Evaluation of Cardiac Reserve in Hyperthyroid Patients with or without Beta-Adrenoreceptor-Blockade by Handgrip Exercise

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Key words: Graves' disease, Thyroid hormones, Beta-blocker, Cardiac reserve, Handgrip exercise, Left Ventricular function

Abstract

To evaluate latent left ventricular dysfunction in patients with Graves' disease, hemodynamic response to isometric exercise were examined in 93 patients and 18 controls by impedance cardiography. All patients were treated with anti-thyroid drugs and 64 patients were still clinically thyrotoxic with elevated triiodothyronine (T3) in serum. The remaining 29 patients were clinically free of thyrotoxicosis with normal serum T3. Thirty three of 93 patients received beta-blocker.

The distinct elevation of cardiac index (CI), associated with elevation of cardiac work index (CWI) and total peripheral resistance index (TPRI), was observed during the exercise in control group. Values for CWI and TPRI were apparently elevated in all patients studied, and the magnitude of the alterations in CWI and TPRI before and during the exercise was almost the same as that observed in control group. However, the CI values were almost unchanged before and during the exercise in hyperthyroid patients without beta-blockade, suggesting the impaired cardiac reserve in hyperthyroidism. Moreover, it was noteworthy that CI values before and during the exercise were also unchanged even in euthyroid patients without beta-blockade. This result supports the contention that a biochemical euthroid state may be achieved many weeks before normalization of contractile response to exercise.

There was a significant correlation between serum T3 and CI at rest in 60 patients without beta-blockade, but this correlation was lost in 33 patients, who received beta-blocker. The beta-blocker induced reduction of the resting CI was evident in hyperthyroid patients, and this reduction of CI values was also observed in these patients with beta-blocker during exercise, showing negative inotropic effects of the beta-adrenoreceptor blocking drugs. Thus, beta-blocker may be beneficial in lowering heart rate in severe hyperthyroidism, but the beta-blockade should
be avoided in euthyroid patients, who showed the delayed recovery of left ventricular function after antithyroid treatment.

**Introduction**

Since palpitation and dyspnea on exertion are common in hyperthyroidism, it was important to elicit latent left ventricular dysfunction in hyperthyroidism. Left ventricular ejection fraction (LVEF) in patients with hyperthyroidism has been measured by several investigators, using radio-nuclide ventriculography at rest and during dynamic ergometer exercise. The LVEF in hyperthyroidism was unchanged or even reduced during dynamic exercise, and this reduction was independent of beta-adrenoreceptor activation. These data demonstrated that hyperthyroidism is associated with impaired functional cardiac reserve from a direct effect of excess thyroid hormones. In more recent work, the effect of isometric exercise on left ventricular function has been evaluated and delayed recovery of left ventricular function after antithyroid treatment has been shown in hyperthyroid patients. However, this study was undertaken in only 15 cases.

Therefore in the present study, cardiac response to isometric handgrip was examined in hyperthyroid Graves' patients and in those maintained in euthyroid state by antithyroid drugs, and, moreover, the effect of beta-adrenoreceptor blockade was also evaluated in these patients.

**Methods**

1) Patients: The study group included 93 patients with Graves' diseases, referred to Kansai Medical University Hospital. All patients were clinically free of heart failure at the time of the study and none of the patients had evidence of cardiovascular disease on the basis of history, clinical examination, electrocardiogram (ECG) or chest X ray. All patients were in sinus rhythm during the study and patients with renal or hepatic dysfunction or other endocrine disorders were not included. All patients were treated with antithyroid drugs (Methimazole) for at least 1 month and up to 3 years. Sixty four patients were still clinically thyrotoxic with high level of serum triiodothyronine (T₃) and were classified as hyperthyroid group. The remaining 29 patients were clinically free of thyrotoxicosis with entirely normal serum thyroxine (T₄) and T₃ and were classified as euthyroid group. Thirty three of 93 patients received beta-blocker (propranolol) with daily dose of 30 mg for at least 1 month before and at the time of the study.

Eighteen subjects with no evidence of renal, hepatic or endocrine diseases were also studied as control group. None of the controls received medications before and during the study.

