Effect of Procainamide on the Induction of Ventricular Fibrillation by Sequential Ventricular Stimulation

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The effect of procainamide on ventricular vulnerability to fibrillation was studied in 13 anesthetized open-chest dogs. Epicardial electrograms were recorded through forty bipolar electrodes placed on the surface of exposed ventricles. Ventricular fibrillation (VF) was induced by sequential extrastimulation. The number of extrastimuli required to induce repetitive extrasystole (RE) or VF were defined as repetitive extrasystole threshold (RET) or ventricular fibrillation threshold (VFT). The epicardial electrograms at the onset of ventricular arrhythmia were divided every 100 msec after the last extrastimulus, and the ratio of recordings with activation time of more than 50 msec during each divided period was defined as "chaotic score". Intravenous injection of procainamide at the dose of 20 mg/kg failed to increase RET but successfully increased VFT from 4.4 ± 0.9 to 7.0 ± 1.8 in hearts with necrosis. Procainamide significantly reduced chaotic score from 36 ± 12% to 14 ± 7% at 5 sec after the induction of ventricular arrhythmias.

We concluded that the antifibrillatory action of procainamide is based on a reduction of the number of chaotic multiple reentries, but not on the prevention of reentry per se.

Antiarrhythmic action of drugs has been classified into two categories: antiectopic action and antifibrillatory action. The suppression of abnormal focal excitation by antiarrhythmic drugs has been studied in detail. As for the antifibrillatory action, beryllium tosylate has been demonstrated to have predominant antifibrillatory action in a experimental study. However, the quantitative measurement of the antifibrillatory effect of drugs has not yet been established.

An earlier study by Moe et al. discussed the propagation of fibrillating wavefront and demonstrated that, at the beginning of ventricular fibrillation (VF), fibrillating wavefronts gradually invade on the ventricular surface, and that some electrograms showed regularly periodic excitation in spite of the continuous fibrillating deflections in other electrograms.

The purpose of this study was to clarify the effect of procainamide on the temporal progression of VF subsequent to the sequential ventricular stimulation, i.e. antifibrillatory action of procainamide.

METHODS

Experimental preparation: Thirteen dogs weighing from 8.0 to 12.0 kg were anesthetized with intravenous sodium pentobarbital. Under artificial ventilation with room air, the chest was opened through median sternotomy. The heart was exposed and supported in a pericardial cradle. The arterial pressure was monitored and the arterial blood was checked to keep pH and PaO₂, and PaCO₂ within the physiological range throughout the experiment.

The repetitive extrasystole threshold (RET) and ventricular fibrillation threshold (VFT): The

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Japanese Circulation Journal Vol. 51, February 1987 203
rectangular extrastimuli 2 msec in duration were given to the right ventricle after every 10th paced atrial beat at the strength of three times diastolic threshold using a digital programmable stimulator (MEC, TAF-400A) and a constant current isolator (MEC, ME-6212S). The interval between the last paced beat and the first ventricular extrastimulus (S1) was set at the length of 5 or 10 msec longer than effective refractory period. The coupling interval between S1 and the second extrastimulus (S2), and that between S2 and the third extrastimulus (S3) were set in the same manner. Intervals of subsequent extrastimuli were fixed after S3. Repetitive extrasystole (RE) was defined as two or more non-paced ventricular beats induced by sequential extrastimulation (Fig. 1). RET or VFT were represented by the number of extra-stimuli required to induce RE or VF. If VF was not preceded by any RE, RET was assumed to be the same as VFT. If RE and/or VF failed to be induced, RET and VFT were counted as "10".

In order to reduce RET and VFT, localized transmural necrosis was produced by intramural injection of 100 units/kg of protease (Miles Scientific) into the anterior wall of left ventricle. Then procainamide at a dose of 20 mg/kg was given and determination of both RET and VFT was repeated. The study was performed in 8 dogs.

Chaotic score: Forty bipolar electrodes (separation: 1.5 mm) were attached on the ventricular surface of the whole heart. Each signal was amplified with a capacitance coupled amplifier having a smooth frequency response between 40-500 Hz (HOTTA MUSEN ADA 8000-60). The digitized potentials were retained in 8k byte memory with memory system which holds data up to 16 seconds. When ventricular arrhythmia was induced, 16 seconds were allowed to stop the digitization and stored the events in the memory. The event was reproduced on an ink-jet recorder at a paper speed of 100 mm/sec.

As shown in Fig. 2, after the last extrastimulation each electrogram was divided every 100 msec, and the ratio of the recordings with activation time of more than 50 msec in each section was defined as "chaotic score". The electrogram with an equivocal activation time was excluded in the analysis. "Chaotic score" defined was to represent the spatial spread of continuous activity. Chaotic score was measured in 5 hearts in control state and after the injection of procainamide at the doses of 10 mg/kg and 20 mg/kg.

