Cardiovascular Effects of Chloroquine with Special Reference to Its Antifibrillatory Action

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Intravenous injections of chloroquine terminated experimental atrial fibrillation in open chest dog preparations. Chloroquine and quinidine possess equal vasodilating properties when injected intra-arterially in the same dosage. Chloroquine and quinidine were equally effective in decreasing resting excitability of isolated cat papillary muscle; conduction velocity was markedly slowed by quinidine, but only slightly decreased by chloroquine.

The actions of quinidine upon isolated heart muscle and the intact heart have been well investigated. It is a generally accepted fact that quinidine decreases the excitability of heart muscle and at the same time decreases the conduction velocity of impulses traveling through the muscle. According to Lewis, this latter depression might be responsible for the failure of quinidine to terminate arrhythmias attributed to the existence of a circus movement. Recently there have been several reports concerning the antiarrhythmic action of the antimalarial drug, chloroquine, in experimental animals and man. Indirect evidence shows that chloroquine also depresses cardiac excitability, but information as to other cardiovascular effects of this drug is lacking. The experiments in this paper describe the cardiovascular effects of chloroquine in the open chest dog preparation and the effects of quinidine and chloroquine on excitability and conductivity in isolated heart muscle.

Methods

A. Heart in Situ. Mongrel dogs, weighing 10 to 14 Kg. were anesthetized with an intravenous injection of a combination of equal amounts of pentobarbital-sodium veterinary solution (60 mg./ml.) and Dial-urethane solution (100 and 400 mg./ml. respectively); the dosage of the mixture was 0.25 ml./Kg. In later experiments anesthesia was induced with 70 mg./Kg. chloralose injected intravenously. A tracheal cannula was inserted; a femoral vein was cannulated for subsequent intravenous injections and systemic blood pressure was induced with 70 mg./Kg. chloralose injected through the right auricular appendage. When the chest was opened by splitting the sternum, artificial respiration was instituted with a respiratory pump. The pericardium was opened longitudinally and a Walton-Boniface strain gage was sutured to the right ventricle to measure changes in contractility. Electrocardiogram records of lead II were obtained with a direct writing electrocardiograph in some experiments. Atrial fibrillation was produced by applying a 0.05 per cent solution of aconitine to the right auricular appendage, according to the method of Scherf. In those experiments in which leg blood flow of the dog was measured, a Shipley-Wilson rotameter was inserted between the right and left femoral arteries. Intra-arterial injections of quinidine and chloroquine were made through the arterial cannula carrying the blood to the leg.

B. Isolated Papillary Muscle. The papillary muscle of the cat was used to measure changes in excitability and conductivity induced by exposure to quinidine or chloroquine. The chordae tendineae end of the muscle was attached to a fixed hook, while the base was attached to a weak spring, so that slight tension was imposed on the muscle. The preparation was placed in a bath containing modified Locke solution of the following composition: 0.9 per cent sodium chloride, 0.02 per cent calcium chloride, 0.04 per cent potassium chloride, 0.02 per cent sodium bicarbonate and 0.25 per cent glucose. A mixture of 95 per cent oxygen and 5 per cent carbon dioxide was bubbled through the bath from a sintered plastic tube. The temperature of the bath was maintained at 37 C.

Electrical stimuli from a Grass Stimulator were delivered to the muscle through a pair of platinum
CARDIOVASCULAR EFFECTS OF CHLOROQUINE

Fig. 1. Antifibrillatory effects of chloroquine. Ordinate, heart rate or blood pressure (mm. Hg) and ventricular force of contraction (Gm.). Abscissa, time (min.). Shaded areas, periods of auricular fibrillation. See text.

Electrodes. A Grass Stimulator Isolation Unit was used to minimize artefacts. A resistor of 5,000 ohms was connected in series with the stimulator and isolation unit. The amount of current applied was varied by altering the input voltage. The face of the oscilloscope tube was previously calibrated, so that the height of the action potential could be expressed in millivolts. Action potentials were recorded through a pair of platinum electrodes by means of a condenser-coupled amplifier and a cathode ray oscilloscope.