2) Measurements: Serum T₄ and T₃ were measured by the commercial radioimmunoassay.
kits, purchased from Dainabot Radioisotope Laboratories (Tokyo, Japan). The normal ranges of T₄ and T₃ were 4.5 to 13.5 µg/dl and 84 to 160 ng/dl, respectively. The determination of serum free T₄ (FT₄) was carried out by the radioimmunoassay kit provided by Amersham (Tokyo, Japan). The normal subjects showed free T₄ values ranging from 1.07 to 2.44 ng/dl. There were no significant differences in T₄, T₃ and FT₄ values of the same serum determined in two consecutive assays. Moreover, the coefficients of variation for triplicate determinations within an assay in those hormones were 11.2% in a normal subject, thyrotoxic and hypothyroid patients.

3) Procedure: The impedance cardiography was used to measure hemodynamic parameters as previously reported. The ECG (lead II) and heart sound of the third intercostal space along the left sternal border were also recorded simultaneously. The stroke volume (SV) was obtained from the cardiograph and the stroke index (SI) was calculated by adjusting to 1 m² body surface area (BSA). Heart rate (HR) was calculated from the R–R intervals. Systolic (BPs) and diastolic blood pressure (BPd) were measured in the nonexercising arm using the automatic sphygmomanometer BO-103 (Nippon Cohlin, Inc.) and mean blood pressure (mBP) was calculated: mBP = 1/3 × (BPs – BPd) + BPd. Cardiac Index (CI), total peripheral resistance index (TPRI), and cardiac work index (CWI) were also calculated: CI (l/min/ m²BSA) = SI × HR, TPRI (dyne·sec·cm⁻⁵) = mBP/SI × HR, CWI (dyne·sec·cm⁻¹) = mBP × CI.

Isometric handgrip exercise was performed with a continuous handgrip effort on a Smedley’s hand dynamometer at an intensity of 50% of previously determined maximal voluntary contraction for 1 minute in the supine position. The measurements were obtained after 20 minutes supine rest and at the last 10 seconds of the handgrip exercise.

4) Statistical analysis: Results were expressed as mean ± standard deviation (SD). Comparisons have been made by means of student’s t test for grouped data. A paired t test was used to compare the values before and after handgrip exercise. A p-values below 0.05 were considered significant. Correlation coefficients were calculated by the standard technique.

Results

Forty nine of 64 patients in hyperthyroid group had elevated T₄ and FT₄ levels. The remaining 15 patients had entirely normal T₄ and FT₄ levels, despite maintenance of clinically thyrotoxic state. Moreover, serum T₄ or FT₄ levels did not relate significantly to CI values at rest in all patients of hyperthyroid group. On the other hand, all patients in hyperthyroid group had elevated T₃ levels and a significant relation existed between T₃ levels and CI values at rest (r = 0.31, p < 0.05). In view of these findings, the patients in hyperthyroid group were divided into 2 groups, severe hyperthyroid and moderate hyperthyroid group, based upon the results of
measurements of serum $T_3$. All patients of severe hyperthyroid group had serum $T_3$ levels of 320 ng/dl or more, whereas $T_3$ levels in all patients of moderate hyperthyroid group ranged from 170 to 316 ng/dl.

No significant relation was found between CI values at rest and serum $T_3$ levels in all patients with beta-blockade. On the other hand, a highly significant relation between CI values at rest and serum $T_3$ levels was found in the patients, who did not receive beta-blocker ($r=0.56$, $p<0.001$, Fig. 1). Therefore, each group was further divided into 2 groups, based on whether beta-blocker was given or not. The patients of group I in severe hyperthyroid group did not receive beta-blocker and those of the group II received beta-blocker. The patients without beta-blockade in moderate hyperthyroid group were classified as group III and those treated with beta-blocker as group IV. The patients of euthyroid group were also divided into group V.

**Table 1** Number of cases and mean ages in each group of patients with Graves' disease

<table>
<thead>
<tr>
<th>Serum $T_3$</th>
<th>$320 \leq T_3$ (ng/dl)</th>
<th>$160 &lt; T_3 &lt; 320$</th>
<th>$84 \leq T_3 \leq 160$</th>
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<tbody>
<tr>
<td>Beta-blocker (−)</td>
<td>Male 3</td>
<td>Male 4</td>
<td>Male 1</td>
</tr>
<tr>
<td>Group I</td>
<td>Female 16</td>
<td>Group III</td>
<td>Female 18</td>
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<tr>
<td>Age 30±11</td>
<td>Age 30±12</td>
<td>Age 28± 9</td>
<td>Age 27±11</td>
</tr>
<tr>
<td>Beta-blocker (+)</td>
<td>Male 5</td>
<td>Male 4</td>
<td>Male 4</td>
</tr>
<tr>
<td>Group II</td>
<td>Female 8</td>
<td>Group IV</td>
<td>Female 6</td>
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<tr>
<td>Age 30±11</td>
<td>Age 30± 8</td>
<td>Age 32± 8</td>
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$T_3$, triiodothyronine.
Table 2  Summary of hemodynamic indices at rest and during handgrip exercise

