAP did not change remarkably. Thus, the degree of alternate changes in the amplitude of MAP increased. After 0.2 mg/kg of verapamil, the decrease in the amplitude of MAP was significantly attenuated, and no alternate changes in the amplitude of MAP were observed (Figure 6a). The amplitude of MAP at T_4 was not significantly different from that at T_1 in control or 1.5 h after verapamil. Nevertheless, alternate changes were not observed. The effect of verapamil on the decrease in the resting potential is shown in Figure 6b. After verapamil, the decrease in the resting potential was significantly attenuated at T_1, T_2 and T_3, while the resting potential at T_4 was not significantly different from that in the control. One and a half hours after verapamil, the decrease in the resting potential was comparable to that in the control.

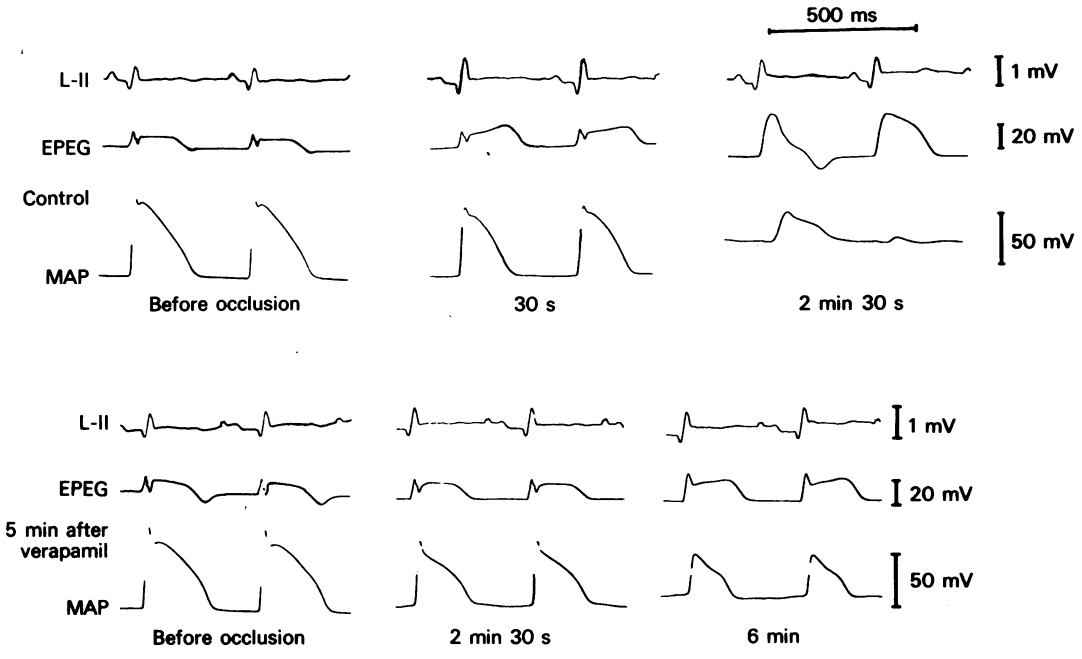

Figure 5 Changes in monophasic action potentials (MAP) during the period of ST-T alternans and effects of verapamil. The amplitude of MAP and the resting potential were reduced, as ischaemia progressed. At 2.5 min after the start of the occlusion, a typical ST-T alternans appeared, and the amplitude of MAP changed alternately. These changes were attenuated by verapamil.

Effects of diltiazem on ST-T alternans and associated conduction abnormalities

Results obtained from seven dogs are shown in Figure 7. Diltiazem at a dose of 0.5 mg/kg markedly inhibited ST-T alternans (a), and significantly attenuated the TQ depression at T_1, T_2 and T_3, but not at T_4 (b). The maximal conduction delay and alternate change in the conduction delay were also attenuated (c, d). Conduction abnormalities were not observed even after a longer period of occlusion. ST-T alternans, TQ depression and conduction abnormalities were again observed 1.5 h after the drug. The blood pressure was not significantly affected by diltiazem.

