



Can Color Doppler Ultrasonography Differentiate Thyrotoxicosis in Graves' Disease from Subacute Thyroiditis?



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Abstract

Background and objectives: Color flow Doppler (CFD) can determine thyroid vascularity. It can be used for confirmatory diagnosis of thyroiditis and Graves' instead of radioactive iodine uptake (RAIU). This study analysed thyroid blood flow, peak systolic velocity (PSV) by CFD and thyroid volume by Gray scale sonography in thyrotoxicosis.

Methods and materials: Thyrotoxic cases (N=78; Graves: M/F=21/27, age: 35.73±1.38; subacute thyroiditis: M/F=09/21, age: 35.37±1.61 (M±SEM, yrs)) were recruited and divided into Graves' and subacute thyroiditis holding RAIU as gold standard. CFD and Gray scale sonography were done for all.

Results: Goiter was tender in 33% of subacute thyroiditis. Neither free thyroxine (FT4: 3.38±0.22 vs. 2.78±0.23ngm/dl, P=0.549) nor thyroid stimulating hormone (TSH: 0.05±0.01 vs. 0.06±0.2μIU/ml, P=0.084) were statistically different between the two groups. Echo pattern was predominantly homogeneous in Graves and heterogeneous in subacute thyroiditis (60.4% vs. 43.3%, P=0.007). Gray scale sonography revealed increased thyroid volume in 73%, normal in 20.8% and decreased in 6.3% of Graves which were 33.3%, 56.7% and 10.3% respectively in subacute thyroiditis (p=0.002). All Graves' had increased flow while 76.7% of the subacute thyroiditis had decreased flow by CFD (P<0.001). Mean (±SEM) PSV of inferior thyroid artery was significantly higher in Graves' than that of subacute thyroiditis (40.70±2.54 vs. 26.71±4.05cm/sec, P=0.003) and correlated with RAIU at 2h (r=0.330, P= 0.003) and 24hrs (r=0.325, P=0.004) as well as blood flow (r=0.663, P<0.001). Sensitivity and specificity of CFD were 93.7% & 83.3% respectively.

Conclusion: It is concluded that CFD may be a cost effective, convenient, safe and noninvasive technique with high sensitivity, specificity and diagnostic accuracy.

Keywords: Color doppler ultrasonography; Graves' disease; Subacute thyroiditis

Introduction

Thyroid disease is common and the prevalence increases with age. It is one of the major health hazards in many countries including Bangladesh [1]. Thyrotoxicosis refers to the classic physiological manifestations of excessive quantities of thyroid hormone. Differentiation between hyperthyroid Graves' disease and destructive thyrotoxicosis in thyroiditis is very important for management purpose.

Radioactive iodine uptake (RAIU) is recognized as the most accurate test, but iodine-containing foods or drugs can interfere with the results. In addition, RAIU is expensive, not easily accessible and contraindicated during pregnancy and lactation [2]. On the other hand, color flow Doppler (CFD) is a useful, inexpensive, noninvasive and widely available. Its evaluation can be both qualitative (visual assessment of thyroid vascularity) and quantitative [measuring peak systolic velocity (PSV), end

diastolic and mean velocities in the inferior thyroid arteries]. Normal PSV in intrathyroidal arteries ranges between 15 to 30cm/sec but it can rise to over 100cm/sec in certain pathologic conditions like Graves' disease [3]. CFD reveals a spectacular thyroid inferno with marked hypervascularity both in systole and diastole. Return of normal thyroid appearance may be possible during remission. Contrary to Graves' disease, vascularity is markedly diminished in subacute thyroiditis. In Graves disease, gray scale ultrasound reveals diffusely enlarged thyroid (2-3 times its normal size) which is hypoechoic and heterogeneous whereas in subacute thyroiditis it shows characteristic focal hypoechoic areas (map like) and enlargement of one or more lobes.

The aim of the study was to evaluate the utility of CFD in differentiation of hyperthyroid Graves' disease from subacute

thyroiditis as well as comparing its sensitivity and specificity in light of RAIU test.