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>BPs (mmHg)</th>
<th>BPd (mmHg)</th>
<th>mBP (mmHg)</th>
<th>SI (ml)</th>
<th>CI (l/min/m²)</th>
<th>CWI (dyne ⋅ sec ⋅ cm⁻¹)</th>
<th>TPRI (dyne ⋅ sec ⋅ cm⁻⁵)</th>
</tr>
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<tbody>
<tr>
<td>Group I</td>
<td>C</td>
<td>95±15 106±17***</td>
<td>126±14 148±16***</td>
<td>49±19 76±24***</td>
<td>75±11 100±16***</td>
<td>76±19 69±17**</td>
<td>7.1±1.6 7.2±1.5</td>
<td>6.5±1.8 8.8±2.2***</td>
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<td></td>
<td>HG</td>
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<tr>
<td>group II</td>
<td>C</td>
<td>84±17 97±17***</td>
<td>129±15 159±26***</td>
<td>51±18 77±27***</td>
<td>77±11 104±19***</td>
<td>60±20 54±20***</td>
<td>5.0±1.5 5.1±1.5</td>
<td>5.0±1.8 7.0±2.5***</td>
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<tr>
<td>group III</td>
<td>C</td>
<td>75±11 90±11***</td>
<td>118±14 143±22***</td>
<td>53±15 81±14***</td>
<td>74±9 102±12***</td>
<td>75±20 66±21***</td>
<td>5.6±1.5 5.8±1.6</td>
<td>5.3±1.5 7.7±2.1***</td>
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<td></td>
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<tr>
<td>group IV</td>
<td>C</td>
<td>79±10 90±12***</td>
<td>123±10 150±20***</td>
<td>48±16 77±21**</td>
<td>73±9 102±18***</td>
<td>72±16 60±10**</td>
<td>5.7±1.2 5.4±1.0</td>
<td>5.3±1.1 7.2±2.2*</td>
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<td></td>
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<tr>
<td>group V</td>
<td>C</td>
<td>69±9 77±10***</td>
<td>114±7 131±9 ***</td>
<td>67±16 80±14***</td>
<td>83±12 97±10***</td>
<td>73±17 67±16***</td>
<td>5.0±1.2 5.1±1.2</td>
<td>5.3±1.4 6.4±1.5***</td>
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<tr>
<td>HG</td>
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<tr>
<td>group VI</td>
<td>C</td>
<td>68±12 79±14***</td>
<td>115±11 142±20***</td>
<td>60±11 86±14***</td>
<td>78±8 105±15***</td>
<td>70±9 60±12***</td>
<td>4.6±0.7 4.7±1.1</td>
<td>4.7±1.0 6.8±1.7***</td>
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<tr>
<td>HG</td>
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<td></td>
</tr>
<tr>
<td>control</td>
<td>C</td>
<td>65±10 78±14***</td>
<td>118±12 141±17***</td>
<td>69±12 92±15***</td>
<td>86±11 108±14***</td>
<td>71±17 66±10*</td>
<td>4.8±1.2 5.2±1.4**</td>
<td>5.1±1.3 7.2±2.3***</td>
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HR, heart rate; BPs, systolic blood pressure; BPd, diastolic blood pressure; mBP, mean blood pressure; SI, stroke index; CI, cardiac index; CWI, cardiac work index; TPRI, total peripheral resistance index; C, at rest; HG, during handgrip exercise.

The values were compared before and after the exercise (* P<0.05, ** P<0.01, *** P<0.001)
(without beta-blockade) and group VI (with beta-blockade). The mean ages and number of cases in each group are listed in Table 1.

In control group, values for SI at rest ranged from 56 to 99 ml/m² BSA (mean ±SD, 71 ±17) and the CI value at rest averaged 4.8 ±1.21/min./m² BSA (Table 2). The resting TPRI and CWI values in this group averaged 1,537 ±555 dyne·sec·cm⁻⁵ and 5.1 ±1.3 dyne·sec·cm⁻¹, respectively (Table 2).

