Hemodynamics of Hyperthyroidism

The Effects of Autonomic Nervous Blocking and Anti-Thyroid Drug Treatment

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Summary

This work was intended to analyze the sympathetic and parasympathetic factors affecting the hemodynamics of hyperthyroidism.

Seven patients with hyperthyroidism, diagnosed based on the determinations of BMR, $^{131}$I-uptake, $T_3$-resin sponge uptake ($T_3$-RSU), and serum level of thyroxine ($T_4$) were subjected to the study. The hemodynamic estimation was done (1) at rest, (2) after vagus blocking by the injection of $0.04 \text{mg/Kg b.wt.}$ atropine and $0.2 \text{mg/Kg b.wt.}$ propranolol before (hyperthyroid state $= H$) and after (euthyroid state $= E$) anti-thyroid drug therapy. Cardiac output was measured by the dye-dilution method, and the value was calculated according to the standard Hamilton formula.

The following results were obtained. (1) The vagal tone is lower in $H$ than in $E$, on the other hand, sympathetic $\beta$-receptor tone is higher in $H$ than in $E$. (2) The sympathetic $\alpha$-receptor tone in $H$ may be equivalent to that in $E$. (3) There might exist inotropic factors which affect the hemodynamics, other than autonomic nervous system in $H$.

Additional Indexing Words:
Dye-dilution method  Systolic time interval  Intrinsic heart
Propranolol  Atropine  Effects of anti-thyroid drug treatment

It has been described that the cardiovascular manifestations of hyperthyroidism include sinus tachycardia, atrial fibrillation, high output cardiac failure, and others. Theoretically, the hemodynamic characteristics of hyperthyroidism can be understood as a hyperkinetic heart syndrome, consisting of high cardiac output and low peripheral arterial resistance. However, the exact mechanism which makes the heart hyperkinetic has not been fully clarified. Among the many theories on this subject, some investigators think that increased cardiac output in hyperthyroidism is induced by sinus tachycardia, while others think that combined tachycardia and increased cardiac performance make the cardiac output high. These proposals

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are based mostly on the investigations done by using drugs, such as ad-
renergic drugs,\textsuperscript{5)-7) adrenergic-blocking agents,\textsuperscript{5,8)-13) or thyroxine,\textsuperscript{4,14) or by comparing the hemodynamic states before and after treatment of hyper-
thyroidism.\textsuperscript{8,15) It is strange that most investigators have left out the possible role of the
parasympathetic nervous system in analyzing the effects of the sympathetic
nervous system on the hyperthyroid heart. To exclude the contribution of the
autonomic nervous system to the cardiovascular function in this disorder, one should apply atropine or propranolol in full doses. If the dosage of these
drugs is not satisfactory, the autonomic nervous system will not be completely
blocked;\textsuperscript{16} and the experimental results will be uninterpretable. With this
thought in mind, the author attempted to evaluate in the present paper first
the hemodynamics of hyperthyroid patients at rest, and second the significance
of parasympathetic innervation and sympathetic $\beta$-receptors in the hyper-
thyroid heart. For the latter purposes the hemodynamic responses were
measured after the administration of full doses of atropine sulfate or pro-
pranolol after vagal blockade with atropine in both hyperthyroid and eu-
thyroid states. Furthermore, possible factors other than the nervous system
affecting the hyperthyroid heart were studied in the intrinsic heart which was
made by blocking both vagus and sympathetic nerves.

\textbf{Materials and Methods}

The patients were selected consecutively from adults who presented to the
2nd Department of Medicine, Kanazawa University Hospital, with signs and symp-
toms of thyrotoxicosis. Criteria for inclusion were; abnormalities of (1) BMR,
$^{131}$I uptake, $T_3$-resin sponge uptake ($T_3$-RSU), and the serum level of thyroxine ($T_4$); (2) no clinical evidence of congestive heart failure; (3) presence of sinus rhythm.

The hemodynamic analysis was done by dye-dilution method and left ventri-
cular systolic time intervals were obtained by noninvasive technique.

