

Red cell Distribution Width as a Predictor of Left Atrial Spontaneous Echo Contrast in Echocardiography

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Abstract: Red cell distribution width (RDW) represents the heterogeneity of red blood cells (anisocytosis). Spontaneous echo contrast (SEC) is thought to be a manifestation of red cell aggregation and it has been linked to the development of thromboemboli. The aim of this study was to evaluate the association between RDW levels and the presence of left atrial SEC (LASEC).

One-hundred and 72 patients who underwent transesophageal echocardiography for various indications were enrolled in the study. All patients were categorized into 2 groups according to the presence of LASEC and into 4 groups according to the severity of LASEC. The baseline clinical characteristics, echocardiographic measurements, and laboratory findings, including RDW, were compared between the groups.

The RDW (%) level was higher in the LASEC group (14.95 ± 1.32) compared with the non-LASEC group (12.20 ± 1.45 ; $P = 0.0001$). When the relationship between RDW and SEC was evaluated according to the increasing grade of SEC, a significant positive correlation was found ($r = 0.645$, $P < 0.0001$). In the ROC analysis, an RDW level $> 13.8\%$ had 70% sensitivity and 89.2% specificity in predicting LASEC (area under the curve = 0.834, $P < 0.0001$, 95% CI 0.656–0.773). In multivariate analysis, RDW levels $> 13.8\%$ and the presence of atrial fibrillation were independently associated with LASEC (odds ratio [OR] 1.697; 95% confidence interval [CI] 1.198–2.085; $P = 0.001$ and OR 1.586; 95% CI 1.195–2.098; $P = 0.003$, respectively).

Elevated RDW value is associated with the presence and the severity of SEC. RDW may be a useful marker and independent predictor for the presence of SEC.

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Abbreviations: AF = atrial fibrillation, CBC = complete blood count, CHF = congestive heart failure, CI = confidence interval, EF = ejection fraction, HT = hypertension, LA = left atrium, LAA = left atrial appendage, LAAV = left atrial appendage emptying peak flow velocity, LASEC = left atrial spontaneous echo contrast, LV = left ventricle, LVEDD = LV end-diastolic diameter, LVESD = LV end-systolic diameter, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MS = mitral stenosis, PLT = platelet,

RBC = red blood cell count, RDW = red cell distribution width, ROC = Receiver operating characteristics, SEC = spontaneous echo contrast, TEE = transesophageal echocardiography, WBC = white blood cell counts, WHO = World Health Organization.

INTRODUCTION

The red blood cell distribution width (RDW), part of a routine complete blood count, is a measure of the variability in the size of circulating erythrocytes, and it has been utilized in the differential diagnosis of anemia.¹ RDW is an easy, inexpensive, routinely reported test, whose assessment might allow the acquisition of significant diagnostic and prognostic information in patients with cardiovascular and thrombotic disorders.² Recently, in a number of studies, RDW has been associated with the presence and outcomes of several cardiovascular diseases, including acute myocardial infarction, stable angina, heart failure, peripheral vascular disease, stroke, postinterventional thrombosis in acute myocardial infarction, slow coronary flow syndrome, and isolated coronary artery ectasia.^{3–11}

Spontaneous echo contrast (SEC) is defined by dynamic smoke-like echoes within the left atrial (LA) cavity or left atrial appendage (LAA).¹² It has been shown especially in low-flow states, such as atrial fibrillation and rheumatic mitral valve disease.¹³

The presence of SEC has been shown to be a marker of increased thromboembolic risk, hypercoagulable and inflammatory states.^{13,14} SEC is thought to be a manifestation of red cell aggregation, arising from an interaction between red cells and plasma proteins, such as fibrinogen, at low shear rates.¹⁵ The blood products and their interaction responsible for SEC formation have not been exactly resolved.

In this study, we aimed to evaluate the association between RDW levels and the presence of SEC.

