Effect of the Thyroid State on Myocardial
Contractility and Ventricular Ejection
Rate in Man

By Morteza Amidi, M.D., Donald F. Leon, M.D., William J. deGroot, M.D.,
Frank W. Kroetz, M.D., and James J. Leonard, M.D.

SUMMARY
Although the circulatory changes in various thyroid states are well
recognized, the alterations of myocardial contractility of hypothyroidism and hyperthyroidism have
remained controversial. The changes in the length of the ejection time (ET) and
isovolumic contraction time (ICT) are used as indicative of alterations in inotropic
state of the myocardium. Isovolumic contraction time, ejection time, and pre-ejection
period were measured externally in 10 normal, 13 hyperthyroid, and five hypothyroid
subjects. Cardiac outputs, mean rate of left ventricular ejection index, and predicted
ejection times were calculated. More shortening of ICT and ET in hyperthyroid and
more prolongation of these intervals in hypothyroid subjects than could be attributed
to other factors were interpreted as indicative of increased and decreased myocardial
contractility, respectively. Catecholamine depletion in hyperthyroid subjects with ade-
quate administration of intramuscular reserpine induced no changes in cardiac output
and oxygen consumption and caused no alteration in different phases of ventricular
systole; consequently it had no effect on enhancement of hyperthyroid myocardial
contractility.

Additional Indexing Words:
Phonocardiography  Electro-mechanical systole  Central venous pressure
A-V difference

HE HEMODYNAMIC alterations which
occur in various thyroid states are well
recognized. The increase in oxygen consump-
tion, heart rate, cardiac output, and ventricu-
lar systolic ejection rate in hyperthyroidism
and the decrease in these parameters in hypo-
thyroidism have been documented in the past.1-4 The mechanism or mechanisms re-
sponsible for these changes have been the
subject of numerous investigations.

The similarity between hyperthyroid symp-
tonatolgy and that of sympathetic system
stimulation has been suggestive of some
thyroid-sympathetic interrelationship.5 Al-
though the chronotropic effect of thyroid
hormone on the myocardium was clearly
demonstrated in 1931 by Yater and Marko-
witz,6,7 its possible inotropic effect has re-
mained controversial.

The effect of various levels of thyroid ac-
tivity on the heart may be postulated to be
due to one or combinations of the following
mechanisms: first of all, the participation of
the heart in increased or decreased general
by guest on April 24, 2017 http://circ.ahajournals.org/ Downloaded from

body metabolism; secondly, the servo adjustment of the myocardium to fulfill the general body requirements of blood flow and oxygen consumption; and thirdly, the direct or indirect effect of the thyroid hormone on the cardiac muscle regardless of any other influences.

Buccino and his co-workers have recently shown that the thyroid state exerts an inotropic effect on the isolated papillary muscle of hyperthyroid and hypothyroid cats. The accelerated rate of muscular shortening and abbreviation of time to peak tension in hyperthyroid and the opposite situation in hypothyroid muscle were demonstrated.

It was the purpose of this study to evaluate the effect of various thyroid states on myocardial contractility in intact man using reliable, yet simple, laboratory techniques. Changes in myocardial contractility in various thyroid states were estimated from changes in the different phases of ventricular systole while all other parameters involved in their duration were taken into consideration. The effect of adequate reserpine therapy on these changes was used to investigate possible thyroid-catecholamine interaction.

### Methods

Ten healthy volunteers, 13 hyperthyroid, and five hypothyroid subjects were studied. All subjects were hospitalized and introduced to the laboratory environment 2 to 3 days prior to study. Laboratory confirmation of the clinical diagnosis was obtained (tables 1 and 2). Subjects with any associated problems were eliminated from the study, and heart failure, coronary artery disease, high output state of other causes, hypertension, cardiomegaly, and pericardial effusion were specifically excluded in the subjects selected. All subjects were studied prior to any therapy.