At first, before treatment of thyrotoxicosis, hemodynamical and mechano-
cardiographical studies were done at 3 states; (1) at rest; (2) immediately after
intravenous injection of 0.04 mg/Kg of atropine sulfate; and (3) 2 min after intra-
venous injection of 0.2 mg/Kg of propranolol following the injection of 0.04 mg/Kg
of atropine sulfate. The injection of atropine sulfate or propranolol was performed
within 5 min. The same measurements were done after improvement of hyper-
thyroidism by anti-thyroid drug therapy. The time intervals of 2 measurements
were from 12 to 17 weeks (average 14 weeks) as listed on Table I.

The patients were in the supine position without premedication. A 19-
gauge 300 mm polyethylene catheter for the injection of indocyanine green was
inserted percutaneously into an antecubital vein of right upper limb after localized
anesthesia with xylocain. At the opposite upper limb, 21-gauge Medicut canula\textsuperscript{®}
was inserted into the brachial artery to sample blood containing indocyanine green
for the measurement of cardiac output and to monitor the brachial arterial pressure. The brachial arterial pressure was determined with the transducer and the mean arterial pressure was obtained by electrical integration. The dye-dilution analysis of cardiac output was performed following injection of the indocyanine green (10 mg) with the flash of 10 ml of physiological saline into the central vein and withdrawal of the blood from the brachial artery. A withdrawal perfusion pump (Constant flow system, Gilford) provided a constant flow rate of 37 ml per minute. Two points calibration curves were made in each study. The output signal of the cuvette (SU 861 D, Waters) was coupled to the input of the dye-densitometer (D 400, Waters) and to a National pen recorder VP 2654. The records were obtained at a paper speed of 3 mm per second.

The area under each dye curve was measured by planimetry and the cardiac output was calculated by the standard Hamilton procedure. Hemodynamic parameters were calculated according to the formula as follows:

Cardiac index (CI) = cardiac output / body surface area (BSA)

Stroke index (SI) = CI / heart rate (HR)

Total peripheral resistance index (TPRI)

= mean blood pressure (MBP) × 1332 × 60 / CI / BSA

Left ventricular work index (LVWI)

= MBP × CI × 13.6 / 1000 / BSA

Stroke work index (SWI) = LVWI / HR

Left ventricular work index (LVWI)

= MBP × CI × 13.6 / 1000 / BSA

External carotid wave, intra-brachial arterial pressure curve, electrocardiogram and phonocardiogram were recorded immediately before each cardiac output determination. A microphone was placed over the precordium in a position optimal for recording the initial high frequency vibrations of the first and second heart sounds. For the carotid pulse recordings a Fukuda TY 302 transducer was used. All the parameters were recorded on a Fukuda EMR 401 and San-ei recording oscillograph with the method indicated by Weissler, Harris, and Schoenfeld, left ventricular ejection time, pre-ejection period and isovolumetric contraction time.
were measured from the above recordings, and ET/PEP and mean systolic ejection rate were calculated as follows:

\[
\text{ET/PEP} = \frac{\text{left ventricular ejection time (ET)}}{\text{pre-ejection period (PEP)}}
\]

Mean systolic ejection rate (MSER) = \( \frac{\text{SI}}{\text{ET}} \)

**RESULTS**

(1) Patients studied:

The study population consisted of 5 men and 2 women whose ages averaged 27-year-old (range 19 to 47). The results of the thyroid function tests (BMR, \(^{131}\text{I}\) uptake, T\(_3\)-RSU, and T\(_4\)) for all the patients when they initially presented and after they were successfully treated were shown in Table I.

