Influence of Reserpine and \( \beta \)TM 10 on Digitalis-Induced Ventricular Arrhythmia

By Jay Roberts, Ph.D., Ryuta Ito, M.D., Joseph Reilly, Ph.D., and Vincent J. Cairoli, B.S.

Roberts and co-workers have concluded that ventricular rhythmicity is related, at least in part, to the action of endogenous catecholamines on ventricular pacemakers.\(^1\,\,^2\) It is likely, therefore, that changes in ventricular rhythm induced by cardioactive agents may be a consequence of an action involving catecholamines. Digitalis glycosides were examined to test this hypothesis. Evidence was presented in a preliminary communication,\(^3\) which suggested that extra beats induced by ouabain in the isolated papillary muscle may be due to catecholamine release. The present report is an extension of this study but is concerned also with experiments designed to explore the in vivo relationship between digitalis-induced ventricular arrhythmia and catecholamines.

Three different preparations were employed: the isolated cat papillary muscle, the dog with surgically induced heart block, and the cat in which ventricular rhythm disturbance was induced by the combined action of the digitalis material and vagal stimulation. Reserpine and trimethyl [2-(2,6-dimethylphenoxy) propyl] trimethyl-ammonium chloride (\( \beta \)TM 10) were employed to reduce catecholamine activity. Reserpine has been reported to deplete tissue catecholamines,\(^4\,\,^5\) while \( \beta \)TM 10 prevents their release.\(^6\) These agents diminished the capacity of digitalis glycosides to induce ventricular arrhythmia and it was concluded, therefore, that the ventricular arrhythmia caused by digitalis is due, at least in part, to catecholamine release.

Methods and Results

I. EFFECT OF OUABAIN ON THE ISOLATED CAT PAPILLARY MUSCLE

A. Method: Papillary muscles were removed from the right ventricle of the cat according to the method of Cattell and Gold\(^1\) and immersed in a glucose-free, bicarbonate buffered, Krebs-Henseleit solution.\(^1\) The stimulus was applied across the base of the muscle at a frequency of 60 per minute and the intensity was adjusted to just over threshold (4 to 10 volts, pulse duration 0.5 to 1 msec). The electrogram was recorded in a manner similar to that described by Garb and Chenoweth,\(^1\,\,^2\) and a Statham strain gauge connected to a Sanborn polygraph was employed to record the tension developed by the muscle. The diameter and length of the muscles ranged from 1 to 2 mm and from 7 to 10 mm, respectively. Ouabain was added to the bath when the tension developed by the muscle had decreased to a steady level (on the average 50% of the initial tension); this usually occurred in one to two hours. Some cats were injected intraperitoneally with 10 mg/kg of reserpine (Serpasil, Ciba) 24 to 26 hours before the heart was removed to obtain the papillary muscle.

B. Results: Our preliminary report\(^3\) indicated that the positive inotropic action of ouabain (0.2 \( \mu \)g/ml) was diminished after reserpine. Experiments have now been carried out using three concentrations of ouabain: 0.2, 1, and 5 \( \mu \)g/ml. The data are summarized in table 1. Statistical analysis of the data (Student’s \( t \)-test) indicates that the tension developed in reserpine-treated muscles after ouabain was not significantly different from that in non-reserpine muscles (0.10 > \( P \) > 0.05). As indicated in our preliminary publication,\(^3\) the incidence of ouabain-induced extra beats in reserpine pretreated muscles was significantly reduced. Extra beats, which were produced only by the larger doses of ouabain (0.2 and 1 \( \mu \)g/ml) occurred in 23 of 39 prep-
arations, while after reserpine, they occurred in 12 of 38 muscles [Chi square test (0.05 > P > 0.01)]. Extra beats occurred approximately 47 and 20 minutes respectively after the administration of 0.2 and 1 µg/ml of ouabain.

Of the 23 muscles exhibiting extra beats, only 5 continued to beat in the absence of electrical stimulation while none of the 12 reserpine pretreated muscles developed spontaneous beating.

