The Action of Cardiac Glycosides on Experimental Auricular Flutter

By Alfred Farah, M.D. and T. A. Loomis, M.D.

The effect of cardiac glycosides on auricular flutter produced by the method of Rosenblueth and Garcia Ramos is studied. In the denervated heart these drugs produce an increase in the effective refractory period, a decrease in conduction velocity and excitability. The flutter is reverted to a sinus rhythm because of the increase in the effective refractory period. In the innervated heart these glycosides can change the auricular flutter to auricular fibrillation. This change is mediated through the vagus since atropine or cutting the vagi promptly reverts the fibrillation to a sinus rhythm. The change from auricular flutter to fibrillation was never observed in vagotomized dogs.

Rosenblueth and Garcia Ramos have developed a method for the production of a long lasting, self-perpetuating type of auricular flutter in anesthetized dogs. Evidence has been presented by these investigators which indicates that this phenomenon is due to a circus movement traveling around a central obstacle.

The action of cardiac glycosides on the heart has been extensively studied; little is known, however, concerning the action of these drugs in auricular flutter. One reason for this has been the lack of reliable methods for producing this condition in experimental animals. With the appearance of the method of Rosenblueth and Garcia Ramos it was thought possible to elucidate some of the complex events which occur in flutter as a result of the administration of cardiac glycosides. In the present study the effects of three pure glycosides, g-strophantin, digitoxin and lanatoside C have been studied on experimental auricular flutter in dogs produced by the method of Rosenblueth and Garcia Ramos.

Methods

All experiments were performed on dogs weighing between 6 and 24 kilograms. Anesthesia used was Dial urethane* (0.6 to 0.7 cc. per Kg., intraperitoneally) or preliminary Pentothal anesthesia (15 mg. per Kg. given intravenously) followed by the infusion of chloralose (50 to 60 mg. per Kg.). Auricular flutter was produced in 44 dogs. In 30 of these experiments the heart was decentralized by vagotomy and removal of the sympathetic chain bilaterally from the stellate to the sixth thoracic sympathetic ganglion inclusive. To allow maximum exposure of the right side of the auricle the animal was rotated on its long axis so that the heart fell towards the left side. Small steel electrodes were clipped to the auricle for purposes of stimulating and recording electrograms. The auricular electrogram and electrocardiogram were recorded simultaneously on a multichannel Grass ink-writing oscillograph. In a number of these experiments multiple auricular electrograms were recorded from various portions of the auricle.

In all experiments flutter was initiated by briefly stimulating directly the auricle at a rate of 15 to 20 impulses per second. In 7 experiments this resulted in the production of auricular flutter which persisted at least 60 to 90 minutes. In all the other experiments this procedure resulted in a flutter which reverted to a normal sinus rhythm within 15 to 60 seconds. In the latter animals a narrow band of auricular tissue connecting the superior and inferior vena cava was crushed by means of hemostats. Restimulation of the auricle resulted in a stable auricular flutter. Arterial blood pressure was recorded by means of a mercury manometer connected to the femoral or common carotid artery. Pulse rates were recorded in seven experiments by means of a bellows type of arterial manometer.

The maximal rate of stimulation was determined on dogs weighing 6.5 to 17.6 Kg. and anesthetized with Dial urethane (0.6 to 0.7 cc. per Kg. given intraperitoneally). Under artificial respiration the chest was opened by means of a midline incision and the heart was eradiated in the opened pericardial sac. Stimulating and recording electrodes consisting of small steel clips were attached to the auricular tissue. The impulse as well as the action potentials

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of auricular and ventricular muscle were recorded on the oscillograph. A monophasic square wave stimulus of known intensity, duration and frequency was used. To minimize the shock artifact the stimulating electrodes were placed at right angles to the recording electrodes. Another procedure employed was the use of a statically shielded transformer and a separate secondary winding with an adjustable balanced ground connected to the amplifier ground. The maximum rate the auricle would follow was determined at voltages varying between 1 to 20 volts. Following two or three control observations the drug to be studied was given intravenously and 15 to 90 minutes later the maximum rate was redetermined.