(2) The hemodynamics of hyperthyroidism at rest:

The results of hemodynamic measurements were listed in Table II and Fig. 1. The heart rate in the hyperthyroid state (98.3 ± 9.9 beats/min) was

**Table II. Hemodynamical Data at Rest, and after Injection of Atropine or Both Atropine and Propranolol**

<table>
<thead>
<tr>
<th></th>
<th>Before or after anti-thyroid treatment</th>
<th>At rest (±SD)</th>
<th>After atropine injection (±SD)</th>
<th>After atropine &amp; propranolol inj. (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR beats/min</td>
<td>before</td>
<td>98.3 ± 9.9</td>
<td>131.9 ± 17.1</td>
<td>97.7 ± 17.4</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>71.0 ± 11.7</td>
<td>113.4 ± 10.4</td>
<td>94.0 ± 7.0</td>
</tr>
<tr>
<td>MBP mmHg</td>
<td>before</td>
<td>83.4 ± 9.3</td>
<td>92.5 ± 11.6</td>
<td>90.1 ± 10.1</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>91.2 ± 7.7</td>
<td>98.2 ± 13.6</td>
<td>96.9 ± 14.1</td>
</tr>
<tr>
<td>CI L/min/M(^2)</td>
<td>before</td>
<td>7.34 ± 2.65</td>
<td>8.00 ± 2.64</td>
<td>6.62 ± 2.52</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>4.96 ± 1.27</td>
<td>5.52 ± 1.18</td>
<td>4.82 ± 1.28</td>
</tr>
<tr>
<td>SI ml/beat/M(^2)</td>
<td>before</td>
<td>74.0 ± 20.4</td>
<td>59.5 ± 12.6</td>
<td>63.2 ± 12.6</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>70.2 ± 10.5</td>
<td>48.8 ± 7.3</td>
<td>51.8 ± 11.9</td>
</tr>
<tr>
<td>TPRIM dyn-sec-cm(^{-4})-M(^{2})</td>
<td>before</td>
<td>984.1 ± 386.4</td>
<td>992.8 ± 381.3</td>
<td>1,605.0 ± 758.0</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>1,606.7 ± 516.4</td>
<td>1,521.5 ± 543.0</td>
<td>1,750.5 ± 662.9</td>
</tr>
<tr>
<td>LVWI Kg/M(^2)</td>
<td>before</td>
<td>8.63 ± 2.96</td>
<td>10.27 ± 2.58</td>
<td>7.50 ± 0.73</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>6.51 ± 1.29</td>
<td>7.65 ± 1.08</td>
<td>6.55 ± 1.08</td>
</tr>
<tr>
<td>SWI Gm-cm/M(^2)</td>
<td>before</td>
<td>87.2 ± 23.1</td>
<td>77.5 ± 10.6</td>
<td>79.9 ± 15.8</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>93.4 ± 14.8</td>
<td>68.2 ± 8.2</td>
<td>70.5 ± 11.7</td>
</tr>
<tr>
<td>PEP msec</td>
<td>before</td>
<td>75.7 ± 16.2</td>
<td>82.9 ± 20.0</td>
<td>89.3 ± 20.5</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>117.1 ± 22.9</td>
<td>100.7 ± 18.4</td>
<td>112.9 ± 21.6</td>
</tr>
<tr>
<td>ET/PEP</td>
<td>before</td>
<td>3.43 ± 1.01</td>
<td>2.79 ± 1.02</td>
<td>3.01 ± 1.03</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>2.59 ± 0.46</td>
<td>2.51 ± 0.56</td>
<td>2.86 ± 0.33</td>
</tr>
<tr>
<td>ICT msec</td>
<td>before</td>
<td>31.4 ± 11.1</td>
<td>38.6 ± 11.4</td>
<td>47.1 ± 16.6</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>74.3 ± 12.7</td>
<td>70.7 ± 15.7</td>
<td>77.9 ± 15.5</td>
</tr>
<tr>
<td>MSER ml/sec/M(^2)</td>
<td>before</td>
<td>307 ± 91</td>
<td>284 ± 66</td>
<td>250 ± 40</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>240 ± 35</td>
<td>203 ± 28</td>
<td>201 ± 50</td>
</tr>
</tbody>
</table>
Fig. 1.
more tachycardic than that in the euthyroid state (71.0±11.7 beats/min). The difference between these values was statistically significant (p<0.005). The cardiac index in the hyperthyroid state (7.34±2.65 L/min/M²) was higher than that of the euthyroid state (4.96±1.27 L/min/M²), but the difference between 2 states was statistically not significant (p<0.10). The stroke index in hyperthyroidism was not different from that in euthyroidism.

