THYROID DOPPLER ULTRASONOGRAPHY AND RESISTIVE INDEX IN THE EVALUATION OF THE NEED FOR ABLATIVE OR ANTITHYROID DRUG THERAPY IN GRAVES’ HYPERTHYROIDISM

Chih-Yuan Wang¹,²,³ and Tien-Chun Chang²

Background and Purpose: Graves’ disease (GD) is the most common hyperthyroid disorder, but the therapeutic strategy for choosing between medical or ablative therapy has not been standardized. Thyroid hypervascularity is an important diagnostic feature in GD. This study collected Doppler ultrasonography data from patients with GD, Hashimoto’s thyroiditis, and simple goiter to develop a hemodynamic index for use in the evaluation of when antithyroid drugs (ATDs) should be withdrawn or ablative therapy given in GD.

Material and Methods: Thyroid Doppler ultrasonography was used to measure the resistive index (RI) and pulsatility index (PI) in various thyroid diseases. We studied 88 patients, including 13 untreated GD patients, 14 euthyroid GD patients after withdrawal of ATDs for more than 12 months, 14 euthyroid GD patients with normal thyroid stimulating hormone (TSH) concentrations after regular ATD treatment for 12 months (well controlled), 16 hyperthyroid GD patients with undetectable TSH concentrations after regular ATD treatment for more than 12 months (poorly controlled), 13 Hashimoto’s thyroiditis patients, and 18 patients with simple goiters.

Results: The PI and RI were significantly different between patients with untreated (median PI/RI 1.36/0.79) or medically well-controlled (median PI/RI 0.66/0.51) GD, but no significant differences in PI and RI were found between patients with untreated or medically poorly controlled (median PI/RI 1.24/0.74) GD. An RI cut-off of at least 0.7 with undetectable TSH was found to be suggestive of the need for ablative therapy in GD patients who had received regular ATD treatment for more than 12 months, because of its statistically high sensitivity and specificity in all untreated and poorly controlled GD patients. An RI of less than 0.6 with normal TSH was suggestive of the need for withdrawal of ATDs in GD patients receiving regular medical treatment, because of its statistically high sensitivity and specificity in all treated euthyroid GD patients.

Conclusions: This study has developed an RI-derived hemodynamic index that determines the need for ablative or ATD therapy in patients with GD. A large-scale, prospective study is needed to confirm its clinical value.

Graves’ hyperthyroidism is characterized by thyroid hypervascularity. Doppler ultrasonography is a non-invasive method for evaluating changes in thyroid blood flow during the course of hyperthyroidism [1–3]. Recently, there have been reports that an increased thyroid blood flow predicts disease relapse in hyperthyroidism; these studies showed increased thyroid blood flow and peak systolic velocity in either the thyroid artery or the thyroid tissue in Graves’ disease (GD) patients [3, 4].

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Quantitation of volumetric flow is not the only method for extracting clinically useful information from the Doppler waveform, as the shape of the waveform can also provide information about the mechanical parameters of the arterial system, including distal impedance. The recognition of certain arterial pulsatile Doppler waveforms might make it possible to investigate distal vascular disease. The resistive index (RI) and pulsatility index (PI), two hemodynamic indices determined using duplex Doppler ultrasonography, are well recognized as valuable means of investigating peripheral vascular disease [5-7]. The RI is especially important clinically, as a higher RI indicates higher peripheral impedance [6, 7]. The advantage of these simple indices is that the Doppler waveform can be analyzed as either frequency or velocity versus time. The RI and PI can be measured independently in each vessel of interest using color Doppler ultrasonography. Since previous reports have indicated that blood flow is increased in the thyroid gland in Graves’ hyperthyroidism, variations in the RI and PI should be investigated in various thyroid diseases.

In the present study, data on RI and PI in patients with untreated and treated (including well-controlled and poorly-controlled patients) GD, Hashimoto’s thyroiditis, and simple goiters were collected to develop a hemodynamic index for the evaluation of whether antithyroid drugs (ATDs) should be withdrawn or ablative therapy should be given in GD.

Materials and Methods

Patient groups
The study included 88 patients divided into six groups: untreated hyperthyroid GD (13 females; mean age 29.8 yr); euthyroid GD after withdrawal of ATDs for more than 12 months (13 females, 1 male; mean age 39.6 yr); euthyroid GD with normal TSH concentrations after regular ATD treatment for 12 months (well-controlled group; 12 females, 2 males; mean age 38.4 yr); hyperthyroid GD with undetectable TSH concentrations after regular ATD treatment for more than 12 months (poorly-controlled group; 14 females, 2 males; mean age 37.2 yr); euthyroid patients with Hashimoto’s thyroiditis (13 females; mean age 39.8 yr); and euthyroid patients with simple goiters (16 females, 2 males; mean age 40.5 yr).