After the muscle had been properly prepared, a control period of approximately one hour was permitted. Resting excitability was measured by determining the minimal amount of current necessary to produce an action potential at each of the following durations of stimuli: 10, 5, 2, 1, 0.5, 0.2 and 0.1 msec. This procedure was repeated several times during the control period. Conduction velocity was determined by measuring the distance from the stimulus artefact to the beginning of the action potential and also by the width of the action potential itself.

Immediately before readings were made, the level of the bath was lowered to about one centimeter below the muscle to prevent short circuiting of the stimulating and recording electrodes. After a series of control readings had been made, the normal Locke solution was drained and replaced by Locke solution containing the drug for a concentration of 3 mg./100 ml. The drug preparations used were quinidine sulfate (Merek) and chloroquine hydrochloride (Aralen, Winthrop-Stearns). The quinidine or chloroquine solution was in contact with the muscle for 25 min., during which time measurements of excitability and conductivity were made at 5, 10 and 25 min. after drug exposure. At the end of 25 min. the Locke solution containing the drug was drained and replaced by normal Locke solution. Recovery of the muscle was followed for 1 hour.

RESULTS

Heart in Situ

The work of previous investigators offers evidence for the antiarrhythmic action of chloroquine. This was confirmed in 5 anesthetized dogs in which atrial fibrillation was induced by the local application of aconitine on the right auricular appendage. In those experiments in which chloroquine was not injected, the fibrillation persisted for at least 15 min. A typical experiment was as follows. After the aconitine-induced arrhythmia was present for approximately 5 min., chloroquine was injected intravenously in a dose of 0.5 mg./Kg. every minute. Following the third injection, the atrial fibrillation reverted to normal sinus rhythm (see electrocardiogram, figure 1). The other measurements reflected the successful termination of the arrhythmia: 1. The ventricular contractions, recorded with a strain gage sutured to the right ventricle, became slower and regular and of uniform size. 2. Carotid blood pressure returned to normal after being slightly depressed during fibrillation. The total amount of chloroquine necessary to stop atrial fibrillation in 5 dogs ranged from 0.2 to 1.5 mg./Kg. Several explanations can be offered for the wide dosage range required to stop fibrillation: 1. Speed of injection may have varied in different experiments.

Fig. 2. Cardiovascular effects of chloroquine. See legend of figure 1.
FIG. 3. Effect of large intravenous injections (2 mg./Kg.) of quinidine sulfate (A) and chloroquine diphosphate (B). Ventricular force is in Gm., femoral blood flow in ml./min.

experiments. 2. Rate of diffusion into myocardial cells may not have been comparable in all animals. 3. The size of the heart may have influenced the amount of drug necessary to terminate the arrhythmia. 4. Rate of metabolism of the drug may have varied from one dog to another. 5. Intensity of fibrillation stimulus may not have been constant.

The remainder of figure 1 shows the effect of chloroquine on a ventricular tachycardia and a repeat in the same animal of an aconitine-induced atrial fibrillation terminated by intravenous injections of chloroquine. The last application of aconitine, which followed shortly the third series of chloroquine injections, failed to produce any arrhythmia.

The dosages of chloroquine sufficient to terminate atrial fibrillation invariably produced a consistent decrease in the force of right ventricular contraction. To investigate more fully the cardiovascular effects of chloroquine, unencumbered by fibrillation, the following experiments were performed.

Cardiovascular Effects of Chloroquine. Chloroquine was administered intravenously until a 50 per cent reduction in force of contraction had been obtained. Measurements of systemic blood pressure and ventricular rate were recorded and the results of one experiment are illustrated in figure 2. Nine successive doses (each of 0.5 mg./Kg./min.) of chloroquine were administered to produce the desired fall in contractile force. There was a small decrease in the animal's blood pressure and a moderate decrease in ventricular rate which accompanied the marked fall in force of contraction. In our experiments the strain gage was invariably sutured to the right ventricle, but from previous work we would expect the same qualitative changes in contractile force regardless of the site of attachment of the unit. All of these effects were transitory and a return to control levels was seen shortly after the first series of chloroquine injections was stopped. Subsequent intravenous injections of chloroquine produced a 50 per cent reduction in ventricular force of contraction with smaller amounts of drug. This would indicate that in spite of the return to control measurements, a residual depressant effect of the drug remained.