The total peripheral resistance index in the hyperthyroid state (984.1±386.6 dyn·sec·cm⁻⁵·M²) was lower than that in the euthyroid state (1,606.7±516.4 dyn·sec·cm⁻⁵·M²). The difference was significant (p<0.05).

The pre-ejection period, as respect to contractility of left ventricular myocardium, in the hyperthyroid state (75.7±16.2 msec) was significantly (p<0.01) shorter than that in the euthyroid state (117.1±22.9 msec). The ET/PEP was significantly (p<0.025) higher in the hyperthyroid state (3.43±1.01) than in the euthyroid state (2.59±0.46).

(3) The hemodynamic response to atropine injection:

Table III. Hemodynamical Changes Induced by Injection of Atropine Sulfate or Propranolol after Atropinization

<table>
<thead>
<tr>
<th></th>
<th>Before or after anti-thyroid treatment</th>
<th>Atropine inj. (±SD)</th>
<th>p value</th>
<th>Propranolol inj. (±SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR beats/min</td>
<td>before</td>
<td>+33.6 ± 8.4</td>
<td>0.001</td>
<td>−34.1 ± 10.3</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>+42.4 ± 6.1</td>
<td>0.001</td>
<td>−19.4 ± 5.9</td>
<td>0.001</td>
</tr>
<tr>
<td>MBP mmHg</td>
<td>before</td>
<td>−2.4 ± 4.8</td>
<td>n.s.</td>
<td>+6.7 ± 9.7</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>−1.3 ± 2.6</td>
<td>n.s.</td>
<td>+5.7 ± 8.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>CI L/min/M²</td>
<td>before</td>
<td>+1.33±0.94</td>
<td>0.025</td>
<td>−1.81±1.97</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>+0.57±0.50</td>
<td>0.05</td>
<td>−0.70±0.71</td>
<td>0.10</td>
</tr>
<tr>
<td>SI ml/beat/M²</td>
<td>before</td>
<td>−14.5±12.8</td>
<td>0.05</td>
<td>+3.7±18.3</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>−21.3±8.6</td>
<td>0.001</td>
<td>+3.0±7.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>TPRI dyn·sec·cm⁻⁵·M²</td>
<td>before</td>
<td>+25.3±198.5</td>
<td>n.s.</td>
<td>+262.9±113.1</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>−82.2±177.9</td>
<td>n.s.</td>
<td>+227.9±211.6</td>
<td>0.05</td>
</tr>
<tr>
<td>LVWI Kg·M/M²</td>
<td>before</td>
<td>+1.86±1.92</td>
<td>0.10</td>
<td>−2.76±2.27</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>+1.55±1.21</td>
<td>0.05</td>
<td>−1.12±0.91</td>
<td>0.05</td>
</tr>
<tr>
<td>SWI Gm·cm/M²</td>
<td>before</td>
<td>−8.52±21.2</td>
<td>n.s.</td>
<td>+2.4±24.2</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>−25.1±11.7</td>
<td>0.001</td>
<td>+2.3±9.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>PEP msec</td>
<td>before</td>
<td>+7.1±9.1</td>
<td>0.10</td>
<td>+6.4±4.8</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>−16.4±15.5</td>
<td>0.005</td>
<td>+12.1±10.4</td>
<td>0.001</td>
</tr>
<tr>
<td>ET/PEP</td>
<td>before</td>
<td>−0.64±0.27</td>
<td>0.001</td>
<td>+0.22±0.36</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>−0.07±0.41</td>
<td>n.s.</td>
<td>−0.15±0.24</td>
<td>n.s.</td>
</tr>
<tr>
<td>ICT msec</td>
<td>before</td>
<td>+7.1±7.6</td>
<td>0.05</td>
<td>+8.6±7.5</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>−4.3±14.6</td>
<td>n.s.</td>
<td>+7.1±13.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>MSER ml/sec/M²</td>
<td>before</td>
<td>−23±55</td>
<td>n.s.</td>
<td>−33±59</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>−37±27</td>
<td>0.02</td>
<td>−2±35</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
The results were listed in Tables II and III and Fig. 1. The heart rate was significantly increased in both hyperthyroid and euthyroid states. The increase of heart rate in the hyperthyroid state was less than that in the euthyroid state (p<0.05). The increase of cardiac index was higher in hyperthyroidism (+1.33±0.94 L/min/M²) than euthyroidism (+0.57±0.59 L/min/M²), but the difference was statistically not significant (p>0.10). The stroke index decreased in both states. The total peripheral resistance index did not change in both states. The pre-ejection period was shortened in the euthyroid state (p<0.05) while it was not changed significantly in the hyperthyroid state, and the isovolumetric contraction time was prolonged in the hyperthyroid state (p<0.05) while there was no significant change in the euthyroid state.