Materials and Methods

This study included 78 patients with thyrotoxicosis (Graves disease: n=48, M/F=21/27, age (M±SEM, yrs): 35.73±1.38; subacute thyroiditis: n=30, M/F=09/21, age (M±SEM, yrs): 35.37±1.61) recruited from May 2014 to April 2015 in the department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU). Informed written consent was taken from all participants. Free thyroxine (FT₄), thyroid stimulating hormone (TSH) and RAIU and complete blood count with ESR were done for each subject. Thyroiditis and Graves’ disease were discriminated on the basis of low versus high uptake. A color Doppler ultrasound scanner (Toshiba Ultrasonography system and color Doppler, Model no: SSA-550A, Toshiba medical system, Tokyo, Japan) equipped with a 7.5MHz broadband linear array high resolution transducer was used and both CFD and Gray scale ultrasound were performed at National Institute of Nuclear Medicine and Allied sciences (NINMAS), BSMMU campus. Thyroid blood flow was seen by color Doppler power mode. PSV of the inferior thyroid artery of >30cm/sec was

considered significantly high and suggestive of Graves disease and <30cm/sec for thyroiditis [3]. RAIU was considered as the gold standard. High RAIU was suggestive of Graves’ disease and low RAIU considered for thyroiditis. All data were analyzed by SPSS (version 22.0).

Results

Though few clinical manifestations were statistically different between the two entities, altogether they were not conclusive (Table 1). Virtually all goiter of both the groups were diffuse (p=NS). However, consistency of goiter was mostly soft in Graves’ and firm in subacute thyroiditis (p<0.001). Similarly, tenderness was absent in Graves’ disease except one case whereas 33% of subacute thyroiditis had tender goiter (p<0.001). FT₄ in both Graves’ and subacute thyroiditis were above the upper normal limit (3.38±0.22 and 2.78±0.23ngm/dl respectively, m±SEM; P=0.549) and TSH less than the lower limit (0.05±0.01 and 0.06±0.02µIU/ml respectively, P=0.084). RAIU at 2hrs (21.35±1.43 vs. 5.02±0.30, mean±SEM; P<0.001) and at 24hrs (37.81±1.72 vs. 2.94±0.35, mean±SEM; p<0.001) were higher in Graves’ disease than that of subacute thyroiditis (Table 2).

Table 1: Clinical findings in the participants (n=78).

Variable	Graves’ Disease (n=48)	Sub Acute Thyroiditis (n=30)	P
Palpitation	45 (93.8%)	23 (76.7%)	0.039
Weight loss	42 (87.5%)	17 (56.7%)	0.003
Heat intolerance	20.0 (41.7%)	04 (13.3%)	0.011
Hyper defecation	08 (16.7%)	02 (6.7%)	0.301
Excessive Sweating	34 (70.8%)	08 (26.7%)	<0.001
Neck pain	03 (6.3%)	23 (76.7%)	<0.001
Fever	04 (8.3%)	13 (43.3%)	<0.001
Sore Throat	04 (8.3%)	12 (40.0%)	0.001
Tremor	24 (50.0%)	13 (43.3%)	0.644
Pulse (M±SEM,bpm)	104±2	98±2	0.01
Goiter			
Diffuse	47 (97.9%)	30 (100.0%)	1
Nodular	01 (20.1%)	00 (0.0%)	
Consistency			
Soft	36 (75.0%)	11 (36.7%)	<0.001
Firm	12 (25.0%)	19 (63.3%)	
Tenderness	01 (2.1%)	10 (33.3%)	<0.001
Bruit	06 (12.5%)	01 (3.3%)	0.24
Eye Sign	07 (14.6%)	00 (0.0%)	0.039

Within parenthesis are percentages over column total.

Table 2: RAIU in Graves' disease and subacute thyroiditis.

RAIU	Graves Disease (n=48)	Subacute Thyroiditis (n=30)	P*
02hr (Mean±SEM)	21.35±1.43	5.02±0.30	<0.001
24hr (Mean±SEM)	37.81±1.72	2.94±0.35	<0.001

*by student's t-test.

