To compare and determine color Doppler ultrasonography (CDU) parameters that is the most reliable parameter for predicting thyroid functional status between euthyroid and hyperthyroid states.

We retrospectively reviewed data from a total of 256 patients (197 females and 59 males) who had undergone CDU from December 2003 to April 2008. Patients’ age ranged from 11-81 yr with average of 38.6 yr. The mean age of females was 37.0 ± 14.3 yr and that of males was 43.8 ± 14.2 yr. The parameters included the pulsatility index (PI), resistive index (RI), peak systolic velocity (PSV), blood volume flow (VF), inferior thyroid artery diameter (DIAM), end diastolic velocity (ED), time-averaged maximum velocity (TA\(\text{max}\)), time-averaged mean velocity (TA\(\text{mean}\)), and acceleration (ACCE). We then evaluated the differences among these CDU parameters between the euthyroid group and the hyperthyroid groups. The Student’s t test was used to compare the means of the CDU parameters. The receiver operating characteristic (ROC) curve was used to determine the optimal cutoff values of the CDU parameters to predict thyroid functional status between the groups.

All CDU parameters, except for PI (p= 0.195) and RI (p= 0.544), showed significantly different results (p < 0.001) between these two groups, including VF, DIAM, PSV, ED, ACCE, TA\(\text{max}\), TA\(\text{mean}\). Then, we selected the PSV, VF and TA\(\text{max}\), the most common parameters in clinical practice, to further determine which parameter is the most reliable parameter for predicting thyroid functional status. Area under the ROC curve for VF was 0.8061; for PSV, 0.8210; and for TA\(\text{max}\), 0.8024, without significant differences between these parameters for predicting thyroid functional status between the groups. According to the ROC analysis, the optimal cutoff values of the PSV, VF and TA\(\text{max}\) were 25cm/sec, 8mL/min and 17cm/sec respectively.

PSV, VF and TA\(\text{max}\) are useful parameters in predicting thyroid function between euthyroid and hyperthyroid states according to the ROC analysis. The cutoff values of these parameters for differentiating thyroid functional status have powerful predictive accuracy and do not differ significantly. Because that VF measurement was easily affected by the DIAM, the main factor influenced by the physician’s procedure and individual vascular variation, we suggest that PSV or TA\(\text{max}\) are the most reliable parameter for predicting thyroid functional status between euthyroid and hyperthyroid states.

Color Doppler Ultrasonography (CDU) is widely used to evaluate the status of the thyroid glands [1] and can be performed easily on outpa-
tient basis. Hypervascularity in thyroid parenchyma is seen in patients with autoimmune thyroid diseases (AITD) such as Graves’ disease (GD) and Hashimoto’s thyroiditis (HT), and especially in those with hyperthyroidism [1-7]. CDU is also a useful modality for evaluating the progression of these diseases [8-9].

CDU has been applied to the follow-up of thyroid diseases. In facts, the progressive decrease of intraparenchymal blood flow is regarded as a reliable index of the effectiveness of medical treatment and is hence helpful in the clinical surveillance of the disease [8, 11-15]. However, the CDU response does not appear necessarily early, changes in the hormonal and clinical status almost always precede the normalization of the CDU pattern [13, 16].

None of the previous studies definitely reported the most reliable CDU parameter for predicting thyroid function. Therefore, this study was designed to determine whether the measurement of CDU parameters in the inferior thyroid artery (ITA) can predict thyroid functional status precisely and to determine the most reliable parameter for predicting this status between euthyroid and hyperthyroid states.

**PATIENTS AND METHODS**

**Patients information, data collection and exclusion criteria**

We retrospectively analyzed the CDU parameters obtained from 256 patients investigated for thyroid disorders between December 2003 and April 2008 at the Chia-Yi Chang Gung Memorial Hospital, whose diagnosis included normal thyroid, nodular goiter, autoimmune thyroid disease and diffuse goiter according to the sonographic findings. Patients with a history of thyroidectomy, 131I therapy or pregnancy were excluded from this study. Patients’ age ranged from 11-81 yr with average of 38.6 yr. The mean age of females was 37.0 ± 14.3 yr and that of males was 43.8 ± 14.2 yr. The female to male distribution of patients was 3.3:1 (197 females and 59 males).