(4) The hemodynamic changes induced by propranolol injection:

The results were shown in Table II and III and Fig. 1. The heart rate in the hyperthyroid state (-34.1±10.3 beats/min) was more significantly (p<0.01) decreased than in the euthyroid state (-19.4±5.9 beats/min). The cardiac index was tended to decrease in the hyperthyroid state (-1.81±1.97 L/min/M²), and decreasing of the cardiac index in the hyperthyroid state was greater than in the euthyroid state. But the difference was statistically insignificant (p>0.10). The stroke index was not changed. The total peripheral resistance index was increased in both states, but the value was not different between them statistically.

The pre-ejection period was prolonged in both hyperthyroid (+6.4±4.8 msec) and euthyroid state (+12.1±10.4 msec), and the isovolumetric contraction time was prolonged in the hyperthyroid state (+8.6±7.5 msec) and the euthyroid state (+7.1±13.2 msec).

(5) The hemodynamics of hyperthyroidism in intrinsic heart:

The intrinsic heart was made by blocking of both vagus and sympathetic nervous system with the injection of atropine and propranolol satisfactorily. The results were listed on Tables II and IV and Fig. 1. The heart rate was not different between both hyperthyroid and euthyroid states. The cardiac index and the stroke index tended to lower in the euthyroid state than in the hyperthyroid state, but not statistically significant. The total peripheral resistance indexes were not changed in intrinsic heart after the treatment of hyperthyroidism. When comparing the hemodynamics of intrinsic heart in hyperthyroidism and euthyroidism an interesting feature was seen in the results of systolic time intervals. That is, the pre-ejection period and the isovolumetric contraction period significantly prolonged after the treatment of hyperthyroidism. The ET/PEP also decreased significantly, indicating that the left ventricular performance of intrinsic heart in hyper-
EFFECT OF HYPERTHYROIDISM

Table IV. Hemodynamical Change Induced by Treatment of Hyperthyroidism at Rest and Intrinsic Heart

<table>
<thead>
<tr>
<th></th>
<th>At rest (±SD)</th>
<th>p value</th>
<th>Intrinsic heart (±SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR beats/min</td>
<td>-27.3 ± 16.9</td>
<td>0.005</td>
<td>-3.7 ± 17.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>MBP mmHg</td>
<td>+11.9 ± 11.1</td>
<td>n.s.</td>
<td>+7.9 ± 13.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>CI L/min/M²</td>
<td>-2.44 ± 2.91</td>
<td>0.10</td>
<td>-1.80 ± 2.86</td>
<td>n.s.</td>
</tr>
<tr>
<td>SI ml/beat/M²</td>
<td>-3.8 ± 24.0</td>
<td>n.s.</td>
<td>-11.3 ± 21.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>TPRi dyn·sec·cm⁻³·M²</td>
<td>+622.6± 587.6</td>
<td>0.05</td>
<td>+480.7± 658.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>LVWI Kg·M⁻³</td>
<td>-2.12 ± 3.28</td>
<td>n.s.</td>
<td>-0.98 ± 1.14</td>
<td>n.s.</td>
</tr>
<tr>
<td>SWI Gm·cm/M²</td>
<td>+6.1 ± 31.7</td>
<td>n.s.</td>
<td>-9.4 ± 20.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>PEP msec</td>
<td>+41.4 ± 16.8</td>
<td>0.01</td>
<td>+23.6 ± 21.5</td>
<td>0.05</td>
</tr>
<tr>
<td>ICT msec</td>
<td>+42.9 ± 11.9</td>
<td>0.001</td>
<td>+30.7 ± 16.4</td>
<td>0.02</td>
</tr>
<tr>
<td>ET/PEP</td>
<td>-0.84 ± 0.72</td>
<td>0.025</td>
<td>-0.75 ± 0.72</td>
<td>0.05</td>
</tr>
<tr>
<td>MSER ml/sec/M²</td>
<td>-68± 110</td>
<td>n.s.</td>
<td>-49± 71</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