MATERIALS AND METHODS

Study Group

We assessed clinical, laboratory, and echocardiographic data of 172 patients who underwent transesophageal echocardiography (TEE) at our institution for various indications from January 2014 through September 2014. Patients with anemia, according to World Health Organization (WHO) criteria¹⁶ (hemoglobin value for males < 13 g/dL, for females < 12 g/dL), chronic renal failure, hematological diseases, vitamin B12, folate, or iron deficiencies, who had recent blood transfusions or bleeding, infectious diseases, collagen vascular diseases, or malignancy were excluded.

The study protocols have been approved by the local ethics committee, and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of

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Helsinki. All patients gave written informed consent before their inclusion in the study.

Laboratory Analysis

Hemoglobin, hematocrit, 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 (CBC) using a Coulter LH 780 Hematology Analyzer (Beckman Coulter, Inc, Brea, CA). The reference range of RDW in our central laboratory is 11.5% to 14.5%. The routine CBC tests were performed on all patients on the same day.

Echocardiographic Analysis

Tran thoracic echocardiography was carried out 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-chamber and 4-chamber views were obtained in all patients. M-mode echocardiograms were derived from the 2-dimensional images, and left ventricular (LV) dimension and left atrial diameter were measured in parasternal long axis view. LV ejection fraction (EF) was calculated by using the modified Simpson method.¹⁷

TEE was performed in all patients using a 5 MHz biplane phased array transducer (Vivid S5, GE, Horten, Norway) by the same examiner, who was blinded to the laboratory details. The left atrial appendage emptying peak flow velocity (LAAV) was measured with pulsed Doppler by placing the sample volume 1 cm into the mouth of the LAA. The mean LAAV was determined by averaging 5 consecutive cardiac cycles. The LA and LAA were evaluated for thrombus and SEC, which was graded from 0 (none) to 4 (severe) according to previously described criteria.¹³ It was graded as 0 = none (absence of echogenicity); 1 = mild (minimal echogenicity located in the LAA or rarely in the main cavity of the LA); 2 = mild to moderate (more dense swirling pattern than grade 1 but with similar distribution); 3 = moderate (dense swirling pattern in the LAA, less intense in the main LA cavity, may fluctuate in intensity but constantly detectable throughout the cardiac cycle); and 4 = severe (intense echo density and very slow swirling pattern in the LAA and with similar intensity in the main LA cavity) (Figures 1 and 2).

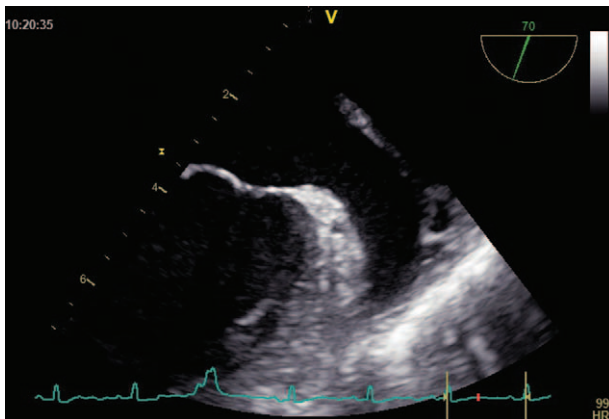


FIGURE 1. Transesophageal echocardiogram showing a left atrial appendage without spontaneous echo contrast in a patient.

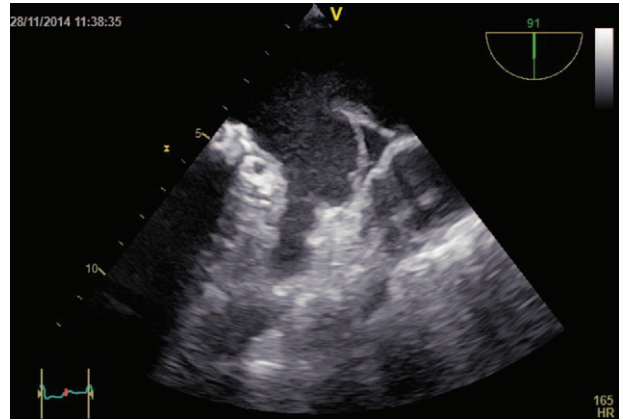


FIGURE 2. Transesophageal echocardiogram showing severe left atrial spontaneous echo contrast in a patient.

