Comparison of the Action of Ouabain on the Heart in Hypothyroid, Euthyroid and Hyperthyroid Dogs

By Anders Rosen, M.D., and Neil C. Moran, M.D.

Although it is assumed that digitalis glycosides are relatively ineffective in heart failure and atrial fibrillation associated with disorders of thyroid gland function, there is little experimental work to support this belief. Frye and Braunwald observed that administration of triiodothyronine to euthyroid and hypothyroid patients with chronic atrial fibrillation increased the dose of cardiac glycosides required to slow the ventricular rate. No experimental work has been done on the effect of cardiac glycosides on cardiac contractile force following changes in thyroid function.

That disorders of thyroid function may alter the toxicity of digitalis is also a common belief. Digitalis intoxication is considered to occur more frequently in patients with thyrotoxicosis than in those in a euthyroid state. Caution in the use of digitalis in such cases has been, therefore, advisable. Older experimental work on the influence of altered thyroid state on digitalis toxicity, which has been reviewed by Lendle, suggests that the toxicity of digitalis is increased in hyperthyroidism and decreased in hypothyroidism. However, we know of no recent experimental work concerned with this problem.

The aim of the present study was to evaluate ouabain-induced changes in cardiac contractile force in hypothyroid, euthyroid and hyperthyroid dogs, as well as to determine possible differences in the amount of ouabain required to induce arrhythmias and to produce death in the various groups of dogs.

Methods

Thirty-one mongrel dogs of either sex weighing 7.0 to 12.1 kg were divided into three groups: hypothyroid, hyperthyroid and euthyroid. Hypothyroidism was produced as follows: With pentobarbital anesthesia the thyroid glands were surgically removed in four dogs. Following recovery from the operation methimazole (1-methyl-2-mercaptimidazole) was administered orally (10 mg/kg daily) for six to eight days. When methimazole administration was stopped, the animals were fasted for three days (the dogs received only distilled water) after which NaI (25 mCi) was administered iv. Methimazole and fasting were used to increase the uptake of I131 by aberrant or residual thyroid tissue. In two additional dogs only I131 was used. The individual treatment of each dog is seen in table 1. The term thyroideectomy will be used to indicate both surgical and radio-iodine removal of the thyroid gland. Following thyroideectomy the animals were kept on a low iodine, vegetable diet made up of the Remington low iodine diet (Nutritional Biochemical Corporation) to which was added Graham crackers, canned baked beans and vegetable soup. Dogs 1, 2, and 3 (table 1), in which the parathyroid glands had been removed, received 15 g of calcium lactate daily in the food to prevent hypocalcemic tetany. Studies were done six to seven weeks after the I131 injection.

To produce a hyperthyroid state nine dogs were given thyroxine subcutaneously daily, 0.3 or 0.5 mg/kg for the first two days and 1.0 mg/kg per day thereafter. The animals were given food ad libitum. Studies were done after nine to eleven days of treatment (18-24 hours after the last thyroxine injection). Serum potassium levels were determined with a flame photometer before and at the conclusion of the treatment. There was no significant change following thyroxine treatment.
Table 1

<table>
<thead>
<tr>
<th>Dog</th>
<th>Thyroidectomy</th>
<th>Methimazole, mg X days</th>
<th>Fasting days</th>
<th>T4, μg</th>
<th>% decrease in serum T4</th>
<th>% decrease in O2 consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bilateral 10 X 8</td>
<td>25</td>
<td>72</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Bilateral 10 X 8</td>
<td>25</td>
<td>72</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Bilateral 10 X 6</td>
<td>72</td>
<td>5</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Unilateral 10 X 6</td>
<td>25</td>
<td>72</td>
<td>50</td>
<td></td>
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<tr>
<td>5</td>
<td>—</td>
<td>—</td>
<td>72</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dog 6 was not considered to be hypothyroid and was not included in the group of hypothyroid dogs.