II. EFFECT OF ACETYLSTROPHANTHIDIN IN THE DOG WITH A-V BLOCK

A. Method: A-V block (proven by electrocardiogram) was induced in mongrel dogs by ligating the bundle of His according to the method of Taufic et al. In five animals, the experiments were performed one to two hours after heart block was induced; four others were used for experimentation one week after recovery from the operation. All the experiments were conducted under sodium pentobarbital anesthesia (30 mg/kg, intravenously). The electrocardiogram (usually Lead II) and carotid blood pressure, using a Statham pressure transducer, were recorded on a Sanborn polygraph. A dose of 100 µg/kg of acetlystrophantbidin (ac. stroph.)* (0.1% solution in 95% alcohol) was injected intravenously to induce ventricular tachycardia. After the effects of this dose had disappeared, 20 mg/kg of βTM 10 was injected intravenously; one and one-half to three hours later, ac. stroph. (100 µg/kg) was given once more. In another group of animals, ac. stroph. was given before and ten minutes after hexamethonium (2 mg/kg, intravenously).

B. Results: Although doses of 20 µg/kg of ac. stroph. caused acceleration of the ventricular rate, only doses as large as 100 µg/kg did it consistently (fig. 1). Within five minutes after the injection of the 100 µg/kg dose, the ventricular rate began to increase. In a few cases, acceleration was preceded by a slight decrease in ventricular rate. In nine dogs, the increase in the ventricular rate induced by 100 µg/kg reached a peak on an average of 13 minutes and lasted 38 minutes. Ventricular acceleration terminated abruptly and was immediately followed by bradycardia and in some cases by asystole. Ventricular bradycardia persisted for approximately 30 minutes and was characterized by cyclic changes in ventricular rate including periods of asystole.

Ventricular acceleration induced by ac. stroph. was largely prevented by βTM 10 (fig. 1). The data are summarized in table 2. Ac. stroph. (100 µg/kg) increased the ventricular rate 175 beats per minute; the average duration of acceleration was 36 minutes. After βTM 10, which slowed the ventricular rate (fig. 1 and table 2) the same dose of ac. stroph. caused an increase in rate of 21 beats per minute, which was maintained for only eight minutes. This increase was usually followed by bradycardia.

The results with βTM 10, an agent reported to prevent the release of catecholamines from the sympathetic nerve terminals, suggest that the ac. stroph.-induced ventricular tachycardia is related to the release of catecholamines from stores in the terminal of the postganglionic adrenergic neurone. To examine the possibility that the release of catecholamines from these stores was a consequence of an action of ac. stroph. on sympathetic pathways central to the postganglionic site, ganglionic transmission was blocked with hexamethonium. The effect of ac. stroph. was much the same after hexamethonium (32 to 161 beats/min) as without it (42 to 181 beats/min). See table 2.

Ventricular acceleration induced by ac. stroph. was accompanied by an increase in mean blood pressure from an average of 100 to 182 mm Hg. Whereas βTM 10 diminished the rate of the ac. stroph.-induced ventricular tachycardia, it did not affect the ac. stroph. pressor effect. After βTM 10, which reduced the mean blood pressure from an average of 130 to 70 mm Hg, the administration of ac. stroph. increased the mean blood pressure to an average of 150 mm Hg, an effect comparable to that in the controls. Hexamethonium also did not block the pressor effect of ac. stroph. These observations are in accord with those of Ross et al., who showed that digitalis caused direct vasoconstriction in the dog.

III. THE EFFECT OF ACETYLSTROPHANTHIDIN ON VENTRICULAR RHYTHMICITY IN THE CAT

A. Method: A modification of the "vagus-amine test" of Roberts et al. was used to determine the

*Kindly supplied by Dr. K. K. Chen of the Eli Lilly Laboratories.
FIGURE 1

Effect of βTM 10 on ventricular acceleration induced by ac. stroph. in dogs with complete heart block. Note failure of ac. stroph. to induce ventricular acceleration. Anesthesia: sodium pentobarbital 30 mg/kg iv. Heart block was produced nine days prior to the experiment. The electrocardiogram was recorded on Lead II. The atrial (AR) and the ventricular rates (VR) are shown in the upper left hand corner of each trace. Trace A shows the control electrocardiogram. With the exception of trace E, the time in minutes indicated below the trace represents the interval elapsed since the intravenous injection of ac. stroph (100 μg/kg). βTM 10 was injected intravenously shortly after trace D was taken. Ac. stroph. was administered approximately three hours after βTM 10 and the effect of the digitalis material is depicted in trace F.