The cardiac glycosides employed were g-strophanthin, digitoxin* and lanatoside C.* Stock solutions, containing 2 to 5 mg. per cc. were prepared in 95 per cent ethanol and used as such. All injections were given intravenously either into a femoral vein or directly into the superior vena cava. The volume of ethanol injected did not exceed 0.15 cc. per Kg.

**Results**

For purposes of convenience the results obtained will be divided into two groups, namely (a) results obtained in the decentralized heart and (b) those obtained in the innervated heart.

*Decentralized heart.* In these experiments both vagal and sympathetic supply was cut. In 29 out of 32 experiments repeated stimulation of the auricles previous to the production of the crush injury did not result in a long lasting flutter. Following the crush, restimulation resulted in a long lasting type of flutter similar to that observed by Rosenblueth and Garcia Ramos.1 In 3 animals weighing 19, 21 and 24 Kg. with hearts weighing 140, 158 and 162 Gm., respectively, flutter was initiated before the crush lesion was made. The results from these three experiments were qualitatively similar to those observed in the crushed preparations and the results have been combined with the above experiments. Control observations were made for 40 to 80 minutes before the drug to be studied was administered. Following the administration of the drug continuous records were obtained until there was a reversion to a sinus rhythm or the auricular rate had been stabilized at a new level. The control auricular flutter rate varied between 330 and 560 beats per minute. The ventricular rate was usually half that of the auricle. Blood pressure varied between 80 and 110 mm. of mercury. In 4 out of 7 experiments the pulse rate was slower than the ventricular rate, the pulse deficit being 30 to 90 beats per minute. Figure 1 illustrates the characteristic response to the administration of a cardiac glycoside. In this instance 0.045 mg. per Kg. of g-strophanthin produced a reduction in the auricular flutter rate from 420 to about 340 beats per minute before reversion to sinus rhythm occurred. The decrease in ventricular rate was proportional to the decrease in auricular rate. The pulse rate gradually increased until the pulse deficit disappeared. Following reversion to sinus rhythm attempts to restart the flutter by repeated auricular stimulation were unsuccessful (figure 1). In general, qualitatively similar results were obtained with digitoxin, lanatoside C and g-strophanthin (table 1). Control injections of ethyl alcohol in a dosage of 0.2 to 0.3 cc. per Kg. did not appreciably or consistently change the auricular or ventricular rate during auricular flutter.

There was no correlation of the percentage reduction in auricular flutter rate at the time

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* Kindly supplied by the Sandoz Pharmaceutical Co.
of reversion to sinus rhythm with the control rate of flutter. In some of the experiments there was a change of only 8 per cent and in another a 39 per cent change in rate was necessary before reversion to sinus rhythm occurred. Table 1 summarizes the data obtained in the 32 experiments considered in this report.

Quantitative differences between the various glycosides were observed. The dosage necessary for reversion to a sinus rhythm was lowest for g-strophanthin, highest for digitoxin and intermediate for lanatoside C (table 1). The same sequence of effectiveness has been observed regarding the toxicity or therapeutic efficacy of these glycosides. The dosage is expressed as a percentage of the lethal dose it is apparent from table 1 that, for all three compounds studied, about 30 to 45 per cent of the lethal dose caused the flutter to revert to a sinus rhythm. This ratio may still be within the therapeutic range since, for the production of cardiac irregularities, approximately 60 per cent of the lethal dose has to be administered.

There are distinct differences in the speed of action of these glycosides. The differences are associated with dosage as well as the type of glycoside used. The higher the dosage the more rapidly maximum effects are attained (table 1). Furthermore, comparing biologically equivalent amounts of these three glycosides, it is apparent that strophanthin acts most rapidly while digi-

redetermined. Twelve experiments of this type were conducted and the results were qualitatively consistent. A sufficient quantity of the glycoside always reduced the maximum rate of stimulation the auricle would follow. Figure 2 is representative of these experiments. It can be seen that 0.06 and 0.12 mg. of lanatoside C per Kg., given intravenously, reduced the maximum rate, by about 25 and 55 per cent respectively. In figure 3 the data obtained with g-strophanthin in 18 determinations on 6 dogs have been summarized. There is a direct relationship between the dosage of g-strophanthin and the percentage reduction in maximum rate. Figure 2 also shows that the injection of lanatoside C resulted in an increase in the voltage

