



# Predictive value of red cell distribution width on left atrial thrombus or left atrial spontaneous echo contrast in patients with non-valvular atrial fibrillation

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## Abstract

**Objective** To evaluate the predictive value of red cell distribution width (RDW) on left atrial thrombus (LAT) or left atrial spontaneous echo contrast (LASEC) in patients with non-valvular atrial fibrillation (AF). **Methods** We reviewed 692 patients who were diagnosed as non-valvular AF and underwent transesophageal echocardiography (TEE) in Guangdong Cardiovascular Institute from April 2014 to December 2015. The baseline clinical characteristics, laboratory test of blood routine, electrocardiograph measurements were analyzed. **Results** Eighty-four patients were examined with LAT/LASEC under TEE. The mean RDW level was significantly higher in LAT/LASEC patients compared with the non-LAT/LASEC patients ( $13.59\% \pm 1.07\%$  vs.  $14.34\% \pm 1.34\%$ ;  $P < 0.001$ ). Receiver–operating characteristic curve analysis was performed and indicated the best RDW cut point was 13.16%. Furthermore, multivariate logistic regression analysis indicated that RDW level  $> 13.16\%$  could be an independent risk factor for LAT/LASEC in patients with AF. **Conclusion** Elevated RDW level is associated with the presence of LAT/LASEC and could be with moderate predictive value for LAT/LASEC in patients with non-valvular AF.

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**Keywords:** Atrial fibrillation; Left atrial spontaneous echo contrast; Left atrial thrombus; Red cell distribution width

## 1 Introduction

Atrial fibrillation (AF), as one of the most common cardiac arrhythmia, is associated with significant morbidity and mortality and essential risk factor for thromboembolic events.<sup>[1]</sup> The development of thrombi within the left atrium is supposed to be the pathogenesis of thrombo-embolism.<sup>[2]</sup> Nowadays transesophageal electrocardiograph (TEE) is the gold-standard for identifying left atrium thrombus (LAT) or left atrial spontaneous echo contrast (LASEC) which has been regarded as a precursor of LAT. However, the mechanisms and pathways underlying LAT or LASEC have not yet been fully clarified.

Red cell distribution width (RDW) is a measure of the variability in the size of circulating erythrocytes. Its clinical value has been confined to the differential diagnosis among several causes of anemia.<sup>[3]</sup> Several studies have shown that RDW is associated with the presence and outcomes of several cardiovascular diseases.<sup>[4–6]</sup> But very limited data were found regarding the predictive value of RDW for the development of LAT or LASEC in patients with non-valvular AF.<sup>[6]</sup> Therefore, we would aim to reveal the relationship between RDW and the development of LAT/LASEC in patients with non-valvular AF.

## 2 Methods

### 2.1 Study population

We retrospectively reviewed the clinical, laboratory, and electrocardiograph data of patients with AF who underwent TEE prior to radiofrequency catheter ablation or cardioversion in our institution from April 2014 to December 2015. Patients with valvular heart disease or severe anemia (hemoglobin level  $< 10$  g/dL) were excluded from the pre-

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sent study. Our study was approved by the local ethics committee.

## 2.2 Laboratory data

The blood routine tests were performed on all patients prior to radiofrequency catheter ablation or cardioversion. Hemoglobin (HGB), hematocrit (HCT), red blood cell count (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet (PLT), white blood cell counts (WBC), and RDW were measured by an automated complete blood count. The reference range of RDW is from 11.0% to 16.0% in our laboratory.

## 2.3 Electrocardiograph data

Transthoracic echocardiography was performed using a Vivid S5 (2–4 MHz phased array transducer; GE, Horten, Norway) system. Standard parasternal long-axis and short-axis views and apical 2- and 4-chamber views were obtained in all patients. Left atrial diameters were measured in parasternal long axis view. LV ejection fraction (LVEF) was calculated by using the modified Simpson method. TEE was performed without anesthesia or sedation in all the patients by using a 5 MHz biplane phased array transducer (Vivid S5, GE, Horten, Norway). The left atrium and left atrial appendage were imaged in different tomographic planes to detect the presence of LAT or LASEC. SEC was classified according to previously described criteria.<sup>[7]</sup> LASEC was defined as minimal echogenicity located in the left atrial appendage (LAA) or rarely in the main cavity of the left atrium. LAT was defined as dense swirling pattern in the LAA, less intense in the main atrium cavity, may fluctuate in intensity but constantly detectable throughout the cardiac cycle or intense echo density and very slow swirling pattern in the LAA and with similar intensity in the main atrium cavity. All patients were divided into LAT/LASEC group or non-LAT/LASEC group basing on the result of TEE.