Effect of ac. stroph. on ventricular rhythmicity in the cat. In the "vagus-amine test" the sinus rate is slowed by vagal stimulation to a critical point, namely, a rate just short of that at which the A-V node or the ventricle escapes ("critical" sinus slowing). In this circumstance, ectopic beats are
TABLE 1

Effect of Reserpine Pretreatment on Positive Inotropic Action of Ouabain on Isolated Cat Papillary Muscle

<table>
<thead>
<tr>
<th>Ouabain Concentration µg/ml</th>
<th>No. of experiments</th>
<th>Untreated Increase in tension ± SE</th>
<th>Reserpine treated Increase in tension ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.04</td>
<td>11</td>
<td>0.210 ± 0.042</td>
<td>0.483 ± 0.147</td>
</tr>
<tr>
<td>0.2</td>
<td>18</td>
<td>0.294 ± 0.049</td>
<td>0.182 ± 0.036</td>
</tr>
<tr>
<td>1.0</td>
<td>21</td>
<td>0.455 ± 0.049</td>
<td>0.315 ± 0.056</td>
</tr>
</tbody>
</table>

*The tensions developed in these muscles are not significantly different from those developed in the non-reserpinized muscles (0.10 > P > 0.05).

TABLE 2

Effect of ßTM 10 and C6 on Ventricular Acceleration Induced by Acetylstrophanthidin (100 µg/kg) in Dogs with A-V Block

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of dogs</th>
<th>Avg. control rate beats/min</th>
<th>Avg. maximum heart rate after ac. stroph. beats/min</th>
<th>Avg. duration of acceleration min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac. stroph.</td>
<td>5*</td>
<td>49</td>
<td>224</td>
<td>36</td>
</tr>
<tr>
<td>Ac. stroph. after ßTM 10 20 mg/kg</td>
<td>5*</td>
<td>19</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Ac. stroph.</td>
<td>4*</td>
<td>42</td>
<td>181</td>
<td>41</td>
</tr>
<tr>
<td>Ac. stroph. after C6 2 mg/kg</td>
<td>4*</td>
<td>32</td>
<td>161</td>
<td>33</td>
</tr>
</tbody>
</table>

*Same group of animals.
†Same group of animals.

induced by agents which raise the rhythmicity of the A-V node or of the ventricle.

Cats were anesthetized with Dial-urethane (Ciba) (0.5 to 0.7 ml/kg intraperitoneally) and the "critical" sinus slowing was produced by stimulating the vagus nerve with pulses of nine volts, 0.5 msec duration, at a frequency of 2 to 30 per second. The smallest or threshold dose of ac. stroph., which induces escape in the setting of "critical" sinus slowing was determined in non-treated and reserpine-treated animals. In the absence of vagal stimulation, threshold doses of ac. stroph. rarely affected cardiac rhythm. In the few cases in which such changes in rhythm occurred, the animals were not used.

The experiments were conducted in 14 non-treated cats and in 30 cats pretreated with reserpine in doses of 1, 5, and 10 mg/kg (intraperitoneally) 24 hours prior to determining the threshold dose of ac. stroph. (table 3). The electrocardiogram (Lead II) was recorded on a direct-writing instrument and carotid blood pressure was obtained using a Statham pressure transducer. In 11 of the 17 cats pretreated with 5 mg/kg of reserpine, after the threshold dose of ac. stroph. was determined, norepinephrine (4 µg/ml in 5% glucose) was infused for three to four hours (total dose of 80 to 400 µg/kg); in the remaining six animals, isoproterenol (1 µg/ml in 5% glucose) was infused for one-half to three hours (total dose of 20 to 80 µg/kg). During the infusion of norepinephrine, the blood pressure and heart rate usually increased, while during the isoproterenol infusion the heart rate was accelerated but blood pressure was not affected. Two hours after the termination of the infusions, heart rates had returned to the pre-infusion level whereas the blood pressure fell below it. At this time the ac. stroph. threshold dose was again determined. In another group of four cats pretreated with reserpine (5 mg/kg), after infusions of 5% glucose administered at the same rate as the amines, the ac. stroph. threshold was again determined (not shown in the tables). The threshold dose was not affected.

