Myocardial Contractile Response to Norepinephrine, Isoproterenol, and Calcium Chloride in Hyperthyroid Guinea Pigs

By M. Jay Goodkind, M.D.

ABSTRACT
Myocardial contractility, measured as the maximum left ventricular systolic pressure response to aortic constriction, is greater than normal in the hyperthyroid guinea pig. The effect of inotropic agents on this response was determined in anesthetized, open-chest, euthyroid, and hyperthyroid guinea pigs. Norepinephrine and isoproterenol in single doses, 1 μg/kg, and isoproterenol infused intravenously, 1, 4 and 10 μg/kg/min, caused a smaller increase in myocardial contractile response to aortic constriction in hyperthyroid than in euthyroid animals. Hyperthyroid guinea pigs also responded to an infusion of calcium chloride, 11 mg/kg/min, with an increase in maximum systolic pressure which was less than normal. With each drug the maximum systolic pressure level attained during aortic constriction was greater in the euthyroid than in the hyperthyroid animals. Cardiac pacing of euthyroid guinea pigs at 430 beats/min, a rate similar to the spontaneous rate of the hyperthyroid guinea pig, did not alter the inotropic response to infused calcium, though single injections and intravenous infusions of isoproterenol had less of an effect than in the spontaneously beating normal heart. These results suggest that the increased myocardial contractility of the hyperthyroid guinea pig may have reached a near maximum level. As a result, the added inotropic effects of isoproterenol and calcium in these animals are less than in normal controls.

ADDITIONAL KEY WORDS active inotropic agents tachycardia aortic constriction maximal systolic pressure cardiac pacing thyroxine pressure work afterload

Although early reports suggested that the cardiovascular system of thyroid-stimulated animals was hypersensitive to catecholamines, recent studies have failed to support this belief (1-7). Indeed, epinephrine and norepinephrine may produce less of an increase of myocardial contractile force in the hyperthyroid animal both in vitro and in vivo than in normal animals (1, 4, 6, 7). Studies from this laboratory using the maximum left ventricular systolic pressure response to aortic constriction in guinea pigs as a measure of myocardial contractility have shown that this response in the hyperthyroid animal is greater than...
normal (8). In addition to the stimulus of aortic constriction to ventricular contractility, the present study examines the effect of a second inotropic stimulus, either sympathomimetic drugs or calcium chloride, and the role of tachycardia in the left ventricular response to the two simultaneously administered stimuli in order to evaluate the mechanism for the increased in-vivo myocardial contractility of the hyperthyroid animal.

Methods

Adult male guinea pigs of the Hartley strain (400 to 1000 g) were fed a standard Purina guinea pig feed and water ad libitum. The hyperthyroid state was produced by the daily injection of sodium L-thyroxine, 100 µg/animal/day ip, for 7 to 10 days in randomly selected animals. On this regimen animals lost an average of 78.9 g of body weight and developed tachycardia. A comparison of the hemodynamic data for groups of euthyroid and hyperthyroid guinea pigs and euthyroid guinea pigs electrically paced at a heart rate of 430 beats/min has been previously published (8). It indicated that thyroxine treatment produces a significant increase in cardiac function over that of the normal animals and that of normal animals paced at a rapid ventricular rate.

The animal preparation and technique for measuring pressures in these studies have been described previously (8). In brief, a loop around the ascending aorta permitted repeated gradual constriction of that vessel. Left ventricular systolic and diastolic pressures were recorded from a needle cannula in the ventricular apex before and during constriction of the aorta. The maximum rate of rise of left ventricular systolic pressure (dP/dt max) was obtained with an R-C circuit. Body temperature was kept constant with a heating pad and thermistor control unit. Hearts of normal animals were paced at an increased rate with supramaximal square-wave stimuli of 2-msec duration, 8 v, and a frequency of 430 beats/min delivered by an American Electronics Laboratories 104A stimulator via bipolar needle electrodes applied to the right ventricular apex.

Myocardial contractility was estimated in these studies as the maximum left ventricular systolic pressure achieved during gradual constriction of the ascending aorta.1 The significance of this measurement of ventricular function as a measure of ventricular contractility in vivo has been discussed previously (8, 9). Determinations of ventricular systolic and diastolic pressures and maximum systolic pressure were made before, during, and after administration of each drug. After single injections of a drug, measurements were made at a time previously shown to coincide with the maximum cardiovascular response to that drug. A separate group of euthyroid and hyperthyroid guinea pigs was used to study each of the drugs examined. Sympathomimetic drugs (norepinephrine, phenylephrine, and isoproterenol) were administered as a bolus via the left ventricular cannula in concentrations which resulted in the delivery of 1 ml of fluid/kg body weight. Isoproterenol, 1, 4, and 10 µg/kg/min, was infused into the external jugular vein for a period of 3 minutes with a syringe-type pump (Harvard Apparatus Co.). Ventricular pressures were measured before the start and between the second and third minutes of the infusion. At least 5 minutes were allowed to elapse after an injection or infusion so that the effect of the drug would be dissipated before beginning a new control period. Doses of these drugs were calculated as the base of the compound.

