Assessment of Cardiac Reserve in Patients with Hyperthyroidism*

Rex B. Shafer, M.D.; and Jesus A. Bianco, M.D.

Radionuclide multigated cardiac imaging was performed to assess functional cardiac reserve in patients with hyperthyroidism. In 11 normal individuals, submaximal supine exercise increased heart rate (HR) by 60 percent, systolic blood pressure (BP) by 54 percent, and the left ventricular ejection fraction (LVEF) by 13 percent. All of these increments were statistically significant (p < 0.001). Eight patients with hyperthyroidism were studied. Their mean ± standard error of the mean (SEM) serum thyroxine level was 17.7 ± 0.5 μg percent. There was a negative correlation between serum thyroxine levels and LVEF, both at rest and during exercise, in the patients with hyperthyroidism. Our data suggest that hyperthyroidism is associated with impaired functional cardiac reserve.

It is well established that thyroid hormones induce positive inotropic and chronotropic effects on the heart in hyperthyroidism. Positive inotropic effects of thyroxine (T₄) have been demonstrated in papillary muscle, left atrial and right ventricular muscles, and hearts of conscious dogs. In hyperthyroid patients, studies employing systolic time intervals have shown that thyrotoxicosis results in shortening of the left ventricular (LV) isovolumic contraction and ejection times, shortening of the LV pre-ejection period, and lowering of the LV pre-ejection period/ejection time ratio. Similarly, echocardiographic investigations have confirmed presence of enhanced LV contractile state in patients with Graves' disease. These investigations have also reported normal cardiac size in hyperthyroid patients.

To date, little has been reported on the LV functional reserve in patients with hyperthyroidism. Availability of exercise radionuclide ventriculographic studies has allowed us to assess the exercise response in patients with clinical and chemical manifestations of thyrotoxicosis.

METHODOLOGY

Control Subjects

The control group consisted of 11 men whose age range was 24-45 years (mean 37). None had clinical or angiographic evidence of ischemic heart disease, or of other cardiac disease. Six patients had undergone coronary angiographic examination and were found to have normal coronary arteries. The remaining five individuals were healthy volunteers who were asymptomatic, had normal ECGs and no clinical or family history of cardiac disease. All had normal thyroid function.

Patients with Thyrotoxicosis

Eight male patients, ages 25-56 years (mean 43), had diffuse toxic goiter (Graves' disease) with clinical criteria of hyperthyroidism, ie, weight loss, muscle fatigue, heat intolerance, tachycardia, tremor and nervousness. Symptoms had been present from three months to one year with a mean of four months. Laboratory criteria for hyperthyroidism included elevated total T₄, total triiodothyronine (T₃), T₃ resin sponge uptake (T₃ RU), and 24-hour ¹³¹iodine uptake. Total serum T₄ of the group determined by radioimmunoassay was 17.7 ± 0.5 μg percent (mean ± SEM). The normal values for T₄ in our laboratory are 4-10 μg percent. No patient had clinical evidence of coronary disease, and all the patients had normal rest and exercise ECG and chest x-ray film findings. Two patients were receiving oral propranolol at the time of study (patient 12, 20 mg per day and patient 16, 100 mg per day).

Exercise Radionuclide Ventriculogram

The multigated cardiac study was performed using methodology previously described. Briefly, after red blood cell labeling with ⁹⁹ᵐtechnetium, the patient was placed in the modified 45° LAO projection, utilizing a 37-PMT large field-of-view Anger scintillation camera. Data collection was conducted under R-wave synchronization. Data were organized in the histogram mode employing 28 frames. Framing rate, at rest and during exercise, was pre-set by the minicomputer (Unicam, Medical Data Systems), in accordance with the prevailing heart rate (range 20-40 m/sec/data frame). The LV edge was defined by the minicomputer in each frame using threshold and second derivative criteria. The LV ejection fraction (LVEF) was computed as end-diastolic counts minus end-systolic counts/end-diastolic counts. Background activity was determined in the end-systolic frame from an area adjacent to the lateral wall of the LV; this background was subtracted from each matrix element in the region of interest of each frame in the cardiac cycle. Each data

