Ventricular Fibrillation Threshold Measured by Continuous 50 cps Stimulation for the Evaluation of the Antifibrillatory effect of the Drugs

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The role of electrophysiologic parameters on the induction of ventricular fibrillation (VF) by continuous 50 cycle per second (cps) electrical stimulation was studied in 21 open chest dogs. The current strength of the 50 cps stimulation required to induce VF when applied to the ventricle for 2 seconds was defined as the ventricular fibrillation threshold (VFT). The intravenous injection of antiarrhythmic drugs raised the VFT in a dose dependent manner. The changes in VFT were associated with a rise in excitation threshold. The slopes of the regression equations relating the excitation threshold to VFT were almost identical, that is, 2.8 with lidocaine, 3.4 with procanamide and 3.2 with disopyramide. Prolongation of refractory period increased the cycle length of ventricular excitations just prior to VF but was not correlated with the changes in VF. Localized myocardial ischemia induced by coronary ligation also resulted in the elevation of VFT. The slope of the regression equation between excitation threshold and VFT was 1.9 which was slightly lower than that observed at the administration of the drugs. The fact that the VFT was mainly attributed to the changes in excitation threshold at the site where the test stimulus was applied would limit the usefulness of the 50 cps continuous stimulation method for the evaluation of vulnerability to VF.

The effects of the drugs which prevent ventricular fibrillation (VF) are evaluated by determining the ventricular fibrillation threshold (VFT) with electrical stimulation methods. However, there are various kinds of stimulation methods to induce VF, in each of which different mechanism of VF are likely to be involved. Thus the effect of antifibrillatory drugs is considered to differ depending on the methods used. In order to clarify the implications of the VFT measurement method, we investigated changes in VFT during the administration of antiarrhythmic drugs as well as during localized myocardial ischemia using a continuous 50 cps electrical stimulation method.

METHOD

Twenty one mongrel dogs of either sex weighing 7–13 kg were anaesthetized with intravenous administration of pentobarbital sodium (30 mg/kg). Under artificial respiration using room air, the heart was exposed through a median sternotomy and cradled in the pericardium. The femoral vein and the femoral artery were cannulated for drug administration and blood pressure monitoring respectively. Electrocardiographic lead II, bipolar left ventricular electrogram, stimulation artefacts and blood pressure were recorded using an ink jet recorder.

The heart was paced through a bipolar hook electrode placed on the right atrial appendage at a cycle length of 400 ms. Using a digital program-
mable stimulator (MEC, TAF-400A) and a constant current isolator (MEC, ME-6212S) the test stimulation was applied after every twenty basic beats through a bipolar hook electrode placed on the apex of the left ventricle. The test stimulus consisted of a train of pulses, 2 msec in duration delivered at 20 msec intervals (50 cps), the onset of which was adjusted to start 100 msec after the beginning of QRS complex and to continue for 2 sec. As shown in Fig. 1, when the current strength of the test stimulation was increased in steps of 0.02 ma, ventricular tachycardia, accelerated ventricular tachycardia and then VF developed. VF was electrically defibrillated as soon as possible. We designated the least amount of current required to induce ventricular tachycardia as ventricular tachycardia threshold (VTT), the cycle length of ventricular tachycardia at this point as ventricular tachycardia cycle (VTC), the least amount of current required to induce VF as VFT and the cycle length of ventricular tachycardia just prior to VF as VFC. The diastolic excitation threshold of the ventricle was measured by a conventional single pulse stimulation method and refractory period was determined with the pulse stimulus at the current strength of twice diastolic excitation threshold.

The effects of antiarrhythmic drugs on VF were studied in 18 dogs. Antiarrhythmic drugs, procainamide, 10, 20 and then to 40 mg/kg, disopyramide, 1.0, 2.5, 5.0 and 10.0 mg/kg, and lidocaine, 0.5, 1.0, 2.0, 4.0 and 8.0 mg/kg, were administered intravenously in a cumulative dosage. The VFT was measured at the control state and 5 min after the administration of the drug. In 3 dogs, the VFT was determined during and after myocardial ischemia, for which the left anterior descending coronary artery was occluded for 180 min and then released. The VFT was measured every 30 min at the ischemic and non-ischemic regions.

The values measured were expressed as mean ± standard deviation. Differences in mean values were analyzed using the paired Student t test. A p value less than 0.05 was considered to be statistically significant.

