Properties of Hyperthyroid Rat Myocardium

By W. V. Whitehorn, M.D., W. C. Ullrick, Ph.D., and B. R. Andersen, M.D.

With the technical assistance of Ryo Kubota

Electric and mechanical properties of right and left ventricular muscle of hyperthyroid rats have been studied in vitro. Excitability was not modified but refractory period was lengthened in left ventricular muscle. Developed tension was significantly reduced in both ventricles, the greater reduction being on the right. The results suggest direct and disproportionate effects of thyroid hormone on right and left ventricular myocardium.

INTEREST in the effects of increased thyroid activity on the heart is old. Numerous studies have been concerned with effects on cardiac rate, rhythm, size, output, morphology, and electrical activity. Metabolic activity has been observed under in vitro and in vivo conditions, and changes in chemical composition of myocardium have been reported. The extensive reviews of Rasmussen, Raab, Andrus, Barker, and Werner cover the voluminous literature. Modern techniques of cardiac catheterization have been applied by Bing, Leight et al., and Rowe et al. to human hyperthyroidism, and Brewster et al. have emphasized the importance of interrelationships with epinephrine and norepinephrine in the metabolic and hemodynamic actions of the thyroid hormones. In spite of this impressive literature, information on basic electrical and mechanical properties of hyperthyroid cardiac muscle is scanty. Studies on isolated tissue have generally not included such observations, and in vivo experiments are complicated by the presence of neural, hormonal, and hemodynamic factors. It seemed of interest to determine the electric and mechanical properties of isolated myocardial bundles from hyperthyroid rats for gaining information regarding basic and direct effects of thyroid hormones on cardiac function. After preliminary observations on right ventricular muscle, we have extended and expanded these studies to include left ventricular tissue as well.

METHODS

The experimental animals were male rats of the Sprague-Dawley strain weighing approximately 150 gm. at the start of the experiment. All animals received a standard diet of Purina Checkers ad libitum. Body weights, heart rates from lead I of the electrocardiogram, and metabolic rates by a modification of the technic of Blood and d'Amour were determined twice on the entire group during a pretreatment period of one week. Two main groups of experiments were performed.

Series A. Right Ventricular Strips. Animals were randomly divided into an experimental and a control group. Experimental animals received 100 mg./day of powdered thyroid (Armour, U.S.P.), moistened and incorporated in the diet. Treatment was continued for 17 days. Body weights, heart rates, and metabolic rates were determined on the eleventh day of the treatment period and on the day of termination for both experimental and control groups. Animals were killed by decapitation, the heart was rapidly removed, and a right ventricular strip was prepared according to the method of Feigen et al. and placed in a specially designed clamp and bath. The great vessels and atria were trimmed from the remainder of the ventricles, the wet weight of the latter was determined, and the tissue was placed in a drying oven at 100 C. for subsequent determination of dry weight. The tension on the isolated muscle bundle was adjusted to 1 Gm., its length measured with a calibrated micrometer, and its threshold determined to a square wave stimulus of 6 msec. duration delivered once per second. The muscle was then allowed to equilibrate for a period of 45 minutes, during which time stimulation was continued. Following the equilibration period, the thresholds to square wave stimuli of 10, 6, 4, 2, 1, 0.6, 0.4, and 0.2 msec. duration were measured. The test shocks were delivered 500 msec. after the driving stimulus at a frequency of 1 per second.
HYPERTHYROID RAT MYOCARDIUM

TABLE 1.—General Data, Series A

<table>
<thead>
<tr>
<th></th>
<th>Control (N = 9)</th>
<th>Thyroid-fed (N = 10)</th>
<th>P (group comparison)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal body weight (Gm.)</td>
<td>332± 7*</td>
<td>288±10</td>
<td>.01</td>
</tr>
<tr>
<td>Heart rate (beats/min.)</td>
<td>405±23</td>
<td>525±23</td>
<td>.01</td>
</tr>
<tr>
<td>Heart weight (mg. dry)</td>
<td>171±10.2</td>
<td>205±18.1</td>
<td>.01</td>
</tr>
<tr>
<td>Heart wt./body wt. ratio</td>
<td>0.517± .011</td>
<td>0.713± .015</td>
<td>.01</td>
</tr>
<tr>
<td>Total metabolic rate, cal./sq.m./hr., (fasting)</td>
<td>30.8±1.36</td>
<td>45.2±1.65</td>
<td>.01</td>
</tr>
</tbody>
</table>

*S.E. of mean.

TABLE 2.—Electrical Properties, Series A

<table>
<thead>
<tr>
<th></th>
<th>Control (N = 11)</th>
<th>Thyroid-fed (N = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory period, msec.</td>
<td>67±5.2</td>
<td>51.3±7.2</td>
</tr>
<tr>
<td>Rheobase (ma.)</td>
<td>0.064±0.020</td>
<td>0.090±0.014</td>
</tr>
<tr>
<td>Chronaxe msec.</td>
<td>1.16±0.28</td>
<td>0.87±0.16</td>
</tr>
</tbody>
</table>

FIG. 1. Passive length-tension relationships. Series A. Right ventricular strips.

