The Effect of Disopyramide Phosphate on Ventricular Fibrillation Threshold of Normal and Ischemic Ventricles

Tsunemi TAJIMA, M.D. and Yutaka DOHI, M.D.

SUMMARY

The effect of disopyramide phosphate (DP) infusion (1 mg/Kg and 2 mg/Kg BW) on ventricular fibrillation threshold (VFT) was studied in anesthetized dogs. In the 1 mg/Kg group, the VFT increased 47% above the control level immediately after infusion. In the 2 mg/Kg group, a delayed increase in VFT was observed after the initial period and VFT was not correlated with the plasma concentration of DP. This phenomenon was abolished by pre-treatment with methacholine. These results suggested an anticholinergic action of DP on the VFT. In the ischemic dogs produced by acute coronary occlusion, DP prevented a decrease in VFT.

Additional Indexing Words:
Disopyramide phosphate Plasma concentration Ventricular fibrillation threshold Anticholinergic action

VENTRICULAR fibrillation is one of the major causes of death in patients with acute myocardial infarctions. Ventricular tachyarrhythmias or premature ventricular contractions falling within the vulnerable period of the previous beat may initiate ventricular fibrillation. The determination of the ventricular fibrillation threshold (VFT) has been used experimentally to assess quantitatively the influence of drugs upon the resistance of the heart to fibrillation. Several investigations\(^1\),\(^2\) have demonstrated that procainamide and quinidine are effective in suppressing both ventricular arrhythmias and raised VFT. However, there are no data regarding the effects of disopyramide phosphate (DP), a type 1 antiarrhythmic agent, despite its effectiveness in suppressing ventricular arrhythmias.\(^3\) The purpose of the present investigation is to determine whether DP can alter electrical stability of normal and ischemic myocardium, as measured by the VFT. Furthermore, in parallel experiments, we studied whether the anticholinergic property of DP
might influence the value of VFT.

**METHODS**

Experiments were performed using 40 mongrel dogs anesthetized by an intravenous injection of sodium pentobarbital (30 mg/Kg). After endotracheal intubation and ventilation with a respirator, the heart was exposed through a left lateral thoracotomy and suspended in a pericardial cradle. A heated operation table was used to maintain constant rectal temperature. Arterial blood pressure was continuously monitored with a Statham strain gauge transducer from a polyethylene catheter inserted into a femoral artery. Blood gases were intermittently measured. The sino-atrial node was crushed to permit atrial pacing at a constant rate (150/min). For intermittent occlusion of the left anterior descending branch of the left coronary artery, the artery was dissected free for a few millimeters near its origin. The fibrillation current was delivered through bipolar platinum electrodes sutured to the anterior right ventricle. Each electrode wire was 1 mm in diameter and they were separated by an interelectrode distance of about 8 mm. The test current consisted of a train of 16 to 20 pulses, each 4 msec in duration and 6 msec apart, for a total duration of 160 to 200 msec. The pulse train was synchronized with the lead II surface electrocardiogram and was programmed to begin 50 msec after the onset of the last paced QRS complex every 10 paced beats. With use of a constant current source, the strength of the pulse train was increased in 1 milliampere increments until ventricular fibrillation occurred. VFT was then defined as the minimal current that induced fibrillations. The VFT of ischemic ventricles was determined immediately after a 3 min period of acute coronary occlusion. The ligated coronary artery was immediately released and defibrillation was accomplished as soon as possible by direct current countershock. Fifteen min were allowed for recovery before the next VFT determination was made. DP was infused in a single dose of 1 or 2 mg/Kg body weight over a 5 min period. In some dogs, during continuous infusion of the muscarinic agent-methacholine (0.3 to 0.6 µg/Kg/min dose of drug without any effect on VFT), DP was infused in a dose of 2 mg/Kg and VFT was determined. Blood samples were collected every 15 min to determine the plasma concentration of DP.

Experiments were divided into 5 groups: 1) VFT in the control study (5 dogs); 2) influence of DP on the VFT in the non-ischemic myocardium (7 dogs in a dose of 1 mg/Kg and 8 dogs in a dose of 2 mg/Kg); 3) influence of 2 mg/Kg disopyramide on the VFT during continuous infusion of methacholine in the non-ischemic myocardium (7 dogs); 4) VFT in the ischemic
ventricles (7 dogs); 5) VFT after infusion of 2 mg/Kg disopyramide during ischemia (6 dogs).

Student's t-test was used to analyze results.

