Myocardial Mechanics in Hyperthyroidism: Importance of Left Ventricular Loading Conditions, Heart Rate and Contractile State

TED FELDMAN, MD, KENNETH M. BOROW, MD, FACC, DAVID H. SARNE, MD, ALEX NEUMANN, BS, ROBERTO M. LANG, MD

Chicago, Illinois

Hyperthyroidism has been reported to affect all of the major determinants of left ventricular performance in a manner that would augment ventricular shortening characteristics. The hypothesis tested in this study is that reduced afterload in conjunction with increased preload and heart rate, rather than augmented contractility, accounts for much of the increase in left ventricular performance noted previously in these patients. To investigate this hypothesis, 11 hyperthyroid patients were evaluated serially over 4 ± 2 months. With therapy, serum total thyroxin (T₄) decreased significantly (p < 0.001). Ventricular hemodynamics were assessed by two-dimensional targeted M-mode echocardiograms and calibrated carotid pulse tracings. Ventricular preload was estimated by end-diastolic dimension, whereas afterload was measured as end-systolic wall stress. Overall left ventricular performance was quantitated by the extent and velocity of shortening, whereas myocardial work was assessed by ventricular systolic stress-length relations.

Overall left ventricular performance reflects the net interaction of preload, afterload, heart rate and contractility. It is generally believed that hyperthyroidism affects all of these factors in a manner that enhances ventricular shortening characteristics (1–7). This is based on the fact that total plasma volume (8) (and presumably ventricular preload), heart rate and contractility are augmented whereas afterload (as measured by systemic vascular resistance) is reduced (5,7). Previous clinical studies of hyperthyroidism have used traditional ejection phase indexes (for example, ejection fraction, shortening fraction and systolic time intervals) to assess changes in overall left ventricular performance. Unfortunately, these indexes are unable to separate thyroid hormone-induced alterations in ventricular contractility that have been demonstrated in isolated muscle (9,10) from changes in preload, afterload and heart rate in patients with hyperthyroidism (2,5,7,11–13). In addition, the relative contribution of each of these factors to the augmented myocardial mechanics in humans with hyperthyroidism has yet to be established.

Recently, several noninvasively determined indexes of ventricular function have been shown to be clinically useful in the assessment of subtle abnormalities in left ventricular contractile state (14–16). The most promising of these is the relation between left ventricular end-systolic wall stress and rate-corrected velocity of fiber shortening (15). This index is independent of preload, incorporates afterload, heart rate and left ventricular mass and is sensitive to alterations in left ventricular contractile state (15).

With therapy, overall left ventricular performance declined (p < 0.01). This change was associated with no change in end-diastolic dimension or end-systolic wall stress, and a 24% fall in heart rate (p < 0.01). This latter finding has been shown previously to have no significant effect on left ventricular contractile state over the range of heart rates encountered in this study. In all cases, the end-systolic stress/rate-corrected shortening velocity relation fell with attainment of normal thyroid status, characteristic of a decline in contractility. There was a strong positive correlation between left ventricular contractility and serum thyroid hormone level (r = 0.83). In addition, ventricular minute work declined with therapy (p < 0.01). Thus, the hyperkinesia of hyperthyroidism in humans is due to augmented contractility rather than altered loading or chronotropic conditions.

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The purpose of this study was to determine the effects of clinical hyperthyroidism on left ventricular mechanics in humans. The specific questions addressed included: 1) What is the contribution of altered loading conditions and heart rate to overall left ventricular performance in hyperthyroidism? 2) What is the effect of hyperthyroidism on left ventricular contractile state, myocardial oxygen consumption and cardiac work, and how are these affected by therapy? 3) How well do standard thyroid function tests correlate with changes in left ventricular contractility?

Methods

Study patients. Eleven patients with hyperthyroidism secondary to Graves’ disease (1 male, 10 female; mean age 34 ± 13 years) who presented to the endocrine clinic of the University of Chicago were evaluated. In addition to typical clinical signs and symptoms, the diagnosis was confirmed by the presence of elevated serum thyroxine (T4) (mean 21 ± 6 μg/dl [p < 0.001]; range 13 to 32; normal range 5 to 12), serum triiodothyronine (T3) (mean 378 ± 117 ng/dl [p < 0.001]; range 229 to 624; normal range 70 to 175) and free thyroxine index (mean 27 ± 7 [p < 0.001]; range 15 to 36; normal range 6 to 11). Serum thyroxine and triiodothyronine were determined by radioimmunoassay and the free thyroxine index was calculated as the product of the serum thyroxine and a normalized resin thyroxine uptake (17). The time interval from onset of symptoms to the first echocardiographic examination was 5 ± 3 months (range 2 to 12). Patients were excluded from the study if they 1) had known cardiovascular disease not related to hyperthyroidism (for example, history of myocardial infarction or ventricular arrhythmia), 2) were receiving beta-adrenergic blocking agent therapy, or 3) demonstrated left ventricular contractility.