Patients received treatment for 14 to 17 days. Control animals received injections of the alkaline thyroxine vehicle. Body weights, heart rates, and metabolic rates were followed, as in series A. Upon termination, a left ventricular columna carneae was prepared as previously described. Stimulation was accomplished as in series A. The muscle was allowed to equilibrate at equilibrium length, and active and passive length-tension relationships were determined by increasing the muscle length in increments of 10 per cent of equilibrium length, until the point of maximum active tension development had been passed. Other observations were similar to those made for series A.

RESULTS

Series A. Right Ventricular Strips. General data are summarized in table 1. Thyroid-fed animals showed significant depression of growth rate, elevation of heart rate, absolute increase in heart weight, and increase in heart to body-weight ratio. The mean elevation of total fasting metabolic rate in the experimental group was about 50 per cent. Measurement of electric properties of the right ventricular strips failed to reveal significant differences between control and hyperthyroid tissue. Mean values for rheobase, chronaxie, and refractory period are listed in table 2. The differences are not significant. Raising length-tension relationships are indicated in figure 1. The slightly reduced extensibility suggested by the experimental curve is not significant. Figure 2 presents the length-de-
veloped tension relationships for this series. It is clearly apparent that mean tension production at any diastolic tension is markedly reduced in the hyperthyroid muscles. The mean maximum tension produced by control strips was 171.6 ± 13.5 mg./mg. dry weight of muscle as compared with a mean maximum of 68.4 ± 8.0 mg./mg. muscle for the experimental group. This difference is highly significant statistically. In both groups maximum tension was developed at about 120 per cent of equilibrium length under the conditions of this experiment.

Series B. Left Ventricular Columnae Carneae. General data for this series are presented in table 3. Results are generally similar to those found in series A. The 50 μg. dose of thyroxine, however, while it produced significant loss of weight, tachycardia, and cardiac enlargement, did not produce a significant elevation of metabolic rate. The increases produced by the larger dose of thyroxine or by thyroid feeding are proportionately similar to those occurring in series A. The lack of weight loss in the thyroid-fed animals of series B is unexpected, since in all other respects this group was clearly hyperthyroid.

Electrical properties of left ventricular muscle bundles are given in table 4. It is again apparent that hyperthyroidism produced no significant changes in rheobase or chronaxie. In contrast to findings in series A, however, there was significant lengthening of the refractory period in all thyroid-treated groups.

Passive length-tension relationships for series B are plotted in figure 3, and length-developed tension curves in figure 4. Resting length-tension relationships were not affected by thyroid treatment. As in series A, however, it is apparent that tension production of muscles from all thyroid-treated groups was less than that of controls. Mean maximum developed tensions and statistical comparisons are given in table 5. There were no significant differences in tension production between the 3 thyroid-treated groups, although mean maximum tension production was somewhat higher in the low thyroxine animals. In general, the reduced capacity to develop tension was less marked in the left ventricular columnae of thyroid fed animals than in right ventricular
TABLE 3.—General Data, Series B

<table>
<thead>
<tr>
<th></th>
<th>Control (N = 10)</th>
<th>50 μg. thyroxine (N = 10)</th>
<th>100 μg. thyroxine (N = 9)</th>
<th>Thyroid-fed (N = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal body wt. (Gm.)</td>
<td>276.7± 7.6</td>
<td>252.4± 8.1*</td>
<td>243.4±15.0*</td>
<td>286.9±17.0</td>
</tr>
<tr>
<td>Total nonfasting metabolic rate (cal./M²/hr.)</td>
<td>44.4± 3.1</td>
<td>50.8± 3.2</td>
<td>70.1± 5.8*</td>
<td>66.8± 5.1*</td>
</tr>
<tr>
<td>Heart rate (beats/min.)</td>
<td>455±15.7</td>
<td>509±14.5*</td>
<td>575±21.0*</td>
<td>567±10.7*</td>
</tr>
<tr>
<td>Ventricle body wt. ratio (mg./Gm.)</td>
<td>.554±.027</td>
<td>.789±.029*</td>
<td>.807±.031*</td>
<td>.782±.038*</td>
</tr>
</tbody>
</table>

*Significantly different from control group (p < 0.05).

TABLE 4.—Electrical Properties, Series B

<table>
<thead>
<tr>
<th></th>
<th>N Control</th>
<th>50 μg. thyroxine</th>
<th>100 μg. thyroxine</th>
<th>Desiccated thyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory period (msec.)</td>
<td>9 47.3 ± 4.2</td>
<td>10 59.7 ± 3.6*</td>
<td>8 75.0 ± 6.3*</td>
<td>10 62.8 ± 3.6*</td>
</tr>
<tr>
<td>Rheobase (μA.)</td>
<td>10 88.6 ±14.9</td>
<td>9 94.4 ±25.9*</td>
<td>8 123.3 ±16.8</td>
<td>8 99.9 ±24.2</td>
</tr>
<tr>
<td>Chronaxie (msec.)</td>
<td>10 1.68± 0.50</td>
<td>8 1.46± 0.46</td>
<td>8 0.93± 0.37</td>
<td>8 1.33± 0.41</td>
</tr>
</tbody>
</table>

*Significantly different from control group (p = 0.05 or less).

strips of similarly treated animals of series A, averaging about 42 per cent of control values for left ventricular and about 60 per cent for right ventricular muscle.

