The Electrophysiological Actions of Lidocaine on Ischemic Ventricular Muscle as Compared with Procainamide

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For the purpose to evaluate the effects of lidocaine on the ventricular arrhythmias occurring as complications of acute myocardial ischemia or infarction, the electrophysiological actions of lidocaine were estimated, as compared with those of procainamide, on the right ventricular papillary muscle of the rabbit heart superfused with hypoxic, hyperkalemic and/or acidic Krebs-Ringer solution.

Lidocaine (1 to 5×10^{-5} M) and procainamide (1.7 to 3.4×10^{-5} M) depressed the maximum rate of action potential upstroke ($\dot{V}_{\max}$) and prolonged both of the effective refractory period (ERP) and the diastolic interval needed for the premature $\dot{V}_{\max}$ to recover to 98% in magnitude of the basic $\dot{V}_{\max}$ (98% recovery time) dose-dependently, without decreasing the resting potential.

Among the ischemic components, low pH (pH 6.9) and high potassium (10 mM) extracellular environments potentiated the depressant actions of lidocaine in synergic manner, but no significant enhancement of the actions of procainamide were observed under exposure to any components of ischemia.

Mechanisms underlying the difference of the depressant actions on ischemic myocardium between lidocaine and procainamide were discussed in the light of recent concepts of actions of local anesthetics, and came to the conclusion that lidocaine is the most preferable antiarrhythmic agent for the management of ventricular arrhythmias during acute ischemia or infarction.

THE clinical management of cardiac arrhythmias has made extensive progress with recent advances in research concerning the electrophysiology of the mechanisms of arrhythmias and the actions of antiarrhythmic agents.

Antiarrhythmic agents are classified into 4 groups according to their electrophysiological and pharmacological characteristics^{1,2}: membrane depressants or first channel blockers (class I), β -receptor antagonists (class II), amiodarone

and amiodarone-like compounds, the antiarrhythmic effects of which are not explainable otherwise than by the "pure" prolongation of the action potentials (class III) and calcium antagonists or slow channel blockers (class IV).

From the view point of managing life-threatening ventricular arrhythmias occurring as complications of acute myocardial ischemia or infarction, lidocaine which has a potent local anesthetic action and, accordingly, is classified into class I, is currently used as the agent of first choice to suppress ventricular arrhythmias in the coronary care unit.³⁻⁵ However, the precise mechanism of the antiarrhythmic action of this agent are still controversial. Nevertheless many investigators

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Fig.1. Illustration of measured parameters.

APD₈₀: Action potential duration measured at the level of 80% recovery of repolarization.

ERP: The shortest coupling interval between the basic and premature stimuli, producing a premature contraction successfully.

V_{max}: The maximum rate of action potential upstroke.

98% recovery time: The diastolic interval needed for the premature V_{max} to recover to 98% in magnitude of the basic V_{max}.

have extensively studied electrophysiologic actions of the agent on cardiac tissues under physiologic conditions⁶⁻¹³ or exposure to ischemia^{14,15} or hypoxia.¹⁶

In this study, changes in the mode of electrophysiological actions of lidocaine on ischemic myocardial cells were measured in papillary muscle preparations of the rabbit heart exposed to the abnormal environments including hypoxia, high extracellular potassium and low pH, which may play essential roles in arrhythmogenesis during acute ischemia, and the specific antiarrhythmic actions of this drug were analyzed through comparison with the mode of action of procainamide, one of the most familiar class-I agents.

METHODS

Adult guinea pigs were killed by a blow to the back of the head. The heart was excised and immersed into a cooled Krebs-Ringer solution. The papillary muscle of the right ventricle about

Fig.2. A typical recordings showing effects of procainamide on the action potentials and effective refractory periods under exposure to each component of the ischemic environments.