## 2.4 Statistical analysis

Numerical variables were expressed as mean  $\pm$  SD and categorical variables were expressed as percentage. Comparisons between the two groups were made using the Student *t* test or Mann-Whitney *U* test or chi-square tests, as appropriate. Receiver–operating characteristic (ROC) analysis was used to detect the cutoff value of RDW in prediction of LAT/LASEC in patients with non-valvular AF. Multivariate logistic regression analysis was performed to identify the independent predictors of LAT/LASEC. *P* < 0.05 was considered significant. All statistical analysis was car-

ried out using SPSS 19.0 for Windows (SPSS Inc. Chicago, Illinois).

## 3 Results

### 3.1 Baseline characteristics of the LAT/LASEC and Non-LAT/LASEC groups

A total of 692 patients with non-valvular AF (67.9% males; mean age of  $54.5 \pm 12.23$  years) were included into the study. Eighty-four patients were identified with LAT/LASEC during TEE examination. The clinical baseline, laboratory and electrocardiography characteristics were summarized on Table 1. The CHADS<sub>2</sub> ( $1.60 \pm 1.62$  vs.  $0.44 \pm 0.88$ , *P* < 0.001) and CHA<sub>2</sub>DS<sub>2</sub>-VASc score ( $2.42 \pm 2.05$

**Table 1. Baseline characteristics of patients with or without LAT/LASEC during TEE examination.**

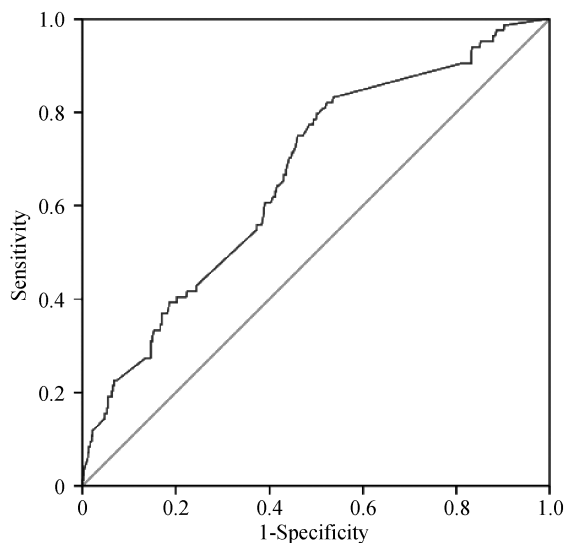
	Non-LAT/LASEC group (n = 608)	LAT/LASEC group (n = 84)	<i>P</i>
Clinical characteristics			
Male	422 (69.4%)	48 (57.1%)	0.024
Age, yrs	$53.73 \pm 12.18$	$60.32 \pm 11.01$	0.072
CHF	57 (9.4%)	23 (27.4%)	<0.001
Hypertension	54 (8.9%)	39 (46.4%)	<0.001
Diabetes mellitus	16 (2.6%)	15 (17.9%)	<0.001
Vascular disease	29 (4.8%)	22 (26.2%)	<0.001
Previous stroke	12 (2.0%)	7 (8.3%)	<0.001
Warfarin	135 (22.2%)	18 (21.4%)	0.814
CHADS <sub>2</sub> score	$0.44 \pm 0.88$	$1.60 \pm 1.62$	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	$0.82 \pm 1.16$	$2.42 \pm 2.05$	<0.001
Laboratory examinations			
RDW	$13.59\% \pm 1.07\%$	$14.34\% \pm 1.34\%$	<0.001
HGB, g/L	$139.60 \pm 14.63$	$140.72 \pm 13.67$	0.507
PLT, 109/L	$201.65 \pm 51.46$	$197.79 \pm 60.39$	0.529
WBC, 109/L	$6.75 \pm 1.91$	$6.59 \pm 1.62$	0.461
RBC, 109/L	$4.62 \pm 0.62$	$4.64 \pm 0.46$	0.667
HCT, %	$41.30\% \pm 4.11\%$	$41.68\% \pm 3.89\%$	0.426
MCV, fl	$90.62 \pm 7.31$	$90.02 \pm 7.98$	0.486
MCH, pg	$30.71 \pm 2.80$	$30.45 \pm 3.10$	0.433
MCHC, g/L	$338.56 \pm 11.87$	$337.83 \pm 12.21$	0.599
Echocardiogram parameters			
LAD, mm	$35.46 \pm 5.86$	$41.57 \pm 5.64$	<0.001
LVEF	$65.56\% \pm 7.04\%$	$64.26\% \pm 5.94\%$	0.107