Similar results were obtained when one large intravenous dose (2 mg./Kg.) of chloroquine was injected (fig. 3B). Here the ventricular contractile force was decreased to approximately one sixth of the control, but there was no significant fall in systemic blood pressure. In contrast to this, intravenous injection of quinidine sulfate (2 mg./Kg.) produced a marked fall in systemic blood pressure, but there was little effect on the force of ventricular contraction (fig. 3A).

It is surprising that with such a severe depression of myocardial contractility, seen with intravenous chloroquine injection, the
CARDIOVASCULAR EFFECTS OF CHLOROQUINE

blood pressure of the animals remained reasonably constant. This might be explained on the basis of an increase in vascular resistance. To investigate the effects of chloroquine on peripheral resistance, leg blood-flow measurements were made following intra-arterial injections of chloroquine. Equivalent intra-arterial doses of quinidine were also administered in order to compare the actions of the two drugs in the same animal.

The effect of intra-arterial injections of chloroquine and quinidine on vascular resistance of the hind limb is illustrated in figure 4. When 50 μg. of either drug was injected into the femoral artery of the dog, the blood flow through the leg increased. This increase in leg blood flow was approximately the same with each drug, when equal amounts were injected.

In view of the fact that chloroquine possesses vasodilating properties similar to those of quinidine, in addition to its depressant effect on ventricular force of contraction, one would expect a significant fall in systemic blood pressure to follow intravenous injection of chloroquine, but this did not occur. Neither cardiac output nor stroke volume measurements were made in these experiments. However, Cotten and Maling have shown that changes in ventricular contractile force are not always accompanied by corresponding changes in stroke volume. Either cardiac output was maintained at near control levels or some other unknown mechanism was operative in order for the systemic blood pressure to remain relatively high following intravenous injections of chloroquine.

The marked hypotension observed with intravenous injections of quinidine can be attributed to its vasodilating action and in part, to its depressant effect on ventricular force of contraction.

Since chloroquine proved to be effective in terminating an acenitine-induced atrial fibrillation, it seemed advisable to investigate its action on the more fundamental properties of cardiac muscle. The state of myocardial excitability and conductivity has been previously related to the production of various arrhythmias. Experiments described below show a comparison of the effects of chloroquine and quinidine on the excitability and conductivity of isolated heart muscle.

Isolated Papillary Muscle

Excitability. The changes in excitability of isolated papillary muscle were measured by determining the amount of current necessary to produce an action potential at various durations of stimuli. From these figures strength-duration curves were constructed for the period before, during and after addition of the drugs to the bath. Figures 5 and 6 illustrate the results obtained with quinidine and chloroquine. In 5 experiments quinidine without exception caused a shift of the curve upward and to the right, indicating an increase in both the rheobase and chronaxia,
therefore a decrease in excitability. This decrease persisted for as long as one hour after the drug had been removed from the bath.

The addition of chloroquine in 6 other isolated muscle preparations produced a similar decrease in resting excitability. Since the same concentration (0.003 per cent) was used with both drugs, it appears that these agents are equally effective in raising the threshold of equally effective in raising the threshold of response to electrical stimuli. However, there is a difference in the tendency of the muscle to recover after the drug-induced depression. After chloroquine was removed from the bath, the muscle returned to nearly control levels of excitability within an hour. In contrast, when quinidine was removed from the bath, the muscle showed little recovery of excitability. This ability of the muscle to recover more rapidly after chloroquine was also observed in the studies on conductivity which are described below.

Conductivity. Quinidine caused a marked decrease in conduction velocity as illustrated in figure 7. It can be seen that the distance between the stimulus artefact and the beginning of the action potential is greater after the drug than before. In addition the action potential itself was wider while quinidine was present in the bath. Both of these observations indicate that quinidine produced a decrease in conduction velocity in the muscle.

Similar measurements were made with chloroquine present in the bath in the same concentration. A comparison with quinidine is given in table 1. From these results it is apparent that while quinidine and chloroquine produced equal depression of excitability of isolated heart muscle, the latter had appreciably less depressant action on conductivity.