TABLE 1.—The Action of Cardiac Glycosides on Auricular Flutter in the Denervated Heart of the Anesthetized Open-Chested Dog

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Per Cent of Lethal Dose</th>
<th>Number of Experiments</th>
<th>Percentage Reduction in Auricular Rate</th>
<th>Number Reverting to a Sinus Rhythm</th>
<th>Time for Maximum Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg. per Kg.</td>
<td></td>
<td></td>
<td>Average</td>
<td>Maximum</td>
<td>Minimum</td>
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<tr>
<td>g-strophanthin</td>
<td>0.09</td>
<td>90</td>
<td>2</td>
<td>22</td>
<td>30</td>
<td>14</td>
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<td></td>
<td>0.06</td>
<td>60</td>
<td>2</td>
<td>17</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>0.045</td>
<td>45</td>
<td>3</td>
<td>25</td>
<td>32</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>0.03</td>
<td>30</td>
<td>4</td>
<td>14</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>0.02</td>
<td>20</td>
<td>3</td>
<td>9.5</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>lanatoside C</td>
<td>0.16</td>
<td>80</td>
<td>2</td>
<td>22</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>0.08</td>
<td>40</td>
<td>5</td>
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<td>3</td>
<td>13</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>digitoxin</td>
<td>0.3</td>
<td>100</td>
<td>1</td>
<td>8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>0.15</td>
<td>50</td>
<td>2</td>
<td>13</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
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<td>20</td>
<td>3</td>
<td>13</td>
<td>19</td>
<td>8</td>
</tr>
</tbody>
</table>

Determination of the Maximum Rate. The method employed is an adaptation of the one employed by Dawes in the isolated auricle of the rabbit. In our experiments the maximum rate of stimulation which the in situ auricle will follow was determined. The heart was denervated and recording and stimulating clips were applied to the auricle. The maximum rate was determined at progressively increasing voltages. Following two to three control observations the glycoside was administered and 15 to 90 minutes later the maximum rate was
necessary to produce stimulation of the auricle, especially at the higher rates of stimulation. This change indicates a decrease in the excitability of this tissue. Similar results have been obtained with digitoxin and g-strophanthin. In two of the above experiments auricular flutter was produced following the determination of the maximum rate. Administration of digitoxin or g-strophanthin in a dosage of 0.1 and 0.045 mg. per Kg., respectively, resulted in a reversion of the flutter to a sinus rhythm. Following this reversion the maximum rate was redetermined and in the digitoxin experiment the maximum rate was reduced 18 per cent while in the g-strophanthin experiment this decrease was 15 per cent.

Results in the Innervated Heart. Twelve experiments were conducted with innervated hearts. In six experiments persistent auricular flutter was initiated in the normal auricle. In six experiments persistent auricular flutter was initiated following the production of the crush injury between superior and inferior vena cava. In these latter experiments the administration of lanatoside C or g-strophanthin produced results similar to those seen in the denervated hearts. The number of experiments is not sufficient to allow any conclusions concerning the establishment of quantitative differences between innervated and denervated hearts.

In 6 dogs auricular flutter was started in the intact (without crush) innervated auricle. All of these animals weighed over 16.5 Kg. and the heart weights exceeded 130 grams. Following control periods lasting 40 to 60 minutes lanatoside C in a dose of 0.06 to 0.1 mg. per Kg. was given by vein. In five out of six of these experiments the injection of lanatoside resulted in a primary reduction in auricular rate which was then followed by a sudden increase in rate (figs. 4 and 5). This increase in rate in all instances exceeded 800 beats per minute. Electrograms indicated marked irregularity in both the rate and configuration of those impulses.

Fig. 2. The action of lanatoside C on the maximum rate of the auricle in situ. Male dog, 7.8 Kg. Anesthesia Dial urethane. Denervated heart. O—O Control determination of the maximum rate. O—O The maximum rate following 0.06 mg. per Kg. of lanatoside C intravenously. O— O The maximum rate following an additional 0.06 mg. per Kg. of lanatoside C.