Patients who had undergone radioiodine therapy or surgery were excluded from the study. The diagnosis of GD or Hashimoto’s thyroiditis was made on the basis of clinical and laboratory criteria. GD patients had elevated concentrations of free thyroid hormones and undetectable or clearly reduced TSH concentrations in the serum, anti-TSH receptor antibody in the serum, and diffuse increased uptake of radionuclide on scintiscan. The diagnosis of Hashimoto’s thyroiditis was based on the findings of palpable goiter and presence of anti-thyroidperoxidase autoantibodies in the serum. The diagnosis of simple goiter was based on the findings of thyroid ultrasonography, normal thyroid function, and absence of anti-thyroglobulin and anti-thyroidperoxidase autoantibodies.

Thyroid Doppler ultrasonography
Doppler ultrasonography was carried out using a commercially available color Doppler apparatus (HPM2410A, Hewlett Packard, Andover, MA, USA). Patients were scanned in the supine position with the neck hyperextended, using a 7.5-MHz linear electronic transducer. Blood flow measurements were performed on the inferior thyroid arteries because of their conspicuous contribution to thyroid vascularization. The angle of insonation was kept at 60° or less. The angle correction cursor was parallel to the direction of flow. The RI and PI were calculated and recorded with software dedicated to the analysis of data on thyroid vascularization.

Resistive index and pulsatility index
RI values, calculated using the formula of Pourcelot [6], and PI values, calculated using the formula of Gosling and King [5], were computed over two or more cardiac cycles at each pixel with sufficient color data. Because the color Doppler ultrasound data represent the mean frequency shift (or mean velocity values), the computed RI and PI are estimates of true RI and PI.

The RI was calculated as:

\[
\text{RI} = \frac{\text{[maximum systolic frequency shift]} - \text{[minimum end diastolic frequency shift]}}{\text{[maximum systolic frequency shift]}},
\]

while the PI was calculated as:

\[
\text{PI} = \frac{\text{[maximum systolic frequency shift]} - \text{[minimum end diastolic frequency shift]}}{\text{[mean frequency shift]}}.
\]

Sensitivity and specificity
For various RI and PI values, sensitivity and specificity were calculated for further application. The sensitivity was calculated as:

\[
\text{Sensitivity} = \left( \frac{\text{true positive}}{\text{true positive} + \text{false negative}} \right) \times 100\%
\]

The specificity was calculated as:

\[
\text{Specificity} = \left( \frac{\text{true negative}}{\text{true negative} + \text{false positive}} \right) \times 100\%.
\]

Statistics
Differences in the RI and PI in the six groups were analyzed using Kruskal-Wallis one-way analysis of variance on ranks, and Dunn’s method was used for all pairwise multiple comparisons.
Results

Hemodynamic indices

The distribution of the RIs and PIs in the six groups are shown in Figs. 1 and 2, respectively. Table 1 shows the median RI and PI values for the six groups and significant differences between groups; the values for patients with untreated hyperthyroid GD and patients with hyperthyroid GD receiving ATDs were significantly higher ($p < 0.01$). Table 2 shows the results of pairwise comparisons of the RI and PI between various groups.

![Fig. 1. Distribution of resistive index in patients with Graves' disease (GD) and other thyroid diseases.](image1)

![Fig. 2. Distribution of pulsatility index in patients with Graves' disease (GD) and other thyroid diseases.](image2)

Table 1. Median resistive index (RI) and pulsatility index (PI) in Graves' disease (GD) and other thyroid diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>RI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroid GD</td>
<td>0.79</td>
<td>1.36</td>
</tr>
<tr>
<td>Euthyroid GD without medication</td>
<td>0.56</td>
<td>0.78</td>
</tr>
<tr>
<td>Euthyroid GD with medication</td>
<td>0.51</td>
<td>0.66</td>
</tr>
<tr>
<td>Hyperthyroid GD with medication</td>
<td>0.74</td>
<td>1.24</td>
</tr>
<tr>
<td>Hashimoto's thyroiditis</td>
<td>0.55</td>
<td>0.74</td>
</tr>
<tr>
<td>Simple goiters</td>
<td>0.57</td>
<td>0.76</td>
</tr>
</tbody>
</table>

The comparison of the RI and PI in the six patient groups revealed significant differences between untreated hyperthyroid and well-controlled euthyroid GD patients. In addition, significant differences in the RI and PI were found between untreated hyperthyroid and euthyroid GD patients after withdrawal of ATDs for more than 12 months. No significant differences in the RI and PI were found between untreated hyperthyroid and poorly-controlled hyperthyroid GD patients. The RI and PI were similar in well-controlled euthyroid GD patients and euthyroid GD patients after withdrawal of ATDs.

