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Superior thyroid artery mean peak systolic velocity for the diagnosis of thyrotoxicosis in Japanese patients

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Abstract. Thyrotoxicosis with diffuse thyroid disease can be caused by Graves' disease (GD) or destructive thyroiditis (DT). Optimal treatment of the underlying condition requires a prompt and accurate method for the diagnosis of thyrotoxicosis. This study evaluated measurement of the mean peak systolic velocity of the superior thyroid artery (STA-PSV) by ultrasonography in detecting thyrotoxicosis in Japanese patients. We recruited 44 patients with untreated GD, 13 with DT, 55 with treated GD, and 49 subjects without thyroid disease. Blood samples were taken to analyze thyroid function and STA-PSV was measured by ultrasonography. The mean STA-PSV was the highest in the untreated GD group, followed by treated GD patients and then those with DT. Receiver operating characteristic curves of the STA-PSV values demonstrated that the area under the curve required discriminating untreated GD from DT was 0.941. The optimal sensitivity and specificity were 83.7% and 92.3%, respectively, using 45 cm/sec as the cutoff value. In conclusion measurement of STA-PSV by ultrasonography is useful for the diagnosis of thyrotoxicosis in Japanese patients.

Key words: Thyroid artery, Thyrotoxicosis, Ultrasonography, Graves' disease, Destructive thyroiditis

THYROTOXICOSIS is caused by both Graves' disease (GD) and destructive thyroiditis (DT), including painless thyroiditis, postpartum thyroiditis, and subacute thyroiditis [1]. GD can be treated with antithyroid drugs, radioisotope therapy, or subtotal thyroidectomy, while DT is often managed by conservative therapy. Thus, correct and prompt diagnosis to distinguish between these underlying conditions is important with regard to the selection of appropriate treatment for thyrotoxicosis. Several tests, including high radioactive iodine uptake (RAIU), serum anti-thyrotropin (TSH) receptor antibody and thyroglobulin levels, and amount of urinary iodine extraction, are regarded as useful information to discriminate GD from DT [2]. However, these tests are not necessarily available in general hospitals and clinics in Japan, and it could take several days to obtain the results. Ultrasonography with pulsed Doppler equipment is a noninvasive and cost-effective method for rapidly obtaining useful information in these cases. High intrathyroidal blood flow [3, 4, 5, 6] and increased mean peak systolic velocity (PSV) of the thyroid artery [3] are well known signs of GD. However, the cutoff values for these tests for discrimination of GD from DT have not been determined, especially in Asian populations. Most previous studies used blood flow at the inferior thyroid artery (ITA) to analyze the association between blood velocity with prognosis and activity of GD [7]. However, measurement of the superior thyroid artery (STA) flow is superior for obtaining stable flow velocity data from almost all subjects. This study therefore evaluated the usefulness of STA-PSV in distinguishing GD from DT in Japanese patients with thyrotoxicosis.

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Abbreviations: GD; Graves' disease, DT; destructive thyroiditis, FT3; free triiodothyronine, FT4; free thyroxine, ITA; inferior thyroid artery, Untreated GD; untreated Graves' disease, NT; subjects without thyroid disease, Treated GD; treated Graves' disease, ROC; receiver operating characteristic, STA-PSV; mean peak systolic velocity of superior thyroid artery, TSH; thyrotropin.

Materials and Methods

Patients

A total of 57 patients with thyrotoxicosis were enrolled in this study. After measuring TSH receptor antibodies (TRAb) levels and technetium Tc 99m pertechnetate ($^{99m}TcO_4^-$) uptake, 13 patients were finally diagnosed with DT and 44 patients with untreated GD. As control, 55 treated GD patients who received regular treatment and 49 subjects without thyroid disease were also enrolled. All subjects were Japanese and enrolled from the outpatient clinic of Juntendo University Hospital. The ethics committee of Juntendo University approved the study protocol.