To achieve optimal detection of SEC was standardized by varying both the gain and compress settings throughout their full range during each study. The CBC and TEE were performed on the same day.

Statistical Analysis

The Statistical Package for Social Sciences software, version 15.0 (SPSS Inc, Chicago, IL), was used to perform all statistical calculations. Categorical variables were presented as frequency and percentage. The χ^2 test and the Fisher exact test were used to compare categorical variables. The Student *t* test was used for variables with normal distribution and the values were presented as mean \pm standard deviation (SD). Continuous variables without normal distribution were analyzed using the Mann–Whitney *U* test and obtained values were presented as median (50th) values and interquartile ranges (25th and 75th). Linear relationships between continuous variables were assessed using the Pearson correlation test. Multivariate logistic regression analysis was used to identify the independent associations of the risk of SEC. Parameters with a *P* value of <0.2 in univariate analysis were included in the model. Receiver-operating characteristics (ROC) analysis was used to determine the cut-off value and the sensitivity and the specificity of RDW. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. *P* values of <0.05 were considered statistically significant.

RESULTS

All patients were categorized into 2 groups according to their SEC grade; patients with SEC grade 0 were assumed to be SEC absent, and all others were assumed to be SEC present. The baseline demographic, clinical, echocardiographic, and laboratory characteristics of the study population are shown in Table 1.

There was no significant difference between the 2 groups regarding age, sex, hypertension, echocardiographic parameters including LV end-diastolic diameter, EF, and laboratory parameters, including hemoglobin, hematocrit, RBC, MCV, MCH, MCHC, WBC, and platelet count. Compared with the no-SEC group, the SEC group had a higher percentage of atrial fibrillation (38 [37.3%] vs 54 patients [77.1%], $P=0.001$), mitral stenosis (MS) (12 [11.7%] vs 13 patients [18.5%], $P=0.015$), and congestive heart failure (CHF) (19 patients [18.6%] vs 21 patients [30.0%], $P=0.083$). Left atrial diameter

TABLE 1. Baseline Demographic, Clinical, Echocardiographic, and Laboratory Characteristics of the Study Population

	Spontaneous Echo Contrast (LA or LAA)		P
	Absent (n = 102)	Present (n = 70)	
Age, years	54.7 ± 16.6	55.3 ± 11.6	0.848
Male sex, n (%)	45 (44.1%)	35 (50.0%)	0.447
AF, n (%)	38 (37.3%)	54 (77.1%)	0.001
CHF, n (%)	19 (18.6%)	21 (30.0%)	0.083
HT, n (%)	41 (40.2%)	36 (51.4%)	0.146
MS, n (%)	12 (11.7%)	13 (18.5%)	0.015
LA diameter, cm	4.45 ± 0.84	5.16 ± 0.68	0.001
LVEDD, cm	5.07 ± 0.78	5.11 ± 0.88	0.984
LVESD, cm	3.28 ± 0.86	3.73 ± 1.07	0.014
EF (%) [*]	57 (32–63)	55 (31–62)	0.231
LAAV, cm/s	56.13 ± 16.26	30.71 ± 16.85	0.001
RBC, × 10 ¹² cells/L	4.81 ± 0.58	4.82 ± 0.49	0.358
Hemoglobin, g/dL	13.63 ± 1.92	13.56 ± 1.90	0.513
Hematocrit, %	41.40 ± 3.55	41.10 ± 3.85	0.518
MCV, fl	89.91 ± 8.57	89.92 ± 7.98	0.754
MCH, pg	30.22 ± 3.41	30.19 ± 2.89	0.675
MCHC, g/dL	33.14 ± 0.75	33.19 ± 0.84	0.813
RDW, %	12.20 ± 1.45	14.95 ± 1.32	0.0001
WBC, × 10 ⁹ cells/L	8.05 ± 3.69	7.98 ± 3.15	0.895
PLT, × 10 ⁹ cells/L	235 ± 86.26	225 ± 67.85	0.421

