Red Cell Distribution Width Predicts the Left Ventricular Reverse Remodeling After ST Segment Elevation Myocardial Infarction Undergone Primary Percutaneous Coronary Intervention

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Abstract

Objectives: Previous studies have shown that red blood cell distribution width (RDW) is associated with some cardiac diseases. We investigated whether RDW was associated with left ventricular (LV) reverse remodeling after ST segment elevation myocardial infarction.

Materials and Methods: This retrospective study analyzed 300 patients with ST segment elevation myocardial infarction who underwent a follow-up echocardiography. We recorded the clinical characteristics, laboratory values

and echocardiographic signs of the patients on admission and in the third month. The patients were categorized into two groups according to echocardiographic assessment after 3 months: LV reverse remodeling and non-reverse remodeling.

Results: The RDW levels were significantly lower in the patients who had LV reverse remodeling than the patients who had non-reverse remodeling (15.4±2 vs 17.8±3.6, p<0.001). In the multivariate logistic regression analysis,

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the independent predictors of reverse remodeling were Diabetes Mellitus (p=0.001), history of coronary artery bypass grafting surgery (p=0.031), ST segment resolution (p=0.021), Thrombolysis in myocardial infarction flow classification (p=0.023) and RDW level (p<0.001). According to the receiver operating characteristic curve analysis, it was found that RDW (for the 17.3 level) had an estimate for LV reverse remodeling.

Conclusion: We suggest that the RDW level that is counted during routine complete blood count test might be useful to estimate LV reverse remodeling.

Keywords: Myocardial infarction, reverse remodeling, red blood cell distribution width (RDW), STEMI

Introduction

Heart failure (HF), which occurs mostly as post-myocardial infarction, is still one of the leading causes of mortality and morbidity in the world[1]. After acute myocardial infarction (AMI), secondary to functional myocardial injury, the myocardium receives adaptive responses to save the same contractile function. As a result of these responses, in the broadest sense, left ventricular (LV) remodeling is a general term used to define an interstitial, molecular and genetic change that occurs by clinical changes in size, shape and function of LV after a cardiac injury[2]. LV remodeling after AMI is accepted as an important indicator of the prognosis and development of HF[3]. The physiology of LV remodeling includes the size of the infarction area, oxidative stress, collagen synthesis, cytokine activation, ventricular dilatation, ventricular hypertrophy, scar formation and neurohormonal responses[4]. The term reverse remodeling is defined as a process that involves the regression of pathological myocardial hypertrophy, chamber shape distortions and dysfunction[5]. In other words, reverse remodeling is defined as myocardial tissue damaged by various factors, which initiates the healing process by stopping the remodeling process, as a result of various therapeutic treatments or elimination of injuring factors. Major guideline-directed HF therapies such as angiotensin converting enzyme inhibitors and beta blockers target the neurohormonal pathways in attempts to prevent remodeling and provide reverse remodeling[6]. Revascularization therapies [coronary artery bypass grafting surgery (CABG) and primary percutaneous coronary intervention (PPCI)] aim to decrease ischemia time and limit myocardial injury and thus support the reverse remodeling process[7]. LV reverse remodeling plays a key role for improving LV function and myocardial recovery.

Red blood cell distribution width (RDW) is obtained with a basic hemogram test in clinical practice, it is a quantitative measure of the size variability of circulating erythrocytes, and values above normal indicate a more heterogeneous population of cells[8]. Recent studies have shown that RDW may be an important predictor of cardiovascular disease progression and inflammatory process[9]. Recently, more focus has been on the predictive and prognostic value of RDW in patients with coronary heart disease, HF, atrial fibrillation and acute pulmonary embolism[10-12]. However, even though RDW has been linked with an increased risk of adverse outcomes in patients with HF, there are a few studies to show its relationship with the severity of LV dysfunction, and surprisingly, little is known about the correlation between RDW and the prognosis of LV dysfunction[13,14]. We investigated whether RDW was associated with LV reverse remodeling after ST segment elevation myocardial infarction (STEMI).

Materials and Methods

Population

The participants were retrospectively recruited from the cardiology clinic at the Atatürk University Training

and Research Hospital between September 2014 and September 2015. A total of 300 patients (239 males, mean age: 57.4±10.5 years) with the diagnosis of STEMI, who underwent PPCI of the culprit lesion after coronary angiography, were included. STEMI was diagnosed according to the criteria of the European Society of Cardiology in 2018[15]. The inclusion criteria were as follows: 1) having chest pain having started in the last 12 hours; 2) undergoing PPCI during coronary angiography; 3) being older than 18 years. On the other hand, patients with anemia (hemoglobin <13 gr/dL for men, <12 gr/dL for women), clinical evidence of cancer, active infection, active or chronic inflammatory or autoimmune diseases, pregnancy, known history of HF or previously LVEF < 35%, and those using steroids were excluded from the study.

The study protocol was approved by the Clinical Trials Ethics Committee of Atatürk University (decision no and date: 4/17 and 02.06.2015).

Procedure

All patients' age, gender, medical history, risk factors [smoking, Diabetes Mellitus (DM), hypertension (HT) etc.], family history, presence of comorbidities (anemia, chronic renal insufficiency, chronic obstructive pulmonary disease), medications, clinical and laboratory data were recorded. Chest pain duration and Killip classes were determined at the time of admission[16].

