Low Efficiency of Oxygen Utilization During Exercise in Hyperthyroidism*

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Study objective: The mechanism of exercise intolerance in hyperthyroidism has not been fully elucidated. This study was undertaken to determine if hyperthyroidism reduced the efficiency of submaximal exercise.

Study design: We measured cardiorespiratory variables up to the anaerobic threshold (AT) during ramp-loading cycle ergometry in 12 patients (New York Heart Association functional class II or III). Studies were performed in the hyperthyroid state and repeated in the euthyroid state after 10 months of medical treatment. In 10-W steps from rest to the AT, we measured oxygen uptake (Vo2) as a measure of total body work rate, and pressure rate product (PRP) as a measure of cardiac work rate. Loading watts at AT divided by the increment of Vo2 from rest to the AT (ΔWatt/ΔVo2) was calculated as an index of work efficiency (where Δ means the increment of each value from rest to the AT).

Results: Vo2 and PRP at the AT were not significantly different between hyperthyroid and euthyroid states (Vo2, 16.6±3.0 vs 17.5±2.3 mL/min/kg; PRP, 220±41 vs 218±28×102 mm Hg/min). However, loading watts at AT were significantly lower in the hyperthyroid than the euthyroid state (28±22 vs 60±14 W; p<0.01). Vo2 and PRP while hyperthyroid were significantly higher than when euthyroid at every 10-W step during ramp-loading exercise. Furthermore, ΔWatt/ΔVo2 was significantly lower in hyperthyroid than euthyroid states (p<0.001). There was a significant inverse correlation between triiodothyronine and ΔWatt/ΔVo2 (r=-0.654, p<0.001).

Conclusion: Hyperthyroidism causes low work efficiency, which may limit exercise tolerance.

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Key words: exercise capacity; hyperthyroidism; work efficiency

Abbreviations: AT=anaerobic threshold; HR=heart rate; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association (functional class); PRP=pressure rate product; ΔPRP=increment of PRP from rest to the AT; T3=triiodothyronine; T4=thyroxine; TSH=thyrotropic hormone; VCO2=carbon dioxide output; Vt=minute ventilation; VO2=oxygen uptake; ΔVo2=increment of VO2 from rest to the AT; ΔWatt=loading watts at AT; ΔWatt/ΔVo2=loading watts at AT divided by the increment of VO2 from rest to the AT

Patients with hyperthyroidism commonly complain of exercise intolerance, despite elevated resting cardiac output.1-4 Several hypotheses have been proposed to explain this finding. First, thyrotoxicosis may cause left ventricular dysfunction during exercise.5-7 However, although some studies have shown an abnormal response of left ventricular ejection fraction to exercise,5-7 cardiac output is high at rest and increases normally during exercise.4,5 Furthermore, elevated skeletal muscle blood flow during exercise was reported recently in hyperthyroid rats.8 Therefore, cardiovascular limitation due to cardiac dysfunction cannot fully explain the exercise limitation. Second, other studies have shown respiratory muscle weakness in hyperthyroid patients.9,10 In one article, however, patients remained dyspneic with exercise even after respiratory muscle power recovered with successful antithyroid treatment.9 This led the authors to conclude that respiratory muscle weakness alone could not explain the dyspnea during exercise. A third mechanism proposed by Martin et al9 is that skeletal muscle myopathy induced by hyperthyroidism may limit exercise tolerance. They demonstrated that pharmacologically induced hyperthyroidism decreased skeletal muscle mass and impaired muscle oxidative and glycolytic capacity. Finally, Ben-Dov et al11 measured the O2 cost of muscle work in clinical hyperthyroidism. The ratio of oxygen uptake (Vo2) increment to work rate increment was not significantly different between their hyperthyroidism.
perthyroid patients and normal control subjects. However, two subjects were retested when euthyroid showed slight improvements in work efficiency. Decreased skeletal muscle efficiency could cause exercise limitation at reduced workloads despite normal or supranormal cardiac output.