All study patients were initially treated with propylthiouracil. This was followed by subtotal thyroidectomy in five patients and treatment with iodine-131 in two patients. All patients had sinus rhythm throughout the study period. Results were compared with data obtained from 11 age-matched (34 ± 12 years) normal control subjects. Written informed consent was obtained according to a protocol approved by the Clinical Investigation Committee of The University of Chicago Hospitals and Clinics.

Experimental protocol. The experimental protocol has been described previously in detail (14–16). Simultaneous recordings of the two-dimensional targeted M-mode echocardiogram (Hewlett-Packard Ultrasound Imager), phonocardiogram, electrocardiogram, indirect carotid pulse tracing and blood pressure measurements were performed under baseline hyperthyroid conditions. Repeat studies were done approximately 7, 21, 35 and 49 days after initiation of therapy. Measurements of serum thyroxine and free thyroxine index were made at the time of each of these studies.

Recordings and measurements. Peak systolic, diastolic and mean arterial blood pressure determinations were made with the Dinamap 1846P Vital Signs Monitor (Critikon). This device has been shown to accurately estimate central aortic pressures over a wide range of values independent of the patient’s cardiac index, systemic vascular resistance, left ventricular ejection fraction and body surface area (18). Left ventricular end-systolic and end-diastolic dimensions (Des, Ded) and wall thicknesses (hes, hed) were measured from the echocardiographic recordings as previously described (14–16). Left ventricular mass index (LVMI) was calculated according to a modification of the method of Devereux et al. (19):

\[
LVMI = 1.04 [(Ded + 2hed)^3 - (Des)^3] - 13.6/body surface area.
\]

Total systemic resistance was calculated as mean arterial pressure divided by the echocardiographically derived cardiac output and converted to dynes·cm⁻⁵ (20). This assumes that the left ventricle contracts in a symmetric manner, a finding confirmed for each subject in our study by two-dimensional echocardiographic imaging. The left ventricular percent fractional shortening (%AD) was calculated as end-diastolic dimension minus end-systolic dimension divided by end-diastolic dimension. The left ventricular end-systolic pressure was estimated by linear interpolation to the height of the incisura using a calibrated carotid pulse tracing (18). The left ventricular ejection time (LVET) was measured from the carotid pulse tracing in the standard manner (21). The rate-corrected left ventricular mean velocity of fiber shortening (Vcf) was calculated as:

\[
Vcf = \frac{\%AD}{LVET/RR} = \frac{\%AD}{LVET} (V/RR),
\]

where %AD = percent change in ventricular dimension and RR = the interval between cardiac cycles as determined from the electrocardiogram (15).

Three to five cardiac cycles for each M-mode echocardiographic recording were digitized using a Franklin Quantico 1200 off-line data analysis system (Bruce Franklin, Inc.). This device has a digitizing pad with a sampling rate of 80/cm (400/s). The Quantico 1200 is programmed to correct for pulse transmission time by aligning the dicrotic notch of the carotid pulse tracing with the first high frequency component of the aortic component of the second heart sound. Left ventricular meridional wall stress (σ) was calculated using the angiographically validated formula (22):

\[
\sigma = \frac{(P)(D)(1.35)}{(b)(1 + (h/D)(4))}
\]

where σ is in g/cm²; P (pressure) is in mm Hg; D (dimension) and h (thickness) are in cm; and 1.35 is the factor to convert
P<sub>e</sub>, (end-systolic pressure) from mm Hg to g/cm<sup>2</sup>. Peak systolic and end-systolic wall stresses were calculated. Mean wall stress during left ventricular ejection was calculated as the average of instantaneous wall stress values from onset to end-ejection. Stress-time and stress-dimension plots calculated by the Quantic 1200 were digitized. Left ventricular stress-time (g/s/cm<sup>2</sup>) and systolic stroke work indexes (g/cm per m<sup>2</sup> body surface area) were calculated as the integral of the instantaneous stress-time and stress-dimension plots, respectively, from onset to end-ejection. Both indexes were multiplied by heart rate, giving left ventricular stress-time per minute and left ventricular minute work index.

