

# Quantitative Index for Diagnosis of Thyroid Disease using Pulsatile Flow Detection Ultrasound (PFD-US)

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**Abstract:** *Purpose: To investigate blood flow pulsatility degree as a quantitative index and to evaluate clinical usefulness of the index using pulsatile flow detection ultrasound (PFD-US).*

*Patients and Methods: Eighty patients (43 with untreated Graves' disease and 37 with untreated Hashimoto's disease) were examined by PFD-US with a 9 MHz electronic linear array transducer. PFD color mapping was imaged as pulsatile flow in red and low pulsatile flow in blue. The number of red and blue pixels were counted respectively. We defined pulsatile flow/ low pulsatile flow (P/LP) ratio as dividing red/blue pixels, for a blood flow pulsatility index.*

*Results: The mean P/LP ratio of Graves' disease ( $2.14 \pm 1.90$ , mean  $\pm$  one standard deviation) was statistically higher ( $p < 0.0001$ ) than that of Hashimoto's disease ( $0.85 \pm 0.58$ ).*

*Conclusion: The P/LP ratio, namely, quantitative index of degree of pulsatility was useful for differentiation between Graves' disease and Hashimoto's disease.*

**Keywords:** pulsatile flow detection ultrasonography (PFD-US), Graves' disease, Hashimoto's disease

## 1. Introduction

Pulsatile flow detection (PFD) is an ultrasonographic (US) technique that can demonstrate both pulsatile and low-pulsatile flow with a different color coding at the same time in both real time and static two-dimensional (2D) images. We investigated blood flow pulsatility degree as a quantitative index and to evaluate clinical usefulness of the index using PFD-US. We defined P/LP ratio as an index the ratio between area of pulsatile flow and area of low-pulsatile flow using PFD-US. The ratio was calculated simply by counting the number of pixels of pulsatile flow vs. that of low-pulsatile flow on a PFD-US image. The ratio was a quantitative index for blood flow pulsatility.

In both of Graves' disease and Hashimoto's disease in active inflammation status, they simply show hypervascularity using conventional power and color Doppler flow mapping. While applying PFD-US to thyroid disease, we had an impression of pulsatile flow dominance in Graves' disease and low-pulsatile flow dominance in Hashimoto's disease. We studied P/LP ratio to classify between Graves' disease and Hashimoto's disease with hypervascular status.

The purpose of the study was to investigate blood flow pulsatility degree as a quantitative index for evaluating usefulness of the index using PFD-US.

## 2. Materials and Methods

This retrospective study was approved by local ethics committee.

### Subjects

Eighty patients (19 men and 61 women) with diffuse thyroid disease (43 with untreated Graves' disease and 37 with untreated Hashimoto's disease with hypervascular status on color Doppler imaging) were examined from December 1999 through January 2004 and data were analyzed retrospectively. The mean age was 41.1 years (age range, 24-77 years). The patients with thyroid disease were required to have routine US examination for observation of thyroid size, echogenicity, vascularity, neck lymph nodes, rule out of thyroid tumor and Plummer disease by using gray-scale mode, color/power Doppler and PFD. The final diagnosis was obtained by hormonal assays, serum free triiodothyronine (FT3), serum free thyroxine (FT4), thyroid stimulating hormone (TSH), and immunological antibody assays, anti-thyroglobulin antibody, anti-thyroid peroxidase antibody, thyroid stimulating hormone receptor antibody, and/or by a radioisotope iodine uptake test.

### Ultrasonography

A LOGIQ500 PRO® (GE Healthcare Japan, Tokyo Japan) equipped with PFD was used with a 9 MHz electronic linear array transducer. Adjusted PFD parameters are shown in Table. We set up the PFD color mapping as follows, pulsatile flow was shown as red and low-pulsatile flow was shown as blue. PFD color gain was set up highest level without clutter noise in each case. PFD type and resolution were specific parameters in PFD-US. PFD type controlled sensitivity for pulsation by using an algorithm of difference of velocity/frame and variance. We set up the lowest sensitivity for pulsatility and suitable for strong pulsatile flow. This setting displayed weak pulsatile flow as low-pulsatile.