Many authors, including those cited above, have used exercise duration or maximal $V_{O_2}$ as the index of exercise capacity. This may be limited by symptoms or patient motivation, and it is therefore not entirely objective. Recently, some authors have used the anaerobic threshold (AT) obtained by respiratory gas analysis on a ramp-loading cycle ergometer as a more objective measure of exercise capacity.\textsuperscript{12,13} Therefore, in this study, we measured the AT in 12 hyperthyroid patients before and after they were rendered euthyroid with medical therapy. We compared loading watts, $V_{O_2}$, and pressure rate product (PRP) at 10-W steps during exercise up to the AT in hyperthyroid and euthyroid states to examine the possible contribution of work inefficiency to exercise intolerance in patients with hyperthyroidism.

### MATERIALS AND METHODS

#### Patients

Twelve hyperthyroid patients (7 men and 5 women) with a mean age of 40 years (range, 26 to 63 years) were studied (Table 1). All patients were diagnosed as having toxic goiter (Graves’ disease) and had elevated plasma triiodothyronine ($T_3$) and thyroxine ($T_4$) levels and suppressed thyrotropic hormone (TSH) levels (Table 1). None had cardiovascular, pulmonary, or hematologic disease. All patients showed sinus rhythm by ECG during this investigation. All complained of exercise intolerance. Nine of them were in class II [New York Heart Association (NYHA)] and three were in NYHA class III.

### Table 1—Patient Profile in the Hyperthyroid and Euthyroid States

<table>
<thead>
<tr>
<th>Patient No./Age, yr/Sex</th>
<th>NYHA</th>
<th>$T_3$, ng/dL</th>
<th>$T_4$, pg/dL</th>
<th>TSH, μU/mL</th>
<th>Treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/28/M</td>
<td>III</td>
<td>328</td>
<td>15.3</td>
<td>&lt;0.01</td>
<td>MMI→PTU</td>
</tr>
<tr>
<td>2/50/F</td>
<td>III</td>
<td>383</td>
<td>16.8</td>
<td>&lt;0.01</td>
<td>MMI</td>
</tr>
<tr>
<td>3/54/F</td>
<td>III</td>
<td>377</td>
<td>15.6</td>
<td>&lt;0.01</td>
<td>MMI</td>
</tr>
<tr>
<td>4/63/M</td>
<td>II</td>
<td>391</td>
<td>17.4</td>
<td>&lt;0.01</td>
<td>MMI</td>
</tr>
<tr>
<td>5/53/M</td>
<td>II</td>
<td>390</td>
<td>16.7</td>
<td>&lt;0.01</td>
<td>MMI</td>
</tr>
<tr>
<td>6/42/M</td>
<td>II</td>
<td>574</td>
<td>23.8</td>
<td>&lt;0.01</td>
<td>MMI</td>
</tr>
<tr>
<td>7/26/F</td>
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<td>602</td>
<td>17.9</td>
<td>&lt;0.01</td>
<td>MMI</td>
</tr>
<tr>
<td>8/37/F</td>
<td>III</td>
<td>538</td>
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<td>&lt;0.01</td>
<td>MMI→PTU</td>
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<tr>
<td>9/32/F</td>
<td>II</td>
<td>599</td>
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<td>&lt;0.01</td>
<td>MMI</td>
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<tr>
<td>10/29/M</td>
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<td>612</td>
<td>26.4</td>
<td>&lt;0.01</td>
<td>MMI</td>
</tr>
<tr>
<td>11/33/M</td>
<td>II</td>
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<td>19.2</td>
<td>&lt;0.01</td>
<td>MMI</td>
</tr>
<tr>
<td>12/30/M</td>
<td>II</td>
<td>587</td>
<td>23.2</td>
<td>&lt;0.01</td>
<td>MMI</td>
</tr>
<tr>
<td>Mean</td>
<td>40</td>
<td>469</td>
<td>19.4</td>
<td></td>
<td>136\textsuperscript{1} 7.5\textsuperscript{1}</td>
</tr>
<tr>
<td>1 SD ±12</td>
<td>±118</td>
<td>±4.0</td>
<td></td>
<td></td>
<td>±17 ±1.4</td>
</tr>
</tbody>
</table>

*MMI=methimazole; PTU=propylthiouracil.

\textsuperscript{1}Significant difference compared to hyperthyroid state (p<0.01).