RESULTS

Plasma concentration of DP: Fig. 1 shows plasma concentrations of DP after a single dose of 1 mg/Kg and 2 mg/Kg body weight. As shown in this figure, plasma levels of DP declined rapidly from a maximum value immediately after the infusion. The slope of the decrease was most steep.

![Graph showing plasma concentration of disopyramide phosphate](image)

Fig. 1. Plasma concentration of disopyramide phosphate in a dose of 1 mg/Kg (closed circles) and 2 mg/Kg (open circles). The ordinate and abscissa show plasma disopyramide concentration (mean ± standard deviation (SD), μg/ml) and time course after disopyramide infusion (minutes), respectively. Note the steep curve during the first 15 min.
during the first 15 min in the 2 mg/Kg group. Thirty min after infusion, the concentration of DP was less than half of the initial value. The slope of decrease was rather gradual later than 60 min after the infusion.

Time course of VFT in the control study (Fig. 2): In the 5 control dogs, the mean VFT was 10.5±4.2 (SD) mA in the initial period of observations. During following 180 min, the range of VFT was less than 3 mA.

Influence of DP on the VFT in the normal myocardium: The effect of DP on the VFT was studied without acute coronary occlusion. Fig. 3 illustrates the time course of changes in the VFT after infusion of DP. In the 1 mg/Kg administered group, the mean VFT increased from 12 to 17.5 mA immediately after DP infusion. This increase is statistically significant (p<0.05). It then decreased gradually. The average percent increase of VFT immediately

![Fig. 2. Time course of VFT in the control study without disopyramide infusion. The mean value of VFT was 10.5 mA in the initial measurement and during next 180 min, the range of VFT was less than 3 mA.](image)

![Fig. 3. Time course of VFT after infusion of disopyramide. The left and right sides of this figure illustrate the 1 mg/Kg and 2 mg/Kg administered group, respectively. In the latter group, the maximum rise in VFT was attained in 15 min following a small initial VFT increase.](image)
Fig. 4. Time course of VFT after infusion of 2 mg/Kg disopyramide. Before, during and after the infusion of disopyramide, methacholine was infused at a constant rate. The VFT reached a maximum value immediately after infusion of disopyramide, in sharp contrast to the right panel of Fig. 3. After the infusion was about 47%. In the 2 mg/Kg administered group, however, an immediate rise after DP was not observed. However, the VFT increased significantly (p<0.01) to a maximum value of 23.5 mA (about 150% of the control value) at 14 min after DP administration followed by gradual decrease in values. This pattern of the time course of VFT after DP was not correlated with the plasma concentration of DP. To examine whether this delayed rise in VFT in the 2 mg/Kg group might be influenced by the anticholinergic property of DP, we infused a muscarinic agent, methacholine, continuously before and after a 2 mg/Kg infusion of DP. Fig. 4 illustrates the results of this study. After methacholine pretreatment, DP induced an immediate increase in VFT to a maximum value (about 185% of the control value). A delayed rise in VFT (Fig. 3) was not seen.

Time course of VFT in the ischemic ventricles without DP infusion (Fig. 5): In the 7 dogs studied, the mean value of the VFT before coronary occlusion was 12.5±5.5 mA. After coronary ligation, the value decreased from 12.6 to 7.4 mA, a 41.5% decrease from the control value. After this initial decrease, the VFT was measured every 15 min during the next 120 min. It declined slightly from the initial decreased value until 120 min.

Time course of VFT in the ischemic ventricles after DP infusion: The control
Fig. 5. Time course of VFT in the ischemic ventricles without disopyramide infusion. The mean value of VFT before ischemia was 12.6 mA. After ischemia, the value decreased from 12.6 to 7.4 mA. Subsequent values were almost the same or lower than the initial decreased value during next 120 min.

Fig. 6. Time course of VFT after infusion of 2 mg/Kg disopyramide during ischemia by acute coronary occlusion. Disopyramide prevented a reduction in VFT during acute ventricular ischemia.

mean VFT (Fig. 6) was 14.5 mA. During ischemia prior to 2 mg/Kg DP administration, the VFT decreased from 14.5 to 9 mA, a 38% decrease from the control value. After DP infusion, the mean VFT during acute coronary occlusion increased to a maximum of 17 mA after 15 min of infusion. This maximum value exceeded the control value (p<0.05). These values of VFT after DP contrasted with the results of control studies (Fig. 5), indicating that DP prevented a reduction in VFT during acute ventricular ischemia.
DISCUSSION