**Statistical analysis.** Paired t tests were performed to compare maximal pretreatment and minimal posttreatment values. An unpaired t test was used to compare normal control subjects with patients before and after therapy and the Bonferroni correction was used for these multiple comparisons. A probability (p) value of less than 0.05 was considered statistically significant. Correlations between the serial thyroid function studies and the end-systolic indexes of left ventricular contractility were determined. The correlation coefficients were calculated by least squares linear regression analysis. Group data are expressed as mean values ± standard deviation.

**Results**

**Clinical course.** The mean duration of follow-up was 4 ± 2 months (Fig. 1). Serum total thyroxine (T<sub>4</sub>) decreased from 21 ± 6 to 5 ± 3 μg/dl (p < 0.001) whereas free thyroxine index decreased from 27 ± 7 to 5 ± 3 (p < 0.001). Patients pretreated with propylthiouracil were clinically and biochemically euthyroid before undergoing surgery. All patients became euthyroid within 8 weeks of initiation of treatment.

**Left ventricular hemodynamics (Table 1).** Left ventricular hemodynamics obtained in the study patients before and after therapy were compared with values from the age-matched normal subjects. The major disparities between the control and pretreatment values reflected differences in left ventricular ejection phase indexes and heart rates. In contrast, there were no hemodynamic differences between the control and posttreatment data. There were no significant changes in peak systolic, end-systolic, diastolic or mean aortic pressures between the groups. When pre- and post-treatment values were compared, heart rate declined by 24% from 91 ± 16 beats/min before therapy to 69 ± 13 after therapy (p < 0.01) (Fig. 2, top). Although left ventricular end-diastolic dimension (a measure of preload) did not change after therapy (Fig. 2, bottom), left ventricular end-systolic dimension increased by 7% (p < 0.05). With therapy the rate-corrected ejection time increased by 6% (p < 0.05) and cardiac output fell by one-third (p < 0.05). This resulted in a 32% increase in total systemic resistance (an index of peripheral vascular tone). During the course of treatment, end-systolic wall stress (a measure of left ventricular afterload) did not change significantly. In addition, there were no changes in mean or peak wall stress, ventricular wall mass index or systolic stress-time index per minute. In contrast, total left ventricular minute work index declined by 37% (8,743 ± 2,004 versus 5,478 ± 1,629 g/cm/m<sup>2</sup>; p < 0.01). The net effect on overall left ventricular performance (Fig. 3) was a 14% decline in percent fractional shortening and an 18% fall in rate-corrected shortening velocity (p < 0.01 for both).

**Left ventricular end-systolic stress/velocity of shortening relation.** Figure 4 compares the relation between end-systolic wall stress and rate-corrected velocity of fiber shortening for the study group with the previously published mean (± 2 SD) value for this relation generated from a normal population over a wide range of end-systolic stresses (15). In all cases initially increased contractility declined significantly with therapy. There is no overlap of rate-cor-
Table 1. Summary of Hemodynamic Data in 11 Patients