Oxygen consumption was measured in the basal state prior to the study by micro-Scholander analysis of duplicate samples of expired air collected

### Table 1

**Characteristics of Hyperthyroid Subjects**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>PBI (ug%)</th>
<th>24-hour 131I uptake (%)</th>
<th>Hemoglobin (g%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.R.</td>
<td>23</td>
<td>F</td>
<td>10.7</td>
<td>77</td>
<td>10.4</td>
</tr>
<tr>
<td>D.C.</td>
<td>29</td>
<td>F</td>
<td>13.5</td>
<td>46</td>
<td>11.5</td>
</tr>
<tr>
<td>H.I.</td>
<td>26</td>
<td>M</td>
<td>12.6</td>
<td>64</td>
<td>14.7</td>
</tr>
<tr>
<td>J.H.</td>
<td>16</td>
<td>F</td>
<td>11.2</td>
<td>72</td>
<td>11.5</td>
</tr>
<tr>
<td>C.L.</td>
<td>36</td>
<td>M</td>
<td>11.3</td>
<td>—</td>
<td>11.5</td>
</tr>
<tr>
<td>S.V.</td>
<td>42</td>
<td>M</td>
<td>12.8</td>
<td>84</td>
<td>13</td>
</tr>
<tr>
<td>A.N.</td>
<td>29</td>
<td>F</td>
<td>—</td>
<td>75</td>
<td>12.2</td>
</tr>
<tr>
<td>A.V.</td>
<td>34</td>
<td>F</td>
<td>9.7</td>
<td>78</td>
<td>12.1</td>
</tr>
<tr>
<td>N.S.</td>
<td>27</td>
<td>M</td>
<td>9.2</td>
<td>68</td>
<td>13</td>
</tr>
<tr>
<td>J.F.</td>
<td>20</td>
<td>M</td>
<td>15.9</td>
<td>65</td>
<td>14.8</td>
</tr>
<tr>
<td>R.J.</td>
<td>30</td>
<td>F</td>
<td>11.6</td>
<td>59</td>
<td>12.6</td>
</tr>
<tr>
<td>B.W.</td>
<td>48</td>
<td>F</td>
<td>18</td>
<td>68</td>
<td>12.1</td>
</tr>
<tr>
<td>J.G.</td>
<td>35</td>
<td>M</td>
<td>19.6</td>
<td>65</td>
<td>14.5</td>
</tr>
<tr>
<td>Average</td>
<td>30</td>
<td></td>
<td>13</td>
<td>68</td>
<td>12.6</td>
</tr>
</tbody>
</table>

### Table 2

**Characteristics of Hypothyroid Subjects**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>PBI (ug%)</th>
<th>24-hour 131I uptake (%)</th>
<th>Hemoglobin (g%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.B.</td>
<td>53</td>
<td>F</td>
<td>2.6</td>
<td>4.7</td>
<td>13</td>
</tr>
<tr>
<td>M.W.</td>
<td>60</td>
<td>F</td>
<td>1.4</td>
<td>0.3</td>
<td>11.5</td>
</tr>
<tr>
<td>M.P.</td>
<td>49</td>
<td>F</td>
<td>1.9</td>
<td>0.5</td>
<td>11</td>
</tr>
<tr>
<td>I.B.</td>
<td>64</td>
<td>F</td>
<td>2.2</td>
<td>3.9</td>
<td>13</td>
</tr>
<tr>
<td>U.P.</td>
<td>56</td>
<td>F</td>
<td>2.5</td>
<td>2.4</td>
<td>12</td>
</tr>
<tr>
<td>Average</td>
<td>56</td>
<td></td>
<td>2.1</td>
<td>2.3</td>
<td>12</td>
</tr>
</tbody>
</table>