RESULTS

Effects of antiarrhythmic drugs

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As shown in Fig. 2, all three drugs studied elevated VFT dose-dependently. The VFT was raised from 0.57 ± 0.16 to 1.43 ± 0.70 mA by procainamide at a dose of 40 mg/kg, from 0.70 ± 0.25 to 1.24 ± 0.47 mA by disopyramide at 5 mg/kg and from 0.56 ± 0.15 to 1.23 ± 0.79 mA by lidocaine at 4 mg/kg. The VFC was also prolonged from 140 ± 28 to 227 ± 58 msec, from 128 ± 16 to 157 ± 23 msec and from 146 ± 11 to 168 ± 30 msec, respectively. Fig. 3 shows the relation between VFT and VTT and that between refractory period and VFC. It was noted that the changes in VFT were well correlated with VTT (r = 0.89 with procainamide, r = 0.62 with disopyramide and r = 0.85 with lidocaine). The slopes of the regression equations relating VTT to VFT were almost identical at 3.4 with procainamide, 3.2 with disopyramide and 2.8 with lidocaine. The VTT was equal to diastolic excitation threshold determined by conventional

Japanese Circulation Journal Vol. 52, March 1988
methods. The prolongation of refractory period was correlated with the changes in VFC after the administration of procaainamide ($r = 0.80$) and disopyramide ($r = 0.81$), but not correlated with the changes in VFT.

Effects of myocardial ischemia

Figure 4 shows the course of the changes in VFT and VTT during coronary occlusion and reperfusion in a representative case. During the coronary occlusion, the VFT at the ischemic area was elevated in parallel with the elevation of VTT, while the VFT as well as the VTT at the non-ischemic area did not change. The slope of the regression equation relating VTT to VFT was 1.9. The value was slightly lower than that observed after the administration of the drugs.

DISCUSSION

The VFT measured by the continuous 50 cps electrical stimulation method was elevated with procaainamide, disopyramide and lidocaine. This result is consistent with the previous observations in which VFT was determined by a method using a single pulse or a train of pulses of short duration. In the present study, the elevation of VFT correlated well with the changes in VTT, that is, diastolic excitation threshold. The prolongation of refractory period correlated with prolongation of VFC but not with VFT. This finding indicates that as the refractory period was lengthened, VF was induced following ventricular responses of longer cycle length. It should be noticed that the changes in VTC, VFC and the refractory period of the ventricle did not cause any alterations in VFT determined with the continuous 50 cps stimulation method.

The changes in VFT were different in ischemic and nonischemic areas. However, the changes in VFT were found to parallel those in VTT in both areas. There would be some localized inhomogeneities in electrophysiological properties within or around the ischemic area, which might enhance the vulnerability to VF. This would explain the lower slope of the regression equation between VFT and VTT in cases with myocardial ischemia. Therefore the VFT measured with the continuous 50 cps stimulation method was considered to be mainly influenced by the changes in diastolic excitation threshold at the area where the test stimulus was applied.

The development of VF can be classified into 4 stages. Stage 1 is the phase in which localized activities are generated in a certain area of ventricular muscle. The genesis of these activities can be attributed to some specific localized myocardial pathology. In stage 2, the local activities propagate to surrounding ventricular muscle, initiating ectopic ventricular excitation. Stage 3 is characterized by repetitive ventricular responses in the form of accelerating ventricular tachycardia. In stage 4, accelerated ventricular responses cause disorganized excitation, finally degenerating into VF. Hitherto, a method using a single pulse or a train of pulses of short duration has been widely employed to determine VFT. In such methods the stimulus is applied
during the vulnerable period of one cardiac cycle and the current strength required to induce VF is defined as the VFT. This method is considered to give the VFT of stage 1 through 4. On the other hand, a continuous 50 cps stimulation method is regarded as measuring the VFT of stage 2 through 4. The present study demonstrated that the VFT thus determined is mainly influenced by excitation threshold and is not affected by the changes in other electrophysiological properties such as refractory period. The results suggest that the threshold at stage 2 at the area where the stimulus is given is largely reflected in the VFT measured by the continuous 50 cps stimulation method and that the application of the stimulation for a period as long as 2 sec would make the precise evaluation of vulnerability of the ventricle at stage 3 or 4 difficult.

REFERENCE
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