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Before Therapy</th>
<th>After Therapy</th>
<th>p Values*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (beats/min)</strong></td>
<td>71 ± 13</td>
<td>91 ± 16</td>
<td>69 ± 13</td>
<td>Control vs. Before Therapy: &lt; 0.05</td>
</tr>
<tr>
<td><strong>Pp (mm Hg)</strong></td>
<td>122 ± 10</td>
<td>129 ± 16</td>
<td>122 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Pm (mm Hg)</strong></td>
<td>86 ± 8</td>
<td>89 ± 12</td>
<td>88 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Pw (mm Hg)</strong></td>
<td>101 ± 10</td>
<td>98 ± 13</td>
<td>95 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Dae (cm)</strong></td>
<td>4.79 ± 0.30</td>
<td>4.70 ± 0.48</td>
<td>4.68 ± 0.56</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Dae (cm)</strong></td>
<td>3.22 ± 0.23</td>
<td>2.98 ± 0.40</td>
<td>3.20 ± 0.47</td>
<td>NS</td>
</tr>
<tr>
<td><strong>CO (liters/min)</strong></td>
<td>4.5 ± 0.7</td>
<td>6.2 ± 1.8</td>
<td>4.1 ± 1.1</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>SVR (dyne's-cm⁻5)</strong></td>
<td>1,546 ± 256</td>
<td>1,228 ± 321</td>
<td>1,813 ± 427</td>
<td>NS</td>
</tr>
<tr>
<td><strong>LVET (ms)</strong></td>
<td>318 ± 23</td>
<td>307 ± 20</td>
<td>325 ± 25</td>
<td>NS</td>
</tr>
<tr>
<td><strong>σw (g/cm²)</strong></td>
<td>49 ± 10</td>
<td>47 ± 9</td>
<td>55 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td><strong>σe (g/cm²)</strong></td>
<td>144 ± 28</td>
<td>137 ± 19</td>
<td>136 ± 26</td>
<td>NS</td>
</tr>
<tr>
<td><strong>σa (g/cm²)</strong></td>
<td>97 ± 15</td>
<td>92 ± 15</td>
<td>95 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td><strong>%ΔD</strong></td>
<td>33 ± 4</td>
<td>37 ± 3</td>
<td>32 ± 3</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>Vcf (circ/s)</strong></td>
<td>1.11 ± 0.13</td>
<td>1.47 ± 0.19</td>
<td>1.04 ± 0.11</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Vcfc (circ/s)</strong></td>
<td>1.04 ± 0.14</td>
<td>1.20 ± 0.08</td>
<td>0.98 ± 0.06</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>LV mass index (g/m²)</strong></td>
<td>105 ± 23</td>
<td>99 ± 25</td>
<td>100 ± 29</td>
<td>NS</td>
</tr>
<tr>
<td><strong>STI (gsov/cm²)</strong></td>
<td>28 ± 5</td>
<td>22 ± 5</td>
<td>27 ± 7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>MSTI (gsov/cm² per min)</strong></td>
<td>1,943 ± 414</td>
<td>2,042 ± 474</td>
<td>1,785 ± 366</td>
<td>NS</td>
</tr>
<tr>
<td><strong>MWI (g/cm per m²)</strong></td>
<td>6,544 ± 1,221</td>
<td>8,743 ± 2,004</td>
<td>5,478 ± 1,629</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

*Corrected for multiple comparisons. CO = cardiac output; Dae and Dae = end-diastolic and end-systolic dimension, respectively; % ΔD = percent shortening fraction; ETe = rate-corrected ejection time; HR = heart rate; LVET = left ventricular ejection time; MSTI = wall stress-time index per minute; MWI = minute work index; Pp, Pm and Pw = peak, mean and end-systolic pressure, respectively; STI = wall stress-time index; SVR = total systemic resistance; σw, σe and σa = peak, mean and end-systolic wall stress, respectively; Vcf and Vcfc = shortening velocity and rate-corrected shortening velocity, respectively.

The correlation coefficient for total serum thyroxine was also highly positive (r = 0.77).

**Discussion**

This study used left ventricular force-shortening-velocity characteristics to define myocardial mechanics before and after therapy in patients with hyperthyroidism. The following discussion addresses the effects of preload, afterload, contractility and heart rate on overall left ventricular performance and myocardial oxygen requirements in these patients.

**Preload.** In spite of the increase in total body plasma volume known to accompany hyperthyroidism (8), our subjects did not show a change in left ventricular end-diastolic dimension with therapy. This suggests that preload is not an important determinant of the augmented ventricular performance in hyperthyroidism. Furthermore, it suggests that total body plasma volume and left ventricular preload are not synonymous.

**Afterload.** Total systemic vascular resistance increased as patients became euthyroid. Previous investigators have found similar changes (3,7,23). Interestingly, the rise in total systemic resistance (a measure of peripheral arterial...
Figure 2. Plot of heart rate and left ventricular end-diastolic dimensions for individual patients. Heart rate declined 24% with treatment for hyperthyroidism. There was no change in end-diastolic dimension, a measure of left ventricular preload. Abbreviations as in Figure 1.

Figure 3. Left ventricular shortening characteristics (percent fractional shortening and heart rate-corrected velocity of shortening [Vcf]) decreased significantly with the change from the hyperthyroid to the treated state. Abbreviations as in Figure 1.

tone) in our study was not associated with changes in left ventricular afterload as measured by end-diastolic pressure or mean systolic wall stress. This means that afterload reduction is not responsible for the hyperdynamic state associated with untreated hyperthyroidism. This is an example of disparity between peripheral vascular tone and the forces acting on myocardial fibers (that is, afterload) and reflects differences between the peripheral and cardiac effects of thyroid hormone.