Circulation, Volume XXXVIII, August 1968
over 5 minutes in Douglas bags. With the patient in the recumbent position, the brachial artery was cannulated percutaneously with a 15-cm polyethylene catheter (PE no. 160, I.D., 0.045 inch) and a 90-cm polyethylene catheter (PE no. 50, I.D., 0.023 inch) was placed percutaneously into an antecubital vein and advanced into the thorax until central venous pressure with intrathoracic respiratory variation could be recorded. The catheters were connected to P 23 G Statham strain-gauge transducers* leveled 5 cm below the sternal angle. Brachial artery and central venous pressures were recorded with a polybeam recorder.† Cardiac output was measured from duplicate indicator-dilution curves inscribed from continuous brachial artery sampling through the Gilford densitometer‡ and injection of indocyanine green through the central venous catheter. Immediately before or after the measurement of cardiac output, a simultaneous recording of the electrocardiogram, the chest wall phonocardiogram, and the indirect carotid pulse contour was made. The phonocardiogram was recorded by placing contact microphones§ at the apex and in the third intercostal space at the left sternal border so that the first heart sound (S₁) and aortic closure sound (A₂) could be clearly identified. The indirect carotid pulse contour was obtained from pulse displacement

*Statham Instrument, Inc., Hato Rey, Puerto Rico.
†Electronics for Medicine, DR8 or DR12, White Plains, New York.
‡Gilford Instruments Laboratory, Oberlin, Ohio.
§Pulse sound microphone, Electronics for Medicine, White Plains, New York.

Figure 1

Simultaneous recording of phonocardiogram, carotid pulse tracing, and electrocardiogram illustrating the measurement of ejection time, duration of systole (S₁-A₂), and electro-mechanical systole (Q-A₂) by 0.02 sec time markings.
Figure 2

The actual left ventricular ejection time of 10 normal subjects measured from carotid pulse tracing is shown in the first column and predicted ejection time calculated by regression formula is shown in the second column. \( P < 0.50 \geq 0.40 \).

of a strain-gauge.* Recordings were made at paper speeds of 100 to 200 mm/sec, with time markers of 0.02 sec (fig. 1). The duration of systole (S1-A2) was measured from the first major vibration of S1 to the first major vibration of second heart sound A2. The left ventricular ejection time (ET) was measured from the beginning of the carotid upstroke to the trough of the incisura. The external isovolumic contraction time was calculated by subtraction of ET from the duration of systole (S1 to A2). The pre-injection period (PEP) was calculated by subtraction of ET from the duration of total electro-mechanical systole (Q to A2).

In each subject 10 consecutive, well-inscribed complexes were measured and the average was recorded to the nearest 0.002 sec.

In each subject the predicted ejection time (PET) with respect to stroke volume (SV) and heart rate (HR) was calculated by using the regression formula reported by Weissler and co-workers:9

\[ \text{PET} = 0.286 + 0.0011 (\text{SV} - 82) - 0.0009 (\text{HR} - 73). \]

This formula was in complete agreement with our findings since the actual ejection time of the 10 normal subjects was statistically equal to

---

*Statham Instruments, Inc., Hato Rey, Puerto Rico.
their predicted ejection time calculated by this formula (fig. 2).

The actual mean rate of left ventricular ejection index (MRLVEI) and the predicted mean rate of left ventricular ejection index (PMLVEI) were calculated by dividing the stroke volume index (SVI) by ET and predicted ET, respectively.

The study was repeated in six of the hyperthyroid subjects after catecholamine depletion by the intramuscular administration of 5 to 20 mg of reserpine daily for 3 to 5 days. Bradycardia, somnolence, decreased tremor, and perspiration were observed in these subjects. Treatment with reserpine was continued until sympathetic blockade by abolition of the post-Valsalva overshoot of the blood pressure was assured.10 11

The data were statistically analyzed by the group-means method.12

**Results**

The results of hemodynamic measurements are shown in tables 3 and 4. As can be seen, the increased cardiac output and oxygen consumption in hyperthyroidism were not altered by adequate reserpine therapy. The increase in stroke volume after reserpine therapy was due to bradycardia. The stroke volume index of hyperthyroid subjects, 61 ± 6 ml/m², was

![Figure 3](image_url)

*The actual ejection time (●) and predicted ejection time (○) of five hypothyroid subjects are plotted against stroke volume index. Broken lines represent time difference between actual and predicted ejection times.*
The actual ejection time (●) and predicted ejection time (○) of 13 hyperthyroid subjects are plotted against stroke volume index. Broken lines represent time difference between actual and predicted ejection times.