Resistive index as an indicator of appropriate therapy

Because PI is calculated from the mean frequency shift, the effect of noise interference in the Doppler ultrasound must be considered, and RI is therefore more reliable than PI. RI has been widely used in predicting several peripheral vascular diseases, including renal transplant rejection and stenosis of hemodialysis grafts [8, 9].

In the present study, we tried to establish an RI cut-off that could be used to evaluate whether ATDs should be withdrawn or whether ablative therapy was indicated in patients with GD by investigating the effect of various cut-off values on the sensitivity and specificity of RI in the prediction of hyperthyroid state in patients with GD after ATD treatment. As shown in Fig. 1, an RI of at least 0.70 was only seen in untreated hyperthyroid and poorly-controlled GD patients. The sensitivity and specificity of RI in the detection of the hyperthyroid state in patients with GD after ATD treatment for various RI cut-off values are shown in Table 3. A cut-off of 0.70 resulted in 100% specificity and 92.3% sensitivity, while RI cut-offs of 0.60 and 0.50 resulted in 100% sensitivity in both cases and respective specificities of 82.1% and 21.4%. An RI value of less than 0.60 was considered suggestive of the need for withdrawal of ATDs in well-controlled GD patients because of the lower positive predictive estimation, and suggestive of the need for ablative therapy (radioiodine...
Table 2. Pairwise comparisons of resistive index (RI) and pulsatility index (PI) in various Graves’ disease (GD) groups (Dunn’s method)

<table>
<thead>
<tr>
<th></th>
<th>RI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q</td>
<td>p  ≤ 0.05</td>
</tr>
<tr>
<td>HGD vs EGD with medication*</td>
<td>5.95</td>
<td>Yes</td>
</tr>
<tr>
<td>HGD vs EGD without medication*</td>
<td>4.66</td>
<td>Yes</td>
</tr>
<tr>
<td>HGD vs HGD with medication</td>
<td>1.09</td>
<td>No</td>
</tr>
<tr>
<td>HGD with medication vs EGD with medication*</td>
<td>5.16</td>
<td>Yes</td>
</tr>
<tr>
<td>HGD with medication vs EGD without medication*</td>
<td>3.79</td>
<td>Yes</td>
</tr>
<tr>
<td>EGD without medication vs EGD with medication</td>
<td>1.32</td>
<td>No</td>
</tr>
</tbody>
</table>

*Significant difference for both parameters. HGD = untreated Graves’ hyperthyroidism; EGD = euthyroid GD.

Discussion

Color Doppler ultrasonography has been reported to show color spots or abundant vascular bands in the thyroid parenchyma of patients with Graves’ hyperthyroidism [1–4, 8–11]. An increased thyroid blood flow with high concentrations of TSH receptor autoantibodies and increased numbers of vessels in the thyroid parenchyma have been reported to predict relapses or surgery in medically poorly-controlled GD patients (undetectable TSH concentrations and RI ≥ 0.70) because of the higher negative predictive estimation (Table 4).

Table 3. Accuracy of resistive index (RI) in detecting the hyperthyroid state after treatment in Graves’ patients

<table>
<thead>
<tr>
<th>RI</th>
<th>Sensitivity(%)</th>
<th>Specificity(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.5</td>
<td>100</td>
<td>21.4</td>
</tr>
<tr>
<td>≥ 0.6</td>
<td>100</td>
<td>82.1</td>
</tr>
<tr>
<td>≥ 0.7</td>
<td>92.3</td>
<td>100</td>
</tr>
<tr>
<td>≥ 0.8</td>
<td>46.1</td>
<td>100</td>
</tr>
<tr>
<td>≥ 0.9</td>
<td>30.8</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4. Suggested therapeutic resistive index (RI) criteria for Graves’ patients

<table>
<thead>
<tr>
<th>RI</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.70</td>
<td>Ablative therapy</td>
</tr>
<tr>
<td>0.60–0.69</td>
<td>Indeterminate*</td>
</tr>
<tr>
<td>0.50–0.59</td>
<td>Withdrawal of ATDs</td>
</tr>
<tr>
<td>&lt; 0.50</td>
<td>Withdrawal of ATDs</td>
</tr>
</tbody>
</table>

*The use of ablative therapy is suggested but this does not suggest that antithyroid drugs (ATDs) should be discontinued.

or surgery) in medically poorly-controlled GD patients (undetectable TSH concentrations and RI ≥ 0.70) because of the higher negative predictive estimation (Table 4).