Data are presented as mean  $\pm$  SD or *n* (%). CHF: chronic heart failure; HCT: hematocrit; HGB: hemoglobin; LAD: left atrial diameter; LAT/LASEC: left atrial thrombus or left atrial spontaneous echo contrast; LVEF: Left ventricular ejection fraction; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; PLT: platelet; TEE: transesophageal echocardiography; RBC: red blood cell counts; RDW: red cell distribution width; WBC: White blood cell counts.

vs.  $0.82 \pm 1.16$ ,  $P < 0.001$ ) were higher in patients with LAT/LASEC. Significant difference was observed between the two groups in term of RDW ( $14.34\% \pm 1.34\%$  vs.  $13.59\% \pm 1.07\%$ ,  $P < 0.001$ ). However, HGB, PLT, WBC, RBC, HCT, MCV, MCH and MCHC levels were not markedly different between the two groups. The mean RDW level in patient with previous stroke was significantly higher than those without previous stroke ( $14.29\% \pm 1.25\%$  vs.  $13.66\% \pm 1.12\%$ ,  $P = 0.018$ ). Furthermore, the RDW level was weakly correlated with CHADS<sub>2</sub> score ( $r = 0.148$ ,  $P < 0.001$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VASc score ( $r = 0.164$ ,  $P < 0.001$ ).

### 3.2 Predictive value of RDW on LAT/LASEC in Patients with non-valvular AF

ROC curve was used to determine the best cutoff value of RDW for predicting LAT/LASEC. The RDW with 13.16 % predicted LAT/LASEC was identified as the best cutoff point with a sensitivity of 82.1% and a specificity of 52.3% in the study population (Figure 1). After adjustment for age, gender, chronic heart failure, hypertension, diabetes, previous stroke and vascular disease, multivariate logistic regression analysis showed that RDW>13.16% (OR = 2.967,  $P = 0.001$ ) was the independent predictor for LAT/LASEC. Additionally, after adjustment for CHA<sub>2</sub>DS<sub>2</sub>-VASc score, RDW > 13.16% (OR = 2.911,  $P = 0.001$ ) still was the independent predictor (Table 2).



**Figure 1.** The ROC curve analysis for RDW in predicting LAT/LASEC in patients with non-valvular AF. Area under the curve = 0.666,  $P < 0.001$ , 95% CI: 0.626–0.726. The RDW with 13.16 % predicted LAT/LASEC was identified as the best cutoff point with 82.1% sensitivity and 52.3% specificity. AF: atrial fibrillation; LASEC: left atrial spontaneous echo contrast; LAT: left atrial thrombus; RDW: red cell distribution width; ROC: receiver-operating characteristic.

**Table 2.** Multivariate logistic regression analysis for LAT/LASEC in patients with non-valvular AF.

Variables	Odds ratio	95% CI	P-value
Model 1			
RDW > 13.16%	2.967	1.603–5.489	0.001
CHF	2.770	1.472–5.212	0.002
Hypertension	4.703	2.475–8.938	< 0.001
Diabetes mellitus	2.422	0.972–6.037	0.058
Age $\geq$ 65 yrs	1.128	0.610–2.086	0.702
Vascular disease	3.071	1.384–6.814	0.006
Previous stroke	0.620	0.182–2.111	0.444
Age $\geq$ 75 yrs	1.361	0.352–5.265	0.656
Female	1.595	0.935–2.721	0.087
Model 2			
RDW > 13.16%	2.911	1.612–5.258	0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc (per score)	1.745	1.486–2.049	< 0.001

RDW: red cell distribution width; Model 1: chronic heart failure, hypertension, diabetes mellitus, age, previous stroke, vascular disease, gender and RDW>13.16%; Model2: CHAS<sub>2</sub>DS<sub>2</sub>-VASc scoring system and RDW > 13.16%. AF: atrial fibrillation; CHF: chronic heart failure; LAT/LASEC: left atrial thrombus or left atrial spontaneous echo contrast; RDW: red cell distribution width.