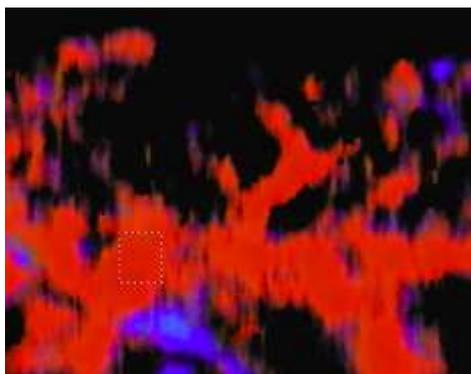
**Table : Scan condition**

<b>Gray-scale mode</b>	
<b>Gain</b>	0 ~ low
<b>Depth</b>	4 cm
<b>Transducer</b>	739L 9MHz electronic linear array
<b>Color mode</b>	
<b>Slant scan</b>	0
<b>Packet size</b>	middle
<b>Penetration</b>	on
<b>High resolution</b>	on
<b>PFD mode</b>	
<b>Adaptive color enhancement</b>	on
<b>Color map</b>	pulsatile flow: red low pulsatile flow: blue
<b>Persistence</b>	mild
<b>Sampling frequency</b>	1.97 KHz
<b>PFD type*</b>	low sensitivity
<b>Resolution</b>	middle smoothness medium color indication

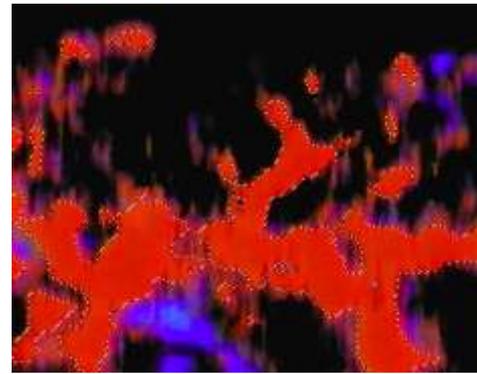
PFD type\*: PFD type controls sensitivity for pulsatility by using an algorithm of difference of velocity/frame and variance.

**P/LP ratio**

We defined P/LP ratio as the ratio between area of pulsatile and area of low-pulsatile flow using PFD-US. The ratio was calculated simply by counting the number of pixels of pulsatile flow vs. that of low-pulsatile flow on a PFD-US image. Oblique longitudinal static image was captured in a commercially available personal computer as JPEG files. The number of red (pulsatile flow) and blue (low-pulsatile flow) pixels were counted respectively using commercially available application software PHOTOSHOP7® (Adobe Systems Inc. Cal., USA). Photoshop application had a function called “Color Range” to extract pixels with approximate color (hue) out and its histogram function provided the number of pixels with the selected color (Fig. 1). By using this function, the number of pixels of each red and blue on an image were separately counted. Pixels were counted three times and used average for decreasing sampling errors. The P/LP ratio was then calculated as red pixels/blue pixels. Red pixels divided by blue pixels equaled P/LP ratio.



**a**



**b**

**Figure 1: The extraction of pixels by using Photoshop Application**

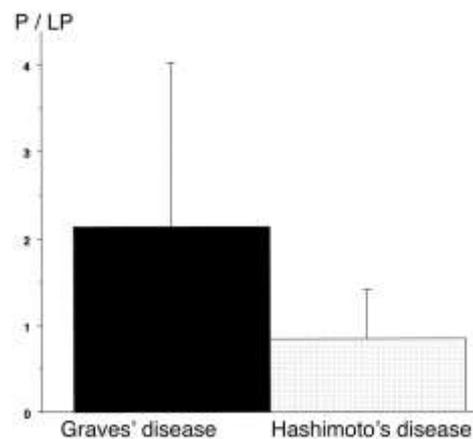
a: Sample red pixels with rectangle ROI (region of interest).  
b: “Color range” selects red pixels by surrounding them with dotted lines.

**Statistical analysis**

The value of P/LP ratio was compared between in Graves’ disease and in Hashimoto’s disease. P/LP ratio was expressed as mean ± one standard deviation in Graves’ disease and Hashimoto’s disease, respectively. Statistical analysis was performed using commercially available application software Stat view® version 4.51 (Abacus, Berkeley, Calif. USA). Analysis of variance was performed using an F-test. When variance was equal to the P/LP ratio between Graves’ disease and Hashimoto’s disease, the comparison was performed using Student’s t-test. Meanwhile, when variance was not equal, the comparison was performed using Welch’s t-test and Mann-Whitney’s U-test. A p value of less than 0.05 was considered to indicate a statistically significant difference.

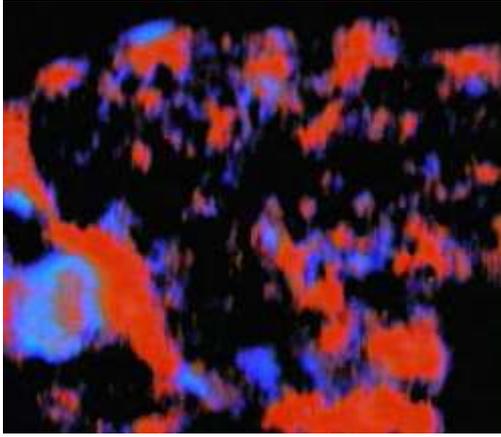
**3. Results**

The mean P/LP ratio of Graves’ disease (mean ± one standard deviation 2.14 ± 1.90: range 0.40~9.22) was statistically higher (Welch’s t-test p < 0.0002, Mann-Whitney U-test p < 0.0001) than that of Hashimoto’s disease (0.85 ± 0.58: 0.18~1.63) (Fig.2, 3). The variance of P/LP ratio of Graves’ disease was statistically different from that of Hashimoto’s disease (F-test p < 0.0001).