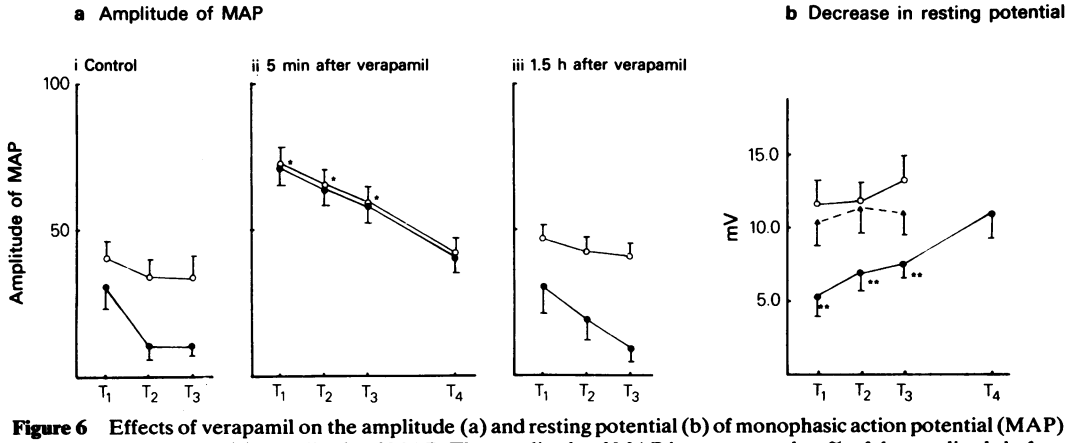

Figure 6 Effects of verapamil on the amplitude (a) and resting potential (b) of monophasic action potential (MAP) during LAD occlusion. (a) Amplitude of MAP. The amplitude of MAP is represented as % of the amplitude before each occlusion: (○) larger MAP; (●) smaller MAP. (b) Decrease in the resting potential: (○) control-2; (●) 5 min after verapamil; (▲) 1.5 h after verapamil. Five dogs were used. $^{*}P<0.05$; $^{**}P<0.01$ vs control-2.