AF = atrial fibrillation, CHF = congestive heart failure, EF = ejection fraction, HT = hypertension, LA = left atrium, LAAV = left atrial appendage emptying peak flow velocity, LVEDD = LV end-diastolic diameter, LVESD = LV end-systolic diameter, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MS = mitral stenosis, PLT = platelet count, RBC = red blood cell count, RDW = red blood cell distribution width, WBC = white blood cell count.

^{*}Median values (50th) and interquartile ranges are presented.

and LV end-systolic diameter (LVESD) were higher (4.45 ± 0.84 vs 5.16 ± 0.68, *P* = 0.001; 3.28 ± 0.86 vs 3.73 ± 1.07, *P* = 0.014, respectively) in the SEC group, whereas LAAV was lower (56.13 ± 16.26 vs 30.71 ± 16.85, *P* = 0.001) in the same group.

The main objective of this study, RDW (%) level, was higher in the SEC group (14.95 ± 1.32) compared with the no-SEC group (12.20 ± 1.45; *P* = 0.0001). To determine the best cutoff value of RDW for predicting LASEC, ROC analysis was performed. ROC curve analysis data indicated that when a 13.8% cutoff value was used, the RDW for predicting LASEC could achieve a sensitivity of 70.0% and a specificity of 89.2%. The area under the ROC curve for RDW, which was used to show LASEC, was calculated as 0.834 (*P* < 0.0001) (Figure 3). The cutoff value of 13.8% for RDW was found to be moderately sensitive and highly specific for predicting LASEC. When the relationship between RDW and SEC was evaluated according to the increasing grade of SEC, a significant positive correlation was found (*r* = 0.645, *P* < 0.0001) (Figure 4).

In addition, we observed a modest correlation between RDW and LA diameter and there was a modest negative correlation between RDW and EF (*r* = 0.468, *P* < 0.0001; *r* = -0.555, *P* < 0.0001, respectively). In addition, we found a modest correlation between SEC and LA diameter (*r* = 0.405, *P* < 0.0001).

Clinical, echocardiographic, and laboratory parameters were evaluated together in multivariate logistic regression analysis, including all risk factors associated with SEC. Multivariate logistic regression analysis was performed to evaluate the independent correlates of the presence of SEC. The

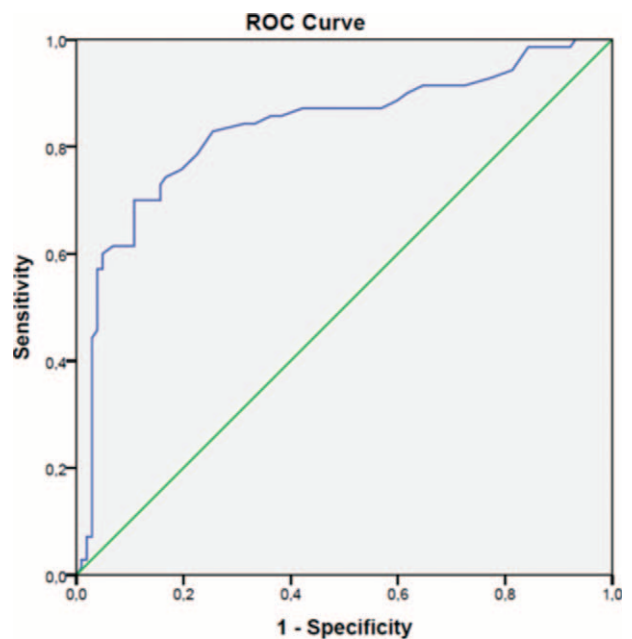


FIGURE 3. The receiver-operating characteristic (ROC) curve analysis for red blood cell distribution width in predicting left atrial spontaneous echo contrast. RDW >13.8% independently predicted LASEC with 70.0% sensitivity and 89.2% specificity (area under the curve = 0.834, *P* < 0.0001, 95% CI 0.656–0.773).

