at high concentration and induce or exaggerate TI that is modulated by cellular calcium at low concentration, and this TI can induce arrhythmias.

-183-

ANTI-ARRHYTHMIC EFFECTS OF Ca-ANTAGONIST AND QUINIDINE SULFATE ON DIGITALIS INDUCED ARRHYTHMIAS

Nobuyuki Ohte, Shunki Yoneda, Toshio Kako, Masaaki Kohketsu, Masanobu Kawaguchi and Takao Fujinami

The 3rd department of Internal Medicine, Nagoya City University Medical School

Anti-arrhythmic effects of Ca-antagonist and quinidine sulfate on ouabain induced arrhythmias were studied on single cultured heart cells. The cells were separated from embryonic heart of ddY strain mice by trypsin treatment and cultured in Falcon dishes containing Eagle's MEM with 10% of calf serum in 5% CO₂ atmosphere for 5 days.

Observation of beat to beat intervals was performed by an optical-television system. Beating behavior detected by a photosensor was converted into voltage change. The electrical signals were made A/D conversion and input to a microcomputer. Mean value (M) and standard deviation (SD) of beating intervals were calculated by the microcomputer. The SD/M was used as an index revealing single cell beating irregularity and it was expressed as a percentage of the control.

The cell showed an increase in beating rate and an augmented irregularity after 10 min of inoculation with ouabain at 10⁻⁵M. After 15 min the index of SD/M increased to more than it was after 10 min. Anti-arrhythmic effects of diltiazem, verapamil and quinidine sulfate were assessed as to how they would reduce increased SD/M by ouabain between 10 and 15 min.

Diltiazem of 10⁻⁸M decreased SD/M to 86.3±26.6% of the control from elevated rate of 131±43.4% by ouabain administration (n=13, p<0.01). Verapamil of 10⁻⁸M reduced SD/M from 133.4±72.8% to 115.3±60.6% (n=9, ns.) and quinidine sulfate of 10 µg/ml also decreased from 202±96.9% to 90.9±46.1% (n=11, P<0.01). Moreover, three agents reduced the beating rate which had been increased by ouabain but differences were not significant.

These findings suggest that diltiazem, verapamil and quinidine sulfate are considered to have anti-arrhythmic effects on digitalis induced arrhythmias.

-184-

DIFFERENT MECHANISM OF AUTOMATIC ACTIVITY IN DISEASED HUMAN ATRIAL MUSCLES EXCISED FROM PATIENTS WITH OR WITHOUT DIGITALIS TREATMENT

Tatsunori Kimura, Sunao Imanishi, Makoto Arita, Hidemi Takasaki*, Tetsuo Hadama*, Joji Shirabe*

Department of Physiology and Surgery*, Medical College of Oita, Oita 879-56

Spontaneously firing action potentials were recorded using microelectrodes in approximately 50% of human atrial specimens perfused with normal Tyrode solution (1.8mM-Ca²⁺, 5.4mM-K⁺). The continuous automaticity (CA) could be divided into two types from the cycle length (CL) of the firing, i.e., Type I and Type II. Type I is CA with CL of 1.5 sec or more, while Type II, CA with

shorter CL than 1.5 sec. Type I was observed in 92% of specimens obtained from patients who received no immediate digitalis therapy before cardiac operation, while 78 % of Type II were those from patients administered with digitalis. Type I increased by an application of caffeine (5-15mM) in dose dependent manner, but almost unchanged in the presence of ryanodine (1µM), a specific blocker of Ca²⁺ release from sarcoplasmic reticulum (SR). In contrast, Type II was depressed markedly by caffeine (5-15mM) or ryanodine (1µM). Type I changed to Type II with Tyrode solution containing either ouabain (1µM) or low Na (75 mM), measures to increase intracellular Ca²⁺ concentrations. It is suggested that pacemaker activity of Type I may be due to slow inward Ca²⁺ current via slow channel, and that the activity of Type II may depend on SR-related cyclic changes in intracellular Ca concentrations.

-185-

COMPUTER SIMULATION OF RE-ENTRANT TACHYCARDIAS IN A TWO DIMENSIONAL MODEL

Yuji Hirano, Tohru Sawanobori and Masayasu Hiraoka

Department of Cardiovascular Diseases, MRI Tokyo Medical and Dental University

We modified the "excitable element" model of van Capelle and Durrer based on the experimental data of frog atrium and constructed a computer simulation model of re-entrant arrhythmias. The propagation of electrical excitation in the sheet consisting of 20 x 20 elements could be analysed visually, as the voltage and the parameter of excitability (which indicates the recovery from refractoriness) of each element were mapped on a color graphic display of the computer. When a limited area with short refractory period was introduced into the model, re-entrant tachycardias could be initiated by giving both basic and extra stimuli at the border of this area. If the model was uniform in refractoriness, however, the basic and extra stimuli should be given to different sites of the sheet in order to produce asymmetrical distribution of refractoriness and to initiate reentry. As observed in biological preparations, re-entrant excitations in the two-dimensional sheet often showed a change in the propagation pathway with a variation of cycle length at individual elements, before establishing the stable circulation of the wavefront. In some cases, the excitation terminated spontaneously after several beats. These diversities of simulated re-entrant arrhythmias in a two-dimensional model were produced by the fact that the distribution of refractoriness in each element of the sheet changed beat by beat, because it was determined by the antecedent wavefront of each excitation.