RAIU: Radioactive Iodine Uptake.

Echo pattern of thyroid was mostly homogeneous in Graves' (60.4%) but heterogenous in subacute thyroiditis (30.0%; p=0.007). As observed by gray scale sonography, increased thyroid volume was found in 72.9% patients of Graves' disease whereas 6.3% had decreased and 20.8% had normal volume. On the contrary, in subacute thyroiditis 56.7% had normal, 33.3% increased, and 10.0% decreased volume (p=0.002) (Table 3).

Table 3: Echo pattern in Gray Scale sonography.

Echo Pattern	Subjects		χ ² , p
	Graves Disease (n=48)	Subacute Thyroiditis (n=30)	
Homogeneous	29 (60.4%)	09 (30.0%)	
Hyperechoic	01 (2.1%)	01 (3.3%)	χ ² =12.08
Hypoechoic	01 (2.1%)	07 (23.3%)	p=0.007
Heterogenous	17 (35.4%)	13 (43.3%)	

Within parenthesis are percentages over column total.

Cent percent of the Graves' disease subjects had increased blood flow by CFD. On the contrary, 76.7% of the subacute thyroiditis subjects had decreased flow, 16.7% had increased flow and 6.7% had normal flow (χ² = 58.87, P<0.001) (Table 4). Mean (±SEM) PSV of inferior thyroid artery was significantly higher in Graves' disease than that of subacute thyroiditis (40.70±2.54 vs. 26.71±4.05, P=0.003). Considering 30cm/sec as cut off value, 93.8% of the Graves' subjects had PSV >30cm/sec; frequency of which was only 16.7% in subacute thyroiditis subjects (p <0.001) (Table 5). Doppler PSV strongly correlate with RAIU in both 2h (r=0.330, p=0.003) and 24hrs (r=0.325, p=0.004; Figure 1 & 2). PSV correlated with thyroid blood flow (r=0.663, p<0.001) as well as thyroid volume (r=0.219, p=0.054). Doppler thyroid blood flow was a strong predictor for diagnosis of Graves' disease and subacute thyroiditis (p<0.001); but none of the others were independently capable as predictor (Table 6).

Table 4: Thyroid blood flow by Color Flow Doppler Sonography.

Thyroid Blood Flow	Subjects		χ ² , P
	Graves Disease (n=48)	Subacute Thyroiditis (n=30)	
Increased	48 (100%)	05 (16.7%)	χ ² =58.87
Normal	00 (0%)	02 (6.7%)	P<0.001
Decreased	0 (0.0%)	23 (76.7%)	

Within parenthesis are percentages over column total.

Table 5: Peak systolic velocity (PSV) of inferior thyroid artery by color flow Doppler Sonography.

PSV (cm/sec)	Subjects		p
	Graves' Disease (n=48)	Subacute Thyroiditis (n=30)	
30 or less	03 (6.3%)	25 (83.3%)	
More than 30	45 (93.8%)	05 (16.7%)	<0.001
Mean±SEM	40.70±2.54	26.71±4.05	0.003

by χ² and student's t-test.

Within parenthesis are percentages over column total.

Table 6: Multiple Regressions analysis showing predictors for diagnosis of Graves' disease and subacute thyroiditis.

Ki	B	SE	Beta	t	p
Constant	1.197	0.613	-	1.953	0.057
Age	0	0.005	-0.009	-0.104	0.917
Palpitation	-0.028	0.134	0.019	0.206	0.837
Weight loss	0.035	0.1	-0.033	-0.351	0.727
Heat intolerance	0.089	0.095	-0.089	-0.939	0.352
Excessive sweating	-0.072	0.091	0.077	0.794	0.431
Hyperdefaecation	-0.058	0.125	0.043	0.464	0.645
Tremor	-0.053	0.083	0.057	0.642	0.524
Goiter-Tender	0.039	0.124	-0.031	-0.314	0.755
Exophthalmos	0.13	0.151	-0.074	-0.863	0.392
FT4	0.003	0.003	0.009	0.092	0.927
TSH	0.662	0.468	0.124	1.417	0.163
RAIU 2h	0.008	0.006	0.187	1.279	0.207
RAIU 24h	0.001	0.004	0.04	0.224	0.824
Doppler thyroid volume	0.002	0.038	0.004	0.048	0.962
Doppler blood flow	0.352	0.073	0.671	4.834	<0.001