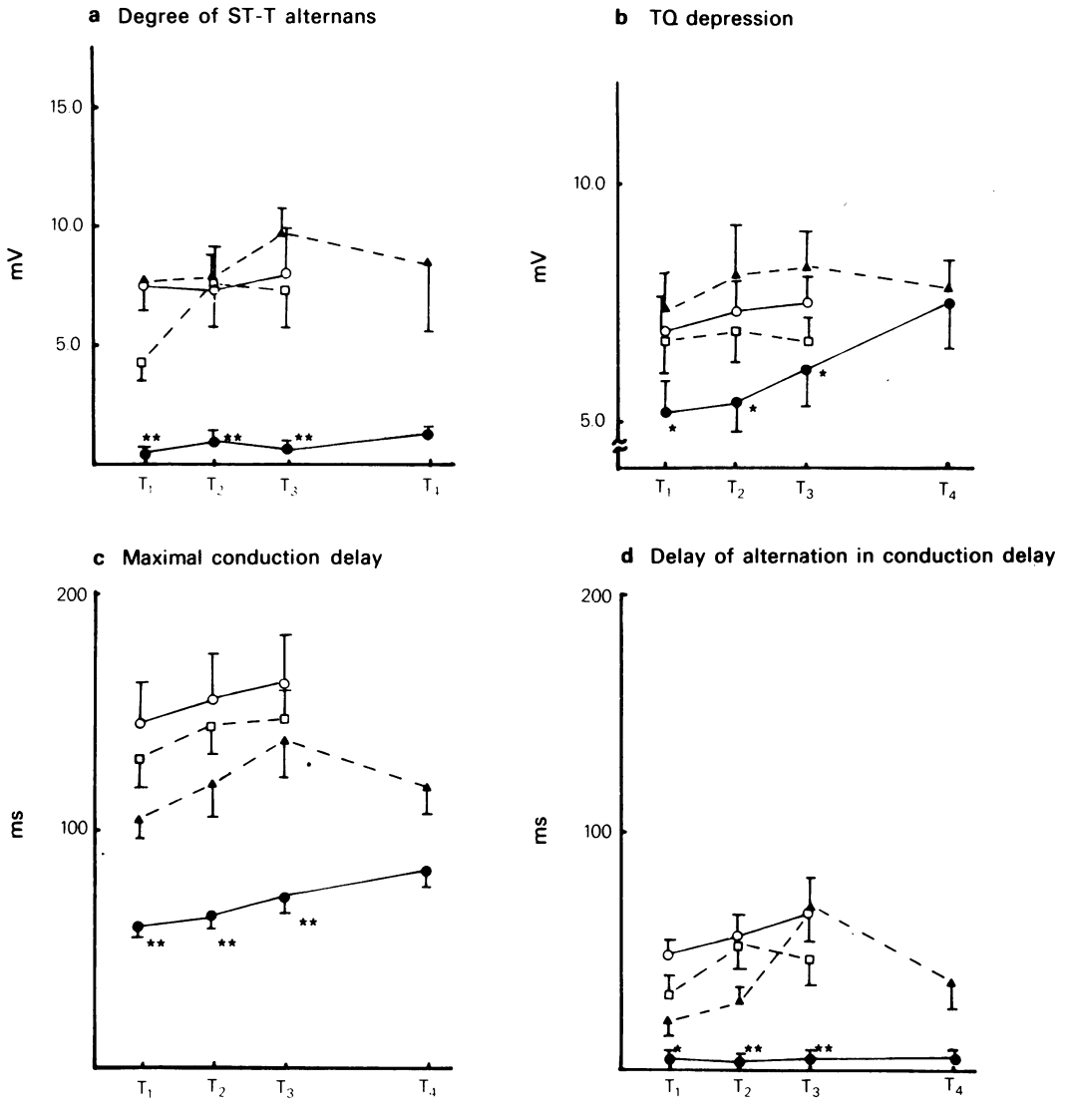

Figure 7 Effects of diltiazem on the degree of ST-T alternans and conduction abnormalities. (□) Control-1; (○) control-2; (●) 5 min after diltiazem; (▲) 1.5 h after diltiazem. Seven dogs were used. $*P<0.05$; $**P<0.01$ vs control-2. Diltiazem reduced the degree of the ST-T alternans, conduction delay and its alternate change.

Effects of dipyridamole on ST-T alternans and conduction abnormalities

Neither the ST-T alternans nor the conduction abnormalities were significantly attenuated by 0.5 mg/kg of dipyridamole in five dogs. The mean blood pressure was 123.0 ± 7.4 mmHg before control-2 occlusion, and was significantly lowered after dipyridamole (97.0 ± 7.2 mmHg, $P<0.05$).

Discussion

Although several types of electrical alternans have been reported (Kimura & Yoshida, 1963; Kleinfeld & Stein, 1968; Lu, Lange & Brooks, 1968; Richetts, Denison & Haywood, 1969; Dolura & Pozzi, 1971; Fish, Edmonds & Greenspan, 1971; Ishikawa & Tateno, 1976; Chung, 1977; Navarro-Lopez, Cinca, Sanz, Periz, Magrina & Betriu, 1978), the alternans

observed in the present study were the alternans of the ST-T segment (ST alternans) and of the ST-T complex (ST-T alternans). Usually, ST alternans was followed by ST-T alternans. During the period of ST alternans, the conduction abnormalities recorded in BPEG were slight. ST alternans was associated with an alternate change in the duration of MAP, supporting our previous idea that ST alternans is a reflection of the alternate change in the repolarization phase (Nakashima *et al.*, 1978). Because the amplitude of MAP did not change to any extent during the period of ST alternans, ST alternans was not accompanied by serious conduction abnormalities.

In contrast to ST alternans, ST-T alternans was associated with a serious conduction delay and its alternate changes. A negative deflection of the ST-T complex was always associated with a longer conduction delay, indicating the existence of a close relation between the two phenomena. During the period of ST-T alternans, the amplitude of MAP decreased and alternately changed. A larger amplitude of MAP was always associated with a negative deflection of the ST-T complex. This fact is consistent with results obtained with the micro-electrode technique in perfused isolated heart (Downar *et al.*, 1977b; Kléber *et al.*, 1978). The initiation of the depolarization phase of MAP was considerably delayed during the period of ST-T alternans, indicating that the conduction of excitation was slowed. The remarkable ST-T alternans is accompanied with 2:1 block. It is probable that a larger action potential associated with the negative deflection of the ST-T complex conducts slowly in the ischaemic area resulting in a considerable conduction delay, and that a smaller action potential associated with the positive ST-T complex is easily blocked resulting in less conduction delay.