Measurement of Oxygen Consumption and Serum Protein Bound Iodine (PBI)

O2 consumption and serum PBI were determined in all but five dogs. The latter are included in the group of euthyroid animals. Prior to administration of thiourea or thyroidectomy, the animals were anesthetized with pentobarbital sodium, 35 mg/kg, intravenously. An endotracheal tube was inserted and tightly fixed in the trachea and attached to a spirometer (Sanborn Waterless Metabolism Tester) for determination of oxygen consumption. At the same time a sample of blood was collected for determination of serum protein bound iodine. Similar determinations of O2 consumption and serum PBI were obtained on the hypothyroid dogs under pentobarbital anesthesia a few days before the experiment and on the thiourea-treated dogs on the day of experiment under a combination of pentobarbital and barbital anesthesia (see below). O2 consumption was corrected to standard temperature and pressure and is expressed in ml/min/m2 body surface area, using the conventional formula.

Surface area (m2) = 0.112 X (weight (kg))^0.62.

The determination of protein bound iodine was performed according to the method of Barker et al.

Weight and Rectal Temperature

Weight and rectal temperature were measured before treatment and on the day of experiment. No significant changes were observed in the hypothyroid and hyperthyroid dogs.

Determination of Effect of Ouabain

When altered states were achieved (determined by O2 consumption and serum PBI), the dogs were anesthetized with a combination of pentobarbital sodium (20 mg/kg in the euthyroid, 20-25 mg/kg in the hyperthyroid, and 20-25 mg/kg in the hypothyroid dogs) and barbital sodium (200 mg/kg in the euthyroid and hyperthyroid dogs, 175-220 mg/kg in the hypothyroid animals). The animals were initially subjected to bilateral cervical vagotomy. The trachea was cannulated and positive pressure artificial respiration was maintained during the experiments. Rectal temperature was maintained at about 37.5°C by means of an electric heating pad placed under the animal. Arterial pressure was determined by means of a Statham physiological pressure transducer connected to a plastic cannula inserted into a femoral artery. A femoral vein was cannulated for intravenous injections. Lead II of the electrocardiogram was recorded. Following thoracotomy and incision of the pericardium a Walton-Brodie strain gauge arch was attached to the right ventricular wall by means of sutures which penetrated deeply into the heart muscle. A direct writing Grass auocillograph was used as recording instrument. The chest was left open throughout each experiment.

The euthyroid dogs were divided into two groups. One group of nine dogs was prepared only as above. In a second group the heart rate was maintained at a rate of 210 ± 3 (mean ± SEM) per minute by means of electrical stimulation (3.0 V, pulse duration 4 msec) through platinum electrodes attached to the right atrium. When a stable level of blood pressure and contractile force was achieved, ouabain was administered intravenously in divided doses as follows: 1/4 cat unit (27.5 μg)/kg was injected over a two-minute period every 15 minutes until the animals died.

The changes in contractile force in each 15-minute period were measured until arrhythmias supervened. The increase in force in response to ouabain was measured and expressed as mean (± standard error) percentage increase. Although the standard error for the force responses to repeated injections of ouabain was relatively large, the error was found to be much less than that obtained in response to continuous infusion of ouabain.
**TABLE 2. General Effects of Thyroidectomy and Thyroxine Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>Before Treatment</th>
<th>After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyroid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal sinus node pacemaker</td>
<td>112 ± 7</td>
<td>112/73 ± 4/6</td>
<td>109 ± 4</td>
<td>109/84 ± 6/6</td>
</tr>
<tr>
<td>Artificial atrial pacemaker</td>
<td>210 ± 3</td>
<td>198/89 ± 6/6</td>
<td>208 ± 3</td>
<td>207/83 ± 9/9</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td>114 ± 6</td>
<td>109/89 ± 4/4</td>
<td>169 ± 8</td>
<td>103/80 ± 4/4</td>
</tr>
<tr>
<td>Thyroxine treatment</td>
<td>208 ± 8</td>
<td>141/83 ± 9/9</td>
<td>122 ± 6</td>
<td>104/79 ± 5/7</td>
</tr>
</tbody>
</table>

* Obtained in anesthetized, vagotomized animals at the time experiment was performed, prior to ouabain administration.