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Table 1—Data in Normal Individuals (n = 11)

<table>
<thead>
<tr>
<th>Patient</th>
<th>HR beats/min</th>
<th>BP mm Hg</th>
<th>DP (×10³)</th>
<th>EF (%)</th>
<th>HR beats/min</th>
<th>BP mm Hg</th>
<th>DP (×10³)</th>
<th>EF (%)</th>
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<td>98</td>
<td>75</td>
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<tr>
<td>Mean ± SEM</td>
<td>73 ± 2</td>
<td>127 ± 2</td>
<td>88 ± 2</td>
<td>66 ± 1</td>
<td>117 ± 1</td>
<td>196 ± 2</td>
<td>232 ± 4</td>
<td>75 ± 1</td>
</tr>
</tbody>
</table>

r (correlation with resting value) | 0.29 | 0.58 | 0.87 | 0.66 |

p (versus resting value) | <0.001 | <0.001 | <0.001 | <0.001 |

HR = heart rate; BP = systolic blood pressure; DP = double product; EF = ejection fraction.

acquisition period, at rest and under exercise, spanned a two to three minute interval as previously described.10 Frames were presented in cinemac display after each acquisition. The validity, variability, and reproducibility of radionuclide LVEF, as calculated in our laboratory, were previously discussed.10

Experimental Protocol

The following protocol was followed in the normal subjects and in the patients with hyperthyroidism. LVEF, heart rate and systolic blood pressure were obtained with the patient supine. Thereafter, both normal subjects and patients performed supine exercise on a bicycle ergometer, beginning at a workload of 100 kpm and increasing by 50 kpm increments until submaximal load was reached (approximately 300 kpm). LV ejection fraction and wall motion were determined at a preselected end-point, under a steady workload. A tightly fitted cloth harness prevented excessive patient motion. The end-point of exercise was defined as at least a doubling of the double product (double product = heart rate X systolic blood pressure/100). LVEF, heart rate and systolic blood pressure were again determined during supine exercise.

Table 2—Data in Hyperthyroid Patients (n = 8)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Serum T4 µg%</th>
<th>HR beats/min</th>
<th>BP mm Hg</th>
<th>DP (×10³)</th>
<th>EF (%)</th>
<th>HR beats/min</th>
<th>BP mm Hg</th>
<th>DP (×10³)</th>
<th>EF (%)</th>
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<td>82</td>
<td>149</td>
<td>190</td>
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<td>70</td>
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<tr>
<td>Mean ± SEM</td>
<td>17.7 ± 0.5</td>
<td>91 ± 2</td>
<td>131 ± 2</td>
<td>119 ± 3</td>
<td>70 ± 1</td>
<td>135 ± 2</td>
<td>180 ± 3</td>
<td>254 ± 6</td>
<td>67 ± 2</td>
</tr>
</tbody>
</table>

r (correlation with resting value) | 0.41 | 0.60 | 0.35 | 0.66 |

p (versus resting value) | <0.001 | <0.001 | <0.001 | NS |

HR = heart rate; BP = systolic blood pressure; DP = double product; EF = ejection fraction; NS = not significant.

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under a steady workload. The means cited in this paper refer to LVEF units, and to their fractional percentage changes. All values are expressed as mean $\pm$ standard error of the mean (SEM).

Statistical significance was ascertained by means of Student's paired t-test. Linear correlations were computed where appropriate. Linear fitting was done by the least-squares method. In all cases an informed written consent was procured prior to the exercise study.

**RESULTS**

Data obtained in the control individuals and in the patients with hyperthyroidism are listed in Tables 1 and 2. In the control group, the increase in double product under exercise was 104 percent (Fig 1). This increment was accompanied by a fractional rise of 13 percent in the LVEF, as compared to rest ($p < 0.001$), (Fig 2).

In the group of patients with hyperthyroidism, there was a 113 percent increase in double product under exercise (Fig 1). However, the mean LVEF did not significantly change during supine exercise (Fig 2).