Calcium chloride, 11 mg/kg/min, was infused into the external jugular vein for 3 minutes, resulting in an increase in whole blood calcium (determined with a Perkin-Elmer Model 303 Atomic Absorption Spectrophotometer) of approximately 30% in a group of euthyroid and hyperthyroid guinea pigs. No difference was observed between the levels of calcium obtained in the two groups of animals. The experimental design used to examine the effect of calcium on left ventricular contractility consisted of measurements of ventricular pressures and maximum systolic pressure during: (1) a control period, (2) an infusion of saline (0.9%) at 1 ml/kg/min, (3) a control period, and (4) an infusion of calcium chloride, 11 mg/kg/min, to give a delivery of the saline solution (0.9%) at 1 ml/kg/min. The effect of calcium infusion was determined by subtracting the effect of saline (period 2 minus period 1) from the effect of calcium (period 4 minus period 3). Although in the final analysis saline infusion alone had no consistent effect on the pressures, commitment to the experimental design required the analysis to include these results in the calculations. Results are, therefore, discussed below as this net change in hemodynamic function.

Data were evaluated by one of two techniques. In early studies, significance was examined by Student's t-test for unpaired data, and in those instances where animals served as their own controls, the t-test for paired data was utilized.
INOTROPIC RESPONSE IN HYPERTHYROIDISM

Results were considered significant if P was less than or equal to 0.05. Data from the animals given infusions of isoproterenol were evaluated by the Mann-Whitney U-test (10). Results were considered significant if alpha was less than or equal to 0.05. All data are expressed as mean values ± se unless indicated otherwise.

**Results**

**NOREPINEPHRINE**

Systolic pressure increased to a similar degree in euthyroid and hyperthyroid guinea pigs over a range of doses of norepinephrine (Fig. 1). Norepinephrine, 1 μg/kg, administered to euthyroid and hyperthyroid animals increased heart rate by the same absolute increment in both groups.

After injection of norepinephrine, the maximum systolic pressure in the euthyroid guinea pigs increased to an average of 171 ± 6.3 mm Hg. In the thyroxine-treated animals, maximum systolic pressure was not affected by norepinephrine (153 ± 4.0 mm Hg), and the difference between this pressure and the control period pressure was significantly less than that obtained from normal guinea pigs (Fig. 2) (P < 0.05). The positive inotropic effect of norepinephrine in euthyroid animals was associated with a decrease in end-diastolic pressure, but no change in end-diastolic pressure occurred in the hyperthyroid animals.

**ISOPROTERENOL**

Isoproterenol, 0.1 μg/kg, increased systolic pressure and dP/dt max to the same degree in the two groups of animals (Table 1). A larger dose, 1.0 μg/kg, produced a greater increase in systolic pressure and dP/dt max in euthyroid, but not in hyperthyroid animals. Heart rate in the hyperthyroid group, on the other hand, increased by the same absolute amount as in the normal controls with a range of doses of isoproterenol, 0.05 to 1.0 μg/kg, (data not shown).

Maximum systolic pressure increased in normal guinea pigs given isoproterenol (Table 1). Isoproterenol increased dP/dt max to the same degree in both groups. A larger dose, 1.0 μg/kg, produced a greater increase in dP/dt max in euthyroid, but not in hyperthyroid animals. Heart rate in the hyperthyroid group, on the other hand, increased by the same absolute amount as in the normal controls with a range of doses of isoproterenol, 0.05 to 1.0 μg/kg, (data not shown).

![Figure 1](http://circres.ahajournals.org/)

**FIGURE 1**

Systolic pressure (LVSP) response to norepinephrine (NE) in euthyroid (N = 7) and hyperthyroid (N = 11) guinea pigs. Each point represents the mean and the vertical bars indicate ± se.