In 10 of the 14 non-reserpinized animals (table 3) in which arrhythmia had been produced through the combined action of ac. stroph. and vagal stimulation, a dose of ac. stroph. which consistently produced ventricular taehycardia and fibrillation in the absence of vagal stimulation was determined (table 4). To induce these arrhythmias it was necessary to employ a considerably larger dose of ac. stroph. (150 µg/kg) than that which induced arrhythmia in combination with vagal stimulation.
TABLE 3
Effect of Reserpine on Arrhythmia Induced by the Combined Action of Acetylstrophanthidin and Vagal Stimulation in the Cat

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of cats</th>
<th>Avg. threshold dose of ac. stroph. µg/kg ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>14</td>
<td>27 ± 3</td>
</tr>
<tr>
<td>Reserpine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>7</td>
<td>68* ± 7</td>
</tr>
<tr>
<td>5 mg/kg</td>
<td>17</td>
<td>63* ± 3</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>6</td>
<td>40* ± 0</td>
</tr>
</tbody>
</table>

*Significantly different from control (Student’s t-test P < 0.001).

TABLE 4
Effect of Reserpine on the Action of Acetylstrophanthidin to Produce Ventricular Tachycardia and Fibrillation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of cats</th>
<th>Incidence of rhythm disturbance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>10/10 (69.1—100)*</td>
</tr>
<tr>
<td>Reserpine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>14</td>
<td>11/14 (49.2—93.3)*</td>
</tr>
<tr>
<td>5 mg/kg</td>
<td>8</td>
<td>6/8 (34.9—96.8)*</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>11</td>
<td>6/11 (16.8—76.6)*</td>
</tr>
</tbody>
</table>

*Induced by 150 µg/kg ac. stroph.

†Numbers in parentheses represent the 95% confidence intervals expressed in per cent occurrence (Binomial Confidence Limits).# Significantly different from control.

The effects of 150 µg/kg of ac. stroph. were also examined in 33 reserpine-treated animals (table 3). The effects of 150 µg/kg of ac. stroph. were also examined in 33 reserpine-treated animals (table 4). One and 5 mg/kg doses of reserpine, which were sufficient to diminish the action of ac. stroph. to induce arrhythmia in combination with vagal stimulation, did not significantly affect the arrhythmia induced by the large dose of ac. stroph. Only the 10 mg/kg dose of reserpine significantly reduced the incidence of ventricular fibrillation. In the six animals which did not exhibit tachycardia or fibrillation, there was marked ventricular bradycardia causing death in three. In the three survivors, although ventricular fibrillation was not produced by 150 µg/kg of ac. stroph., it occurred after a dose of 400 µg/kg.

In addition to the effects on digitalis-induced arrhythmia, reserpine pretreatment resulted in a slower heart rate and a lower blood pressure. Since the change in heart rate was not dose-dependent in the dose range employed, the heart rates after all doses of reserpine were pooled and averaged. In 42 animals the average was 129 beats per minute (SE ±4.6), while in 20 cats not treated with reserpine, it was 200 beats per minute (SE ±6.7). After 1 mg and 5 mg/kg of reserpine, the average mean blood pressure in 10 animals was 69 (SE ±8) and 75 mm Hg (SE ±3.2), respectively, whereas in the 24 non-treated animals it was 127 mm Hg (SE ±3.3).

Discussion

The results of this investigation suggest that, at least in part, the action of digitalis glycosides to induce arrhythmia is related to catecholamine release. After doses of reser-
FIGURE 2
The effect of reserpine on the combined action of ac. stroph. and vagal stimulation in the cat. Anesthesia: Dial-urethane, intraperitoneally. The electrocardiogram was recorded on Lead II. With the exception of trace B, the figures in the upper left hand corner represent the sinus rate (beats/min) before vagal stimulation; the sinus rate after vagal stimulation is indicated in the middle of the record. The arrows below the trace signal the start of vagal stimulation. Trace A shows the effect of a vagal stimulation which produces sinus slowing just short of that at which the ventricle escapes ("critical" sinus slowing). Trace B depicts the effect of ac. stroph. in combination with the vagal slowing shown in trace A. Note the ventricular arrhythmia (prior to vagal stimulation normal sinus rhythm was present). The ventricular rate is indicated in the upper left hand corner. Trace C and D depict similar experiments performed in another cat previously treated with reserpine (5 mg/kg). In trace C, ac. stroph. in a dose which was sufficient to produce arrhythmia in the non-reserpine treated animal failed to evoke ectopic beats, while in trace D, a much larger dose was effective.
pine which deplete tissue catecholamines, the incidence of extra beats induced by ouabain in the isolated cat papillary muscle is reduced, and the threshold dose of ac. stroph. necessary to induce arrhythmia in combination with vagal stimulation in the cat is increased. After repleting amine stores with norepinephrine or isoproterenol in animals which have received reserpine, doses of ac. stroph. of the same magnitude as in animals not receiving reserpine induce arrhythmia. In addition, after βTM 10, an agent which prevents the release of catecholamines from sympathetic nerve terminals, the capacity of ac. stroph. to produce acceleration of the ventricle in dogs with surgically induced heart block is greatly reduced.