In this study, no change was noted in left ventricular mass. Reversible cardiac hypertrophy induced by thyroid hormone has been reported in animals, but left ventricular mass increased above the normal range has yet to be demonstrated in adult humans (25-27). Changes in myocardial protein synthesis induced in animals by thyroid hormone administration have not yet been found in humans.

Contractility. There was a strong positive correlation between thyroid hormone levels and myocardial contractility, measured as deviation of the end-systolic stress-rate corrected velocity of fiber shortening relation from its normal mean regression line (Fig. 5). This finding is consistent with a shift in the force-velocity curve upward and to the right noted previously in isolated cat papillary muscle treated with thyroxine (9). Because our data were acquired over a mean of 4 ± 2 months at multiple stages of therapy, they suggest that left ventricular contractile state correlates closely and in a temporal manner with the patient's biochemical thyroid hormone profile (28).

Heart rate. With antithyroid therapy, heart rate fell from 91 ± 16 to 69 ± 13 beats/min. It is important to consider how this magnitude of change in heart rate could influence left ventricular contractile state. It has been demonstrated that the positive inotropic effect of a steady state increase in cardiac frequency is less marked at physiologic than at room temperature, and in the intact ventricle than in isolated cardiac tissue (29). Also, increases in contractility appear to be considerably smaller in intact conscious dogs than in dogs in the anesthetized state (30). We recently examined this question in 10 normal subjects. A change in heart rate from 55 ± 6 to 86 ± 8 beats/min did not significantly alter...
left ventricular contractility as measured by the end-systolic stress-rate-corrected velocity of fiber shortening relations. This finding is in agreement with other studies performed over the physiologic range for heart rate in humans (31,32). Thus, chronotropic factors do not appear to have contributed significantly to the increased contractility associated with hyperthyroidism.

Myocardial oxygen requirements. The hypermetabolic state in hyperthyroidism is accompanied by increased myocardial oxygen consumption (5,23,33). In this study we used the left ventricular systolic stress-time index per minute to assess relative myocardial oxygen demands. This measure, which incorporates two of the three major determinants of myocardial oxygen consumption (systolic wall stress and heart rate) has been shown previously to reflect changes in myocardial oxygen consumption (34). The remaining major determinant, contractility, should account for most, if any, disparity between expected and actual myocardial oxygen consumption. We found that the left ventricular systolic stress-time index per minute did not change with therapy, reflecting counterbalancing effects of the 24% decrease in heart rate and the 23% increase in stress-time index per beat. The known increase in myocardial oxygen consumption that occurs with hyperthyroidism must therefore be due predominantly either to increased demand caused by augmented left ventricular contractility and external work or to decreased myocardial efficiency. The 60% higher values for left ventricular minute work index noted under pretreatment (that is, hyperthyroid) conditions in our patients suggest that increased left ventricular oxygen demand, not myocardial inefficiency, was the major factor.

Methodologic considerations. It has been suggested that the left ventricular hyperkinesia in hyperthyroidism is mediated by either catecholamine excess or enhanced cate-
cholamine sensitivity. Plasma catecholamine concentrations are normal or decreased in hyperthyroid patients, and myocardial beta-adrenergic binding sites in animals are increased (2,26). Beta-receptor blockade with sotalol, an agent free of intrinsic myocardial depressant properties, abolishes the tachycardia and shortened circulation time in hyperthyroidism, but does not change left ventricular performance (35). This suggests that thyroxine affects the heart independent of circulating catecholamines and the sympathetic nervous system (35). Although we did not measure serum catecholamine concentrations, it does not appear that this information would significantly alter the interpretation of our results.

Systemic vascular resistance was estimated using non-invasive techniques. As afterload (measured as end-diastolic pressure or mean systolic pressure) did not change, a difference in systemic resistance in either direction would not alter our conclusions. Echocardiographic determination of cardiac output in patients with a normal sized left ventricle in the absence of wall motion abnormalities has been shown previously to be accurate (36,37). This is particularly true when all subjects serve as their own control in serial studies using two-dimensionally targeted M-mode echocardiographic imaging. The direction and magnitude of change in systemic resistance with therapy in these patients are similar to those reported by other investigators (7,25).

Conclusions. The hyperdynamic appearance of the left ventricle in hyperthyroidism is due to increased contractility independent of alterations in ventricular preload, afterload and heart rate.

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