Fig. 3. The relation of dosage of g-strophanthin to the per cent reduction in maximum rate. Decentralized hearts. Full circles are averages and maximum and minimum values are indicated in the graph. Determinations were made on 6 dogs. Each point is the average of two to five individual determinations. Abscissa: dosage of g-strophanthin in micrograms per Kg. given intravenously. Ordinate: the percentage reduction in maximum rate.

Multiple recordings made from various portions of the auricle indicated that some of the impulses were transmitted for only a short distance and then disappeared. This was in contrast to the observations made during auricular flutter where an impulse traveled along the total length of the auricle. These rapid and irregular action potentials observed are designated as auricular fibrillation in contrast to the slower and more regular ones which are called auricular flutter.

The condition of auricular fibrillation occurred within 4 to 18 minutes following the administration of lanatoside C. The dosages administered varied between 0.8 and 0.12 mg. per Kg. In one of the experiments following
the administration of 0.12 mg. of lanatoside C per Kg., the condition of fibrillation lasted for about 5 minutes and then suddenly reverted spontaneously to a normal rhythm. Attempts to restart the auricular flutter by repeated stimulation were unsuccessful. In the four other experiments the fibrillation was observed for 12 to 36 minutes. In three of these experiments the injection of 0.1 mg. per Kg. of atropine sulfate resulted in a prompt reversion of the fibrillation to a normal sinus rhythm (fig. 4). Control experiments conducted with the same amounts of atropine in auricular flutter produced negligible changes in the flutter rate (three experiments). In two other experiments the auricular fibrillation following lanatoside C administration could be stopped by cutting both the vagi (fig. 5). Attempts to restart the flutter by repeated stimulation of the auricle were unsuccessful in both the atropine and the vagotomy experiments.

The above results clearly implicate a vagal mechanism in the change of flutter to fibrillation. A similar change can be produced by stimulation of the vagi or by the intravenous injection (15.0 gamma per Kg.) or infusions of acetylcholine (10 gamma per Kg. per minute) or by injection of physostigmine (0.5 mg. per Kg.). The observation has been made that if a crush exists between the superior and inferior vena cava the vagal stimulation either electrically or pharmacologically has to be stronger to convert the flutter to fibrillation. This is a possible reason why cardiac glycosides did not produce a change from flutter to fibrillation in the crushed but innervated auricle.

**DISCUSSION**

Methodical differences in the production of auricular flutter may conceivably result in different pharmacologic responses to various drugs. The method used in the present study was the one studied extensively by Rosenblueth and Garcia Ramos.\(^1\) These investigators have presented good evidence that this type of flutter is a circus movement. Prinzmetal and associates\(^8\) and Sherf and Terranova\(^8\) have studied aconite-produced auricular flutter and fibrillation and these investigators have presented convincing evidence that aconite-induced flutter and fibrillation are due to a rapidly discharging focus. The essential facts presented by Rosenblueth and Garcia Ramos have been confirmed in this laboratory. It is thus possible that, in the dog at least, two causes of flutter have been demonstrated: one type being a
circus movement, the other being a rapidly discharging focus. The present study with digitalis glycosides concerns itself only with the circus type of flutter produced by the method of Rosenblueth and Garcia Ramos.\(^1\)\(^-\)\(^3\) A consistent change observed has been the decrease in auricular flutter rate. Within certain limits the percentage decrease in flutter rate is proportional to the dose of the glycoside administered (table 1). Reversion to a sinus rhythm was consistently seen in all the denervated hearts when a sufficient amount of glycoside was administered. The percentage reduction in flutter rate at the time of reversion to sinus rhythm varied between 8 and 39 per cent. There was no consistent relation between reversal to sinus rhythm and percentage change in flutter rate. In the individual experiment the length of the path in flutter produced by the method of Rosenblueth and Garcia Ramos is constant. Thus a progressive decrease in auricular flutter rate represents a proportional decrease in auricular conduction velocity. Theoretic considerations by Lewis\(^10\) and Wiener and Rosenblueth\(^1\)\(^1\) show that such a decrease in conduction velocity by itself would not result in a reversion to sinus rhythm but rather would tend to perpetuate the auricular flutter. Reversion from circus movement to sinus rhythm indicates that the circus wave met with refractory tissue. This could be caused either by the entrance of ectopic beats or by a lengthening of refractory period proportionately greater than the decrease in conduction velocity. In none of the experiments have we observed the appearance of ectopic beats at the time of reversion to sinus rhythm and thus the former possibility is excluded. Lengthening of the effective refractory period of the auricle by strophanthin has been demonstrated by Lewis and Drury and Iliescu\(^12\) and in the present study we have observed a definite and consistent decrease in the maximum rate of the auricle following the administration of sufficient amounts of the glycosides studied. Maximum rate changes are closely related to changes in effective refractory period which is the time before the muscle will again transmit a propagated impulse to any distance.\(^1\)\(^8\) The lengthening of the effective refractory period by antifibrillating agents is thus of importance in the reversion of flutter to a normal sinus rhythm by these drugs. In our experiments maximum rate was decreased about 15 to 25 per cent by amounts of cardiac glycosides which restored a sinus rhythm in auricular flutter. The decrease in ventricular rate always followed the administration of the glycosides. In most instances the decrease in ventricular rate was proportional to the decrease in auricular rate. With quinidine and procaine a decrease in auricular flutter rate may be accompanied by a relative or absolute increase in ventricular rate.\(^14\)\(^-\)\(^15\) This is probably due to the fact that at slower auricular rates the ratio of ventricular to auricular beats is increased.\(^16\) With the cardiac glycosides studied there was always an absolute change but no relative change in ventricular rate. This difference between cardiac glycosides and quinidine may be due to the well known effects of the former compounds on auriculoventricular conduction.