Protocols

Informed consent was obtained from all patients. This study was approved by the hospital’s review board for clinical studies. Clinical and exercise data and blood chemistry values were measured prior to therapy for hyperthyroidism. Serum $T_3$, $T_4$, and free $T_3$ were measured using commercially available kits ($T_3$RIA Kit; Eiken Chemical Co Ltd, Tokyo, Japan; $T_4$ and free $T_3$ Kits; Japan Kodak Diagnostic Co Ltd, Tokyo, Japan). Serum TSH was determined by immunoradiometric assay (using Diagnost TSH kit; CIB Diagnostic Co Ltd, Chiba, Japan). All patients were then treated with antithyroid drugs (methimazole with or without propylthiouracil). No patients were receiving medications other than those listed. Six months after thyroid hormones reached euthyroid levels (normal $T_3$, $T_4$, and free $T_3$) (Table 1), the second test was performed using the identical protocol. Mean duration between the first and second test was 10 months.

#### Exercise Tests and Measured Variables

Before the study, all patients were accustomed to the system by 3 min of preliminary exercise. Tests were performed on a bicycle ergometer (ISO-power ergometer; Takei Co Ltd, Tokyo, Japan) with subjects breathing through a mouthpiece and one-way valve for exhaled gas collection. After baseline rest of more than 1 h, the trial began with 3 min of resting data collection. The exercise consisted of 10 W of constant work for 3 min followed by increasing ramp-loading (10 W/min). Heart rate (HR), systolic BP, and loading watts were recorded every 30 s during the test. Tidal volume, respiratory rate, $V_{O_2}$, carbon dioxide output ($V_{CO_2}$), and minute ventilation (Ve) were also measured every 30 s by sampling from a mixing chamber (AY-900T gas analyzer; Chest Co Ltd, Tokyo, Japan). The AT was determined using the method of Wasserman\textsuperscript{13} as the point where the $Q_{O_2}$ equivalent increased while the $Q_{CO_2}$ equivalent remained constant. Exercise was discontinued a few minutes after the AT was recognized. We calculated $\Delta V_{O_2}$, $\Delta PRP$, and $\Delta Watt$ as the increment from rest to the AT and used $\Delta Watt/\Delta V_{O_2}$ as the parameter of work efficiency on ramp-loading exercise\textsuperscript{14,15} (see discussion below). We compared these parameters between the two states in 10-W steps up to the AT.
Table 2—Variables at Rest in Hyperthyroid and Euthyroid States

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>HR, /min</th>
<th>BP, Systolic, mm Hg</th>
<th>PRP, ( \times 10^2 )</th>
<th>( V_O_2 ), mL/min/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120</td>
<td>136</td>
<td>163</td>
<td>5.91</td>
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<td>2</td>
<td>82</td>
<td>124</td>
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<td>3</td>
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<td>116</td>
<td>116</td>
<td>5.20</td>
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<td>4</td>
<td>89</td>
<td>132</td>
<td>117</td>
<td>6.42</td>
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<td>5</td>
<td>88</td>
<td>141</td>
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<td>166</td>
<td>212</td>
<td>8.41</td>
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<tr>
<td>7</td>
<td>126</td>
<td>140</td>
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<tr>
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<td>146</td>
<td>7.27</td>
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<td>137</td>
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<tr>
<td>1 SD</td>
<td>±16</td>
<td>±14</td>
<td>±33</td>
<td>±1.1</td>
</tr>
</tbody>
</table>

\*Significant difference compared to hyperthyroid state (p<0.01).