DISCUSSION

The extensive studies that have been carried out on the cardiovascular effects of hyperthyroidism have supplied little or no information on the functional status of the cardiac muscle itself. While clinical and experimental observations clearly indicate the occurrence of arrhythmia, tachycardia, and increased stroke output and stroke work, the presence of varying hemodynamic factors, nervous control, and the coincident action of other hormones prevent interpretation of these findings in terms of basic myocardial properties. The data reported here indicate the modification of certain of these properties as determined in vitro as a result of increased activity of thyroid hormone. Of the most striking of these effects is the reduction in tension production observed in hyperthyroid muscle bundles.

Comparable studies on mammalian myocardial contractility are scant. Hirvonen and Lybeck found that the force of contraction of isolated atria from rats receiving thyroxine was significantly less than that of controls at temperatures ranging from 25 to 41°. At a temperature of 37°, the decrease of 37.5 per cent in contractile force noted by these workers is quite comparable to the decrease in maximal developed tension in our left ventricular thyroid-treated groups, although less than the 60 per cent reduction in right ventricular strips. Other direct studies on hyperthyroid cardiac muscle have not been found, but the defect in tension production noted seems entirely compatible with the depletion of glycogen and phosphocreatine observed by Shelley, Code and Visscher in hyperthyroid rat hearts, and with reported effects of thyroxine on function and structure of mitochondria. The reduction in in vitro tension production here reported is in some contrast with the in vivo studies of Brewster, Isaacs, Osgood and King. When ventricular stroke work per unit of filling pressure was taken as an index of ventricular contractility in thyroid-fed dogs, these workers noted increased contractility during control periods. Follow-
ing induction of epidural procaine block designed to eliminate autonomic influences, indexes of contractility were similar in euthyroid-fed and thyroid-fed animals. It was accordingly concluded that thyroid hormones per se have no observable effect on ventricular dynamics in the absence of sympathetic catechol amines. Since in the experiments of Brewster et al. the heart was neither devoid of neural control nor hemodynamically isolated, these findings cannot be taken to bear directly on the question of direct hormonal action, although they clearly demonstrate the importance of extrathyroidal factors in the in vivo situation. The suggestion of Raab2 and others, that effects demonstrated in isolated hyperthyroid tissues may be due to the presence of endogenously-produced epinephrine or norepinephrine, does not lend itself readily to interpretation of the reduced contractility here described, particularly in the light of the well known sensitivity of hyperthyroid tissues to the action of these amines. It is conceivable, however, that the results obtained are the end result of a series of in vivo interactions in which a basic biochemical defect due to thyroxine excess is accentuated by the actions of other neurohormonal factors, with resultant disturbance of the metabolic and perhaps structural elements of contraction.

The results lend support to earlier suggestions that functional divisions of the heart respond disproportionately to the action of thyroid hormone.19 Goh and Dallam20 found right ventricular slices to be more sensitive than left to the calorigenic action of thyroxine, a finding quite compatible with the greater depression of contractility noted in right ventricular strips in our studies. The lengthening of refractoriness in left, but not in right, ventricular muscle is, however, not readily explained. If the metabolic defect in hyperthyroidism does in fact involve utilization of oxidative energy it is not surprising that that phase of membrane activity most dependent on active metabolism should be involved. The considerations outlined above would, however, lead one to expect that the relative sensitivity of the ventricles would be the opposite of that found. The increase in the left ventricular refractory period is in agreement with the lengthening of the Q-T interval reported by Rasmussen in his hyperthyroid dogs.1

**Summary**

Electric and mechanical properties of right and left ventricular muscle of the hyperthyroid rat have been studied in vitro. Excita-
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bility of hyperthyroid right or left ventricle is not modified. Refractory periods are lengthened in left ventricular muscle bundles. Passive length-tension curves are not abnormal, but developed tension is significantly reduced in hyperthyroid myocardium. Reduction of contractility is more marked in right than in left ventricular bundles.

It is concluded that thyroid hormones produce direct effects on myocardial functions not mediated by other hormones or neurohormones.

SUMMARY IN INTERLINGUA

Esseva studiate in vitro le proprietates electric e mechanica de musculo dextero- e sinistro-ventricular de rattos hyperthyroide. Le excitabilitate dextero- o sinistro-ventricular non es modificate in le stato hyperthyroide. Le periodos refractori es prolongate in le fasces de musculo sinistro-ventricular. Le curvas de longor-tension in stato passive non es anormal, sed le disveloppate tension es significativamente reducite in le myocardio hyperthyroide. Le reduction del contractilitate es plus marcate in fasces dextero-ventricular que in fasces sinistro-ventricular.

Es concludite que hormones thyroide produce efectos directe in le functiones myocardial, non mediate per altere hormones o per neurohormones.

REFERENCES

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