The VFT has been used as an index of vulnerability to fibrillation and may be a useful general indicator for drugs with potential antiarrhythmic properties.\textsuperscript{4} DP is a new antiarrhythmic drug with a pharmacological profile of action similar to quinidine.\textsuperscript{5} DP has been said to possess an important anticholinergic property in addition to its myocardial depressant action.\textsuperscript{6,7} Thus clinically observed effects of DP and quinidine may be the net results of both "excitatory" (anticholinergic) and depressant properties.\textsuperscript{8}

Although several investigators\textsuperscript{1,2} reported studies of the effects of type 1 antiarrhythmic agents on the VFT, there are no data about the effects of DP on the VFT. Yoon et al\textsuperscript{1} studied the effects of procainamide on the VFT of normal and ischemic ventricles with simultaneous procainamide blood levels. Procainamide at therapeutic blood levels increased the mean fibrillation threshold from the control value of 16 to 30 mA (88\% increase) in the normal ventricles. The effect was less pronounced during acute coronary occlusion and the mean fibrillation threshold increased from 8 to 13 mA (63\% increase) at therapeutic procainamide blood levels. The increase, peak level and decrease in blood concentration paralleled changes in fibrillation threshold.

In our DP study, this drug in a dose of 1 mg/Kg increased the mean fibrillation threshold from a control value of 12 to 17.6 mA (47\% increase) in the normal ventricles. As in procainamide studies, the increase, peak level and decrease in blood concentration paralleled changes in fibrillation threshold. However, in a 2 mg/Kg infused group, the VFT curve after infusion was different from the 1 mg/Kg group. The peak level of VFT was delayed and the mean VFT was not dependent on the plasma concentration of DP. We thought that some net effects of DP might influence the results of these VFT values in the 2 mg/Kg administered group. As stated above, DP has been said to possess significant anticholinergic properties in addition to their myocardial depressant action.\textsuperscript{6,7} Yeh et al\textsuperscript{7} found that DP had much more potent vagolytic effect than quinidine. Atropine as a representative of anticholinergic drugs has been said to decrease VFT in normal ventricles.\textsuperscript{9} Thus it is possible that the anticholinergic property of DP over a certain degree of plasma concentration in the immediate phase after 2 mg/Kg infusion antagonized the increase of VFT, which reflects the antifibrillatory action of DP (dose related response). Also, the delayed rise in the 2 mg/Kg group occurs when the plasma DP concentration declines to a level within the range that induces the immediate rise in the 1 mg/Kg group. This implies that the anticholinergic properties of DP are most prominent at
plasma concentrations above 2 μg/ml. In this sense, the delayed rise and immediate rise may be the same phenomenon. Furthermore, as shown in Fig. 4, pretreatment with a muscarinic agent, methacholine, abolished the anticholinergic effects of DP, which then revealed the immediate antifibrillatory action. This result is consistent with the previous findings\(^8,10\) that the anticholinergic properties of DP antagonized the muscarinic action. Winkle et al\(^10\) have shown that DP antagonizes the negative chronotropic effects of muscarinic receptor activation in isolated guinea pig atria. Also, Mirro et al\(^8\) observed that under the influence of increased muscarinic receptor stimulation, the electrophysiological effects of DP were different than those from control study, namely, an anticholinergic effect predominated over the direct effect. Furthermore, Mirro et al\(^11\) evaluated the effects of DP on muscarinic receptors in guinea pig right atrium and canine ventricular myocardium. Their direct examinations with receptor binding assays suggested that the cardiac anticholinergic effects of DP are due to a direct interaction of this compound with muscarinic cholinergic receptors. These previous investigations and our present study support the hypothesis that anticholinergic property may be operative in the immediate effects of VFT after DP infusion at a dose of 2 mg/Kg and that the anticholinergic properties of this drug interact with muscarinic cholinergic receptors, counteracting the antifibrillatory action. It seems that after this initial period, antifibrillatory actions predominated over the anticholinergic properties, as expressed in the VFT curve (Fig. 3). It should also be noted that the present VFT determinations confirmed the anticholinergic properties of DP.

It has been shown that the VFT is decreased during myocardial ischemia in experimental animals.\(^12\)-\(^14\) The present study confirms these observations. The DP infusions in dogs with acute myocardial ischemia prevented the decrease in fibrillation threshold and decreased ventricular vulnerability to fibrillation. This effect on VFT was almost the same as that of procainamide.\(^1\)

**References**

1. Yoon MS, Han J, Goel BG, Creamer P: Effect of procainamide on fibrillation threshold of normal and ischemic ventricles. Am J Cardiol 33: 238, 1974