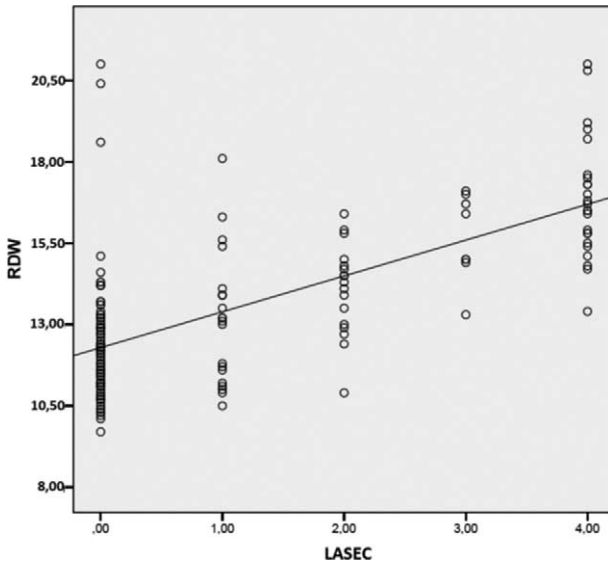


FIGURE 4. Correlations between RDW and grade of LASEC ($r=0.645$, $P<0.0001$). LASEC = left atrial spontaneous echo contrast, RDW = red blood cell distribution width.

variables with an unadjusted $P < 0.020$ in univariate analysis were adjusted to the full model. Multivariate logistic regression analysis was performed, and atrial fibrillation (AF), CHF, MS, LA diameter, LVESD, LAAV, and RDW were included in the analysis. As demonstrated in Table 2, in multivariate logistic regression analysis after adjustment for confounding variables (including AF, CHF, MS, LA diameter, LVESD, LAAV, and RDW), RDW levels $>13.8\%$ and the presence of AF were independently associated with LASEC (OR 1.697, 95% CI 1.198–2.085, $p=0.001$ and OR 1.586, 95% CI 1.195–2.098, $P=0.003$, respectively). This means that an RDW value of $>13.8\%$ increased the risk of LASEC by 1.697 times.

DISCUSSION

We demonstrated that a higher level of RDW (%) was significantly and independently associated with the presence and the severity of LASEC. The other independent indicator of LASEC is the presence of AF. The major findings of the study are as follows: first, the RDW levels were significantly higher in patients with SEC than in patients without SEC. Second, RDW levels of 13.8% could predict the presence of SEC with a sensitivity of 70.0% and a specificity of 89.2% in our study population.

RDW represents the heterogeneity of red blood cells (anisocytosis).¹⁸ Anisocytosis is a pathologic condition that appears as a result of some diseases. Immature red cell production (nutritional deficiencies such as iron, vitamin B12, and folic acid), increased red cell destruction (such as hemolysis), and impaired renal function after blood transfusion are leading causes of pathology leading to elevated RDW.¹⁹ Most of these events also affect erythrocyte maturation or function. If erythrocyte function is distorted, it may be prone to aggregation. Normal RDW values are between 11% and 14.5%.²⁰

SEC may represent a precursor of thrombus formation, and its presence is associated with an increased thromboembolic risk.¹⁴ LASEC is an appearance of red cell aggregation, arising from an interaction between red cells and fibrinogen, at low

TABLE 2. Independent Predictors of LASEC in Multivariate Logistic Regression Analysis