The average ejection time of six hyperthyroid subjects before and after reserpine therapy is shown in dotted columns and their predicted ejection times are demonstrated in hatched columns.

significantly higher than normal, 48 ± 4 ml/m² (P < 0.001).

Although the actual ejection time of hypothyroid subjects (296 ± 22 msec), was statistically equal to that of normal subjects (305 ± 21; P > 0.40), when the effects of low stroke volume and slow heart rate were taken into consideration, it was obvious that hypothyroid subjects had a significantly long-

The converse was noted in hyperthyroid subjects (fig. 4), in whom the actual ejection time was significantly shorter, 222 ± 12 msec, than the predicted ejection time (258 ± 21; P < 0.001).

In hyperthyroid subjects, reserpine induced bradycardia and the resultant increased stroke volume caused the actual ejection time to increase from 225 ± 8 msec to 237 ± 12 msec. However, the relationship between actual ejection time and predicted ejection time did not change with administration of reserpine, and the actual ejection time (237 ± 12 msec) remained significantly shorter than the predicted ejection time (290 ± 12 msec; P < 0.001; fig. 5).

The actual mean rate of left ventricular ejection index (MRLVEI) in hyperthyroid subjects was significantly faster than would be predicted (278 ± 38 ml/syst. sec vs 237 ± 19; P < 0.001) and the inverse was noted in
hypothyroid subjects in whom the actual MRLVEI was slower than the predicted rate (100 ± 17 ml/syst. sec vs 122 ± 13; P < 0.005; fig. 6). The MRLVEI in hyperthyroid subjects was expectedly increased after reserpine therapy because the increase in stroke volume index due to bradycardia was proportionally more than the prolongation of ejection time.

The isovolumic contraction time and the pre-ejection period of hypothyroid subjects were significantly longer and those of hyperthyroid subjects and reserpine-treated hyperthyroid subjects were significantly shorter than those of normal subjects (figs. 7 and 8).

The central venous pressure was normal in hyperthyroid subjects (4 mm Hg) and in hypothyroid subjects (3 mm Hg).

**Discussion**

The reduction of cardiac output and of oxygen consumption in hypothyroidism which was observed in this study are in accord with the results of previous studies. Likewise, the augmentation of these parameters in hyperthyroidism irrespective of catecholamine stores has been documented in other investigations.\(^\text{18-17}\)

In distinction to the studies of isolated muscle preparations, the evaluation of myocardial contractility in the intact subject in various thyroid states is made difficult by the simultaneous presence of multiple changing hemodynamic influences. The resultant combination of effects is so complex, that even after left ventricular catheterization, changes in cardiac performance related to Frank-Starling effect and ventricular contractility cannot be differentiated.\(^\text{18}\)

Changes in the intrinsic contractile state of myocardium are known to be reflected in the duration of the various phases of ventricular systole. These changes could not be defined accurately unless all other influences on these intervals are critically evaluated. In view of these considerations, shortening of the ejection time and isovolumic contraction time should reflect increased velocity of shortening and diminished time to peak tension in the heart, an end-result indicating increased myocardial contractility.\(^\text{19}\) Other inotropic interventions like stimulation of the cardiac sympathetic nerve fibers and digitalization also shorten isovolumic contraction time, ejection time, and total systole by increasing myocardial contractility.\(^\text{20, 21}\)

The isovolumic contraction time and the ejection time are not significantly influenced by aging. Harrison and co-workers\(^\text{22}\) showed that the isovolumic contraction time and the ejection time of 65 healthy persons from 9 to 97 years of age remained essentially constant with increasing age. Thus, the age difference
among the studied groups would not be an important factor in comparative evaluation of data obtained in this study.