Measurement of serological makers

Blood samples were collected from all study subjects. Serum free thyroxine (FT4), free triiodothyronine (FT3), and TSH values were measured using a commercial electrochemiluminescence immunoassay (Roche Diagnostics, Tokyo, Japan; FT4 normal range, 11.61–21.93 pmol/L, and measurable upper limit, 77.4 pmol/L; FT3 normal range, 3.54–6.62 pmol/L, and measurable upper limit, 46.2 pmol/L; TSH normal range 0.5–5.0 μIU/mL). Untreated GD patients showed over-limit values for FT4 in 12 individuals and for FT3 in 3. Mean FT4 and FT3 were tentatively calculated by assigning the over-limit data as upper-limit values (Table 1). Serum TRAb was measured using a two-step radioreceptor assay (DYNO test TRAb Human kit "YAMASA"; Yamasa Corp, Tokyo: normal range <1.0 IU/L).

Color-flow Doppler ultrasonography

Mean PSV-STA and thyroid volume were measured in all subjects by two experts using color-flow Doppler ultrasonography (EUB-525, Hitachi, Tokyo) with a 10-MHz linear transducer. Thyroid volume was calculated using the ellipsoid model ((width x length x thickness x $\pi/3$) for each lobe + (width x length x thickness) for isthmus).

Statistical analysis

For parameters showing normal distribution, Pearson's analysis was used to calculate the correlation coefficients and Student's *t*-test was used to compare differences between groups. For parameters with skewed distribution, Spearman's rank correlation analysis was used to calculate the correlation coefficients and the Mann-Whitney *U*-test to compare differences between groups. The correlation coefficients and differences were calculated using the StatView 5.0 J program for Windows (Abacus Concepts, Berkeley, CA). The sensitivity, specificity, and receiver operating characteristic (ROC) curves were calculated using a two-by-two contingency table. The cutoff values and the resultant optimal sensitivity to specificity ratio were determined based on the ROC curves. Values of $P < 0.05$ were considered statistically significant. All data are expressed as mean ± SD unless otherwise indicated.

Results

Patient characteristics

Table 1 details the clinical characteristics and results of blood tests for the subjects of this study. Gender and age were comparable across groups. Serum FT3 and FT4 values were significantly higher in the untreated GD patients (34.16 ± 19.17 and 66.87 ± 26.54 pmol/L, respectively) than in the other groups, despite 12 patients and 3 patients showing over-limit values for FT4 and FT3, respectively. The same val-

Table 1. Patients' characteristics and results of blood tests

	NT	DT	untreated GD	treated GD
number	54	13	44	53
male/female	12/42	15/29	3/10	27/26
Age (years)	40.2±13.0	43.8±17.0	42.1±14.4	42.1±14.4
FT3 (pmmol/L)	6.57±1.48	15.6±7.4*	34.2±19.2*¶	7.90±3.61*¶§
FT4 (pmmol/L)	22.4±7.4	49.2±20.9*	66.9±26.5*¶	21.1±8.0¶§
TSH (μIU/mL)	1.21±0.58	<0.01*§	<0.01*§	2.8±6.81
TRAb (IU/L)	ND	<1	12. 9±17.0¶	5.5±10.7¶§
Thyroid volume (mL)	ND	22.1±9.3	31.7±18.2	27.4±10.8

*p <0.01, compared with NT, ¶ p <0.01, compared with DT, § p <0.01, compared with untreated GD.
NT; subjects without thyroid disease, DT; patients with destructive thyroiditis, ND; not determined.

ues in DT subjects (15.63 ± 7.44 and 49.15 ± 20.86 pmol/L, respectively) were significantly higher than treated GD patients and subjects without thyroid disease (NT), while the treated GD group showed significantly higher FT3 values than the NT controls. TSH was completely suppressed in untreated GD and DT subjects, and not significantly different between treated GD and NT subjects. TRAb was elevated in both untreated GD (12.89 ± 16.99 IU/L) and treated GD (5.47 ± 10.70 IU/L) patients and the untreated GD group values were significantly higher than those of treated GD patients.

Comparisons of mean STA-PSV

The mean STA-PSV of patients with untreated GD was significantly higher than for the NT, DT, and treated GD groups (78.48 ± 36.28 cm/sec *vs*. 20.76 ± 7.77, 28 ± 12.84, 52.39 ± 28.54 cm/sec, respectively, P <0.01, Fig. 1). Interestingly, the mean STA-PSV of treated GD subjects was also significantly higher than the NT and DT group mean values, while the DT mean was modestly but significantly higher than that of the control NT group.