![Figure 2](http://circres.ahajournals.org/)

**FIGURE 2**

Effect of norepinephrine, 1 μg/kg, and phenylephrine, 1 μg/kg, on maximum systolic pressure (LVSP max) and end-diastolic pressure (LVEDP) response to aortic constriction in euthyroid (E) and hyperthyroid (H) guinea pigs. Each column represents the mean difference from a control measurement, and the vertical bars ± se of the difference. The asterisks indicate a significant difference (P ≤ 0.05) from the control, and crosses indicate a significant difference (P ≤ 0.05) from the euthyroid animals response.
TABLE 1
Effect of Isoproterenol on Left Ventricular Function in Guinea Pigs

<table>
<thead>
<tr>
<th></th>
<th>Systolic pressure (mm Hg)</th>
<th>End-diastolic pressure (mm Hg)</th>
<th>dP/dt max (mm Hg/sec)</th>
<th>Heart rate (beats/min)</th>
<th>Maximum systolic pressure during aortic constriction (mm Hg)</th>
<th>Maximum end-diastolic pressure during aortic constriction (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1 μg/kg (N = 12)</td>
<td>1.0 μg/kg (N = 12)</td>
<td>0.1 μg/kg (N = 19)</td>
<td>1.0 μg/kg (N = 39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euthyroid</td>
<td>+7 ± 1.5</td>
<td>+18 ± 2.3*</td>
<td>+9 ± 2.1</td>
<td>+6 ± 2.0†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.3 ± 0.14</td>
<td>-0.3 ± 0.23</td>
<td>+0.1 ± 0.24</td>
<td>+0.3 ± 0.23‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+10 ± 6.8</td>
<td>+1805 ± 266.5*</td>
<td>+803 ± 176.9</td>
<td>+951 ± 204.2†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroid</td>
<td>+17 ± 3.1</td>
<td>+39 ± 3.7*</td>
<td>+4 ± 1.8†</td>
<td>+7 ± 1.5†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-5.2 ± 1.8†</td>
<td>-5.7 ± 1.05</td>
<td>-0.2 ± 0.42‡</td>
<td>-0.8 ± 0.49‡</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values are expressed as mean difference ± SE of the difference between the left ventricular response before and after administration of isoproterenol. Results significantly different from the response with the 0.1 μg/kg dose are indicated: *P < 0.001, ‡P < 0.01. Results significantly different from the response in euthyroid guinea pigs are indicated: †P < 0.001, †P < 0.05.

1) and the increase was greater with a dose of 1.0 μg/kg than with 0.1 μg/kg. In contrast, 0.1 μg/kg of isoproterenol did not alter the maximum systolic pressure response in hyperthyroid animals, and 1.0 μg/kg produced only a modest increase which was significantly less than the normal. As with norepinephrine, the maximum systolic pressure attained in euthyroid guinea pigs after 1 μg/kg of isoproterenol (184 ± 3.5 mm Hg) was higher than that in the hyperthyroid animals (159 ± 2.2 mm Hg) (P < 0.001). End-diastolic pressure decreased after isoproterenol in normal controls during aortic constriction, but did not change in the thyroxine-treated guinea pigs.

Intravenous infusion of three doses of isoproterenol, 1, 4, and 10 μg/kg/min, resulted in similar changes in systolic pressure, heart rate, and diastolic pressures in euthyroid and hyperthyroid animals. On the other hand, these infusions produced less than normal increments in maximal systolic pressure elevation in hyperthyroid guinea pigs (Table 2).

PHENYLEPHRINE
Following administration of phenylephrine, 1 μg/kg, systolic pressure increased to a similar degree in 7 normal (+6 ± 2.2 mm Hg) and 12 hyperthyroid (+8 ± 2.7 mm Hg) guinea pigs. End-diastolic pressure also increased slightly in the two groups. Heart rate did not change significantly. Myocardial response to aortic constriction (Fig. 2) did not change in euthyroid controls, but the maxi-

TABLE 2
Net Changes in Maximum Systolic Pressure of the Left Ventricle during Infusion of Isoproterenol in Euthyroid and Hyperthyroid Guinea Pigs

<table>
<thead>
<tr>
<th>Dose (μg/kg/min)</th>
<th>Euthyroid</th>
<th>Hyperthyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Net change (mm Hg)</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>59 ± 5.4</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>41 ± 19.7</td>
</tr>
<tr>
<td>10</td>
<td>7</td>
<td>40 ± 9.3</td>
</tr>
<tr>
<td>1 (paced, 430 beats/min)</td>
<td>6</td>
<td>33 ± 8.0†</td>
</tr>
</tbody>
</table>

All values are expressed as mean difference ± SE of the difference between the left ventricular response to aortic constriction before and after administration of isoproterenol. Footnotes indicate values significantly different from euthyroid controls: *P ≤ 0.001, †P ≤ 0.05, ‡P ≤ 0.01.
INOTROPIC RESPONSE IN HYPERTHYROIDISM

TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Euthyroid (N = 15)</th>
<th>Hyperthyroid (N = 8)</th>
<th>Euthyroid, paced (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic pressure</td>
<td>+12 ± 2.8</td>
<td>+10 ± 3.3</td>
<td>+9 ± 3.4</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic pressure</td>
<td>+0.3 ± 0.28</td>
<td>+0.2 ± 0.20</td>
<td>+0.4 ± 0.31</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dP/dt max</td>
<td>+653 ± 194.8</td>
<td>+762 ± 192.7</td>
<td>+711 ± 245.5</td>
</tr>
<tr>
<td>(mm Hg/sec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>+11 ± 4.7</td>
<td>+11 ± 7.6</td>
<td></td>
</tr>
<tr>
<td>(beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum systolic pressure during aortic constriction</td>
<td>+20 ± 2.9</td>
<td>+15 ± 1.5*</td>
<td>+32 ± 5.5†</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic pressure during aortic constriction</td>
<td>−3.0 ± 1.30</td>
<td>−2.9 ± 1.03</td>
<td>−1.0 ± 2.10</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values are expressed as mean difference ± sic of the difference between the left ventricular response to aortic constriction during calcium infusion and during saline infusion. * Significantly different from the response of euthyroid guinea pigs, P < 0.001. † Significantly different from the response of hyperthyroid guinea pigs, P < 0.001.

Euthyroid guinea pigs responded to a calcium infusion with an increase in systolic pressure and no change in end-diastolic pressure (Table 3). Similar results were observed in the thyroxine-treated animals and the changes in pressure were of the same magnitude as the normal responses. With elevation of blood calcium concentration, approximately the same rise in dP/dt max and heart rate occurred in both groups of animals.

Calcium had a greater positive inotropic effect in euthyroid than in hyperthyroid guinea pigs (Table 3). Aortic constriction during calcium infusion also resulted in a greater maximum systolic pressure in euthyroid guinea pigs (173 ± 4.6 mm Hg) than in hyperthyroid animals (152 ± 2.5 mm Hg) (P < 0.01).

EFFECT OF TACHYCARDIA ON THE RESPONSE TO INOTROPIC AGENTS

There were at least three stimuli to the myocardial contractile mechanism in the hyperthyroid guinea pigs described above: aortic constriction, an inotropic agent, and tachycardia. To evaluate tachycardia, the maximum systolic pressure decreased slightly in the hyperthyroid guinea pigs without a change in end-diastolic pressure.

CALCIUM

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Effect of isoproterenol, 1 µg/kg, given by injection, on maximum systolic pressure (LVSP max) and end-diastolic pressure (LVEDP) response to aortic constriction before, during, and after right ventricular pacing at 430 beats/min in euthyroid guinea pigs. Numbers in parentheses below the key indicate the heart rates for each period. Other symbols as in Figure 2.
response to inotropic compounds and aortic constriction was studied in euthyroid animals whose hearts were paced at 430 beats/min, a rate similar to that observed in the hyperthyroid guinea pigs.

Isoproterenol, 1 \( \mu g/kg \), was administered as a bolus injection to seven euthyroid guinea pigs before, during and, in four instances, after electrical pacing of the right ventricle. Left ventricular pressure response to aortic constriction was measured during each of the periods, before isoproterenol and at the peak isoproterenol effect. Electrical pacing of the heart at 430 beats/min in another group of normal animals did not alter systolic and end-diastolic pressures, \( dP/dt \) max, or maximum systolic and associated end-diastolic pressure (8). Isoproterenol produced less of an increment in maximum systolic pressure when the heart was paced at 430 beats/min than when a spontaneous heart rate obtained (Fig. 3). Upon cessation of pacing, each of the four animals studied showed an increase in their response to isoproterenol (\( P < 0.05 \)). The average increase in maximum systolic pressure during the isoproterenol effect in the recovery period, however, was less than the control response to isoproterenol prior to pacing. End-diastolic pressure during aortic constriction in the recovery studies was decreased after isoproterenol, also indicating an increased response to the positive inotropic effect of the drug.

Intravenous infusion of isoproterenol, 1 \( \mu g/kg/min \), given to a group of normal guinea pigs whose right ventricles were stimulated at a rapid rate, produced changes similar to those observed with a bolus injection of the drug. Hearts beating spontaneously at an average rate of 332 beats/min (during isoproterenol) developed a greater maximum systolic pressure response to aortic constriction than did a group paced at 430 beats/min (Table 2). The maximum systolic pressure response of normal animals to isoproterenol infusion, 1 \( \mu g/kg/min \), during ventricular pacing was similar to that of hyperthyroid guinea pigs given the same dose of isoproterenol (Table 2).