Variables	Odds Ratio	95% CI	P
AF	1.586	1.195–2.098	0.003
CHF	0.997	0.962–1.025	0.834
MS	0.995	0.964–1.039	0.246
LA diameter	0.998	0.995–1.007	0.311
LVESD	0.892	0.885–1.004	0.145
LAAV	0.845	0.833–1.010	0.217
RDW $>13.8\%$	1.697	1.198–2.085	0.001

AF = Atrial fibrillation, CHF = congestive heart failure, CI = Confidence interval, LA = left atrium, LAAV = left atrial appendage emptying peak flow velocity, LVESD = LV end-systolic diameter, MS = mitral stenosis, RDW = red blood cell distribution width.

shear rates.¹⁵ This study attempts to demonstrate any association between RDW and SEC with respect to presence and severity. In our study, patients with anemia were excluded, but iron levels, vitamin B12, folic acid, and fibrinogen, which may affect RDW levels, were not measured. Therefore, it remains unclear whether these factors contributed to the relationship between RDW and SEC in our study.

The only study we are aware of to date that investigates the relationship between RDW and SEC is by Zhao et al.²¹ They have similarly shown that RDW was associated with SEC formation and levels $>12.55\%$ predicted presence of LA thrombus or SEC with 64% sensitivity and 60% specificity in nonvalvular atrial fibrillation patients. Our study demonstrated a mildly higher cutoff with higher sensitivity and specificity.

Briley et al²² showed that the severity of SEC was not related to albumin, hematocrit, WBC, or PLT in patients with acute stroke or chronic cerebrovascular disease. They found an association between increasing grades of SEC and increased LA diameter, with a higher percentage of patients in atrial fibrillation. Although it involved different study groups, we similarly found that hematocrit, WBC, and PLT were not related with the presence of SEC, but the LA diameter was associated with the existence of SEC.

Previous studies have shown that RDW is closely related to the prognosis and long-term adverse events of cardiovascular diseases. A higher RDW level ($>14.6\%$) has been found to be associated with an increased risk of acute pulmonary embolism-related mortality in the early phase of hospitalization after adjustment for other confounding variables.²³ Cay et al²⁴ showed that an RDW value of $>13.9\%$ increased the risk of developing deep venous thrombosis by 4.5 times. These studies support that RDW may be a good predictor of a thrombotic state.

The RDW has also been suggested as a useful marker for predicting mortality in patients with acute and chronic heart failure,^{25–27} coronary artery disease,^{4,28} peripheral artery disease,⁶ and stroke.⁷ In most circumstances, this is independent of hemoglobin and hematocrit levels, but it is still unclear whether anisocytosis might be the cause, or a simple epiphenomenon of an underlying disease, such as inflammation, impaired renal function, malnutrition, oxidative damage, or perhaps an element of both.² However, no studies have been performed in patients with SEC. One of the possible explanations for the mechanism underlying the relationship between RDW and SEC may be

anisocytosis. The presence of anisocytosis leads to erythrocyte aggregation and thereby increases the degrees of SEC.

These findings suggest that an increased RDW level may be considered as a risk factor for SEC. RDW, a cheap and easily measurable laboratory parameter, was independently and significantly associated with the presence and severity of SEC. The mechanism of association requires, however, further study.

LIMITATIONS

This study is a single-center study and sampled a relatively small number of people. Although the patients with anemia were excluded in our study, routine iron, vitamin B12, folic acid, fibrinogen, and inflammatory marker levels were not measured.

CONCLUSIONS

Increased RDW significantly predicts the presence and the severity of SEC, which is the precursor of thrombus. RDW might be a useful and easily measurable parameter to identify patients according to the degree of SEC. RDW may be used as a surrogate marker to predict SEC. Further larger studies are warranted to make a final conclusion whether high RDW is an underlying mechanism for SEC formation and whether RDW is associated with stroke.

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