Values for SI at rest in patients of group I tended to elevate, ranging from 60 to 120 (76 ±19, Table 2), as compared with those in control group. However, no significant difference existed between SI values in group I and those in control group. A significant increases of the resting HR were observed in patients of group I (95 ±15 vs. 65 ±10 in control group, p<0.001, Table 2), and, therefore, values for CI at rest, representing the product of SI values and HR, revealed marked elevation in patients of group I (7.1 ±1.6 vs. 4.8 ±1.2 in control group, p<0.001, Table 2). Since the resting mBP values (75 ±11) in group I did not differ from those (86 ±11) in control group, the mean value for the resting CWI, representing the products of mBP and CI, was also significantly elevated in patients of group I (6.5 ±1.8 vs. 5.1 ±1.3 in control group, p<0.05, Table 2). Because of the marked elevation of CI in group I, values of the resting TPRI, representing the quotient of mBP and CI, was markedly reduced (907 ±271), when compared with those in control group (1,537 ±555, Table 2). Values for SI tended to decrease in patients of group II (60 ±20 vs. 71 ±17 in control group, Table 2). The resting HR was significantly increased in group II (84 ±17), as compared with that in control group (65 ±10); the increased HR offset the reduced SI in yielding similar CI values (5.0 ±1.5) to those in control group (4.8 ±1.2, Table 2). The mean values of the resting CWI and TPRI in group II were 5.0 ±1.8 and 1,261 ±390, respectively and values for TPRI tended to reduce, as compared with those of control group (Table 2).

In patients of moderate hyperthyroid group, values for SI at rest did not significantly differ from those of control group, regardless of subdivision into groups III and IV. Mean values for CI at rest both in group III (5.6 ±1.5) and in group IV (5.7 ±1.2) did not significantly differ from that in control group (4.8 ±1.2, Table 2). The resting values for TPRI in group III and IV averaged 1,086 ±382 and 1,017 ±292, respectively; values were significantly lower than those in control group (1,537 ±555, Table 2). The mean values of CWI at rest in both group III and IV did not differ from that in control group.

The resting values for SI, CI, CWI and TPRI in patients of euthyroid group were almost the same as those of control group (Table 2).

In all patients studied in the present paper, values for BPs and BPd were elevated during isometric handgrip exercise and the differences in blood pressure between at rest and during
the exercise in all patients with Graves' disease were almost similar to those in control group (Table 2). The findings suggested that the isometric exercise, employed in the present study, induced vasopressor responses of similar mean magnitude in all patients.

A significant reduction of SI values in control group was observed during the exercise (66±19 vs. 71±17 at rest), while values for CI during the exercise (5.2±1.4) were significantly elevated by the modest increase in HR, when compared with those at rest (4.8±1.2). Moreover, the expected increases of CWI (7.2±2.3) and of TPRI (1,789±641) were observed during the handgrip exercise (Table 2).

In patients of severe hyperthyroid group, values for SI during the exercise were somewhat reduced either in group I or in group II, although the differences were not significant (Table 2). The modest increases in HR during the exercise were observed in all patients of severe hyperthyroid group. Values for CI in 18 of 19 patients in group I were almost unchanged before and during the exercise and the mean CI value during the exercise in this group (7.2±1.5) was almost unchanged, as compared with that at rest (7.1±1.6). Values for CI in all patients in group I were also almost unchanged before and during the exercise (5.0±1.5 at rest vs. 5.1±1.5 during the exercise, Table 2). The exercise induced elevations of CWI and TPRI values were found both in group I and in group II, and the magnitude of the alterations was almost the same as that in control group (Table 2).

Reduction of SI values during the exercise was observed in 21 of 22 patients of group III and in all patients of group IV and this reduction of SI was statistically significant in group IV (60±10 during the exercise vs. 72±16 at rest, Table 2). The modest increases in HR were also observed in all patients of moderate hyperthyroid group. Therefore, values for CI in group III were unchanged before and during the exercise (Table 2). The mean value of CI during the exercise in group IV (5.4±1.0) tended to diminish, when compared with that at rest (5.7±1.2). The almost similar changes of CWI and TPRI values during the exercise were found in all patients of moderate hyperthyroid group, as compared with either in control group or in severe hyperthyroid group (Table 2).