**Changes in Ejection Time**

Ventricular ejection time is dependent on heart rate, stroke volume, mean arterial pressure, and ventricular contractility. There is an inverse relationship between heart rate and ejection time and a direct and independent relationship between stroke volume and ejection time. The changes in ejection time, due to variations in heart rate and stroke volume, have been evaluated by calculation of the predicted ejection time.

The average difference in mean arterial pressure between normal and hypothyroid subjects was 12 mm Hg and between normal and hyperthyroid subjects was 9 mm Hg. Wallace and associates and recently Shaver and co-workers have shown that large changes in mean arterial pressure are required to induce small changes in the duration of ejection. Thus, these differences in mean arterial pressure could not have induced significant alterations in the duration of the ejection time.

In view of these considerations, the inotropic state of the left ventricle is the only remaining determinant which could be held responsible for changes in ejection time. Therefore, the abbreviation of ejection time in hyperthyroidism and its prolongation in hypothyroidism, both of which were more than could be predicted, are indicative of increased and decreased myocardial contractility, respectively. Reserpine-treated hyperthyroid subjects maintained their shortened ejection times relative to predicted ejection times, thereby indicating that the increase in myocardial contractility in hyperthyroidism is not dependent on catecholamine stores. Catecholamine depletion with reserpine in six hyperthyroid subjects seems certain since the dosage used was remarkably more than has been proven by Chidsey and co-workers to cause catecholamine depletion in human left atrial appendage.

**Changes in Mean Rate of Ejection Index**

Increased mean rate of left ventricular ejection index in hyperthyroidism relative to predicted value (278 ± 39 ml/sec vs 234 ± 19; \( P < 0.001 \)) and the opposite situation in hypothyroidism (100 ± 17 ml/sec vs 122 ± 13; \( P < 0.005 \)) reflect the changes in ejection time and stroke volume index which are discussed in detail.

**Isovolumic Contraction Time**

Isovolumic contraction time is dependent on heart rate, stroke volume, ventricular end-diastolic volume, aortic diastolic pressure, and ventricular contractility. Previous work from this laboratory has demonstrated that externally and internally measured isovolumic contraction time correlate perfectly.

---

**Table 5**

<table>
<thead>
<tr>
<th>Hyperthyroid</th>
<th>Euthyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>SV (ml/beat)</td>
</tr>
<tr>
<td>H.I.</td>
<td>119</td>
</tr>
<tr>
<td>D.C.</td>
<td>78</td>
</tr>
<tr>
<td>J.H.</td>
<td>100</td>
</tr>
<tr>
<td>C.L.</td>
<td>105</td>
</tr>
<tr>
<td>S.V.</td>
<td>110</td>
</tr>
<tr>
<td>A.N.</td>
<td>73</td>
</tr>
<tr>
<td>A.V.</td>
<td>99</td>
</tr>
<tr>
<td>N.S.</td>
<td>109</td>
</tr>
<tr>
<td>R.J.</td>
<td>93</td>
</tr>
<tr>
<td>B.W.</td>
<td>91</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>98</strong></td>
</tr>
</tbody>
</table>

*Circulation, Volume XXXVIII, August 1968*
Increasing heart rates enhance myocardial contractility by the Treppe mechanism, but within physiological ranges of heart rate, this mechanism does not significantly affect isovolumic contraction time. This was documented in a study reported by Goldstein and co-workers in which the increase in heart rate due to atropine from an average of 65 beats/min to 111 beats/min in five subjects caused the isovolumic contraction time to decrease from an average of 52 msec to 45 msec (P > 0.50).

