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EFFECTS OF DILTIAZEM ON ELECTRICAL ALTERNANS OF ST SEGMENT AND VENTRICULAR ARRHYTHMIA INDUCED BY ACUTE CORONARY OCCLUSION

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Effects of diltiazem (DZ) on electrical alternans of ST segment (STEA) and ventricular arrhythmia (VA) during coronary occlusion and reperfusion were examined in anesthetized open chest dogs. Standard II ECG, unipolar surface ECG, His bundle electrogram, bipolar surface electrograms and bipolar monophasic action potentials (MAP) both inside (IZ) and outside (NZ) boundaries of the ischemic zone, and blood pressure were simultaneously recorded. Right atrial appendage was paced at a rate of 180/min. Dogs were divided into two groups. Group A (n=16) included dogs with administration of DZ (0.02 mg/kg/min). Group B (n=29) included dogs without DZ. In addition, in other 5 dogs, regional myocardial blood flow (RMBF) were measured in both ischemic center zone and border zone using H_2 clearance method.

Results: In group A, compared with group B, (1) the incidence of VA, particularly VT and VF, significantly decreased during occlusion. (2) the degree of STEA, MAP alternans and conduction delay were significantly attenuated. (3) RMBF in both zones significantly increased before occlusion, but the decrease in RMBF during occlusion did not improve. (4) there were no significant difference in blood pressure during occlusion between both groups. Our results suggest that the mechanism for the decrease in the incidence of VA, degree of STEA and MA alternans by DZ is not due to the improvement of RMBF and the decrease in pressure rate product, but may be due to the reduction of transmembrane Ca flux into ischemic myocardium.

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EFFECTS OF ALPHA- AND BETA-BLOCKING AGENTS ON ISCHEMIA- AND REPERFUSION-INDUCED ARRHYTHMIAS -STUDIES IN THE CONSCIOUS RAT-

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Most studies on ischemia- and reperfusion-induced arrhythmias have been performed either in the isolated heart preparations or in anesthetized animals. Since the use of anesthetics and denervation can influence the severity of arrhythmias, we have developed a conscious rat preparation, in which coronary artery occlusion and also reperfusion can be achieved, and occluded zone size can be measured. Using this new preparation, we have assessed the effects of an alpha-blocking agent, prazosin and a beta-blocking agent, atenolol on ischemia- and reperfusion-induced arrhythmias. Atenolol (1mg/kg body wt, given i.v. 10 min prior to LAD occlusion, n=12) decreased heart rate and significantly reduced the incidence of ventricular fibrillation from 63% (15/24) to 17% (2/12) ($p < 0.05$). In contrast, prazosin (0.1 or 1mg/kg body wt, given i.v. 10 min prior to occlusion, n=12) significantly increased heart rate. It did not alter the incidence of VF, but dramatically increased mortality from 13% (3/24) to 100% ($p <$

0.001) and 87% ($p < 0.001$) during 30 min of ischemia, respectively. The high mortality with prazosin was associated with a high incidence of bradyarrhythmias. Atenolol also significantly reduced the incidence of reperfusion induced VF following 5 min of coronary occlusion from 100% (15/15) to 58% (7/12) ($p < 0.05$). All groups possessed occluded zone of similar size. Thus, in the conscious rat, atenolol affords some protection against ischemia- and reperfusion-induced VF, whilst at the doses studied, prazosin exacerbates arrhythmias and resultant mortality.

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EFFECTS OF PREEXISTING CORONARY STENOSIS ON VENTRICULAR ARRHYTHMIAS AND ST SEGMENT ELEVATION INDUCED BY ACUTE CORONARY OCCLUSION

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After release of 1st 5 min occlusion of left anterior descending coronary artery, 33 dogs were separated into two groups. Group A included 16 dogs with 4 hrs stenosis before 2nd 10 min occlusion. Group B included 17 dogs with 4 hrs no-stenosis before it. Based on the mean value (12.1 ml/min/100g) of regional myocardial blood flow (RMBF) in ischemic center zone (IZ) during 1st occ., dogs with less than 12.1 of RMBF were selected for the analysis in both groups because those were postulated to have poor collateral flow like in human being.

Results: During 1st occ., there were no differences in RMBF in IZ, conduction delay (CD), ST segment elevation in IZ between group A' (n=11) and group B' (n=10).

During 2nd occ., compared with group B', results in group A' were as follows:

- (1) RMBF in IZ was significantly increased (11.6 ± 1.9 vs 5.7 ± 0.7 ml/min/100g, $p < 0.05$, M±SE).
- (2) CD and ST segment elevation were significantly reduced (18.4 ± 5.6 vs 57.6 ± 17.0 ms, $p < 0.05$ and 5.3 ± 2.5 vs 16.1 ± 4.5 mV, $p < 0.05$, M±SE).
- (3) Incidence of occurrence of ventricular arrhythmias (VA) was significantly reduced.

Our results suggest that reduction of CD, ST segment elevation and incidence of VA during 2nd occ. in group A' was due to the increase in collateral flow stimulated by the preexisting coronary stenosis.