FT4: Free Thyroxine

TSH: Thyroid Stimulating Hormone

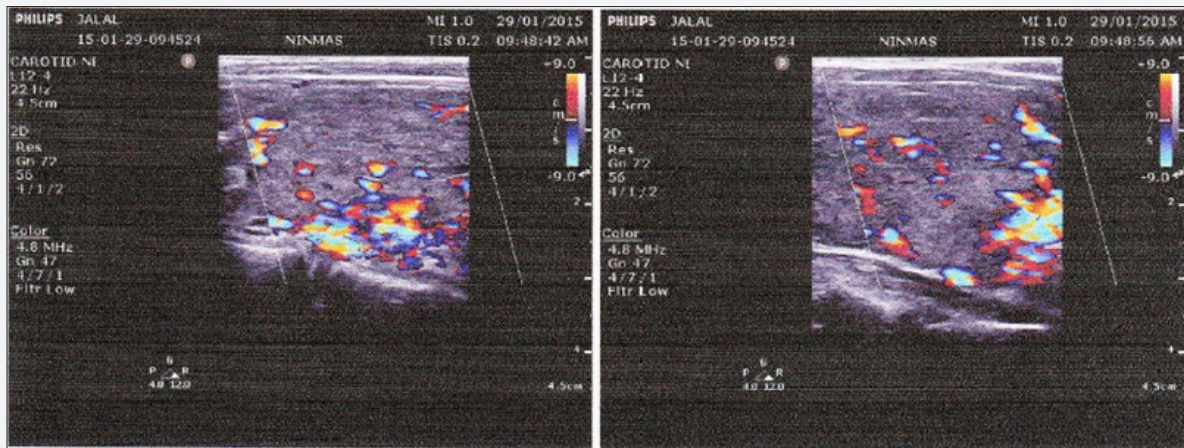


Figure 1: Color flow Doppler (CFD) reveals a spectacular thyroid inferno in a Graves' patient.
*Printed with permission from the patient.

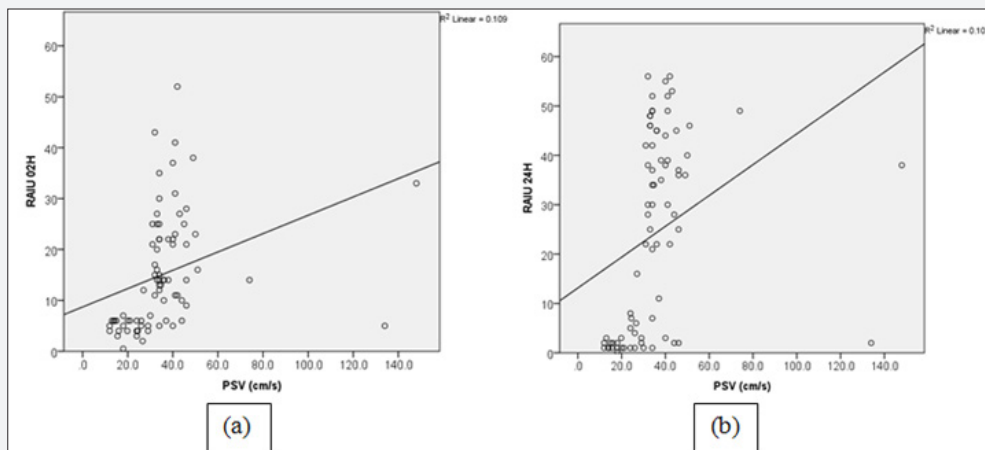


Figure 2: Correlation between peak systolic velocity (PSV) of inferior thyroid artery to (a) 2h and (b) 24h radioactive iodine uptake (RAIU) among the studied subjects.

