Red cell distribution width and its relationship with global longitudinal strain in patients with heart failure with reduced ejection fraction: a study using two-dimensional speckle tracking echocardiography

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Abstract

Background: Red cell distribution width (RDW) is a measurement of size variability of the red blood cells and has been shown to be a powerful predictor of prognosis in heart failure (HF). Recently, global longitudinal strain (GLS) emerged as a more accurate marker of left ventricular (LV) systolic function.

Aim: We aimed to assess the relationship between RDW and standard echocardiographic parameters and LV global strain measured by two-dimensional (2D) speckle tracking echocardiography in patients with HF with reduced EF (HFrEF).

Methods: Fifty-nine HF patients with an EF < 50%, and 40 age-matched controls with normal EF were included in the study. Standard and 2D strain imaging examinations were performed. Blood tests including RDW were scheduled on the same day as the echocardiographic study.

Results: Left atrial volume index, LV end-systolic and end-diastolic dimensions, and E/A and E/e′ ratios were higher and LVEF together with LV GLS were significantly lower in the HFrEF group. RDW showed positive correlations with log B-type natriuretic peptide (r = 0.45, p = 0.0001), left atrial volume index (r = 0.38, p = 0.001), LV end-diastolic dimensions (r = 0.37, p = 0.001), and E/e′ (r = 0.33, p = 0.005) and negative correlations with haemoglobin (r = –0.54, p = 0.0001), LVEF (r = –0.27, p = 0.004) and finally LV GLS (r = –0.41, p = 0.001). HFrEF patients were divided into two groups based on the median RDW value. Patients with higher than median RDW had significantly lower GLS despite similar EF.

Conclusions: Elevated RDW is associated with poorer LV deformation assessed by speckle tracking echocardiography in HF patients with similar EF. Therefore, the degree of anisocytosis could be used as an additional marker to identify these high-risk patients as well as improve treatment strategy.

Key words: red cell distribution width, echocardiography, heart failure, global longitudinal strain

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INTRODUCTION

Red cell distribution width (RDW) is a measurement of size variability of the red blood cells that can be easily measured by automated laboratory equipment as a component of complete blood count. Recently, RDW has been shown to be a powerful predictor of prognosis in heart failure (HF) with reduced ejection fraction (EF) — HFrEF; however, its relationship with the degree of the left ventricular (LV) dysfunction remains to be clarified [1, 2]. Echocardiography is the method of choice for the assessment of ventricular function, the diagnosis and the follow-up of HF. Strain imaging is an established technique for the accurate quantification of ventricular function and LV global longitudinal strain (GLS) has been shown to be a superior marker of contractility than EF [3, 4]. In this study we aimed to assess the relationship between RDW and standard echocardiographic parameters
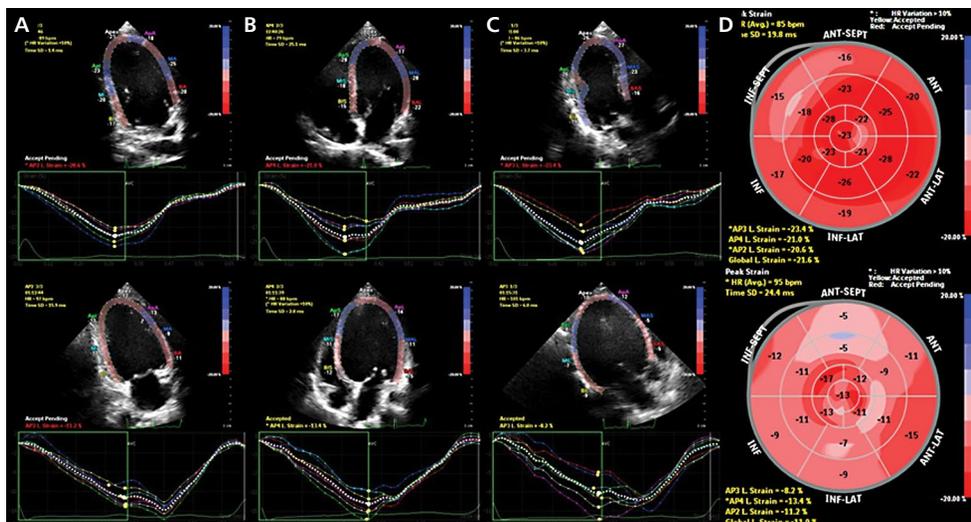
Figure 1. Representative examples of acquisition and analysis of global longitudinal strain (GLS) in a control subject (upper panel) and a patient with heart failure with reduced ejection fraction (HFrEF) (lower panel). Strain is measured from apical two chamber (A), four chamber (B), and three chamber (C) views. Peak systolic strain is defined as the most negative value before aortic valve closure. GLS is the average of the peak systolic strain acquired from three apical views. Seventeen segment bulls-eye plots of left ventricular strain are built automatically by the software at the end of the analysis (D). Note the difference between the control subject with normal GLS (–21%) and the HFrEF patient with severely decreased average GLS (–5%)