Each of the panels from A to D shows changes of the action potentials and V_{max} (tracings are inversely deflected) responded to the basic and the shortest coupling premature stimuli successful in producing a propagated response. The coupling intervals between the basic and premature response, therefore, measure the effective refractory periods.

one mm in diameter was dissected from the heart, mounted in a lucite chamber, and superfused at a rate of 10 ml/min with the Krebs-Ringer solution maintained at $37^{\circ} \pm 0.5^{\circ}\text{C}$ and gassed with 95% O₂ - 5% CO₂. The composition of the superfusing solution is: NaCl 120mM; KCl 4.0 mM; MgSO₄ 1.3 mM; NaH₂PO₄ 1.2 mM; CaCl₂ 1.2mM; NaHCO₃ 25.2 mM; glucose 5.8 mM.

After 30 min of the equilibration period, the

Fig.3. Effect of each component of the ischemic environment on the actions of procainamide. Note that dose-dependent depression of $\dot{V}_{max}$ and prolongation of APD₈₀, 98% recovery time and ERP and not enhanced under exposure to any of ischemic environments.

control measurements were performed. Glass microelectrodes filled with 3M KCl and with a tip resistance of 10 to 30 M Ω were used to record the transmembrane action potential. The upstroke of the action potential was differentiated using an electrotonic differentiator with a time constant of 1 msec.

The preparation was driven basically at a rate of 1 Hz by rectangular pulses 2 msec in duration and 1.5 times diastolic threshold in strength.

After every 8 basic stimuli, a single test impulse with variable coupling interval was introduced to determine the effective refractory period (ERP) and the diastolic interval needed for $\dot{V}_{max}$ of the premature response to return to 98% of that of the basic response (98% recovery time).

The recordings were displayed on a dual beam cathode ray oscilloscope (Textronix Model 5111) and photographed on polaroid film. The following measurements were performed on the polar-

Fig.4. Effect of lidocaine on the action potentials responded to the basic and premature stimuli under each component of the ischemic environment.

oid pictures as shown in Fig. 1: the resting potential, the action potential amplitude, the maximum rate of action potential upstroke ($\dot{V}_{max}$), the action potential duration measured at 80% of repolarization (APD_{80}), the effective refractory period (ERP), and the diastolic interval needed for the premature $\dot{V}_{max}$ to recover to 98% in magnitude of the basic $\dot{V}_{max}$.

Because of difficulties in reducing the superfusing flow rate in the chamber, ischemia was simulated by exposing the preparation to hypoxic, hyperkalemic and/or acidic environments. Hypoxia was produced by equilibrating the superfusing solution with a gas mixture of 95% N_2 + 5% CO_2 . The partial pressure of oxygen in the superfusate was about 50–100 mmHg. The hyperkalemic solution (10 mM) was prepared by adding KCl to the control solution. To produce respiratory acidosis, CO_2 content of

the mixed gas was increased from 5% to 20%, reducing pH of the superfusate from 7.4 to 6.8.

Procainamide was added to the superfusate in concentrations of 1.7 or 3.4×10^{-5} M and lidocaine in concentrations of 1 or 5×10^{-5} M. These concentrations of both drugs were chosen because they are either near or twice the therapeutic range of concentrations. Measurements were made after 30 min of exposure to each concentration of drugs.

Values were quoted as mean $\pm$ SD. Comparisons were made using analysis of paired t -test.

RESULTS

The actions of procainamide and lidocaine on the action potential configuration and the effective refractory period were compared with each other when preparations were superfused with the physiologic solution and each of low pH, high K and hypoxic perfusates.

The panels in Fig. 2 show the effects of procainamide 1.7×10^{-5} M on action potentials responded to the basic stimulus at a rate of 1 Hz and to the shortest coupling stimulus successful in producing premature responses. Under the physiological environment (panel A), procainamide caused a slight decrease in the maximum rate of depolarization ($\dot{V}_{max}$) of action potentials responding both to the basic and premature stimuli without any accompanying change in the level of the resting potential or the amplitude of the action potentials, and, in addition, prolonged duration of the action potentials and the effective refractory period measured as the shortest coupling interval successful in producing premature response. These effects of procainamide on the action potential and the effective refractory period were measured in 5 experiments as shown in Fig. 3. In the presence of procainamide 1.7×10^{-5} M, $\dot{V}_{max}$ was decreased from 198 ± 24.5 to 194 ± 26.0 v/sec, and 80% repolarization time of the action potential (APD_{80}) was prolonged from 156 ± 17.6 to 165 ± 18.5 msec, leading to a prolongation of the effective refractory (ERP) by 11 msec. The difference in measured values before and after administration of procainamide were statistically significant ($p < 0.05$, $n = 5$) in each of these parameters. However, 98% recovery time, the time needed for $\dot{V}_{max}$ of the premature responses to return to 98% of that obtained from the basic response, remained unchanged with procainamide. As shown in the left upper panel of Fig. 3, the