**Thyroid evaluation**

Ultrasonographic studies of the thyroid glands were performed with a real-time ultrasonographic scanner using a 10-MHz multifrequency linear probe (LOGIQ-9; GE Medical Systems, Milwaukee, WI, USA) under the following settings: color pulse repetition frequency, 2-8 kHz; wall filter, 25-80 Hz; and Doppler frequency, 4.4-6.6 MHz. CDU was performed to measure the parameters of the right ITA or left ITA for all patients. As there is no significant difference in the CDU parameters between the lobes of the thyroid gland [10], we did not exclude the group in which only the left ITA was examined. The parameters were calibrated automatically and included the pulsatility index (PI), resistive index (RI), peak systolic velocity (PSV), blood volume flow (VF), ITA diameter (DIAM), end-diastolic velocity (ED), time-averaged maximum velocity (TA_{max}), time-averaged mean velocity (TA_{mean}), and acceleration (ACCE). According to previous literature [8, 17-19], there was high intraobserver and interobserver agreement. The coefficient of variation were 8-10% on CDU parameters. Thyroid function analysis including thyroxine (T4), free T4, triiodothyronin (T3) and thyroid-stimulating hormone (TSH) level were determined by radioimmunoassay (RIA) methods within one month.

**Diagnostic criteria of thyroid functional status**

Patients with a TSH level of less than 0.35 mIU/L and presenting with symptoms of hyperthyroidism (such as palpitation, hand tremor, weight loss, and heat intolerance) were classified as the hyperthyroid group. Patients with a TSH level between 0.35 and 5.5 mIU/L and without marked symptoms of hyperthyroidism presented were classified as the euthyroid group. Of the 256 patients, the euthyroid group included 119 patients (46 normal thyroid, 9 nodular goiter, 27 diffuse goiter and 37 AITD), and the hyperthyroid group included 137 patients (14 normal thyroid, 15 nodular goiter, 5 diffuse goiter and 103 AITD).

**Statistical analysis**

Continuous variables were expressed as the means ± SDs. The mean values of the CDU parameters were compared between the euthyroid group and the hyperthyroid groups by using the Student’s t test. The diagnostic accuracy for predicting thyroid functional status calculated by using changes in the CDU parameters was evaluated with receiver operating characteristic (ROC) analysis [20]. The optimal cutoff value of the CDU parameter for differentiating euthyroid status from hyperthyroid status was defined as the point on the ROC curve with the minimal distance from the left upper corner, which is the 0% false-positive rate and the 100% true-positive rate [21]. The area under the ROC curve (AUC) was calculated with the corresponding 95% confidence interval. The statistical significance of differences
between the ROC curves was based on the 95% confidence interval of the difference between the AUC values. All statistical analyses were performed by using Stata version 10.1 statistical software. (StataCorp. 2008. Stata Statistical Software: Release 10.1. College Station, TX: StataCorp LP). A p value of less than 0.05 was considered to indicate a statistically significant difference.

**RESULTS**

CDU images of patients with hyperthyroidism essentially revealed more vascularity in the thyroid parenchyma and higher values of the CDU parameters than CDU images of patients with euthyroidism. After the analysis of Student’s t test analysis, significant differences were noted in the descriptive statistics of the CDU parameters (mean ± SD) between the euthyroid group and the hyperthyroid groups (Table 1).

Among these significant parameters, we selected PSV, VF and $T_{\text{Amax}}$, the most common parameters in clinical practice, to further evaluate the most reliable parameter for predicting thyroid functional status between the euthyroid group and the hyperthyroid groups. We used the ROC analysis to compare their predictive validity and determine their optimal cutoff values. ROC curves were plotted using measures of sensitivity and specificity based on the cutoff values of the VF, PSV, and $T_{\text{Amax}}$ (Fig. 1). The AUC is a measure of the diagnostic power of a test. The AUC of these three CDU parameters was $VF, 0.8061$ (95% CI: 0.7531-0.8592); $PSV, 0.8210$ (95% CI: 0.7688-0.8732); and $T_{\text{Amax}}, 0.8024$ (95% CI: 0.7491-0.8557). After statistical comparison, no significant difference was observed between these parameters in diagnostic power.