## 4 Discussion

As the increasing morbidity of AF in recent years, the corresponding complications were brought to the forefront. AF was an independent risk factor for stroke. LAT or LASEC were deemed to be associated with increased thrombo-embolism risk.<sup>[3,8–10]</sup> Black, *et al.*<sup>[11]</sup> had shown that red cell aggregation, manifested as LASEC, appeared to be a precursor to thrombosis. TEE was supposed to be the best way to find LAT or LASEC out, but always accompanied with operational risk and patients' sufferings. It seemed necessary to identify some noninvasive predictor for LAT/LASEC in AF patients. RDW was an indication represented the heterogeneity of red blood cells. It could be measured routinely as a part of daily automated CBC and its formula was (SD of erythrocyte volume/mean cell volume)  $\times$  100. RDW had been found to be an independent prognostic factor for cardiovascular outcome and all-cause mortality.<sup>[12,13]</sup> A national retrospective study analyzed by Ani, *et al.*<sup>[14]</sup> showed the elevated RDW was associated with stroke occurrence and strongly associated with cardiovascular and all-cause death in subjects with known stroke. Saliba, *et al.*<sup>[15]</sup> showed that RDW was directly associated with the risk of stroke regardless of anemia status and improved the predictive accuracy for stroke in patients with AF. Kurt, *et al.*<sup>[16]</sup> also showed that RDW value was highly associated with

thrombo-embolism risk shown by CHA<sub>2</sub>DS<sub>2</sub>-VASc score in patients with AF.

Only few studies had assessed the link of RDW with LAT or LASEC.<sup>[17]</sup> The study investigated by Zhao, *et al.*<sup>[18]</sup> had similarly shown the elevated RDW was associated with LAT or LASEC in the condition of matched baseline except previous stroke. However, further multivariate logistic regression analysis showed RDW could not independently predict the presence of LAT/LASEC in patients with non-valvular AF (OR = 1.312, *P* = 0.452). A cross-sectional study by Providencia, *et al.*<sup>[19]</sup> showed RDW was predictors of LAT or LASEC in the condition of mismatched baseline, but the predictive value turned to be negative when adding clinical risk factors from CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc in logistic regression models.

In our study, a total of 692 patients were reviewed to evaluate the relationship between RDW level and LAT/LASEC. Although there were some mismatched baseline characteristics due to the retrospective nature of the study, the independent predictive effect of binary RDW level had been identified via adjustment of those mismatched baseline characteristics and CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system.

The underlying mechanisms of the link between RDW and LAT/LASEC in patients with AF were still largely unclear. It had been reported the RDW level was strongly bound up with oxidative stress and inflammation.<sup>[20]</sup> Oxidative stress influenced RDW level by decreasing erythrocytes lifespan and making them vulnerable to hemolysis. Some studies showed that inflammatory cytokines, such as tumor necrosis factor or IL-6, were related to ineffective erythropoiesis which might indirectly affected the RDW level.<sup>[21]</sup> Oxidative stress and some inflammation factors also had been demonstrated as markers which were correlated with ischemic stroke or LAT.<sup>[22]</sup> Further studies would be essential to clarify the link between RDW and LAT or LASEC in patients with AF.

#### 4.1 Limitation

The present study was a single-center retrospective study with a limited sample size and no follow-up data. As a result, potential cause-effect relationship could not be clarified. Therefore, it was hard to determine the prognostic significance. Then, although the patients with anemia were excluded in our study, some other factors such as routine iron, vitamin B12, folic acid, fibrinogen levels were not measured. Further large-scale and prospective studies would be needed to demonstrate the role of RDW with regard to prediction of LAT/LASEC in patients with non-valvular AF.

#### 4.2 Conclusions

Elevated RDW level is associated with the presence of

LAT/LASEC in patients with non-valvular AF and could be with moderate predictive value for LAT/LASEC. Comparing with the factors of CHA<sub>2</sub>DS<sub>2</sub>-VASc scores, RDW level >13.16% could be an independent risk factor for LAT/LASEC in patients with non-valvular AF.

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