Fig.5. Effect of the ischemic environments on actions of lidocaine. Depression of $\dot{V}_{\max}$ and prolongation of both of 98% recovery time and ERP are potentiated in the presence of lidocaine under exposure to low pH and high extracellular potassium environments.

inhibitory action of procainamide on $\dot{V}_{\max}$ was very similar to that obtained under the physiological environment, even when the preparations were superfused with the low pH, high K and hypoxic solutions, respectively. The prolonging effects of procainamide on the action potential duration and the effective refractory period were unaltered in preparations exposed to the low pH or high K environments. The action potential duration was reduced to a great extent under the hypoxic environment, mainly due to the disappearance of the plateau phase of the action potential. This reducing effect attenuated the

prolonging action of procainamide on the action potential duration as shown in panel D of Fig. 2 and the upper right panel in Fig. 3. The action of procainamide on the effective refractory period was similar to that on the action potential duration. The recovery time of $\dot{V}_{\max}$ was prolonged from 21 ± 3.2 msec under the physiologic environment to 86 ± 16.0 msec with the high K solution, without manifesting any discernible prolongation under low pH or with the hypoxic solution. Such tendency was not affected by procainamide (left lower panel in Fig. 3).

Figures 4 and 5 compare the effects of lido-

Fig.6. Combined effect of components of ischemic environments on actions of lidocaine and procainamide.

Combination of ischemic components potentiated the action of lidocaine on V_{max} and ERP in a synergic manner, but any tendency to potentiate the action of procainamide are not observed.

caine on the action potentials and the effective refractory period among the preparations exposed to the physiologic, low pH, high K and hypoxic environments. Under the physiologic condition, V_{max} of the action potential responded to the basic stimulus was reduced from 189.4 ± 29.3 to 185.6 ± 30.0 v/sec in the presence of

lidocaine 1×10^{-5} M, and to 178.5 ± 30.6 v/sec in lidocaine 1×10^{-5} M, without manifesting any statistical significance. The inhibitory action of lidocaine on V_{max} measured under low pH environment was comparable with that obtained under the physiologic environment: the percent reduction of V_{max} after lidocaine 5×10^{-5} M was

8.8 ± 0.24 under the physiologic environment while it was 11.2 ± 0.40 under the low pH environment. However, this inhibitory action of lidocaine was markedly enhanced under high K and hypoxic environments as shown in Fig. 5; the percent reductions of $\dot{V}_{\max}$ were 29 ± 6.8 with the high K solution, and 19 ± 5.2 with the hypoxic solution.

Action potential duration shortened after exposure to lidocaine. However, the shortening action of lidocaine was not affected by any component of ischemia. The recovery time of $\dot{V}_{\max}$ was prolonged from 24 ± 4.6 msec in the control to 301 ± 84.8 msec in the presence of lidocaine 5×10^{-5} M, with a mean difference of 273 ± 66 msec. When the preparations were exposed to the low pH or high K environment, this prolonging action of lidocaine was augmented by 487 ± 87 msec under low pH and by 553 ± 153 msec with the high K solution. The action of lidocaine on the recovery of $\dot{V}_{\max}$ during hypoxia, on the contrary, was not enhanced in comparison to that under the physiologic environment. Similarly, the action of lidocaine on the effective refractory period was not enhanced after exposure to the hypoxic environment, but it was enhanced significantly when the preparations were superfused with the high K or low pH solution, as could be expected from the data on the recovery time of $\dot{V}_{\max}$.