According to the ROC analysis, the discriminatory powers was measured by the optimal cutoff values. The optimal cutoff values of the PSV, VF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Euthyroid (n=119)</th>
<th>Hyperthyroid (n=137)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>$0.96 \pm 0.29$</td>
<td>$1.03 \pm 0.33$</td>
<td>0.195</td>
</tr>
<tr>
<td>RI</td>
<td>$0.60 \pm 0.10$</td>
<td>$0.62 \pm 0.11$</td>
<td>0.544</td>
</tr>
<tr>
<td>VF (ml/min)</td>
<td>$7.19 \pm 8.08$</td>
<td>$27.23 \pm 34.58$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DIAM (cm)</td>
<td>$0.13 \pm 0.04$</td>
<td>$0.18 \pm 0.06$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSV (cm/sec)</td>
<td>$21.98 \pm 10.39$</td>
<td>$45.96 \pm 27.57$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ED (cm/sec)</td>
<td>$9.17 \pm 5.83$</td>
<td>$17.62 \pm 11.93$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACCE (cm/sec²)</td>
<td>$163.50 \pm 158.89$</td>
<td>$414.82 \pm 597.04$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$T_{\text{Amax}}$ (cm/sec)</td>
<td>$14.56 \pm 7.22$</td>
<td>$28.78 \pm 17.29$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$T_{\text{Amean}}$ (cm/sec)</td>
<td>$7.03 \pm 3.84$</td>
<td>$13.77 \pm 8.38$</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PI, pulsatility index; RI, resistive index; PSV, peak systolic velocity; VF, blood volume flow; DIAM, inferior thyroid artery diameter; ED, end-diastolic velocity; $T_{\text{Amax}}$, time-averaged maximum velocity; $T_{\text{Amean}}$, time-averaged mean velocity; ACCE, acceleration.
and $TA_{\text{max}}$ were 25 cm/sec, 8 mL/min and 17 cm/sec respectively. Table 2 indicates the predictability and accuracy of the optimal cutoff values of the three CDU parameters.

**DISCUSSION**

In a Doppler study, Vitti et al. [7] had evaluated the CDU patterns and PSV values for the treated, the untreated Graves’ disease (GD) and Hashimoto’s thyroiditis (HT) patients. They discovered clear correlation between the patients’ thyroid functional status and the CDU parameters. They found hyper-vascularity and higher PSV values in the majority of the untreated GD patients with hyperthyroidism. Similar findings were reported by Bogazzi et al. [17] for the untreated GD patients. In fact, several previous studies [3, 7-9, 14] have revealed that the PSV and the VF both correlate with the thyroid function status and indicate the progression of thyroid disease. On the other hand, Wang and Chang [6] showed that the RI value was an indicator of thyroid function and can play a role in the treatment planning. However, our study showed that not only the PSV and VF values but also the DIAM, ED, ACCE, $TA_{\text{max}}$, and $TA_{\text{mean}}$ values were significantly higher in the hyperthyroid group than those in the euthyroid group. Further, the RI and PI values were not significantly different between the groups. The conflicting result from the previous study of Wang and Chang may be due to the difference in frequencies of the transducers used in the Wang and Chang (7.5 MHz) study and our study (10 MHz).

As shown in previous studies, most of the CDU parameters correlate with thyroid function. However, none of those studies determined the most reliable parameter to predict thyroid function. In this study, except for the RI and PI values, the values of all CDU parameters (i.e., PSV, VF, DIAM, ED, ACCE, $TA_{\text{max}}$, and $TA_{\text{mean}}$) were significantly higher in the hyperthyroid group than in the euthyroid group. Among these parameters, we selected PSV, VF, and $TA_{\text{max}}$ to determine the most reliable CDU parameter for predicting thyroid functional status between the euthyroid and the hyperthyroid groups: no significant difference in diagnostic power was observed for predicting thyroid functional status.

In one study [18], a few overlaps of the CDU patterns were observed between GD and HT patients. The result is also supported by some reports [7, 9, 17]. This finding reveals that patients with HT have high blood flow values (including PSV and VF) in hypothyroid or euthyroid status. On the other hand, patients with amiodarone-induced thyroiditis or interferon-induced thyroiditis have normal blood flow values even in hyperthyroid status. Optimally, the patients with amiodarone-induced thyroiditis or interferon-induced thyroiditis should be excluded because their data would interfere with the predictive accuracy. However, it is difficult because the echogenic pattern of the patients with amiodarone-induced thyroiditis or interferon-induced thyroiditis would be similar with that of the patients with autoimmune thyroid disease.