Isovolumic contraction time is shortened by an increase in stroke volume. In order to compare the isovolumic contraction time of normal and hyperthyroid subjects, 10 hyperthyroid subjects were selected whose stroke volumes were comparable to those of the 10 normal control subjects (table 5). It was demonstrated that for any given stroke volume the isovolumic contraction time of the hyperthyroid subjects (average, 18 msec) was significantly shorter than that of the matched normal volunteers (average, 46 msec). Since changes in heart rate do not alter the isovolumic contraction time significantly, the difference in isovolumic contraction time between hyperthyroid subjects and normal volunteers, matched for stroke volume, should be attributed to other factors.

Since the heart size was within normal limits in all groups of subjects and there was no clinical evidence of heart failure, it is unlikely that a possible existence of a difference in end-diastolic volume of sufficient magnitude to affect isovolumic contraction time could have been present.

The difference in the arterial diastolic pressure of normal volunteers from that of hyperthyroid and hypothyroid subjects was in the range of 3 to 4 mm Hg, and these pressures were statistically the same; this finding, therefore, eliminated the difference in arterial diastolic pressure as a factor influencing isovolumic contraction time in this study.

In view of these considerations it appears reasonable to conclude that shortening of isovolumic contraction time in hyperthyroidism (to 18 msec) and prolongation of isovolumic contraction time in hypothyroidism (to 75 msec) when compared to the normal (40 msec) are predominantly the results of increased myocardial contractility in hyperthyroidism and decreased myocardial contractility in hypothyroidism.

The isovolumic contraction time of hyperthyroid subjects treated with reserpine remained unaltered, again indicating that increased contractility in hyperthyroidism is not related to the level of catecholamine stores.

**Pre-ejection Period**

Since the precise time of onset of the first heart sound is often difficult to determine, the measurement of external isovolumic contraction time is subject to some small errors. It is generally agreed, however, that the pre-ejection period can be measured very accurately externally. In spite of changes in left ventricular end-diastolic pressure, a highly significant correlation between an increased rate of pressure rise in the ventricle and abbreviation of the pre-ejection period has been demonstrated previously. Shortening of the pre-ejection period by inotropic agents, such

**Figure 9**

*Pre-ejection periods of normal, hypothyroid, and hyperthyroid subjects are shown in hatched columns and the Q-S1 period is in dotted column.*
as isoproterenol and digitalis, has been documented by Harris and co-workers.\textsuperscript{31} Atropine induced tachycardia and right atrial pacing at fast rates do not result in a significant change in the pre-ejection period.\textsuperscript{32}

The pre-ejection period in hyperthyroid subjects (69 ± 11 msec) was shorter and in hypothyroid subjects (143 ± 21 msec) was longer than that in normal volunteers (103 ± 16 msec) (fig. 8). Since most of the shortening or lengthening occurred after the first heart sound (fig. 9), changes in electro-mechanical delay cannot be a major factor in variations of the pre-ejection period. The conclusion and interpretation of these findings are similar to those for isovolumic contraction time.

Critical analysis of the phases of systole, ejection time, isovolumic contraction time, and pre-ejection period clearly indicate enhanced myocardial contractility in hyperthyroidism and depressed myocardial contractility in hypothyroidism. Catecholamine depletion with reserpine repeatedly failed to alter the hemodynamic findings of hyperthyroid subjects toward normal. This study in man is in support of the conclusions made by Buccino and co-workers\textsuperscript{8} in isolated papillary muscle of euthyroid, hypothyroid, and hyperthyroid cat reported recently.

References
18. Ueda, H., et al.: Clinical studies on the cardiac performance by means of transseptal left heart catheterization: Left ventricular function in
Effect of the Thyroid State on Myocardial Contractility and Ventricular Ejection Rate in Man

MORTEZA AMIDI, DONALD F. LEON, WILLIAM J. DEGROOT, FRANK W. KROETZ and JAMES J. LEONARD

_Circulation._ 1968;38:229-239
doi: 10.1161/01.CIR.38.2.229

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1968 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/38/2/229

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/