Holding the RAIU as the gold standard for diagnosis of Graves' disease and subacute thyroiditis, sensitivity and specificity of CFD were 93.7% & 83.3% respectively. Positive predictive value was 90.0%, negative predictive value was 89.2% and diagnostic accuracy was 89.7%.

Discussion

In the present study, importance of relatively easily practicable, convenient and less hazardous modules like blood flow and PSV of inferior thyroid artery by CFD sonography and thyroid volume as well as echo pattern by gray scale sonography were investigated in the light of 2h and 24h RAIU as gold standard. It was clearly observed that cent percent of Graves' disease patient had increased thyroid blood flow in comparison to subacute thyroiditis in which more than three quarters showed decreased flow. Cut off value of 30cm/sec was considered in differentiation between Graves' disease from thyroiditis based on a review of relevant literature [3,4]. Our findings were in agreement with the findings of those investigators revealing more than 90% of the Graves'

patient above the mentioned cut off while 80% of subacute cases were below.

Although echo pattern was found to be different, yet it was not enough to demarcate the two diseases- it was homogeneous in around 60% of Graves and 30% of subacute thyroiditis and by gray scale sonography 70% of Graves patient had increased volume while only 33% of subacute thyroiditis had so. Thus, neither echo pattern nor thyroid volume could be considered for diagnostic differentiation of the two disease status. Rather PSV was found to be free from performance related error and relatively better in distinguishing between the two diseases as well as less hazardous and easy practicable. Holding RAIU as the gold standard, sensitivity and specificity of PSV were 93.75% and 83.33% respectively with 89.7% diagnostic accuracy. The diagnostic performance is very satisfactory and in much agreement with other investigators' findings [5-8].

Though there are similarities of clinical manifestations between Graves' disease and thyroiditis, it was observed in this

study that some clinical manifestations like palpitation, weight loss, heat intolerance, hyperdefaecation, excessive sweating, tremor were more prominent in Graves' than subacute thyroiditis whereas neck pain/ tenderness, fever, sore throat were more prominent in subacute thyroiditis as was expected. 75% of the goiter was soft in Graves' disease while in subacute thyroiditis 63% were firm in consistency. Bruit (12.5%) and eye sign (14.6%) were exclusively seen in patients with Graves'. None of the abovementioned features could clearly distinguish between these two groups as features of thyrotoxicosis overlapped in both the groups.

CFD is a cheap and simple technique with no ionizing radiation exposure and is cost effective in the diagnosis of thyrotoxicosis. A typical CFD thyroid examination takes about 10 minutes [9]. Inferior thyroid artery blood flow could be considered as an acceptable alternative to RAIU test especially when there is a contraindication to nuclear imaging of the thyroid. Radioactive iodine should not be used in situations with recent use of iodinated contrast which interfere with the accuracy of radioactive iodine tests [9]. Phillips et al. found that 45% of patient with newly diagnosed thyrotoxicosis had received iodinated contrast within 2 week before endocrine evaluation for other purposes heralding diagnostic difficulty [10]. Therefore, in these scenario if some diagnostic module avoiding the use of radioisotope can be utilized diagnostic difficulties can be overcome. In such context, we might propose and would fully agree with other investigators [11,12] supporting diagnostic modules like PSV by CFD to discriminate between thyrotoxicosis due to Graves' and subacute thyroiditis.

In summary, the thyroid blood flow is a useful marker in diagnosis of Graves' disease and subacute thyroiditis in initial phase. The high correlation between RAIU and PSV by CFD established this modality as an acceptable alternative. Its role in pregnancy and lactation where nuclear imaging is contraindicated needs to be emphasized. Data of present study suggest that CFD may be a cost effective, quick, safe and

noninvasive technique in contrast to RAIU with high sensitivity, specificity and diagnostic accuracy.

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