Calcium chloride infusion had a different effect on paced normal myocardium (Table 3). Tachycardia did not alter the response to calcium during aortic constriction. End-diastolic pressure at the maximum systolic pressure response was not reduced during the period of elevated blood calcium. Other hemodynamic effects of calcium infusion were not affected by tachycardia.

**Discussion**

The positive inotropic effects of norepinephrine and isoproterenol are decreased in the hyperthyroid guinea pig. Though treatment with thyroxine alone increases the left ventricular contractile response to aortic constriction in hyperthyroid animals above that of normal controls (8), the increment in maximum systolic pressure observed in response to the two beta-receptor stimulating drugs is less than normal. Similar findings have been reported with measurements of ventricular contractile force in vivo, and with in-vitro studies of atrial muscle, papillary muscle and ventricular muscle strips (1, 4). Results of Brewster et al. (11) which indicated that an increased sensitivity to catecholamines existed in hyperthyroid dogs are not supported by results of either the present study or those of other investigators (1, 4). A decreased left ventricular contractile response to calcium suggests that the effect of thyroid hormone on the myocardial contractile apparatus is not limited to adrenergic receptors. The decreased inotropic response to cardiac glycosides in hyperthyroid animals (6, 12, 13) also supports this concept. Thyroid hormone probably increases myocardial contractile ability by a direct effect. For example, thyroxine causes an increase in the myocardial myosin ATPase activity of the guinea pig (14), a change which in skeletal muscle has been correlated with an increase in contractile ability (15).

In addition to a direct effect on the contractile apparatus, thyroxine may alter its response to inotropic stimuli by other less direct effects. Tachycardia, inherent in the hyperthyroid state, affects the myocardial response to inotropic agents. A rapid heart
rate reduces the diastolic interval, and with severe tachycardia coronary blood flow is decreased. In the case of drugs administered as a single bolus, less of the agent would reach the myocardium during tachycardia. To obviate the bolus effect, sustained elevation of isoproterenol and calcium blood levels were achieved by intravenous infusions of the drugs. Like the single injection, however, this too was associated with a smaller positive inotropic effect of the drugs in the hyperthyroid animal.

Hyperthyroidism is associated in vitro with an altered force-frequency relationship in guinea pig atria (7) and papillary muscles (14). Thus, tachycardia places the heart of the hyperthyroid animal on a different portion of the force-frequency curve from the normal. If there is a maximal level of contractile response in cardiac muscle for any given set of circumstances (16), a muscle stimulated by a positive inotropic agent can only increase its contractile tension to this maximum. As a result, myocardium starting at a high level of contractile tension, such as that of the hyperthyroid animal, but having the same maximum as a normal, can only develop a smaller increment in tension than normal if both are stimulated maximally. In the present study, the absolute level of pressure attained by thyroid-stimulated animals was lower than normal under maximal stimulation with aortic constriction plus either calcium or catecholamines. This would suggest that the myocardium of the hyperthyroid animal was on the descending portion of an in-vivo force-frequency curve. The decreased response to isoproterenol and the normal response to calcium infusion of paced hearts could be due to the increased sensitivity of the catecholamine response to such factors as hypoxia or acidosis, both of which may have been present after an episode of electrical pacing. It also suggests that tachycardia per se is not the only factor playing a role in the decreased response of the hyperthyroid animal’s heart to inotropic stimuli.

In contrast to the difference in inotropic effects, the increase in heart rate following administration of catecholamines or calcium was of equal magnitude in both hyperthyroid and euthyroid guinea pigs. Several investigators have noted similar results with catecholamines in other species (1-3, 5, 17). Aoki et al. (17) studied male volunteers before, during, and after treatment with triiodothyronine. They found the same increase in heart rate following the administration of epinephrine and norepinephrine in both normal and hypermetabolic states. However, Van der Schoot and Moran (4) described a decreased chronotropic response to epinephrine and norepinephrine in the hyperthyroid dog. In the latter study anesthesia or a species difference may partly explain the difference in results of the two reports. The difference between the inotropic and chronotropic responses in hyperthyroidism suggests that either the receptors for the two responses differ or they have different sensitivities to the stimuli examined in these studies. Cairoli and Crout (18) suggest that, though the tachycardia of hyperthyroidism responds to various drugs in a normal fashion, the initial set of the intrinsic cardiac pacemaker is higher than normal as a result of the direct action of thyroxine on the sinoatrial node. Similarly, current knowledge indicates that thyroid hormone also alters the contractile response to external agents by a direct effect on the contractile mechanism.

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