**DISCUSSION**

The results of the experiments reported in this paper, demonstrating the effective antiarrhythmic action of chloroquine, are in agreement with those obtained by previous investigators, who used different methods of producing atrial fibrillation. The severe cardiovascular depression associated with quinidine administration is not observed with intravenous injections of chloroquine. Not only is hypotension minimal, but the direct cardiac depression due to chloroquine injections is of a short transitory nature. Arora has administered very large (10 mg./Kg.) intravenous doses of chloroquine and quinidine to dogs and cats and has reported that at this dosage level both drugs produce an equal fall in blood pressure. However, the hypotension so obtained was considerably briefer with chloroquine than with quinidine.

These findings can be correlated with the reports of Scott and Sanabria, who administered chloroquine to human patients. Scott injected chloroquine intravenously (5 to 14 mg./Kg.) in patients infected with falciparum malaria; he found little or no signs of toxicity. Similarly, Sanabria, using chloroquine as an antiarrhythmic drug, encountered no manifestations of toxicity. These observations, while not establishing the superiority of chloroquine over quinidine, provide encouragement for the use of chloroquine in the treatment of clinical arrhythmias.

The more basic question as to how these drugs exert their antifibrillatory effects re-
CARDIOVASCULAR EFFECTS OF CHLOROQUEINE

Table 1.—Interval (msec.) between Stimulus Artifact and Beginning of Action Potential

<table>
<thead>
<tr>
<th></th>
<th>Quinidine</th>
<th>Chloroquine</th>
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<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>During drug exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 min.</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>15 min.</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>25 min.</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Recovery (45 min.)</td>
<td>10</td>
<td>6</td>
</tr>
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mains a problem. The experimental results reported here are in agreement with previous investigators that quinidine decreases myocardial excitability in both isolated cardiac muscle and intact heart. It appears that chloroquine possesses equal potency in reducing the resting excitability of cardiac muscle. While changes in fibrillation threshold and resting excitability do not follow each other in all instances, there is usually a decrease in resting excitability associated with an increase in the fibrillation threshold.

More important than the equally depressant-excitatory capabilities of quinidine and chloroquine, is the relatively minor effect that chloroquine exerts on conduction velocity in papillary muscle. It has been demonstrated that arrhythmias, in particular atrial fibrillation, are most likely to occur when an impulse is irregularly conducted through the surrounding musculature or when there is a decrease in the conduction velocity. A drug, such as chloroquine, which can depress cardiac excitability and yet have no decremental effect on conduction, would be potentially useful in the treatment of arrhythmias.

**SUMMARY**

Chloroquine, administered intravenously in doses of 0.2 to 1.5 mg./Kg. to anesthetized dogs, is capable of terminating experimental atrial fibrillation, while it has little effect on the systemic blood pressure. Intravenous injection of chloroquine does not result in profound hypotension, in spite of its marked vasodilating properties.

Quinidine and chloroquine have been shown to produce equal depression of resting excitability in isolated cat papillary muscle. In contrast to quinidine, chloroquine decreases conduction velocity very little in isolated heart muscle. Following exposure to these agents, the muscle recovers from a chloroquine-induced depression, but shows little tendency to recover after exposure to quinidine.

The possible value of chloroquine in the treatment of clinical arrhythmias is discussed.

**SUMMARIO IN INTERLINGUA**

Chloroquina, administrate intravenosemente in doses de 0.2 a 1,5 mg/kg a canes anestetizate, es capace a terminar fibrillation atrial de origine experimental, sed illo ha pauc effetto super le pression systemic de sanguine. Le injection intravenose de chloroquina non resulta in hypotension profunde, in despecto de su marcate proprietates vasodilatatorii.

Ha essite monstrate que quinidadina e chloroquina produce le mesme depression del excitabilitate in stato de reposo in isolate musculos papillari de cattos. Per contrasto con quinidina, chloroquina reduce le velocitate del conduction in isolate musculos cardiac solmente a grados minimal. Post su exposition al effetto del mentionate agentes, le musculo se restabili ab le depression effectuate per chloroquina sed exhibi pauc tendentia a restablir se ab le effetto de quinidina. Es discutite le valor possibile de chloroquina in le tractamento de arrhythmias clinic.

**REFERENCES**


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Circ Res. 1959;7:86-92
doi: 10.1161/01.RES.7.1.86

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