In patients of euthyroid group, values for SI were also reduced, regardless of subdivision into groups V and VI (Table 2). Although HR was increased during the exercise, values for CI were still unchanged before and during the exercise (5.0±1.2 at rest vs. 5.1±1.2 during the exercise in group V and 4.6±0.7 at rest vs. 4.7±1.1 during the exercise in group VI, Table 2), despite maintenance of clinically euthyroid state. The magnitude of the elevations in CWI and TPRI, induced by the exercise, in all patients of euthyroid group was almost similar to that observed in all other groups including the control group (Table 2).
Discussion

All patients studied in the present paper received antithyroid drugs and, nevertheless, 64 patients were still clinically thyrotoxic together with the elevation of serum T₃ levels. Moreover, a significant relation was found between T₃ levels and the resting values for CI in these patients. Therefore, the present patients were divided into 2 groups, severe hyperthyroid and moderate hyperthyroid groups, based upon the results of serum T₃ measurement. Values for CI at rest were markedly elevated in patients without beta-blockade in severe hyperthyroid group. This finding was consistent with the results obtained previously. The resting CI values in all patients of moderate hyperthyroid group were intermediate between CI values in the patients of severe hyperthyroid group and normal CI values. Moreover, values for CI in euthyroid group were almost similar to those in control group. These results support the validity of the present estimates of CI values by impedance cardiography. Furthermore, the findings also provide validation of the proposed classification in the present study.

It was noteworthy that the values for TPRI at rest were markedly reduced in patients of group I. Since TPRI values in group II were almost identical to those in control group, the reduction of resting TPRI in group I might be due to β₂ receptor stimulating effect of thyroid hormones, although this was tentative speculation pending more extensive findings. In spite of beta-blockade, blood pressure remained unchanged in group II. This result may be explained by almost identical CI and TPRI values in group II to those in control group.

Various forms of stress have been used to detect mild left ventricular dysfunction. The isometric stress can be easily done in that it may be useful to elicit latent left ventricular dysfunction. Therefore, in the present study, cardiac reserve was assessed using the isometric handgrip exercise. The distinct elevation of CI values, associated with elevation of CWI and TPRI, was observed during the exercise in control group. Values for CWI and TPRI were apparently elevated in all patients studied, and the magnitude of the alterations in CWI and TPRI before and during the exercise was almost the same as that observed in control group. On the other hand, the CI values were almost unchanged before and during the exercise in hyperthyroid patients. Moreover, it was remarkable that CI values before and during the stress were also unchanged even in euthyroid patients.

Cardiac performance in patients with hyperthyroidism has been extensively studied using M-mode echocardiography, systolic time intervals and radionuclide cardiac imaging. With regard to cardiac reserve in hyperthyroid state, Shafer and Bianco have demonstrated that LVEF, estimated by radionuclide cardiography, was unchanged before and during the ergometer exercise in thyrotoxic patients. Moreover, even reduced values for LVEF during the exercise in hyperthyroidism were observed by Forfar et al. The present
findings were consistent with the previous results which demonstrated the impaired cardiac reserve in hyperthyroidism\textsuperscript{1,2).} The reversible changes of left ventricular dysfunction were observed in hyperthyroid patients\textsuperscript{2)}, and, moreover, it was demonstrated that a biochemical euthyroid state may be achieved many weeks before normalization of contractile response to exercise\textsuperscript{3)}. This delayed normalization of left ventricular function was also observed in the present study and the findings support the concept of structural changes in the hyperthyroid heart that resolve at a rate appreciably slower than the hyperthyroidism itself\textsuperscript{3)}. 

The beta-adrenoreceptor blockade can produce significant improvement of the cardiovascular status in patients with hyperthyroidism, although correction of the basic metabolic defect required antithyroid drugs. In the present study, beta-blocker treated patients in moderate hyperthyroid group had almost the same CI values at rest as those in control group, despite clinically thyrotoxic state. The beta-blocker induced reduction of the resting CI was also evident in severe hyperthyroid group, associated with markedly elevated T\textsubscript{3} values in serum. No significant relation existed between T\textsubscript{3} and the resting CI values in thyrotoxic patients with beta-blocker. In contrast, a highly significant relation was evident between T\textsubscript{3} levels and CI values at rest in thyrotoxic patients, who did not receive beta-blocker. Moreover, reduction of SI and CI were observed in moderate hyperthyroid group with beta-blocker during handgrip exercise. These results were consistent with previous reports\textsuperscript{13-15)} which show negative inotropic effects of the beta-adrenoreceptor blocking drugs. Beta-adrenoreceptor blockade may be beneficial by lowering the ventricular rate in patients of severe hyperthyroid group. However, it should be emphasized that the beta-blockade must be avoided in euthyroid patients, who showed the delayed recovery of left ventricular function after antithyroid treatment.

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