To evaluate the usefulness of STA-PSV in discriminating untreated GD from DT, we constructed and analyzed ROC curves of the STA-PSV values across the groups. The STA-PSV AUC to discriminate between untreated GD and DT as the cause of thyrotoxicosis was 0.941 (IC95%: 0.86–0.95; Fig. 2). The optimal sensitivity and specificity to discriminate untreated GD from DT were 83.7% and 92.3%, respectively, using 45 cm/sec as a cutoff value.

This result shows that most of untreated GD shows that STA-PSV value is more than 45 cm/sec. On the other hand, 11.4% of untreated GD shows that STA-PSV value is less than 45 cm/sec. In the patients with STA-PSV <45 cm/sec, it is important to discriminate DT from untreated GD. Thus, finally, we analyzed ROC curves of the STA-PSV values across DT and GD with STA-PSV <45 cm/sec. The optimal sensitivity and specificity to discriminate DT from untreated GD were 100% and 34.6%, respectively, using estimated cutoff value 20 cm/sec.

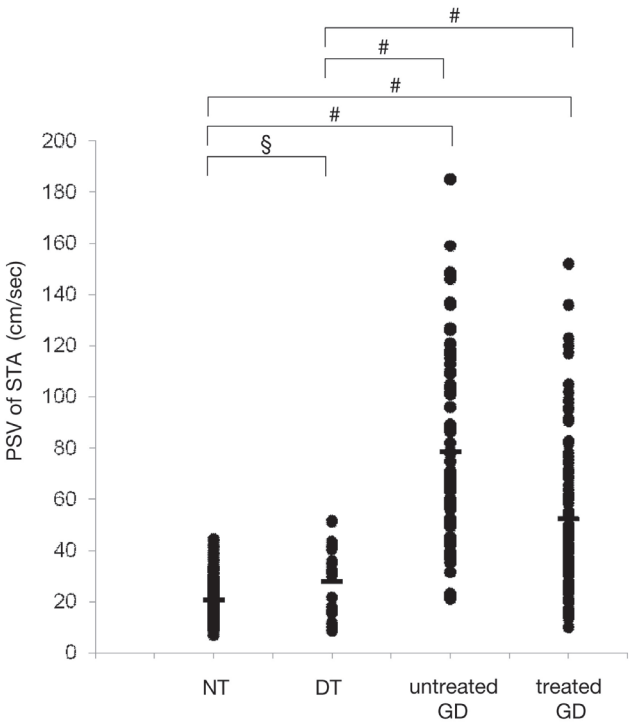

Fig. 1. Each dot represents an individual value of superior thyroid artery mean peak systolic velocity in 49 patients free of thyroid disease (NT), 57 patients with thyrotoxicosis [13 with destructive thyroiditis (DT) and 44 with untreated Graves' disease (untreated GD)], and 55 treated Graves' disease (treated GD). The horizontal lines represent the mean values. $^{\#}P$ <0.001, between the marked groups, $^{\S}P$ = 0.004 between NT and DT.

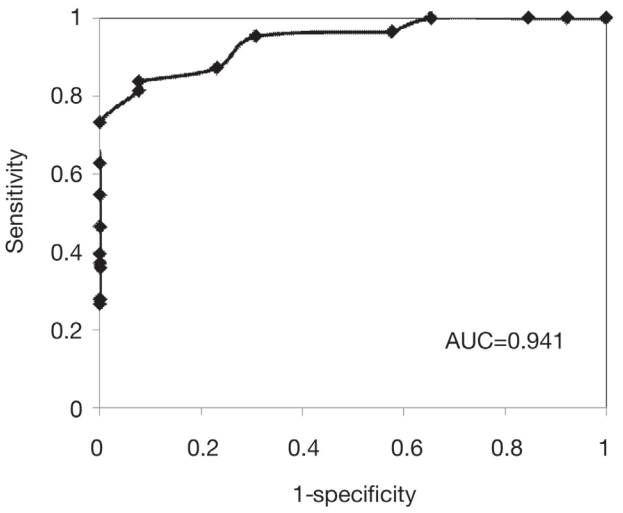

Fig. 2. ROC curves for thyrotoxicosis discrimination obtained with threshold values from 0 to 100 cm/sec for STA-PSV. The area under the curve was calculated by multiplying 1-specificity (0 to 1) by sensitivity (0 to 1).