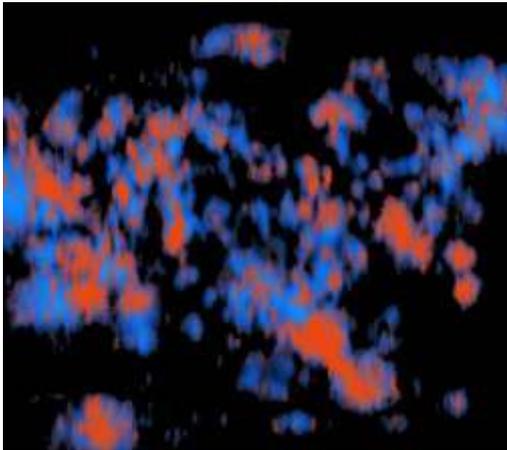
**Figure 2: Mean P/LP ± one standard deviation**

The mean P/LP ratio was 2.14 ± 1.90 for Graves’ disease and 0.85 ± 0.58 for Hashimoto’s disease. Error bar represents one standard deviation.



**Figure 3-a: Graves' disease**

Total number of red pixels is 21024 and that of blue is 11631.  
P/LP ratio is 1.81. High P/LP suggests Graves' disease.



**Figure 3-b: Hashimoto's disease**

Total number of red pixels is 10165 and that of blue is 13476.  
P/LP ratio is 0.75. Low P/LP ratio suggests Hashimoto's disease.

#### 4. Discussion

We showed the degree of pulsatility in quantitative terms with PFD-US. P/LP ratio used to be calculated simply by counting the number of pixels of pulsatile flow vs. that of low-pulsatile flow in PFD-US. The mean P/LP ratio of Graves' disease was statistically higher than that of Hashimoto's disease, and it was useful to differentiate these two diseases in a hypervascular status by setting up constant scanning condition.

Iitaka et al. [1] and Shimosawa et al. [2] noted the usefulness of total blood flow index by using color Doppler US, which was calculated by dividing the area of intrathyroidal blood flow by the area of the thyroid gland in the reports. They defined total flow index as follows: [the area of intrathyroidal blood flow]/[the area of the thyroid gland]. The total flow index in the case of active Graves' disease was the highest, in the case of Hashimoto's disease the index was the second highest and the index in the case of euthyroid was the third. Whereas total flow index is an index of vascularity, P/LP ratio is an index for the blood flow pulsatility.

Hyperthyroidism has effect on the cardiovascular system [3]. It was observed that in cases of Graves' disease, peak systolic velocities of the inferior thyroid artery were significantly higher than that of normal controls [4]. Vitti P et al. [5] also reported

that marked increase of color flow Doppler signals were shown in untreated Graves' disease than in untreated Hashimoto's disease.

Following considerations have been made to find a cause of high P/LP ratio in Graves' disease. And the higher velocity flow displays vascular diameter larger. It is an artifact on color/power Doppler and PFD-US. On the other hand, low velocity flow might be suppressed by the wall-filter algorithm. Then, pulsatile flow vessels are displayed relatively larger, and low-pulsatile flow vessels are displayed relatively smaller.

P/LP ratio is an index that shows blood flow pulsatile degree quantitatively and is clinically useful for a distinction between Graves' disease and Hashimoto's disease. The development of PFD-US was motivated by discriminating artery from vein depicted by separate color-code in real time. PFD-US judges the flow to be pulsatile if the dispersion of its velocity (difference between  $V_{max}$  and  $V_{min}$ ) is relatively high, and low-pulsatile if relatively low. The display of an image was obtained by setting scan condition and by thresholds to separate color-code. The optimum conditions need to be discovered heuristically and individually in each organ and disease. US equipment cannot automatically select reddish / bluish color and it cannot calculate P/LP automatically.

Recently, oxygen becomes the focus of biomarker. Oncocytes and inflammatory cells release angiogenesis factor, and arteries reply, and arterial blood flow increases [6-8]. Detection of increasing pulsatile flow vessels by PFD-US equals detection of increasing oxygen consumption.

If our technology can overcome these challenges, PFD-US will be more clinically useful.

#### 5. Conclusion

The P/LP ratio, namely, quantitative index of degree of pulsatility was useful for differentiation between Graves' disease and Hashimoto's disease.

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#### Conflict of interest

All authors declare that they have no conflict of interest in association with this study.

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