Fig. 2. Determination of chaotic score. Each electrogram was divided every 100 msec after the last extrastimulation. Shaded compartments indicate the recordings with activation time of more than 50 msec. The equivocal compartment with question mark was excluded from the analysis. The ratio of shaded compartments among unequivocal areas was defined as chaotic score.

Fig. 3. The effect of procainamide on the repetitive extrastyle threshold (RET) and ventricular fibrillation threshold (VFT). Both thresholds were represented by the number of extrastimuli required to induce RE or VF. Procainamide brought out the remarkable dissociation of two thresholds, which had been reduced by intramural injection of protease.

Japanese Circulation Journal Vol. 51, February 1987

Fig. 4. The effect of procainamide on the chaotic score. Procainamide lessened the increase of chaotic score significantly as the ventricular tachyarrhythmias developed.
as mean ± standard deviation. Difference of mean value was analyzed with paired t-test. A p value less than 0.05 was considered statistically significant.

RESULTS
RET and VFT: After the production of localized transmural necrosis by protease, RET was lowered from 7.1 ± 1.6 to 4.1 ± 1.0, and VFT was reduced from 7.6 ± 1.6 to 4.4 ± 0.9 (p < 0.01). The administration of 20 mg/kg of procaainamide increased VFT to 7.0 ± 1.8 (p < 0.01), but decreased RET to 3.4 ± 0.7 (p < 0.05) with plasma concentration of procaainamide at 24 ± 9 µg/ml (Fig. 3).

Chaotic score: In intact hearts, immediately after the induction of ventricular arrhythmias, chaotic score increased time-dependently. Chaotic score was 7 ± 8% at 0.5 sec after the induction, and increased to 20 ± 6% and 36 ± 12%, 1 sec and 5 sec after. Injection of procaainamide minimized the increase of chaotic score at the onset of ventricular arrhythmias. The chaotic scores one second after the induction of ventricular arrhythmias were 6 ± 5 after the injection of 10 mg/kg of procaainamide and 6 ± 2% after 20 mg/kg. The values five second after were 14 ± 7% and 12 ± 7% respectively (Fig. 4).

DISCUSSION
The process between the precipitation of ectopic excitations and VF can be classified into several stages. Stage 1 is the phase in which depolarizations of certain number of cells are generated at a localized area of ventricular muscle. The genesis of these activities is attributed to increased ectopic automaticity, reentry, triggered activity or some other mechanisms which result from the specific myocardial pathology. In stage 2, the focal excitation propagate to the whole ventricular muscle, producing ventricular excitation. Stage 3 is characterized by the repetitive ventricular responses in a form of accelerating ventricular tachycardia. In stage 4, accelerating tachycardia disorganized ventricular excitation, finally degenerating into VF. From the clinical point of view, available antiarrhythmic drugs are grouped into 4 classes on the basis of electrophysiological effects. Among them class 3 drugs have been classified to antiarrhythmal agents, which are though to increase overall electrocardial stability, decreasing the capability for multiple microreentrant circuits to exist and diminishing the vulnerability to VF.

Since the sequential stimulation method gives the VFT stages from 3 to 4, the reduction of both RET and VFT after the production of myocardial necrosis, which was demonstrated in the present study, indicates the localized necrosis increases myocardial vulnerability at stage 3. The administration of procaainamide elevated VFT just at it did in earlier study but failed to elevate RET determined with sequential pulse stimulation method. This finding suggests that procaainamide prevents VF at stage 4.

Earlier studies demonstrated a gradual progression of fibrillating wavefronts at the onset of VF, by analyzing the electrograms placed on ventricles. In the present study we also observed the process of the development of VF induced by the sequential extrastimulation. When ventricular arrhythmia was induced, chaotic score, ratio of the recordings with activation time more than 50% during the interval of 100 msec, increased linearly and reached the maximum value in 1 second or so. It was found that procaainamide administration minimized the increase of chaotic score at the initial phase of ventricular arrhythmias. Since RET was decreased by procaainamide, that drug may not inhibit the induction of reentrant circuits itself by sequential ventricular stimulation. Diminution of the prevalence of continuous electrical activities during polymorphous ventricular arrhythmias in the present study suggests that procaainamide prevents the induction of chaotic multiple reentrant pathways. Relatively larger reentrant circuits, on the other hand, are conceivable, if they appear. In other words, under the administration of procaainamide, induced reentrant circuits are large in size rather than small fragmented ones.

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