Table 3—Variables at the AT in Hyperthyroid and Euthyroid States

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>HR, /min</th>
<th>BP, Systolic, mm Hg</th>
<th>PRP, ( \times 10^2 )</th>
<th>Loading Watt</th>
<th>( V_O_2 ), mL/min/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>144</td>
<td>166</td>
<td>239</td>
<td>15</td>
<td>15.6</td>
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<td>138</td>
<td>172</td>
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<td>15.4</td>
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<td>4</td>
<td>139</td>
<td>184</td>
<td>255</td>
<td>50</td>
<td>20.4</td>
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<td>118</td>
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<td>235</td>
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<td>18.8</td>
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<tr>
<td>6</td>
<td>157</td>
<td>191</td>
<td>300</td>
<td>10</td>
<td>17.7</td>
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<tr>
<td>7</td>
<td>144</td>
<td>154</td>
<td>222</td>
<td>10</td>
<td>15.3</td>
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<tr>
<td>8</td>
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<td>147</td>
<td>166</td>
<td>10</td>
<td>12.0</td>
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<tr>
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<td>135</td>
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<td>189</td>
<td>10</td>
<td>18.1</td>
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<tr>
<td>10</td>
<td>140</td>
<td>166</td>
<td>232</td>
<td>10</td>
<td>11.4</td>
</tr>
<tr>
<td>11</td>
<td>126</td>
<td>228</td>
<td>288</td>
<td>70</td>
<td>20.5</td>
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<tr>
<td>12</td>
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<td>184</td>
<td>236</td>
<td>45</td>
<td>19.0</td>
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<tr>
<td>Mean</td>
<td>131</td>
<td>176</td>
<td>229</td>
<td>28</td>
<td>16.6</td>
</tr>
<tr>
<td>1 SD</td>
<td>±16</td>
<td>±30</td>
<td>±41</td>
<td>±22</td>
<td>±3.0</td>
</tr>
</tbody>
</table>

\*Significant difference compared to hyperthyroid state (p<0.01).

Statistical Analysis

All values are expressed as mean±1 SD. Mean data during hyperthyroid and euthyroid states were compared using two-way analysis of variance for repeated measures. The \( \Delta V_O_2 \), \( \Delta PRP \), and \( \Delta Watt/\Delta V_O_2 \) in hyperthyroid and euthyroid states were compared by two-tailed paired t tests. Correlations between \( T_3 \) and \( \Delta Watt/\Delta V_O_2 \) were determined by least squares linear regression analysis. Significance was assumed at p<0.05.

RESULTS

Table 2 shows the resting HR, systolic BP, PRP, and \( V_O_2 \) in hyperthyroid and euthyroid conditions. All values decreased significantly from hyperthyroid to euthyroid states. Table 3 shows the HR, systolic BP, PRP, loading watts, and \( V_O_2 \) at the AT during hyperthyroidism and euthyroidism. The HR, systolic BP, and PRP were not significantly different in the two conditions, but loading watts significantly increased during the euthyroid state. Figure 1 shows the change from rest to the AT in \( \Delta V_O_2 \), \( \Delta PRP \), and \( \Delta Watt/\Delta V_O_2 \) in both states. All of these variables were significantly increased from hyperthyroidism to euthyroidism (\( \Delta V_O_2 \), \( 9.9±3.3 \) vs \( 13.4±2.3 \) mL/min/kg; p<0.01; \( \Delta PRP \), \( 83±41 \) vs \( 124±34\times10^2 \) mm Hg/min; p<0.05; \( \Delta Watt/\Delta V_O_2 \), \( 2.6±1.5 \) vs \( 4.5±1.0 \); p<0.001). The relationship between \( V_O_2 \) and loading watts at 10-W steps up to the AT is shown in Figure 2. \( V_O_2 \) was higher at every step than while euthyroid (p<0.05). Figure 3 shows the relationship between PRP and loading watts. PRP while hyperthyroid was significantly higher than while euthyroid at every step (p<0.05). The relationship between serum \( T_3 \) and \( \Delta Watt/\Delta V_O_2 \) for all patients in both thyroid states is
shown in Figure 4. There was a statistically significant inverse correlation between these parameters (r=−0.654; p<0.001).

**DISCUSSION**

**Case Profiles**

We selected hyperthyroid subjects (Table 1) with no history of arrhythmia, valvular or coronary heart disease, neuromuscular disease, or pulmonary disease which could contribute to their exercise intolerance. Patients performed the identical exercise protocol in hyperthyroid and euthyroid states, and were receiving no medications except those listed in Table 1 to control their hyperthyroidism. In the hyperthyroid state, all patients had increased thyroid hormone levels and suppressed TSH levels. Forfar et al. reported that recovery of left ventricular function is delayed up to 3 months after normalization of serum thyroid hormone levels. Therefore, we performed the second exercise test at least 6 months after thyroid hormone levels returned to normal with treatment.