and LV GLS measured by speckle tracking echocardiography in patients with HFrEF.

METHODS
Study population
Fifty-nine HF patients with an EF < 50% and 40 age-matched controls with normal EF were included in the study. Exclusion criteria were defined as the presence of known haematological diseases such as haemolytic anaemia, chronic obstructive pulmonary disease, malignancy, neoplastic metastasis in the bone marrow, any thyroid or liver dysfunction, infectious diseases, pregnancy, severe arthritis and inflammatory bowel diseases, and any medication that could potentially interfere with the measurement of RDW. The study was approved by our Local Ethics Committee, and informed consent was obtained from all participants.

Echocardiographic study
Standard and two-dimensional (2D) strain imaging examinations were performed using a Philips ultrasound system (Epic 7.0, Philips Healthcare, Inc., Andover, MA) equipped with a 1–5 MHz X5-1 transducer and tissue Doppler imaging technology. At least two consecutive heartbeats were analysed with values represented as mean values. All standard 2D transthoracic echocardiographic images were obtained. Left atrial volume was measured and indexed to the body surface area. LV end-systolic (LVESD) and end-diastolic dimensions (LVEDD) were calculated from M-mode recordings in the parasternal long axis view. LVEF was assessed by using bi-plane Simpson method. Mitral early (E) and late (A) inflow velocities were measured by pulsed wave Doppler, and an E/A ratio was calculated.

Mitral annular peak early (E') and late (A') diastolic velocities were measured by pulsed wave tissue Doppler imaging from the septal and lateral mitral annulus and averaged. The E/E' ratio was calculated to estimate LV filling pressures.

For the assessment of longitudinal strain, standard 2D ultrasound images were recorded with a frame rate between 60 and 80 frames per second from the apical long axis, and two- and four-chamber views. These recordings were then stored digitally for offline analysis. In short, a semi-automatic algorithm was used for tracking the LV myocardial wall. First the LV endocardial border manually defined. Then the endocardium was automatically tracked throughout the cardiac cycle. The LV GLS was obtained by averaging all segmental strain values of three apical views. Peak systolic strain was defined as a peak negative value on the strain curve before the aortic valve closure (Fig. 1). All measurements were made by an expert echocardiographer blinded to clinical information of the patients. Because the GLS values are negative, a lower absolute number represents a worse value.

Laboratory measurements
Peripheral venous blood samples were obtained for routine chemistry including creatinine, haemoglobin, and RDW after an over-night fast. B-type natriuretic peptide (BNP) measurement was performed only for the HFrEF patients. Blood tests were scheduled on the same day as the echocardiographic study, and the analysis was performed with a Beckman Coulter analyser (Pasadena, California, United States).

Statistical analysis

Data management and analysis were performed using SPSS Statistics version 17.0 (SPSS Inc., Chicago, IL). Continuous variables are expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) according to the variable distribution. Normal distributions were confirmed using the Kolmogorov-Smirnov test. We used the χ^2 test for differences in categorical factors between the groups. Comparisons of continuous variables were performed using independent samples t-test for normally distributing variables, otherwise the Mann-Whitney U test was applied to test the differences between groups. Correlations of RDW with various clinical and echocardiographic parameters were tested by Pearson or Spearman's correlation analysis, as appropriate. A p-value < 0.05 was considered statistically significant.