1. Normal Pacemaker. The cardiac positive inotropic response to ouabain, given at 15-minute intervals, was plotted at each 5-minute period. The augmented contractile force following ouabain injection could be studied through the first 15-minute interval and five minutes of the second interval, after which arrhythmias appeared. The mean percentage increase of contractile force at the end of the first 15-minute interval and five minutes of the second interval, after which arrhythmias appeared. The mean percentage increase of contractile force at the end of the first 15-minute interval and five minutes of the second interval, after which arrhythmias appeared. The mean percentage increase of contractile force at the end of the first 15-minute interval and five minutes of the second interval, after which arrhythmias appeared. The mean percentage increase of contractile force at the end of the first 15-minute interval and five minutes of the second interval, after which arrhythmias appeared.

2. Artificial Pacemaker. In the dogs, in which heart rate was maintained at an elevated level by electrical stimulation of the right atrium a normal conduction pattern prevailed throughout the second 15-minute interval, thus allowing studies of the action of ouabain on contractile force for two full intervals. As can be seen in figure 1 the response to ouabain was close to that in the dogs with a normal sinus node pacemaker. At the
Figure 1

Comparison of the positive inotropic effect of ouabain in euthyroid, hypothyroid, and hyperthyroid dogs. Mean increase in right ventricular contractile force, measured with strain gauge arch, shown on ordinate, time on abscissa. Ouabain, 27.5 µg/kg given iv over 2-minute period at arrows.

A. Euthyroid Dogs (heart rate: 160 ± 7)
- Euthyroid dogs with electrical pacemaker (heart rate: 210 ± 3)
- Euthyroid dogs (heart rate: 160 ± 6)

In the euthyroid animals a slow augmentation of contractile force followed the first injection of ouabain (fig. 1). At five minutes the mean percentage increase was 24 ± 2.8 in the euthyroid group with artificial pacemaker and 20 ± 2.8 in the euthyroid dogs with normal sinus rhythm. The rate of force augmentation successively increased during the following ten minutes in the first interval, however, so that at the end of the interval the increase of force was closer to that in the euthyroid dogs (15 ± 1.3 compared to 24 ± 2.8 and 28 ± 4.4 in the euthyroid group with artificial pacemaker and normal sinus rhythm respectively). In the second 15-minute interval the response of contractile force to ouabain in the hypothyroid animals mainly followed the response observed in the euthyroid dogs (fig. 1).

B. Hypothyroid Dogs
- Hypothyroid dogs (heart rate: 140 ± 6)

In the hypothyroid animals a slow augmentation of contractile force followed the first injection of ouabain (fig. 1). At five minutes the mean percentage increase was 1 ± 1.8 compared to 15 ± 2.4 in the euthyroid group with artificial pacemaker and 20 ± 2.8 in the euthyroid dogs with normal sinus rhythm. The rate of force augmentation successively increased during the following ten minutes in the first interval, however, so that at the end of the interval the increase of force was closer to that in the euthyroid dogs (15 ± 1.3 compared to 24 ± 2.8 and 28 ± 4.4 in the euthyroid group with artificial pacemaker and normal sinus rhythm respectively). During the second 15-minute interval, the response was much less augmented in hypothyroid than in euthyroid dogs. It should be noted that the figures for the hypothyroid animals in figure 1 are based on the results obtained in the seven experiments in which no arrhythmias appeared in the second 15-minute interval. The figures during the first interval equal those obtained from all nine experiments.

C. Hyperthyroid Dogs
- Hyperthyroid dogs (heart rate: 208 ± 8)

A contractile force response to ouabain similar to that seen in the euthyroid dogs was observed in the thyroxine-treated animals during the first 10 minutes. By the end of 15 minutes, however, the mean increase of contractile force in the hyperthyroid animals was less than that in the euthyroid dogs (17 ± 2.6% compared to 24 ± 2.8% and 28 ± 4.4% in the euthyroid group with artificial pacemaker and normal sinus rhythm respectively). During the second 15-minute interval, the response was much less augmented in hyperthyroid than in euthyroid dogs. It should be noted that the figures for the hyperthyroid animals in figure 1 are based on the results obtained in the seven experiments in which no arrhythmias appeared in the second 15-minute interval. The figures during the first interval equal those obtained from all nine experiments.