thyroidism is significantly stronger than in euthyroidism.

DISCUSSION

Numerous reports regarding the hemodynamics of hyperthyroidism have appeared. Recent availability of the sympathetic β-receptor blocker, e.g. propranolol, has enabled us to evaluate more properly the sympathetic tone in the hyperthyroid heart. However, with such an approach at least 3 problems should be taken into consideration. Among these, the first issue is how to manage the parasympathetic nervous system which antagonizes the sympathetic nervous system. Second, what dosage of sympathetic β-blocker is sufficient to block the action of sympathetic nervous system in the human heart? The third problem is whether other factors affecting the hemodynamics of hyperthyroidism may exist or not.

In the present study, the author solved the first problem by injection of atropine sulfate, which is known to block vagus nerves, prior to the administration of sympathetic β-blockade. In this way, the author could minimize the antagonism of the vagus nerves after sympathetic β-blockade and also evaluate the effect of the parasympathetic nervous system on the hyperthyroid heart.20) As to the dosages of sympathetic β-blocker and atropine sulfate, the author used full dosage; 0.2 mg/Kg b.wt. for propranolol and 0.04 mg/Kg b.wt. for atropine sulfate according to the papers described by Jose and others.21)-24) It has been confirmed that the drugs in these dosages block essentially all the autonomic nervous system in man; and thus, the so-called intrinsic heart is prepared.
For the last problem, the author compared the hemodynamics of intrinsic hearts without autonomic nervous function before and after anti-hyperthyroid drug treatment. This comparison enabled us to evaluate the difference between the hyperthyroid state and the euthyroid state without consideration of the sympathetic and parasympathetic nervous effects on the hemodynamics of these states.

In this study the heart rate was analyzed as an index of chronotropic effect; the stroke volume, cardiac output, and hemodynamic ratio (ET/PEP) as indexes of the pump function of the heart;\textsuperscript{25,26} the pre-ejection period and isovolumetric contraction time as indexes of cardiac contractility;\textsuperscript{25-27} and the total peripheral resistance as an index of the peripheral arterial condition. The hemodynamic characteristics of hyperthyroidism obtained in this study coincided with the results described in the previous literature, that is, tachycardia,\textsuperscript{3,15} tendency to increase in the stroke volume and cardiac output,\textsuperscript{3,15} decrease in the peripheral arterial resistance,\textsuperscript{1,28} shortening of the pre-ejection period and isovolumetric contraction time,\textsuperscript{29,30} and increase in the hemodynamic ratio. These results suggested that the chronotropism and the left ventricular performance in hyperthyroidism were stronger than those in euthyroidism.