**Evaluation of Exercise Capacity in Hyperthyroidism**

Maximal VO2 is the end point often used when assessing serial cardiocirculatory reserve. VO2 is considered maximal when subjects reach a plateau in VO2 during a graded exercise protocol. However, Jemtel noted that patients with heart failure are often unable to reach a plateau in VO2 because of limitation by their symptoms. The peak VO2 is therefore obtained at peak exercise. Peak VO2 is not an entirely objective measurement because it is dependent on symptoms and motivation. Moreover, Pina and Karalis have demonstrated that measured maximal VO2 varies with different exercise protocols. In contrast, they found that VO2 at the AT was more reproducible and less effort-dependent than was peak VO2. Because hyperthyroid patients often complain of palpitations or dyspnea similar to patients with congestive heart failure, we chose to analyze our data at the AT rather than at peak exercise.

**Parameters Adopted in This Study**

With exercise, not only the loaded muscle but also other muscles do additional work. Below the AT, the energy source for this total work is derived from aerobic metabolism. Thus, VO2 reflects whole-body total work rate. PRP is an index of cardiac work rate that correlates with myocardial oxygen consumption. Therefore, we used VO2 as a measure of total body work rate, PRP as a measure of cardiac work rate, and loading watts as the target organ's (leg) work rate.

Work efficiency is, by definition, external work divided by energy expended in a steady state. However, several studies have used ΔWatt/ΔVO2 as work efficiency with ramp-loading exercise. In addition, Poole and Henson used ΔWatt/ΔVO2 as the parameter of work efficiency to determine the effect of short-term caloric restriction. Therefore, we chose to estimate work efficiency by this formula during ramp-loading exercise:

\[ \eta = \frac{\Delta \text{Watt}}{\Delta \text{VO}_2} \]

where Δ refers to the increase in each variable from rest to the AT. Since VO2 at rest was higher during hyperthyroidism than after treatment, this convention allows us to compare efficiencies while starting from

**Figure 1.** Increment of oxygen uptake (ΔVO2; mL/min/kg) and pressure rate product (ΔPRP; \(10^5\) mm Hg/min) from rest to the AT and ΔWatt/ΔVO2 in hyperthyroid and euthyroid states. Closed circles=mean value of the hyperthyroid state; open circles=that of the euthyroid state. Bars denote 1 SD.

**Figure 2.** Relationship between VO2 (mL/min/kg) and loading watts through the duration of exercise up to the AT in all patients. Closed circles=mean value of the hyperthyroid state; open circles=that of the euthyroid state. Bars denote 1 SD. "n" denotes the number of patients who completed the given step. "10" means the end of a 10-W constant work load for 5 min. VO2 of the hyperthyroid state was significantly higher (p<0.05) than the euthyroid state at every 10-W step.
patients. Closed circles = mean loading
hyperthyroid state the end of
Interpretation of Figure 3.
work body state reflected the
at PRP slopes of different
in patients by reflected the
found. We
AT
of patients hyperthyroid state. During ramp-loading exercise, Vo2
and PRP in hyperthyroidism were significantly higher than when euthyroid at every workload (Figs 2 and 3). In addition, both ∆Vo2 and ∆PRP were significantly higher in the hyperthyroid state than the euthyroid state (Fig 1). There was also a significant inverse relationship between T3 and ∆Watt/∆Vo2 (Fig 4).

Cardiac output is increased at rest in hyperthyroid states by inotropic and chronotropic effects of thyroid hormone on the heart. However, some studies have shown that hyperthyroidism causes left ventricular dysfunction and an abnormal cardiac response during exercise as assessed by echocardiography23,24 or radionuclide ventriculography.5–7 Forfar et al5 showed a small fall in left ventricular ejection fraction (LVEF) during exercise measured by radionuclide ventriculography, which they believed may explain the exercise intolerance. The mean age of their patients was considerably higher than those in the present study. In contrast, in a study of young hyperthyroid patients with normal cardiac reserve on exercise was reported by Smallridge et al.29 Iskandrian et al26 reported that hyperthyroid patients showed significantly lower LVEF during exercise than normal subjects. However, there were no significant differences between patients with hyperthyroidism and normal subjects in cardiac output, BP, end-diastolic volume, end-systolic volume, stroke volume, and HR during exercise. Shafer and Bianco7 reported impaired LVEF response to exercise in hyperthyroid patients. However, they did not measure cardiac output.7 Furthermore, Hansen et al26 found ∆Vo2/∆Watt can be used to sensitively detect impaired oxygen delivery. In their study, left ventricular dysfunction was associated with a decrease in ∆Vo2/∆Watt.26 In contrast, in the present study, ∆Vo2/∆Watt was higher (∆Watt/∆Vo2 lower) in the hyperthyroid state than the euthyroid state. Increased blood flow to skeletal muscle during exercise in hyperthyroid rats was also reported recently.8 Therefore, we believe thyrotoxic left ventricular dysfunction is unlikely to be a significant contributor to the exercise intolerance of hyperthyroidism.