Effect of Ouabain on Heart Rate and Blood Pressure

Heart rate was not significantly changed in any group of dogs following the injections of ouabain. Blood pressure increased slightly in all dogs after the first injection of ouabain. Following the second administration, the rise was more extensive (mean rise of systolic pressure after five minutes approximately 30 mm Hg). Systolic pressure in the hyperthyroid dogs dropped (mean fall approximately 20 mm Hg) during the last ten minutes of the second interval, the response thus being parallel to that of cardiac contractile force in the same dogs (fig. 1).
EFFECT OF OUABAIN ON RHYTHM OF THE HEART

A. Euthyroid Dogs

1. Normal Pacemaker. At the end of the first 15 minutes ouabain had not induced arrhythmias in any dog. At the end of the second interval, however, ouabain had caused irregular rhythm in eight of the nine dogs. The ninth dog showed irregular rhythm after another 15-minute interval had elapsed. The cumulative percentage of the dogs with arrhythmias at the end of each 15-minute interval is shown in figure 2.

2. Artificial Pacemaker. As the hyperthyroid dogs (see below) required a larger dose of ouabain to produce arrhythmias than the euthyroid animals it was suggested that the tachycardia per se in the hyperthyroid group might be responsible for this difference. To study that suggestion, a pacemaker was attached to the right atrium in seven euthyroid dogs, driving the heart at a mean rate (210 ± 3) corresponding to that observed in the hyperthyroid dogs (208 ± 8). It was found that the arrhythmia-producing dose was larger in the euthyroid dogs with artificial pacemaker than in the euthyroid dogs with normal sinus rhythm and was approximately the same as that observed in the thyroxine-treated animals (fig. 2).

B. Hypothyroid Dogs

In the hypothyroid animals arrhythmias were observed late and at a time closely corresponding to that seen in the euthyroid dogs with atrial pacemakers and in the thyroxine-treated animals (fig. 2).

C. Hyperthyroid Dogs

As seen in figure 2 arrhythmias appeared later in the thyroxine-treated dogs than in the euthyroid animals following administration of ouabain. In most of the animals arrhythmias were induced in the third 15-minute interval. The curve of cumulative per cent of dogs with arrhythmias was close to that for the euthyroid group with electrically driven hearts.

THE LETHAL EFFECT OF OUABAIN

A. Euthyroid Dogs

1. Normal Pacemaker. The cumulative per cent fatality after each 15-minute interval is shown in figure 2. No dogs survived the end of the fourth 15-minute interval, at which time the animals had received a full lethal unit (110 μg/kg) of ouabain.

2. Artificial Pacemaker. Artificially elevated heart rate in euthyroid dogs increased the time to lethal effect of ouabain. The curve of cumulative per cent fatality appeared close to that of the hyperthyroid animals (see below and fig. 2).

B. Hypothyroid Dogs

The lethal effect of ouabain occurred later
in the hypothyroid animals than in euthyroid dogs with normal sinus rhythm. The majority of the dogs died in the fifth 15-minute interval, at which time they had received 137.5 μg/kg of ouabain (fig. 2).

C.Hyperthyroid Dogs

As seen in figure 2, the hyperthyroid dogs died following a dose of ouabain which was larger than the lethal dose in the euthyroid animals with a normal sinus node pacemaker. However, there was no noticeable difference in the lethal dose in the hyperthyroid dogs and the euthyroid animals with a heart rate artificially increased to the "hyperthyroid' level.

Discussion

The present study shows that ouabain substantially augments cardiac contractile force in dogs with altered thyroid states. The magnitude of the response and the rate of change of force are in some instances altered. In hypothyroid dogs a moderate dose of ouabain produces an increase in contractile force of approximately the same extent as in the euthyroid animals, although of slower onset and larger doses further increase the force, the magnitude of increase being the same as that observed in the euthyroid animals. Although the number of hypothyroid animals is small it is felt that the results are significant, at least those after a moderate dose of ouabain where the variability is small. In the hyperthyroid dogs the magnitude of force augmentation and the rate of change of force to a moderate dose of the glycoside are approximately the same as in the euthyroid animals whereas larger doses of ouabain cause a smaller positive isotropic response than in the euthyroid animals.