Combined Effects of the Ischemic Components on the Actions of Procainamide and Lidocaine

The actions of procainamide and lidocaine on the action potentials and the effective refractory period were compared under the combined environments of the two (hypoxia and high K) and three components (hypoxia, low pH and high K) of ischemia, respectively. $\dot{V}_{\max}$ of the action potential responding to the basic stimulus was decreased markedly under the combination of hypoxia and low pH, but the inhibitory action of procainamide on the $\dot{V}_{\max}$ was quite similar to that obtained under the physiologic environment as shown in the upper graphs in Fig. 6. The same tendencies were observed when the preparations were exposed to the combination of hypoxia, high K and low pH. On the contrary, the inhibitory action of lidocaine against the $\dot{V}_{\max}$ was markedly augmented under combinations of the ischemic components. In particular, under the combination of the three components, 3 of the 5 preparations became inexcitable in the presence of lidocaine 1×10^{-5} M and all the 5 in

lidocaine 5×10^{-5} M (the lower left graph of Fig. 6).

The prolonging action of procainamide on the effective refractory period, as can be expected from the previous data, was almost unchanged when the preparations were exposed to combinations of hypoxia, high K and low pH, while the prolonging action of lidocaine was enhanced mainly due to a marked delay in the recovery of $\dot{V}_{\max}$ of premature responses in the same manner as illustrated in Fig. 5.

DISCUSSION

The actions of procainamide and lidocaine on the transmembrane action potentials of myocardial fibers have been studied extensively by many researchers, but the modes of these actions are vary according to the kinds of cardiac tissues and different conditions as well as according to different concentrations of the drugs used. In particular, there has been much argument about the electrophysiological actions of procainamide and lidocaine in concentrations of the therapeutic plasma level⁹⁻¹³

Rosen and Gelband et al.¹⁷ have reported that procainamide in concentrations of 5 to 10 $\mu\text{g/ml}$ in blood or 30 $\mu\text{g/ml}$ in a Tyrode solution depressed the maximum rate of depolarization ($\dot{V}_{\max}$) and the amplitude of the membrane action potential without inducing a meaningful decrease in the resting potential. These electrophysiological actions of procainamide stated above were observed also in our experiments, where procainamide in concentrations of 1.7 to 3.4×10^{-5} M (4.6~9.2 $\mu\text{g/ml}$) slightly prolonged the membrane action potential duration, leading to a slight lengthening of the effective refractory period. The prolonging action of procainamide on the membrane action potential duration is presumably attributable to inhibition of the potassium outward current during repolarization,⁸ but the underlying mechanisms are still under debate.^{18,19} With respect to the actions of procainamide on the diseased fibers or those exposed to abnormal environments, few papers have been published. In partially depolarized fibers of human atrial tissue excised during the routine cannulation procedure for cardio-pulmonary bypass, the depressant effects of procainamide on the $\dot{V}_{\max}$ and the amplitude of the action potentials observed were proportionately greater than those in normal fibers.²⁰ In our study, even though $\dot{V}_{\max}$ was decreased from 200 ± 24.5 to 138 ± 21.6 v/sec through a depres-

sion of the membrane responsiveness under exposure to an extracellular high potassium medium (10 mM $[K]_o$), the extent of the depressant action of procainamide on such partially depolarized fibers was comparable to that on fibers under the physiologic condition. Similarly, the dose dependent prolonging actions of procainamide on the recovery time of $\dot{V}_{max}$, the action potential duration and the effective refractory period were not enhanced by any of the ischemic components. These results are consistent with experiments on influence of high extracellular potassium and of low pH on the electrophysiological action of quinidine,^{10,12} a prototype class-I drug.