Martin et al4 have suggested that hyperthyroidism causes exercise intolerance (as measured by peak Vo2) due to decreased skeletal muscle mass. They also found decreased activity of oxidative enzymes in biopsy tissue from normal subjects taking oral T3.4 Other studies reported variable changes in oxidative enzyme capacity: increased,8,27 unchanged,28 and decreased.4

Ben-Dov et al11 studied exercise intolerance in hyperthyroidism using respiratory gas analysis. In their report, the work efficiency in patients with hyperthyroidism did not differ from that in normal subjects. Two patients were restudied after treatment of their hyperthyroid state and their efficiency improved

Figure 3. Relationship between PRP (×10² mm Hg/min) and loading watts through the duration of exercise up to the AT in all patients. Closed circles = mean value of the hyperthyroid state; open circles = that of the euthyroid state. Bars denote 1 SD. "n" denotes the number of patients who completed the given step. "10" means the end of a 10-W constant work load for 3 min. PRP of the hyperthyroid state was significantly higher (p<0.05) than the euthyroid state at every 10-W step.

不同baselines. It is analogous to calculating the slopes of two relationships with differing intercepts.

Interpretation of Findings

We found similar hemodynamics and oxygen uptake at the AT in hyperthyroid and euthyroid states. Total body work rate reflected by Vo2 and cardiac work rate reflected by PRP were similar in both states at the AT, but target organ (leg) work rate was decreased in the

Figure 4. Relationship between serum T3 and ∆Watt/∆Vo2 of all patients in hyperthyroid and euthyroid states. Correlation coefficient and probability value are indicated. Regression equation is also included.

△Watt/△Vo2

(watt/ml/min/kg)

Y=5.19-0.0053X

r=-0.654, p<0.001
slightly. We have extended their findings by studying a larger group of hyperthyroid patients and allowing each patient to serve as his or her own control subject. Our data indicate significant improvement in the work efficiency after effective therapy. We conclude that low exercise capacity is due at least in part to decreased work efficiency.

As to the cause of reduced work efficiency, we speculate as follows: Ianuzzo et al.\(^2\) first demonstrated that hyperthyroidism altered the composition of myosin in rat skeletal muscle, increasing fast myosin and decreasing slow myosin. Others have confirmed that the hyperthyroid state increases fast-twitch or intermediate fibers and decreases slow-twitch fibers in rat and human skeletal muscle.\(^28-30\) Since fast-twitch skeletal muscle is less economic in oxygen utilization during contraction than slow-twitch muscle,\(^31\) this may be one of the causes of reduced work efficiency. Another possibility is that reduced work efficiency is induced by excessive heat production during exercise in patients with hyperthyroidism.\(^32,33\)

In summary, we have measured cardiorespiratory variables up to the AT in both hyperthyroid and euthyroid states with the same exercise protocol. At the AT, HR, systolic BP, and \(V_O_2\) showed no significant difference between the states, but the loading work rate was significantly higher when subjects were euthyroid. \(V_O_2\) and PRP in hyperthyroidism were higher than when euthyroid at each 10-W step during ramp-loading exercise up to the AT. Work efficiency (\(\Delta W_{av}/\Delta V_O_2\)) was decreased in the hyperthyroid state and was inversely correlated with thyroid hormone levels. We conclude that hyperthyroidism decreases the work efficiency of skeletal muscle. This may be an important factor limiting exercise tolerance.

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