Catecholamine release by digitalis glycosides may not, however, be the only way in which catecholamines and digitalis are related. It is possible that the degree to which ac. stroph. must raise ventricular rhythmicity to induce arrhythmia depends on the background rhythmicity of the ventricle. "Intrinsic" rhythmicity of the ventricle has been related to the activity of endogenous catecholamines. If catecholamines are depleted or their release prevented, the "intrinsic" rate of the ventricle falls to relatively much lower levels than that of the atrium. It is conceivable that larger doses of digitalis may be necessary to raise the rhythmicity of the ventricle sufficiently to achieve pacemaker dominance than would be required if the prevailing rhythmicity of the ventricle were at a higher level. The experiments in which arrhythmia is produced through the combined action of ac. stroph. and vagal stimulation are pertinent. The smallest dose of ac. stroph. which produced arrhythmia (see Methods) was determined in both untreated and reserpine-treated cats. In each instance sinus activity is depressed to the same biologic level in that the rate is just above that which permits ventricular escape; therefore, the degree to which ventricular rhythmicity must be raised by ac. stroph. to usurp sinus dominance is the same in all instances. Hence, in these experiments, the level of "intrinsic" rhythmicity and the action of catecholamines in setting the level, are not factors in determining the dose of ac. stroph. necessary to produce arrhythmia. Nevertheless, the presence of catecholamines was essential for small doses of ac. stroph. to be effective; after reserpine the same threshold doses as those in the untreated animals were not effective in evoking ventricular arrhythmia when amine stores were not repleted. This suggests that the arrhythmia induced by such doses is mediated through catecholamine release.

Since large doses of ac. stroph. in combination with vagal stimulation evoked ventricular arrhythmia after reserpine, a mechanism unrelated to catecholamines is involved in this action. This is supported by the observation that reserpine in doses of 1 and 5 mg/kg did not affect the arrhythmias (ventricular tachycardia and fibrillation) induced in the absence of vagal stimulation by a large dose (150 μg/kg) of ac. stroph.

Yelnosky and Erwin reported that in the intact anesthetized dog, ouabain-induced ventricular tachycardia was not affected by reserpine pretreatment and concluded that this arrhythmia is not caused by the release of catecholamines. The doses of ouabain expressed in cat units (0.72—0.88 c. u.) used by these investigators is comparable to the large dose of ac. stroph. (0.75 c. u.) employed in the present study to produce ventricular tachycardia and fibrillation in the absence of vagal stimulation. The arrhythmias induced by the large dose of ac. stroph., however, were not affected by reserpine pretreatment (1 and 5 mg/kg) and to this extent, therefore, our results agree with those of Yelnosky and Erwin. It should be noted, however, that Yelnosky and Erwin did not explore the effect of reserpine pretreatment on arrhythmia induced by ouabain in doses comparable to the small dose of ac. stroph. used in this study. Since it was the response to these doses that was affected by reserpine pretreatment, it is not surprising

\*Ac. stroph. 0.2 mg = 1 cat unit; ouabain 0.1 mg = 1 cat unit.
that they were not able to demonstrate any relationship between digitalis arrhythmia and catecholamine release.

The time-course of reserpine action to deplete catecholamines must also be considered in evaluating the effect of this agent on digitalis-induced arrhythmia. Dick et al. reported that in patients who were previously digitalized, reserpine causes atrial or ventricular arrhythmia. Since large amounts of catecholamines are released during the early phase of reserpine action, the authors suggested that the action of these amines in combination with those liberated by the digitalis material on ectopic foci might account for the development of the rhythm disturbances. In the present study, such an interaction did not occur. The digitalis material was administered 24 hours after reserpine; a point on the time action curve of reserpine at which the catecholamine stores have been largely depleted. In this circumstance, the administration of digitalis material would not result in the liberation of significant amounts of catecholamines and consequently its action to induce arrhythmia is diminished. Thus, to demonstrate the depressant effect of reserpine on the digitalis-induced arrhythmia, the catecholamine stores must be largely depleted before the digitalis material is administered.