Discussion

This study assessed the ability of STA-PSV to discriminate GD from DT in Japanese patients with thyrotoxicosis. The STA-PSV effectively distinguished

the underlying cause of thyrotoxicosis. The sensitivity and specificity to discriminate untreated GD from DT using 45 cm/sec were high enough for clinical use. In the patients with STA-PSV <45 cm/sec, STA-PSV, 20 cm/sec shows high sensitivity to discriminate DT from untreated GD. On the other hand, the specificity is too low to detect DT. Thus to discriminate DT from untreated GD is difficult using STA-PSV value for the patients with STA-PSV between 20 to 45 cm/sec. These seems to be the limitation of using STA-PSV for the diagnosis of thyrotoxicosis.

Previous studies reported that thyroid artery blood flow [8] and PSV [9] correlated well with the FT3 level in GD. Here, we also found a positive correlation between STA-PSV and FT3 values after excluding the over-limit data (data not shown). These results suggested that STA-PSV reflects the thyrotoxicosis status. In addition, previous data demonstrated that thyroid blood flow was increased both in untreated and treated GD patients [9, 10]. The current findings also showed that blood flow in patients with treated GD was not normalized. The high blood flow seemed to result from a progressive increase in vascular density, which is known to correlate positively with the expression and serum level of vascular endothelial growth factor [11, 12]. On the other hand, we found no correlation between PSV and other biological parameters including TV, as reported previously [13, 14]. Thus, thyrotoxicosis status and vascular density might be important determinants of STA-PSV.

Thyroid artery blood flow and PSV have been already used as clinical indices. For GD patients in remission following anti-thyroid drug therapy [3, 6, 13], higher thyroid blood flow, PSV, and intrathyroidal blood flow seemed to be good predictors of an imminent recurrence of GD. In addition, other groups reported the effectiveness of thyroid blood flow [3, 15] and PSV [7, 13, 16] to discriminate thyrotoxicosis, but without showing any cut-off value. Our current study is the first to show a clear cut-off value for these parameters.

Kumar *et al*. [7] reported mean ITA-PSV values of 22.4 ± 5.4 cm/s in DT patients and 57.6 ± 13.1 cm/s in untreated GD patients, both with thyrotoxicosis. These reported values were slightly lower than those calculated in the present study, probably due to different sites of thyroid artery sampling and racial differences between studies.

In this study, we chose STA for measurement of the mean peak systolic velocity because it is more easily detected anatomically than ITA. Indeed, the values were obtained without issues from every subject enrolled in this study. Finally, we analyzed the value of measuring the FT3 to FT4 ratio for the diagnosis of thyrotoxicosis, using available FT3 and FT4 values within measurable ranges. The ROC curve showed that STA-PSV is a better method for the diagnosis of thyrotoxicosis than FT3 to FT4 ratio (data not shown).

In conclusion, this study confirmed that STA-PSV is a potentially useful parameter for the rapid and correct diagnosis of thyrotoxicosis in Japanese patients.

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Conflict of Interest

The authors declare no conflict of interest relevant to this manuscript.

References

1. Amino N, Yabu Y, Miki T, Morimoto S, Kumahara Y, Mori H, Iwatani Y, Nishi K, Nakatani K, Miyai K (1981) Serum ratio of triiodothyronine to thyroxine, and thyroxine-binding globulin and calcitonin concentrations in Graves' disease and destruction-induced thyrotoxicosis. *J Clin Endocrinol Metab* 53 : 113-116.
2. Sayama N, Yoshida K, Mori K, Fukazawa H, Hori H, Nakazato N, Tani, Nakagawa Y, Ito S (1998) Measurement of red blood cell zinc concentration with Zn-test kit: discrimination between hyperthyroid Graves' disease and transient thyrotoxicosis. *Endocr J* 45 : 767-772.
3. Ralls PW, Mayekawa DS, Lee KP, Colletti PM, Radin DR, Boswell WD, and Halls JM (1988) Color-flow Doppler sonography in Graves disease: "thyroid inferno". *AJR Am J Roentgenol* 150 : 781-784.
4. Castagnone D, Rivolta R, Rescalli S, Baldini MI, Tozzi R, Cantalamessa L (1996) Color Doppler sonography in Graves' disease: value in assessing activity of disease and predicting outcome. *AJR Am J Roentgenol*