During LAD occlusion, the TQ level was gradually depressed. Coincidentally with the TQ depression, the resting potential of MAP also gradually decreased. Therefore, the TQ depression is probably a reflection of the decrease in resting membrane potential of myocardial cells, as suggested by Kléber *et al.* (1978).

Verapamil attenuated the degree of ST-T alternans and associated conduction abnormalities. The alternate change in the amplitude of MAP was also inhibited, indicating that the attenuation of ST-T alternans and of the alternate change in the conduction delay is a reflection of the inhibition of the alternate change in the amplitude of the transmembrane action potential of myocardial cells. Verapamil attenuated the delay of the initiation of the depolarization of MAP. This fact is consistent with the disappearance of the conduction delay. The improvement of conduction delay by verapamil has been demonstrated during acute LAD occlusion and in the late myocardial infarction (Elharrar, Gaum & Zipes, 1977; El-Sherif & Lazzara, 1979).

Both the TQ depression and the decrease in the resting potential of MAP were also attenuated by verapamil. Therefore, it is possible that the attenuation of the decrease in the resting potential of myocardial cells may partially contribute to the inhibition of ST-T alternans, conduction abnormalities and changes in MAP. However, 5 min after verapamil, the TQ depression at T_4 was comparable to that in the control, while both ST-T alternans and the conduction delay were still greatly inhibited. The decrease in the resting potential recorded by a suction electrode was also attenuated by verapamil. However, the resting potential at T_4 after verapamil was not significantly different from that in control, while the alternate change in the amplitude of MAP was still inhibited. These facts suggest that the inhibition of either ST-T alternans, or the conduction delay or the alternate change in MAP is not merely due to attenuation of the decreases in the resting potential. Nevertheless, the decrease in the amplitude of MAP is probably caused by the decrease in the resting potential, because the amplitude of MAP markedly decreased at T_4 after verapamil. It has been reported that acidosis and several metabolic factors besides K^+ accumulation in the extracellular space also contribute to electrical abnormalities during ischaemia (Dower *et al.*, 1977a; Vogel & Sperelakis, 1977; Carmeliet, 1978; Opie, Nathan & Lubbe, 1979; Hill & Gettes, 1980; Morena, Janse, Folet, Krieger, Crijns & Durrer, 1980). Therefore, it is probable that verapamil attenuated these metabolic changes resulting in the inhibition of ST-T alternans and conduction abnormalities.

Diltiazem, another powerful calcium antagonist (Nagao, Sato, Iwasawa, Takeda, Ishida, Nakajima & Kiyomoto, 1972; Nakajima, Hoshiyama, Yamashita & Kiyomoto, 1975; Saikawa, Nagamoto & Arita, 1977), also attenuated ST-T alternans and conduction abnormalities. The effect of diltiazem on the TQ depression was similar to that of verapamil. The TQ depression at T_4, 5 min after diltiazem was comparable to that in the control, when ST-T alternans and conduction abnormalities were greatly inhibited. Therefore, as in the case of verapamil, the attenuation of the decrease in the resting potential cannot fully explain the inhibition of the ST-T alternans and of conduction abnormalities. It has been suggested that diltiazem may reduce damage to the ischaemic myocardium by preventing damage to mitochondira (Weishaar, Ashikawa & Bing, 1979; Nagao, Matlib, Franklin, Millard & Schwartz, 1980). This metabolic effect of diltiazem may contribute to its inhibitory effects on ST-T alternans and associated conduction abnormalities. It seems that the mechanisms of action of the two drugs are similar and due to their antagonistic effects on Ca^{2+}.

Unlike the Ca^{2+}-antagonists, dipyridamole, a powerful coronary vasodilator, did not significantly

affect ST-T alternans or conduction abnormalities. In contrast to the Ca^{2+}-antagonists, dipyridamole lowered the blood pressure, suggesting that its vasodilator activity is greater than that of the Ca^{2+}-antagonists. Therefore, it seems that the effects of the Ca^{2+}-antagonists on ST-T alternans are not due to their vasodilator actions but are due to direct effects on myocardial cells.

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