RESULTS

Fifty-nine HFrEF patients fulfilled the inclusion criteria (50 had ischaemic and nine had non-ischaemic cardiomyopathy). All patients were receiving guideline-recommended medical treatment and were clinically stable with New York Heart Association (NYHA) class II functional capacity. The clinical characteristics of HFrEF patients and the control group are shown in Table 1. There were no differences regarding the gender and age of the subjects. Systolic blood pressure (SBP) and plasma haemoglobin levels were significantly lower, while creatinine and RDW were significantly higher in HFrEF patients. The echocardiographic data are shown in Table 2. Left atrial volume index (LAVI), LV dimensions, and E/A and E/e' ratios were higher and LVEF and LV GLS were significantly lower in the HFrEF group.

Red cell distribution width showed significant correlations with various laboratory and echocardiographic parameters. As the distribution of BNP was not normal within the HFrEF group, "log-transformation" of BNP (log-BNP) was used for further statistical analysis. There were positive correlations with log BNP (r = 0.45, p = 0.0001), LAVI (r = 0.38, p = 0.001), LVEDD (r = 0.37, p = 0.001), and E/e' (r = 0.33, p = 0.005) and negative correlations with haemoglobin (r = –0.54, p = 0.0001), LVEF (r = –0.27, p = 0.004), and finally LV GLS (r = –0.41, p = 0.001). From the echocardiographic parameters measured, LV GLS showed the strongest correlation with RDW. The correlation analysis is presented in Table 3. Subsequently, HFrEF patients were divided into two groups based on the median RDW value (Table 4). Patients with higher than median RDW had significantly lower GLS compared to patients with lower than median RDW, despite similar EF.

DISCUSSION

In this study, first we assessed the level of RDW in normal subjects and patients with HFrEF, then we investigated the association between the RDW levels and echocardiographic parameters of LV function, namely GLS, a quantitative marker of LV systolic function in an ambulatory HFrEF patient popula-

Table 1. Comparison of demographic properties and clinical characteristics of HFrEF patients and control group

	HFrEF group (n = 59)	Control group (n = 40)	p
Age [year]	57 ± 13	53 ± 8	NS
Gender (male)	77%	63%	NS
Systolic BP [mmHg]	109.9 ± 9.4	121 ± 10.2	0.02
Diastolic BP [mmHg]	70 (60–85)	73 (60–89)	NS
Creatinine [mg/dL]	0.98 (0.8–1.3)	0.8 (0.7–0.9)	0.03
Uric acid [mg/dL]	6.9 ± 1.9	5.4 ± 0.7	NS
Haemoglobin [g/dL]	12.6 ± 2	14.1 ± 1	0.01
RDW [%]	15 (13.8–17.5)	13.7 (13.2–14.2)	0.0001

Data shown as mean and standard deviation, mean and interquartile range or percentage. HFrEF — heart failure with reduced ejection fraction; BP — blood pressure; RDW — red cell distribution width; NS — nonsignificant

Table 2. Comparison of echocardiographic parameters of HFrEF patients and control group

	HFrEF group (n = 59)	Control group (n = 40)	p
LVEDD [mm]	65 (57–69)	48 (45–50)	0.0001
LVESD [mm]	49 (43–56)	28 (26–32)	0.0001
LVEF [mm]	34 (26–40)	65.5 (64–67)	0.0001
E [mm/s]	76 ± 24	65 ± 17	0.01
A [mm/s]*	55 ± 25	72 ± 13	0.0001
E/A*	1.4 (0.7–3)	0.9 (0.8–1.1)	0.001
e' [cm/s]	5.3 ± 1.3	10.5 ± 1.8	0.0001
E/e'	17 ± 6	10 ± 3	0.0001
LAVI [mL/m²]	42.7 ± 22.1	28.2 ± 9.6	0.0001
LV GLS [%]	–9 ([–7]–[–13])	–20 ([–18]–[–25])	0.0001

Data shown as mean and standard deviation or mean and interquartile range. *The measurements were available for 45 patients in the heart failure with reduced ejection fraction (HFrEF) group; LVEDD — left ventricular end-diastolic dimension; LVESD — left ventricular end-systolic dimension; LVEF — left ventricular ejection fraction; E — mitral early diastolic inflow velocity; A — mitral late diastolic inflow velocity; e' — mitral annular early diastolic tissue velocity; LAVI — left atrial volume index; LV GLS — left ventricular global longitudinal strain

tion. In accordance with previous studies [1–4], we demonstrated that mean RDW level was significantly elevated in the HFrEF group compared with controls.