166 : 203-207.
5. Bogazzi F, Bartalena L, Brogioni S, Scarcello G, Burelli A, Campomori A, Manetti L, Rossi G, Pinchera A, Martino E (1999) Comparison of radioiodine with radioiodine plus lithium in the treatment of Graves' hyperthyroidism. *J Clin Endocrinol Metab* 84 : 499-503.
6. Bogazzi F, Bartalena L, Brogioni S, Mazzeo S, Vitti P, Burelli A, Bartolozzi C, Martino E (1997) Color flow Doppler sonography rapidly differentiates type I and type II amiodarone-induced thyrotoxicosis. *Thyroid* 7 : 541-545.
7. Hari Kumar KV, Pasupuleti V, Jayaraman M, Abhyuday V, Rayudu BR, Modi KD (2009) Role of thyroid Doppler in differential diagnosis of thyrotoxicosis. *Endocr Pract* 15 : 6-9.
8. Hodgson KJ, Lazarus JH, Wheeler MH, Woodcock JP, Owen GM, McGregor AM, Hall R (1988) Duplex scan-derived thyroid blood flow in euthyroid and hyperthyroid patients. *World J Surg* 12 : 470-5.
9. Vitti P, Rago T, Mazzeo S, Brogioni S, Lampis M, De Liperi A, Bartolozzi C, Pinchera A, Martino E (1995) Thyroid blood flow evaluation by color-flow Doppler sonography distinguishes Graves' disease from Hashimoto's thyroiditis. *J Endocrinol Invest* 18 : 857-861.
10. Chang DC, Wheeler MH, Woodcock JP, Curley I, Lazarus JR, Fung H, John R, Hall R, McGregor AM (1987) The effect of preoperative Lugol's iodine on thyroid blood flow in patients with Graves' hyperthyroidism. *Surgery* 102 : 1055-1061.
11. Nagura S, Katoh R, Miyagi E, Shibuya M, Kawaoi A (2001) Expression of vascular endothelial growth factor (VEGF) and VEGF receptor-1 (Flt-1) in Graves disease possibly correlated with increased vascular density. *Hum Pathol* 32 : 10-17.
12. Iitaka M, Miura S, Yamanaka K, Kawasaki S, Kitahama S, Kawakami Y, Kakinuma S, Oosuga I, Wada S, Katayama S (1998) Increased serum vascular endothelial growth factor levels and intrathyroidal vascular area in patients with Graves' disease and Hashimoto's thyroiditis. *J Clin Endocrinol Metab* 83 : 3908-3912.
13. Bogazzi F, Bartalena L, Brogioni S, Burelli A, Manetti L, Tanda ML, Gasperi M, Martino E (1999) Thyroid vascularity and blood flow are not dependent on serum thyroid hormone levels: studies in vivo by color flow doppler sonography. *Eur J Endocrinol* 140 : 452-456.
14. Saleh A, Furst G, Feldkamp J, Godehardt E, Grust A, Modder U (2001) Estimation of antithyroid drug dose in Graves' disease: value of quantification of thyroid blood flow with color duplex sonography. *Ultrasound Med Biol* 27 : 1137-1141.
15. Fobbe F, Finke R, Reichenstein E, Schleusener H, Wolf KJ (1989) Appearance of thyroid diseases using colour-coded duplex sonography. *Eur J Radiol* 9 : 29-31.
16. Saleh A, Cohnen M, Furst G, Godehardt E, Modder U, Feldkamp J (2002) Differential diagnosis of hyperthyroidism: Doppler sonographic quantification of thyroid blood flow distinguishes between Graves' disease and diffuse toxic goiter. *Exp Clin Endocrinol Diabetes* 110: 32-36.