The mechanisms of electrophysiologic actions of lidocaine, a prototype of the local anesthetics, have been extensively advanced these few years. Lidocaine in therapeutic concentrations (2~5 $\mu\text{g/ml}$), the most widely used antiarrhythmic agent for arrhythmia occurring as a complication of acute myocardial infarction, depresses the conduction velocity, prolongs the effective refractory period and decreases excitability in regions of *in vivo* myocardial ischemia but not in normal regions.^{22,23} With respect to the enhancement of lidocaine actions due to the individual components of ischemia in this study, the low pH and high potassemic environments were more potent than hypoxia. According to recent concepts^{11-13,24,25} of the inhibitory actions of local anesthetics and related drugs on the fast Na channels of the excitable membranes including nerve and cardiac fibers, 1) local anesthetics are presumed to have a stronger affinity for the fast Na channels in the inactivated state than those in the activated or resting state; 2) the Na channels bound with lidocaine remain inactivated, resulting in a decrease in the number of Na channels available for excitation of the membrane; 3) the recovery from the inactivated state which proceeds voltage-dependently with the progress of repolarization is modulated by the unbinding process of the drugs from the Na channels, taking a longer time course than that obtained under the physiological condition, where the ratio of the inactivated state of the fast Na channels (closure of the inactivation gate) to the resting state (opening of the inactivation gate) decreases at a time constant of a few hundredths of a second with a decrease in the resting membrane potential. Therefore, the mechanisms underlying the potentiation of the lidocaine action on the ventricular muscle under

a high extracellular potassium environment studied may be explained as follows: Incompleteness of the recovery of the fast Na channels from the inactivated state due to a decrease in the resting membrane potential by several millivolts under the high extracellular potassium environment may enhance the affinity of lidocaine to the Na channels, resulting in potentiation of the depressant action of the drug.

Recent studies^{11-13,26} on the depressant actions of quinidine and quinidine-like drugs suggest that these drugs, as well as lidocaine, voltage-dependently delay the recovery process from the inactivated state of the fast Na channels. However, the time constant for the recovery process in the presence of quinidine requires much longer time (up to several seconds) than that in lidocaine (a few hundredths of a second), because the rate constant which governs the unbinding process between the blocking agents and receptor sites of the fast Na channel is several hundred times faster in lidocaine than in quinidine or procainamide.¹¹ Therefore, it is reasonable to suspect that such a slow recovery of the fast Na channels induced by procainamide will exert little influence on either 98% recovery time of $\dot{V}_{max}$ or the effective refractory period in this experiments, because these parameters were measured with respect to a single premature beat coupled at several hundreds msec with 1 Hz of the basic stimuli. Even taking into account the clinical view point, the recovery process of the fast Na channels over one second may offer a less meaningful parameter to indicate how to prevent premature contractions with short coupling intervals, even though it affects the excitation and conduction velocity irrespective of the difference between the basic rhythm and premature contractions.

The potentiation of the depressant actions of local anesthetics is debated in terms of changes in the rate of unbinding of the drugs from the receptor sites of the Na channels as is already stated. It was proposed by Grant et al²⁷ that increase in protonation of receptor-bound drug under low pH might depress the unbinding rate of the drugs from the receptor sites, resulting in a slowing of the recovery process. The enhancement of the depressant actions of lidocaine under low pH observed in this experiment is consistent with this hypothesis. Lack of any apparent enhancement of procainamide action on the recovery process may be explained in the same manner as that under exposure to the high

extracellular environment. As can be supposed from discussion so far, the combination of low pH and high extracellular potassium environments may enhance the depressant action of lidocaine in synergic manner. A significant potentiation of lidocaine actions in depressing $V_{\max}$ and prolonging the effective refractory period under the combination of hypoxia, low pH and high $[K]_o$ can be reasonably explained by the hypothesis stated above.

In summary, lidocaine in therapeutic concentrations inhibits premature contractions selectively without suppressing the excitability and conductivity of the basic rhythm; furthermore, these antiarrhythmic actions are potentiated under ischemic environments including hypoxia, low pH and high $[K]_o$; it is concluded that lidocaine is the most preferable antiarrhythmic agent for management of ventricular premature contractions and tachyarrhythmias occurring as complications of acute myocardial infarction.

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