Our data indicate that heart muscle responds to moderate (therapeutic) doses of digitalis in hyperthyroidism as well as hyperthyroidism, thus supporting a few clinical observations that the failing myoecardium in hyperthyroidism and hyperthyroidism is, in fact, strengthened by digitalis. Regarding the digitalis requirement in treatment of atrial fibrillation in thyroid disorders reference should be made to the experimental work by Frye and Braunwald. They observed that the effective dose of digoxin in patients with chronic atrial fibrillation is increased three to four times following triiodothyronine treatment. The isotropic action of digitalis does not appear to be reflected by the slowing of the ventricular rate as already pointed out by Frye and Braunwald, and thus their and our observations are probably not contradictory.

Characteristic signs of cardiac toxicity, as observed on the electrocardiogram, are seen in all groups of animals, although larger doses of ouabain were required to produce these effects in hypothyroid and hyperthyroid dogs than in normal animals. The time to death following ouabain administration was also greater in hypothyroid and hyperthyroid than in euthyroid dogs. In hyperthyroid dogs the increase in toxic and lethal doses may be simply a delayed manifestation of the toxic effects of ouabain on the ventricles due to the sinus tachycardia. This seems plausible, as a similar delayed toxicity was observed in euthyroid animals, in which atrial rate was increased by atrial fibrillation in thyroid disorders. Reference should be made to the experimental work by Frye and Braunwald. They observed that the effective dose of digoxin in patients with chronic atrial fibrillation is increased three to four times following triiodothyronine treatment. The isotropic action of digitalis does not appear to be reflected by the slowing of the ventricular rate as already pointed out by Frye and Braunwald, and thus their and our observations are probably not contradictory.

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time of six weeks or more elapsed between administration and experiment, and one dog, which received I-131 but remained euthyroid (table 1), showed a response to ouabain characteristic of that of euthyroid dogs. With respect to calcium it is known that a synergistic effect exists between calcium and ouabain. Parathyroidectomy even appears to reduce calcium absorption from the intestines. There is thus no reason to believe that the administration of calcium to the parathyroidectomized dogs influenced the results in the present study. The hypothyroid dogs receiving calcium also showed the same response to ouabain as those to which no calcium was given.

Our finding of decreased toxicity of ouabain in hypothyroidism, in agreement with some older work, has no known mechanism. However, we can find no correlation with any clinical observation. The present observations in the hyperthyroid animals do not confirm the reports of increased digitalis intoxication in hyperthyroidism. From our data we are more inclined to believe—as has been suggested earlier—that the increased frequency of digitalis intoxication in thyrotoxic patients with chronic atrial fibrillation is due to the large dose of digitalis apparently required for successful treatment.

Biochemical lesions in heart muscle in hyperthyroidism have been reported by several investigators. It has been suggested that uncoupling of oxidative phosphorylation occurs in hyperthyroidism and may cause congestive heart failure. Recently, however, Olson and Piatnek have observed no decrease in high-energy phosphate compounds in the myocardium of hyperthyroid dogs with augmented cardiac output, coronary blood flow, and myocardial oxygen usage. It has also been suggested that anabolic reactions leading to protein synthesis, and hence to the maintenance of the contractile proteins of the heart, may be affected in thyrotoxicosis and thereby influence contractility of the heart. Further work in this field is required, however, to justify a discussion of correlation between the present findings on the action of ouabain and biochemical changes in the myocardium induced by changes in the thyroid state.

Summary

Ouabain-induced changes in cardiac contractile force and differences in the amount of ouabain required to induce arrhythmias and to produce death were evaluated in normal, thyroidectomized and thyroxine-treated dogs. It was found that ouabain, following alterations in thyroid function, still substantially augmented cardiac contractile force in anesthetized open-chest dogs. In both the hypothyroid and the hyperthyroid animals a moderate dose of ouabain produced an increase in contractile force of approximately the same extent as in the euthyroid animals, although of slower onset in the hypothyroid dogs. Larger doses of ouabain caused a smaller positive inotropic response in hyperthyroid dogs than in euthyroid and hypothyroid animals. Changes in thyroid function increased the arrhythmia-producing and the lethal dose of ouabain, which in the hyperthyroid dogs may have been due to the markedly elevated heart rate.

Acknowledgment

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