In the innervated heart the cardiac glycosides studied may change the flutter to auricular fibrillation. This has been observed only in dogs weighing more than 16 Kg. and where flutter could be initiated without a crush injury. In all the experiments so far observed auricular fibrillation produced by cardiac glycosides could be abruptly stopped by vagal cutting or blockade with atropine. The change of flutter to fibrillation can be produced by electrical or pharmacologic stimulation of the vagus. The conclusion to be drawn is that at least in the dog a change from flutter to fibrillation is mediated through the vagus. The well known vagal effects of the cardiac glycosides may conceivably be the cause of this change. Lewis, Drury and Bulger\(^17\) have shown that vagal stimulation decreases the refractory period and at high rates of stimulation increase the conduction velocity in the auricle. Similar conclusions can be drawn from the results of Garcia Ramos and Rosenblueth.\(^18\) The cardiac glycosides produce direct actions on the auricle which tend to stop the flutter (by an increase in the effective refractory period) as well as reflex vagal actions which tend to perpetuate the flutter or even change it to a fibrillation. In the present study we have been able to
demonstrate a dual effect of cardiac glycosides on auricular flutter in the dog. Whether similar mechanisms are operative in man has not been established and must await clinical experimentation. Furthermore, the effects of cardiac glycosides may be different in those types of flutter and fibrillation produced by rapid focal discharges.

Summary

The action of β-strophanthin, digitoxin and lanatoside C was studied on auricular flutter produced in dogs by the method of Rosenblueth and Garcia Ramos.

In the denervated heart these glycosides produce a decrease in auricular flutter rate and in sufficient amounts revert the flutter to a normal sinus rhythm. The decrease in auricular flutter rate is probably due to a decrease in auricular conduction velocity. A second effect of these glycosides that has been demonstrated is a decrease in the maximum rate the auricle will follow. This decrease in maximum rate is probably due to an increase in the effective refractory period and is a possible cause for the reversion to sinus rhythm produced by these glycosides.

In the innervated heart the observation has been made that lanatoside C will change auricular flutter to fibrillation. This change is mediated through the vagus nerve since atropine or vagal cutting will revert the auricular fibrillation to a sinus rhythm.

It is concluded that in the dog the direct action of cardiac glycosides on the auricle tend to increase the refractoriness and decrease the conduction velocity of auricular muscle while the reflex vagal action of these glycosides tends to decrease the refractory period and increase the conduction velocity in this tissue. The net effects on the innervated fluttering auricle are thus dependent on the magnitude of either one of these actions.

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