Next, the euthyroid state responded to the infusion of atropine sulfate with more increased heart rate than the hyperthyroid state.\textsuperscript{31} Therefore, concerning the chronotropic effect, vagal tone seems to be higher in euthyroidism than in hyperthyroidism. The cardiac index increased in both the hyperthyroid and euthyroid states by atropine injection, while the stroke index decreased. The author, however, is careful in evaluating the results of cardiac pump function because over-increasing of the heart rate by injection of atropine sulfate may be inadequate to fill the left ventricle, and consequently, the stroke volume cannot be maintained above the same level after all. The stroke volume might decrease after atropinization in the 2 states. Since the change in cardiac output mostly depend on the change of heart rate in this situation,\textsuperscript{32,33} a justifiable evaluation of cardiac pump function is difficult. Then, measurement of the pre-ejection period, the isovolumetric contraction time, and the hemodynamic ratio were rather helpful as indexes of left ventricular performance.\textsuperscript{34,35} These indexes moved toward the direction of decreased cardiac performance in hyperthyroidism after atropinization, but did not change or moved rather to the direction of increase of cardiac performance in euthyroidism.

Discussing the hemodynamic change after propranolol injection based on our study, the heart rate decreased, the cardiac pump function decreased, and the cardiac contractility also decreased in both the 2 states. These
changes were larger in hyperthyroidism than in euthyroidism.

From these results, the author concludes that the vagal tone is lower in hyperthyroidism than in euthyroidism; on the other hand, the sympathetic $\beta$-receptor tone is higher in hyperthyroidism than in euthyroidism. Especially the tachycardia in hyperthyroidism is the most dominant characteristic which results from the above-mentioned trial of the autonomic nervous function. Increase of left ventricular contractility, which is thought to be another characteristic facet of the hyperthyroid heart, was never relieved by infusion of atropine sulfate and propranolol as demonstrated by comparing the hemodynamics of the intrinsic heart before and after anti-thyroid treatment. The author has compared the intrinsic heart of hyperthyroid state with that of euthyroid state. The pre-ejection period, isovolumetric contraction time, and hemodynamic ratio all changed to decrease the left ventricular contractility or performance after anti-thyroid drug treatment; and the stroke index and cardiac index tended to decrease while the heart rate or total peripheral resistance did not change in this transitional treatment state. From these results, it is more likely that some factors other than the sympathetic and parasympathetic nervous system play a role in the increase of left ventricular contractility in the hyperthyroid state. The author feels that thyroxine might be incriminated as increasing the left ventricular contractility, since basically this hormone has been known to increase the inotropic effect on heart muscle besides the sympathetic nervous system.4),14),36) According to our study, the heart rate of the hyperthyroid state did not differ from that of the euthyroid state in comparison with the intrinsic heart, while the heart rate decreased with anti-thyroid drug treatment without other pharmacological management. McDevitt et al described that the tachycardia in the patients with hyperthyroidism was caused by the direct action of thyroxine,37) but according to above results of our study we think that the thyroxine itself has no effect on the heart rate in the patients with hyperthyroidism. Theilen et al concluded in their report that the increased cardiac output in thyrotoxicosis may be in part secondary to peripheral vasoconstriction by the study of phenylephrine infusion,38) While the total peripheral resistance index in the intrinsic heart showed no difference between the hyperthyroid state and the euthyroid state in our study. This suggests that the sympathetic $a$-receptor may not function differently in the hyperthyroidism as compared with the euthyroidism.

CONCLUSION

1. The hemodynamics of hyperthyroidism are characterized by tachy-
cardia, high cardiac output, low peripheral arterial resistance, and a short pre-ejection period.  

(2) The high cardiac output is mainly caused by tachycardia, although it partly depends on increased cardiac performance.  

(3) The autonomic nervous system affects hyperthyroidism, especially in causing tachycardia. The parasympathetic nervous tone is lower in hyperthyroidism than in euthyroidism. The sympathetic β-receptor tone is higher in hyperthyroidism than in euthyroidism.  

(4) In comparison of the intrinsic heart preparation of hyperthyroidism and euthyroidism, there may be some factor which acts directly on cardiac muscle and strengthens cardiac performance more in hyperthyroidism than in euthyroidism.  

(5) Total peripheral resistance in the intrinsic heart of hyperthyroidism is not different from that of euthyroidism. The α-receptor and any other factors making the peripheral arteries dilate may not affect differently the hyperthyroidism from the euthyroidism.

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