In conclusion, PSV, VF, and $TA_{\text{max}}$ are all useful in predicting thyroid functional status between the euthyroid and the hyperthyroid states according to the ROC analysis, and no significant difference was observed between these three parameters in diagnostic power. In addition, we determine

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No in the euthyroid group</th>
<th>No in the hyperthyroid group</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSV &lt; 25</td>
<td>92</td>
<td>27</td>
<td>0.803</td>
<td>0.773</td>
<td>0.80</td>
<td>0.77</td>
<td>0.789</td>
</tr>
<tr>
<td>$\geq 25$</td>
<td>27</td>
<td>110</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VF &lt; 8</td>
<td>90</td>
<td>38</td>
<td>0.723</td>
<td>0.756</td>
<td>0.77</td>
<td>0.70</td>
<td>0.738</td>
</tr>
<tr>
<td>$\geq 8$</td>
<td>29</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$TA_{\text{max}}$ &lt; 17</td>
<td>89</td>
<td>35</td>
<td>0.745</td>
<td>0.748</td>
<td>0.77</td>
<td>0.72</td>
<td>0.746</td>
</tr>
<tr>
<td>$\geq 17$</td>
<td>30</td>
<td>102</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PSV, peak systolic velocity; VF, blood volume flow; $TA_{\text{max}}$, time-averaged maximum velocity; PPV, positive predictive value; NPV, negative predictive value.
the cutoff values of these three CDU parameters that have reliable predictive accuracy. As measurement of the VF value is easily affected by the DIAM, the main factor influenced by the operator and individual vascular variation, we propose PSV or TA_max are the most reliable parameters for predicting thyroid functional status between euthyroid and hyperthyroid states.

**ACKNOWLEDGEMENTS**

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**REFERENCES**

6. Wang CY, Chang TC. Thyroid Doppler ultrasonography and resistive index in the evaluation of the need for ablative or antithyroid drug therapy in Graves’ hyperthyroidism. J Formos Med Assoc 2001; 100: 753-757
18. Color flow Doppler sonography for the etiologic diagnosis of hyperthyroidism. Thyroid 2007; 17: 223-228
利用彩色都卜勒超音波血流參數以預測甲狀腺功能

韓嘉哲 1  邱世欽 2,3  彭雲杏 1  翁旭惠 4,5,6  何正 1  陳鈊印 1

長庚大學  嘉義長庚紀念醫院  內科部內分泌新陳代謝科 1  放射診斷科 4
大千綜合醫院  內科部 2
中國醫藥大學附設醫院  內科部內分泌新陳代謝科 3
長庚技術學院嘉義分部  呼吸治療系 5
高雄醫學大學  職業安全衛生研究所 6

以統計學方法找出對於分辨甲狀腺功能具有統計意義的彩色都卜勒超音波血流參數，再進一步找出預測準確度最高的參數，並算出其分辨甲狀腺功能的最佳預測值。

總共篩選出 256 位病患，其中包含 197 位女性及 59 位男性。病患年齡介於 11 歲至 81 歲，女性平均年齡 37.0 ± 14.3 歲，男性平均年齡 43.8 ± 14.2 歲。納入評估的甲狀腺血流參數包括 pulsatility index (PI), resistive index (RI), peak systolic velocity (PSV), blood volume flow, diameter (VF), inferior thyroid artery diameter (DIAM), end diastolic velocity (ED), Time-averaged maximum velocity (TA_{max}), Time-averaged mean velocity (TA_{mean}), acceleration (ACCE)。所有病患分成二組，包括甲狀腺功能正常及甲狀腺功能亢進二組。以統計學方法分析在這二組病患中，血流參數是否有統計上的差異，並找出最具統計學差異的血流參數。最後，再利用 ROC analysis 算出此血流參數的最佳預測值。

除了 PI 跟 RI 之外，所有其他的血流參數（包括 PSV, VF, DIAM, ED, TA_{max}, TA_{mean}, ACCE）在甲狀腺功能正常及甲狀腺功能亢進二組病患中皆有統計上的差異（p<0.001）。我們進一步挑選出 PSV & VF & TA_{max} 這三個臨床應用較常見的血流參數做比較。畫出其 ROC curve 並比較其曲線下面積，分析結果顯示這三個血流參數其曲線下面積並無統計上的差異，亦即此三個血流參數在預測甲狀腺功能亢進及正常方面的準確度無明顯差異。這三個血流參數在分辨甲狀腺功能正常及甲狀腺功能亢進最佳預測值分別為 PSV: 25cm/sec; VF: 8ml/min; TA_{max}: 17cm/sec。

PSV & VF & TA_{max} 是用來預測甲狀腺功能很有價值的工具。但因 VF 較易受醫師的操作及病患的先天血管管徑差異所干擾。因此，PSV & TA_{max} 也許是最適合用來預測甲狀腺功能的二項參數。