According to the American Thyroid Association’s treatment guidelines for patients with hyperthyroidism [17], there is no clear and definite standard for the duration of ATD therapy. Life-long thyroid hormone replacement is indispensable for treatment of early or

and long-term outcome in GD patients [2, 10]. These results are supported by those of a recent study showing that thyroid vascularity and blood flow increase when TSH receptor antibody concentrations increase, but are unrelated to serum thyroid hormone concentrations [12]. However, there is still no objective standard for evaluating therapeutic strategy for GD patients.

In this study, we measured hemodynamic indices in the inferior thyroid arteries, rather than the parenchymal vessels, because of their conspicuous contribution to thyroid vascularization. The RI and PI values measured by Doppler ultrasonography were used to evaluate thyroid vascularization in patients with GD, euthyroid Hashimoto’s thyroiditis, or simple goiter. Although the RI and PI have been widely used in investigating peripheral vascular diseases, such as renal transplant rejection, hemodialysis grafts, and carotid stenosis [5–7, 13–16], they have not received much attention for studying thyroid vascularization in various thyroid diseases. The use of a more precise 7.5-MHz linear electronic transducer in our study may play a pivotal role in the accurate estimation of RI and PI, and explain the difference between the results obtained in the present study and a previous study using a 5.0-MHz transducer [10]. Because PI is calculated from the mean frequency shift, the effect of noise interference on Doppler ultrasound must be considered, and RI is therefore more reliable than PI. To our knowledge, the present study is the first to establish an RI cut-off to evaluate the need for withdrawal of ATDs in well-controlled GD (normal TSH concentrations and RI < 0.60), and to suggest that ablative therapy is indicated in medically poorly-controlled GD patients (undetectable TSH concentrations) if the RI is at least 0.70.

According to the American Thyroid Association’s treatment guidelines for patients with hyperthyroidism [17], there is no clear and definite standard for the duration of ATD therapy. Life-long thyroid hormone replacement is indispensable for treatment of early or
late hypothyroidism, but radioactive iodine is still the most commonly used form of treatment in the USA. In addition, no criteria have been reported for selecting patients to receive such treatment. On the other hand, specific indications for thyroidectomy include very large goiter, resistance to radioactive iodine, patients allergic to ATDs, and patients with coincidental thyroid nodules. There are also no objective criteria indicating the need for ablative therapy. Our results suggest that a hemodynamic index (RI) may provide more objective and simpler indications regarding therapeutic strategy. RI is simple to calculate, and a higher RI indicates blood flow into a higher impedance vascular bed.

In multiple comparison studies, no significant difference in RI was found between untreated GD and hyperthyroid GD patients with undetectable TSH concentrations after regular ATD treatment for more than 12 months. In addition, a significant difference in the RI was noted between the untreated GD group and euthyroid GD patients after withdrawal of ATDs for more than 12 months. This indicates that the hemodynamic indices in GD patients poorly controlled by ATDs are similar to those in untreated GD patients. In addition, a high specificity (100%) and high sensitivity (92.3%) in the detection of the hyperthyroid state were achieved when the RI was at least 0.70. Thus, an RI cutoff of 0.70 may be an important indicator of the need for further therapy.

In addition, we found no significant difference in RI between euthyroid GD patients after withdrawal of ATDs for more than 12 months and euthyroid GD patients with normal TSH concentrations after regular ATD treatment for 12 months, showing that ATDs could be withdrawn long term in certain euthyroid GD patients with normal TSH concentrations. RI can also be considered as an indicator in evaluating withdrawal of ATDs (Table 4).

In conclusion, this quantitative Doppler ultrasonographic study of RI and PI in the inferior thyroid arteries suggests that RI provides a rapid method for examining thyroid vascularization and evaluating the need for ablation or continued use of ATDs. An RI cutoff of at least 0.70 with undetectable TSH concentrations was suggestive of the need for ablative therapy in GD patients who had received regular ATD treatment for more than 12 months, and an RI of less than 0.60 with normal TSH concentrations was suggestive of the need for withdrawal of ATDs in GD patients receiving regular ATD treatment. Further prospective studies between thyroid vascular hemodynamic change and the clinical course of GD are needed in patients with Graves’ hyperthyroidism.

References