Figure 3 displays the relationship between serum $T_4$ levels and LVEF in the patients with hyperthyroidism. The graph shows values obtained both at rest and during exercise. There was a negative correlation between the two variables ($r = 0.65, p < 0.01$).

Analysis of LV wall motion at rest and during exercise in both the control group and the hyperthyroid group did not disclose noticeable differences. No wall motion abnormalities developed with exercise in either group.

**DISCUSSION**

The data from this study clearly suggest that functional LV reserve is impaired in patients with hyperthyroidism. While in normal individuals we found the expected increment of LVEF during exercise, there was no significant change in the LVEF with exercise in the group with Graves' disease. The lesser increase in double product in the hyperthyroid patients (2.1 times in hyperthyroid patients compared to 2.6 times in the normal subjects) was most likely due to the higher resting heart rates and systolic blood pressure seen in the hyperthyroid patients.

The impairment of functional reserve is similar to that found in patients with coronary disease, aortic valvular disease, and other cardiomyopathies. Hyperthyroidism, as well as these clinical entities, must be considered when interpreting the exercise radionuclide ventriculogram.
Figure 2. Effect of submaximal exercise on the left ventricular ejection fraction in 11 normal subjects and eight patients with hyperthyroidism. Open circles = rest values; solid circles = exercise values; means ± SEM indicated; NS = nonsignificant.

The negative correlation between serum T₄ level and LVEF in the hyperthyroid patients, at rest and under exercise, further supports the presence of impaired LV function in thyrotoxic patients. We are not aware that this relationship between serum T₄ and LVEF has previously been documented.

Two of the eight hyperthyroid patients were receiving oral propranolol (patient 12, 20 mg per day and patient 16, 160 mg per day). While patient 16 showed a significant fall in LVEF from 61 percent to 52 percent with exercise, this fall should not be attributable to propranolol. Marshall et al. have shown that when oral propranolol was given to subjects in doses of 165 ± 13 mg per day, no measurable change in resting LVEF resulted. More recently, they have reported that the rise of LVEF during exercise is not blunted by oral propranolol given in doses up to 190 mg per day.

Cardiac disease secondary to hyperthyroidism is a concept amply popularized by Samuel Levine, and accepted by many investigators. Biventricular cardiac enlargement may result from excess of thyroid hormones. Cardiac failure, however, is unusual today because of earlier diagnosis and therapy. Additional demands or limitations placed on the LV, as for example hypertensive vascular disease or coronary artery disease, may nevertheless provoke cardiac decompensation in patients with hyperthyroidism.

Thyroid disease as the precipitating cause of heart failure may go unrecognized for a long time before hyperthyroidism is diagnosed. Our experimental data suggest that the depression of LV functional reserve in a given patient with hyperthyroidism will importantly depend on the severity of the hypermetabolic state.

Our investigation did not address the question of the mechanisms whereby altered thyroid state influ-
ences myocardial function. Neither biochemical or histologic information has revealed the primary myocardial defect in patients with hyperthyroidism. Appropriate management of this condition reverses whatever mechanisms are responsible for the cardiomyopathy of hyperthyroidism.

While this study casts little light as to the underlying primary pathogenetic defects in hyperthyroidism, certain conclusions may be drawn from the data. The LV functional reserve is impaired in patients with hyperthyroidism. Early diagnosis may expedite therapy and preclude appearance of heart failure. The degree of derangement of cardiac reserve in these patients probably determines their vulnerability for cardiac decompensation. One would expect that protracted hyperthyroidism with high levels of serum T, would be associated with greater propensity for development of cardiomyopathy. Patients with nonendocrine cardiac disorders may likely show cardiac decompensation with the onset of hyperthyroidism. Timely management of the latter situation should prevent worsening of the former condition.

In summary, this report establishes a decline in LV functional reserve in patients with hyperthyroidism, which appears to vary in intensity in relation to the serum level of thyroid hormones.

REFERENCES
1 Symons C. Thyroid heart disease. Br Heart J 1979; 41:257-262