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THE EFFECT OF CORONARY REOCCLUSION ON REPERFUSION ARRHYTHMIA IN CONSCIOUS DOGS

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The effect of coronary reocclusion on reperfusion arrhythmia was evaluated in 31 mongrel dogs. After induction of anesthesia and left thoracotomy, the snare-type polyethylene occluder was placed around the left circumflex coronary artery. Seven days after operation coronary occlusion was produced by the occluder in the awake state, and reperfusion was carried out 1 hour after coronary occlusion. ECG was recorded continuously at slow speed and standard

speeds using limb leads.

Reperfusion was carried out in 28 cases. Three cases died of ventricular fibrillation (VF) during coronary occlusion. Twenty seven of the 28 cases developed reperfusion arrhythmia (sustained ventricular tachycardia (VT) 15, non-sustained VT 5, VF 2, and frequent ventricular premature contraction (VPC) 5).

Coronary reocclusion was performed within 3 minutes after reperfusion (early coronary reocclusion) in 10 cases. Sustained VT in 8 cases and frequent VPC in 2 cases all disappeared after reocclusion in 1 to 75 seconds.

Coronary reocclusion was performed in 9 cases between 20 and 30 minutes (late coronary reocclusion). Sustained VT after reperfusion in 4 cases which were temporarily suppressed by lidocaine bolus injection and reappeared in 15 to 20 minutes all disappeared in 18 to 100 seconds after reocclusion. Non-sustained VT in 4 cases all disappeared after reocclusion.

These results demonstrate that coronary reocclusion has an interrupting effect on reperfusion arrhythmia.

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A STUDY OF THE ARRHYTHMOGENIC MECHANISM IN HYPOKALEMIA

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The arrhythmogenic mechanism in dogs with hypokalemia was investigated in relation to the effect of α -1 blockade. Hypokalemia was induced by insertion of ion-exchange resin into colon. After the premedication of 60 min, 10 μ g/kg of epinephrine was injected intravenously. Heart mitochondria (Mt) was prepared 5 min after the epinephrine injection and Mt Ca^{2+} content was measured. The severity of arrhythmias was expressed by the arrhythmic ratio (the percentage of ventricular ectopic beats divided by the total heart rate) during 5 min after the epinephrine injection. In the hypokalemia group, dogs with the arrhythmic ratio of over 10% were observed 9 out of 17. However, in the control group ($n=13$) which was maintained normal serum K^+ level, only one dog showed the arrhythmic ratio of over 10%. Furthermore, dogs with the lower serum K^+ levels showed the higher arrhythmic ratio. Ca^{2+} content of heart Mt, which is considered to be the reflection of intracellular Ca^{2+} concentration, was 24.4 ± 5.7 nmoles/mg protein in the control group 5 min after the epinephrine injection, while that from the hypokalemia group was increased to 35.0 ± 13.4 . A good reciprocal correlation between the concentration of serum K^+ just before the epinephrine injection and Mt Ca^{2+} content was observed in the hypokalemia group ($r=-0.79$), while in the control group, no correlation was observed. Clear correlation between Mt Ca^{2+} content and the arrhythmic ratio was also observed in the hypokalemia group. Pretreatment of bunazosin, an α -1 blockade, prevented effectively the increase in Mt Ca^{2+} content, and reduced the arrhythmic ratio. These results indicate that, in hypokalemia, a relatively small dosis of epinephrine, which scarcely effects the dogs maintained with normal serum K^+ level, could induce the severe ventricular arrhythmias probably due to the Ca^{2+} influx to myocardium through α -1 adrenergic responsiveness.

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DESENSITIZATION OF ACh-INDUCED K^+ CURRENT IN ATRIAL CELLS OF THE GUINEA-PIG HEART

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Acetylcholine (ACh) increases K^+ current (I_{ACh}) in atrial tissues. Although it has been generally described that muscarinic increase of K^+ current does not desensitize during continuous application of ACh in cardiac tissues, we found that I_{ACh} does desensitize. Here, we characterize the desensitization phenomenon of I_{ACh} in single atrial cells of the guinea-pig. The tight-seal whole cell clamp technique was used. The pipette solution contained 100 μ M GTP and 1 mM MgCl_2 . Various concentrations of ACh were applied in the bath solution. ACh 10^{-8} - 10^{-4} M increased I_{ACh} dose-dependently. I_{ACh} evoked by ACh more than 10^{-6} M decreased with time after initial activation. The time-course of the decay could be divided into two exponential components. The time-constants of both components were not affected by the membrane potential but depended on the concentrations of ACh. The I_{ACh} in the steady state was 67% (10^{-8} M ACh), 53% (10^{-5} M ACh) & 43% (10^{-4} M) of the peak current, respectively. When 10^{-5} M ACh was applied after perfusion of 10^{-6} M ACh, the peak current evoked by 10^{-5} M ACh decreased to 68% of the control, which was coincident with the decrease of I_{ACh} during perfusion of 10^{-6} M ACh. We interpret this phenomenon as representing the desensitization of muscarinic receptors by ACh.

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ACETYLCHOLINE AND ADENOSINE RECEPTORS LINK WITH A K^+ CHANNEL VIA GTP-BINDING PROTEINS IN CARDIAC ATRIAL CELL MEMBRANE

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Both acetylcholine (ACh) and adenosine (Ado) reduce the heart rate and atrio-ventricular conduction by increasing a K^+ conductance of cardiac cell membrane. To clarify the molecular mechanisms underlying the effects of ACh and Ado, we examined the mode of regulation of K^+ channel