-186-

THE MECHANISM OF INCREASED PLATEAU AND ACTION POTENTIAL PROLONGATION AT

SHORT DIASTOLIC INTERVALS IN A RABBIT VENTRICULAR MYOCYTE

Masayasu Hiraoka and Seiko Kawano

Dept. Cardiovasc. Dis., MRI, Tokyo Medical and Dental University

The ventricular action potential in the rabbit heart shows paradoxical prolongation at the shorter preceding diastolic intervals (PDI) than at the longer one. These changes are suggested to be brought about by the transient increase in slow inward current (I_{Ca}). However, it is not known why I_{Ca} increases at short PDI during the recovery period. Therefore, we examined the underlying ionic mechanism using ventricular myocytes isolated from rabbit heart. The action potential prolongation at 0 mV level (APD_0) and the augmentation of the plateau at shorter PDI than 2 sec were observed in single myocytes as similar as in ventricular tissues. Under voltage clamp conditions, I_{Ca} increased at the PDI between 300 msec and 2 second, but was small at the PDI shorter than 250 msec despite of the APD_0 prolongation and the plateau augmentation. The discrepancy seemed to be resulted from the participation of other current. We found the existence of a transient outward current (I_{TO}) on a membrane depolarization above -20 mV, which overlapped with I_{Ca} . The time course of the recovery of I_{TO} was slower than that of I_{Ca} , the former being longer than 2 second and the latter about 300 msec. At short PDI the net inward current increased due to a slow repriming of I_{TO} compared to that of I_{Ca} . It is concluded that the augmentation and the prolongation of the plateau at short PDI are produced by different recovery kinetics between I_{Ca} and I_{TO} .

-187-

DISSOCIATION BETWEEN INCREASED CYCLIC AMP CONTENT AND "EARLY" ISCHEMIA-INDUCED ARRHYTHMIAS IN THE RAT HEART

K. Kinoshita, K. Tokunaga, A.S. Manning* and D.J. Hearse*.

Dept. of Cardiac Surgery, Kyushu University School of Medicine and * The Rayne Institute, St. Thomas' Hospital, U.K.

Some authors have proposed that increases in myocardial cyclic AMP during ischemia may be a major factor for the induction of the "early" ischemia-induced arrhythmias. We have tested this hypothesis to compare the effects of forskolin, which increases cyclic AMP by direct stimulation of adenylyl cyclase without stimulating the beta-receptor to those of epinephrine in isolated perfused rat heart. Aerobic perfusion with 1 μ M epinephrine and 0.2 μ M forskolin (n=12 in each group) increased cyclic AMP content from 3.0 ± 0.1 to 10.7 ± 0.06 ($p < 0.001$) and 14.1 ± 0.9 nM/g dry wt ($p < 0.001$), respectively.

During 30 min of LAD occlusion, epinephrine increased the incidence of ventricular fibrillation from 8% to 83% ($p < 0.01$). In contrast to epinephrine, forskolin which increased cyclic AMP throughout the ischemic period reduced the severity of arrhythmias. The incidence of ventricular tachycardia was reduced from 100% to 58% ($p < 0.05$) and the total number of premature ventricular complexes was reduced from 561 ± 105 to 79 ± 29 ($p < 0.001$). Both epinephrine and forskolin similarly

increased heart rate and coronary flow prior to and during ischemia.

In conclusion, despite its ability to increase myocardial cyclic AMP content to a greater extent than that of epinephrine, forskolin exerts an antiarrhythmic effect. This would suggest that any increases in cyclic AMP content within an ischemic zone are not responsible for the genesis of the "early" ischemia-induced arrhythmias in the rat heart.

-188-

THE EFFECT OF VAGUS NERVE STIMULATION ON VENTRICULAR FIBRILLATION THRESHOLD

Tetsuro Shirai, Hiroshi Tsunakawa, Fumitaka Ebato, Kenichi Harumi

Division of Cardiology, Showa University, Fujigaoka Hospital

To evaluate the possibility of role of AV nodal ventricular echo on the induction of ventricular fibrillation (VF) and the effect of vagal nerve stimulation (VNS) upon it, we carried out VF induction in 11 dogs weighing from 7 to 12 kg were anesthetized with nembutal, 30-35 mg/kg i.v. Two bipolar electrodes were placed in the left ventricle, and one bipolar electrode was placed in the left atrial appendage. VF was induced by a low current train of 3 msec impulses of 50 HZ. After the ventricular fibrillation threshold (VFT) was determined in control, the effect of VNS upon VFT was examined. VNS was effective if a retrograde ventriculoatrial conduction was blocked completely under ventricular pacing. Result: VNS inhibited the induction of VF under the same VFT which induced VF in control in 3 out of 11 dogs. In remaining 8 dogs VNS didn't inhibit the induction of VF. Inhibition of VF induction by VNS occurred as a result of disappearance of AV nodal ventricular echo immediately after the cessation of train pulse. Conclusion: A ventricular echo has some role to induce the VF and VNF inhibits the induction of VF by blocking the AV nodal retrograde conduction.

-189-

EVALUATION OF SUBSIDIARY PACEMAKER FUNCTION AFTER THE TRANSARTERIAL CATHETER ABLATION OF ATRIOVENTRICULAR JUNCTION BY OVERDRIVE SUPPRESSION AND HOLTER ECG

Kazuo Moroe, Tadayuki Hiroki, Yasushi Sasaki, Keisuke Fukuda, Kikuo Arakawa

The Second Department of Internal Medicine Fukuoka University School of Medicine

To investigate the subsidiary pacemaker function after the transarterial catheter ablation of atrioventricular junction (AVJ), overdrive suppression test and Holter ECG were performed in nineteen mongrel dogs, persisting experimentally induced complete AV block. The energy delivered to the AVJ was divided into three grades, namely of high energy of more than 200J (group A), medium energy of 60 or 100J (group B), and low energy of 20 or 40J (group C).

Result; 1) In right ventricular overdrive