Red cell distribution width is a quantitative measure of anisocytosis, which is the variability in the size of the circulating erythrocytes, and is routinely measured by automated laboratory equipment used to perform complete blood counts [5]. There are several haematological reasons for elevated RDW, including iron deficiency anaemia, haemolytic disorders, thrombotic thrombocytopenic purpura [6, 7], and non-haematological causes such as colon cancer, inflammatory bowel disease, pulmonary hypertension, and aortic

Table 3. Correlation analysis of biochemical and echocardiographic variables and red cell distribution width

Variable	Correlation	
	r	p
Age [years]	−0.161	0.22
Haemoglobin [g/dL]	−0.54	0.0001
Log BNP	0.451	0.0001
WBC [/μL]	−0.072	0.63
Creatinine [mg/dL]	0.053	0.726
CRP [mg/dL]	−0.188	0.307
E [cm/s]	0.187	0.24
A [cm/s]	−0.20	0.07
E/A	0.144	0.36
E/e'	0.33	0.005
LVEF [%]	−0.27	0.004
LVEDD [mm]	0.371	0.001
LVESD [mm]	0.222	0.091
LAVI [mL/m²]	0.383	0.001
LV GLS [%]	0.415	0.001

Log BNP — log transformation of B-type natriuretic peptide; WBC — white blood cell count; CRP — C reactive protein; E — mitral early diastolic inflow velocity; A — mitral late diastolic inflow velocity; e' — mitral annular early diastolic tissue velocity; LVEF — left ventricular ejection fraction; LVESD — left ventricular end-systolic dimension; LVEDD — left ventricular end-systolic dimension; LAVI — left atrial volume index; LV GLS — left ventricular global longitudinal strain

Table 4. Comparison of clinical characteristics and echocardiographic parameters of HFrEF patients grouped based on the median red cell distribution width (RDW) value

	Lower than median RDW group (n = 29)	Higher than median RDW group (n = 30)	p
Age [years]	60 ± 10	55 ± 14	NS
Gender (male)	82%	70%	NS
Log BNP	2.5 ± 0.3	2.6 ± 0.3	NS
Creatinine [mg/dL]	0.98 (0.52–1.54)	0.99 (0.55–6.07)	NS
Haemoglobin [g/dL]	13.5 ± 1.5	11.5 ± 2.1	0.001
Systolic BP [mmHg]	109.7 ± 9	110 ± 10	NS
Diastolic BP [mmHg]	70 (60–80)	70 (60–85)	NS
Atrial fibrillation	18 (5%)	30 (9%)	NS
LVEDD [mm]	62.3 ± 0.9	64.1 ± 0.8	NS
LVESD [mm]	47 ± 1.0	51 ± 0.7	NS
LVEF [%]	34 ± 9	31 ± 9	NS
E [mm]	69 ± 21	83 ± 25	0.04
A [mm]*	61 ± 24	43 ± 25	0.02
E/A*	1.9 ± 2.3	2.3 ± 1.3	NS
e' [cm/s]	5.4 ± 1.4	5.2 ± 1.1	NS
E/e'	16.7 ± 5.7	18.5 ± 7.5	NS
LAVI [mL/m²]	41.1 ± 19	43.18 ± 22	NS
LV GLS [%]	−12 ± 4	−8 ± 3	0.001

Data shown as mean and standard deviation; mean and interquartile range, or number (percentage). *The measurements were available for 24 with "lower" and 21 patients with "higher" RDW. HFrEF — heart failure with reduced ejection fraction; Log BNP — log transformation of B-type natriuretic peptide; BP — blood pressure; LVEDD — left ventricular end-diastolic dimension; LVESD — left ventricular end-systolic dimension; LVEF — left ventricular ejection fraction; E — mitral early diastolic inflow velocity; A — mitral late diastolic inflow velocity; e' — mitral annular early diastolic tissue velocity; LAVI — left atrial volume index; LV GLS — left ventricular global longitudinal strain; NS — nonsignificant

valve surgery [8–10]. Recently, RDW has been regarded as a promising marker for predicting the onset and evolution of HF [11]. In two population-based prospective studies including subjects without cardiovascular diseases, patients with the highest RDW quartiles exhibited a significantly increased risk of developing HF [12, 13].