The vagal actions of reserpine may also be important. The investigation of Lown et al. is especially pertinent. These investigators found that reserpine pretreatment did not reduce the cardio-toxic actions of ac. stroph. in patients with congestive heart failure; in fact, such actions were enhanced in patients who also had atrial fibrillation. They also reported that reserpine increased vagal activity as evidenced by greater cardiac response to carotid sinus massage. It is possible that the slower sinus rate and greater prolongation of A-V conduction time resulting from increased vagal activity would provide a more favorable background for ac. stroph. to produce ventricular arrhythmia. Hence, while reserpine may reduce the response of the ventricular pacemaker to ac. stroph. by depleting catecholamines, the enhancement of vagal activity by reserpine may obscure its depressant effect on the ac. stroph.-induced arrhythmia. Because of this, vagal activity before and after reserpine must be taken into account in a proper evaluation of the relationship between catecholamines and digitalis-induced arrhythmia. In the present study, vagal activity before and after reserpine was comparable since, in both instances the vagus was stimulated to the point just short of that permitting ventricular escape. On the other hand, in the dog with surgically induced heart block vagal activity is of little importance. N-methylatropine does not influence the ventricular rate and vagal stimulation leads to but slight ventricular slowing in less than half the animals.

It has been proposed that reserpine also exerts a direct cardiotoxic effect. In our study, only in the dose of 10 mg/kg did it appear that catecholamine depletion did not entirely account for the action of reserpine. The ac. stroph. threshold dose was not increased to the same degree as with the smaller doses of reserpine, while the incidence of ventricular fibrillation after the large dose of ac. stroph. was reduced. However, a direct cardiotoxic effect does not seem to be a likely explanation for these actions of reserpine, since the amplitude of contraction and the rate of failure of papillary muscles isolated from cats pretreated with 10 mg/kg of reserpine was not significantly different from that of untreated preparations. It would appear therefore that the action or actions responsible for the effects of the higher dosage ranges of reserpine remain to be elucidated.

The hypotension induced by reserpine did not seem to be an important factor in its action to increase the dose of ac. stroph. necessary to induce arrhythmia in combination with vagal stimulation. After the infusions of norepinephrine and isoproterenol, the blood pressure in the reserpine-treated cat remained at low levels although the reactivity of the ventricular pacemaker to ac. stroph. was restored.
While βTM 10 lowered the blood pressure of dogs with surgically induced heart block, this effect also did not appear to be a factor in its action which reduces the responsiveness of the ventricular pacemaker to ac. stroph. Hexamethonium which causes hypotension did not affect the ac. stroph.-induced tachycardia in these animals.

It is also interesting that although catecholamine depletion by reserpine reduced the incidence of ouabain-induced extra beats, the action of ouabain to increase the tension developed by isolated papillary muscle was not affected. While the latter finding differs from that of Tanz, who reported that reserpine pretreatment diminished the positive inotropic effect of ouabain in isolated cat papillary muscles, it is in agreement with the in vivo studies of Yelnosky and Erwin and Morrow et al.

**Summary**

After catecholamine depletion by reserpine, the capacity of the digitalis materials to induce ventricular arrhythmia is diminished. In papillary muscles from cats pretreated with reserpine, the incidence of ouabain-induced extra beats is reduced. The dose of ac. stroph. necessary to induce ventricular arrhythmia in combination with vagal stimulation is increased by reserpine pretreatment. Threshold doses comparable to those in cats not pretreated with reserpine produced arrhythmia after the catecholamine stores were repleted with norepinephrine or isoproterenol.

In dogs with A-V block, βTM 10, an agent which prevents the release of catecholamines, markedly reduces the response of the ventricular pacemaker to ac. stroph.

Since the arrhythmias induced by large doses of ac. stroph. are not affected by reserpine pretreatment, it is concluded that while catecholamine release is the primary mechanism involved in the arrhythmia produced by small doses, another mechanism also plays a role in this action after larger doses.

Only in the dose of 10 mg/kg did it appear that catecholamine depletion did not account entirely for the action of reserpine. The ac. stroph. threshold dose was not increased to the same degree as with the smaller doses of reserpine, and the incidence of ventricular fibrillation induced by the large dose of ac. stroph. was reduced.

Hypotension produced by reserpine and βTM 10 did not seem to be an important factor in depression of the responsiveness of the ventricular pacemaker to ac. stroph.

While the incidence of ouabain-induced extra beats was reduced by reserpine pretreatment, the action of ouabain to increase the tension developed by isolated papillary muscles was not affected.

**References**

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