Regarding to the prognostic value of RDW in patients with HF, it has been concluded that RDW independently predicts one-year mortality in acute HF patients, as well as in patients with chronic HF [14, 15]. High RDW values also predict poor long-term outcome regardless of anaemia status in HF patients [16]. There are no clear conjectural mechanisms to explain the relationship between RDW and cardiovascular diseases yet. Among a number of potential factors, chronic inflammation, oxidative stress, and neurohormonal activation have been hypothesised to play a significant role. Previous studies demonstrated that inflammation causes myelosuppression, decreases renal erythropoietin synthesis, and triggers apoptosis of erythroid precursors in bone marrow, which may result in a higher degree of anisocytosis, and thereby a higher RDW value [17]. In accordance with this data, our results suggest that RDW has a strong negative correlation with haemoglobin and a positive correlation with BNP in HFrEF patients.

Although there is increasing evidence uniformly supporting the prognostic importance of RDW in HF, findings about the association between RDW and the degree of ventricular dysfunction have not been consistent. Oh et al. [18] reported an independent correlation between RDW and echocardiographic signs of diastolic dysfunction (E/E') in acute HF patients. In another study by Al-Naijar et al. [19], increasing RDW was shown to be associated with worsening cardiac function, which is defined as increasing NYHA functional class in HF population. In our study, although all of the patients were in similar NYHA functional class, RDW showed close correlation with echocardiographic indicators of diastolic dysfunction such as increased LVEDD, LAVI, E/A, and E/e', as well as systolic dysfunction such as reduced EF and GLS. Within these echocardiographic parameters, GLS had the most significant correlation with RDW.

In order to compare the laboratory and echocardiographic parameters between HFrEF patients with "higher" and "lower" RDW levels, we divided the patients according to the median RDW. Interestingly, despite having similar EF, patients with higher than median RDW exhibited a worse ventricular systolic function reflected by severely reduced GLS. Speckle tracking echocardiography offers a multidimensional assessment of myocardial contraction [20] and represents myocardial deformation rather than volumetric change as seen by the LVEF method. GLS, obtained by 2D speckle tracking echocardiography, has previously been demonstrated to be superior to EF in various cardiac diseases [21, 22].

Although there is no established absolute value for GLS that indicates high risk in HF, recently published data suggest that worsening GLS is a manifestation of advanced degree of systolic dysfunction and adverse prognosis in HFrEF patients independent from EF [23]. Recently, GLS also appeared to be a better prognosticator and showed a closer relation with BNP than EF in HFrEF patients [24, 25]. Accordingly, despite having similar standard echocardiographic parameters including EF, patients with higher RDW had significantly less favourable GLS in our study.

Limitations of the study
This study had some limitations. First, the size of the study population was relatively small to compare the echocardiographic parameters between different quartiles of RDW, which could enable a more explicit observation of the relation between increasing RDW and worsening GLS. Second, although we excluded several haematological and non-haematological conditions that could affect RDW, the study population included patients with mild degree of anaemia due to chronic disease, which might cause potential interference between haemoglobin and RDW levels. Third, we measured the LVEDD and LVESD based on M-mode recordings and calculated the EF with the biplane Simpson method on echocardiography. The volumetric measurement of EF with cardiac magnetic resonance imaging or three-dimensional echocardiography is more accurate; however, those techniques are not suitable for follow-up of these patients in routine clinical practice. Finally, we did not demonstrate the precise mechanism of association between RDW and systolic deformation. Further studies are required to answer the key question of whether the association between RDW and LV systolic deformation is casual or if elevated RDW occurs as a consequence of underlying metabolic alterations that are commonly observed in HF.

CONCLUSIONS
In conclusion, elevated RDW is associated with poorer LV deformation assessed by speckle tracking echocardiography in HF patients with similar EF. Therefore, the degree of anisocytosis could be used as an additional marker to identify these high-risk patients as well as improve treatment strategy.

Conflict of interest: *none declared*

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