Complete blood counts and biochemical values were recorded for all patients. Hematological indices (hemoglobin, number of white cells, number of platelets and red cell distribution width) were measured and recorded using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland). Percutaneous coronary intervention (stenting and/or balloon angioplasty) was performed on the culprit lesion for coronary angiography after the transfemoral approach using the standard Judkins method. Infarction-related arteries were classified as the left anterior descending artery (LAD), circumflex artery, right coronary artery,

saphenous graft and others. Coronary blood flow was detected by Thrombolysis in Myocardial Infarction (TIMI) classification on the angiographic images after PPCI[17].

Echocardiographic evaluations of the patients were made within the first 24-48 hours and 3 months after hospitalization. The patients were imaged by using GE Vivid 7 (Vivid Seven, General Electric-Vingmed, Milwaukee, WI, USA), which was equipped with a transducer employing harmonic imaging. M-mode echocardiographic measurements were on the basis of the standards. Echocardiograms were taken from the left lateral decubitus position and from the standard echocardiographic windows (parasternal long and short axis, apical 2 and 4 cavities). The LVEF values of the patients were assessed using the Teichhold, Biplane Simpson methods or visually. LVEF, LV systolic and diastolic end-point measurements and interventricular septum measurements were recorded. At the end of three months of STEMI, those with an increase in LVEF by 5% and higher on echocardiography were defined as the group with LV reverse remodeling. The group with an increase under 5% in LVEF was assessed as the group with LV non-reverse remodeling[18,19].

Statistical Analysis

In statistical analysis, the numerical variables were presented as mean ± standard deviation, while the categorical variables were expressed as percentages. The Kolmogorov-Smirnov test was used to determine if the numerical variables were normally distributed. The Student's t-test was used to compare the normally distributed numerical variables between the groups, and the Mann-Whitney U test was used to compare the non-normally distributed numerical variables between the groups. The chi-square test was employed to compare the categorical variables between the groups. The Spearman's or Pearson's correlation analysis was used in the analysis of the relationship between the numerical variables. Variables with a p value of <0.100 in the univariate analyses between the patients who had LV reverse remodeling and LV non-reverse remodeling on a mean

follow-up of three months were subjected to multivariate analysis to determine the independent determinants of LV reverse remodeling. Additionally, ROC curve analysis was performed to determine which value of RDW had the best sensitivity and specificity for estimating LV reverse remodeling. In all statistical analyses, p<0.05 was accepted as the limit of significance. Statistical analyses were performed using the SPSS 20.0 (SPSS Inc, Chicago, IL, USA) package program.

Results

A total of 300 patients with STEMI were included in the study. The mean age of the patients was 57.4±10.5 years, and 79.7% were male. The rate of the patients with HT was 43.3%, and the rate of the patients with DM was 29%. The rate of the patients who smoked was 57.7%, and the rate of patients with dyslipidemia was 40.3%. The rate of the patients with previous history of AMI was 11.7%. 13.3% of the patients were using aspirin, 16.7% were using oral antidiabetics, and 20.3% were using statin. The proportion of the patients with three vessel diseases was 12.3%, and the infarction-related artery was detected as 46.3% of LAD. The mean RDW value of the patients was 16.5±3.2. The mean baseline LVEF value was 46.7±7.5, and the mean EF value after 3 months was 49.5±9.5 (Table 1).

Comparisons between the groups showed a significantly lower incidence of DM (17.3% vs 39.1%, p<0.001) in the LV reverse remodeling group. The glucose levels were lower in the LV reverse remodeling group in the comparison of the groups (143±69 vs 161±90, p=0.04). The mean RDW value was lower in the LV reverse remodeling group than in the non-reverse remodeling group (15.4±2.4 vs 17.8±3.6, p<0.001) (Figure 1). At the end of three months, the patients' LVEF values were significantly higher in the LV reverse remodeling group (53.9±7.8 vs 45.6±9, p<0.001) (Table 1).

In the analyses between the patients in the LV reverse remodeling group and non-reverse remodeling group on a mean follow-up of three months, the variables with a p value <0.100 were analyzed with multivariate analysis to determine the independent predictors of LV reverse remodeling. In the multivariate analysis that was performed, the presence of DM [Odds ratio (OR): 3.4, 95% confidence interval (CI): 1.7-6.7, p=0.001], history of CABG (OR: 11.9, 95% CI: 1.2-13.2, p=0.031), ST segment resolution (OR: 0.514, 95% CI 0.29-0.9, p=0.021), the classes of TIMI (OR: 0.39, 95% CI: 0.18-0.87, p=0.023) and RDW values (OR: 1.30, 95% CI: 1.20-1.43, p<0.001) were determined as the independent predictors of LV reverse remodeling (Table 2).

Additionally, ROC curve analysis was performed to determine which level of RDW had the best sensitivity and specificity to predict LV reverse remodeling. As a result of the ROC curve analysis, the AUC value was 0.722 (0.654-0.789, p<0.001). The predictive value of RDW for reverse remodeling, with 71% sensitivity and 79% specificity, was found to be 17.3 (Figure 2).

Discussion

One of the major results of our study was that the RDW levels on admission predicted the LV reverse remodeling in patients with STEMI undergoing PPCI. A cut-off value of 17.3 for RDW was obtained to predict LV reverse remodeling after a 3-month follow-up. As far as we know, this is the first study in the literature to show a relationship between RDW and LV reverse remodeling. Moreover, other results of the study on the presence of DM, CABG operation history, ST segment depression rate after PPCI and TIMI flow class may be used in STEMI patients as a predictor of LV reverse remodeling. Moreover, this study found that DM, smoking, ST segment resolution, TIMI risk score and glucose levels were associated with LV remodeling development in the patient population of study. It is possible to say that these data were in accordance with the literature.

The most important consequence of morbidity and mortality affecting quality of life in the long term after STEMI is the development of HF as a result of LV systolic

Table 1. The clinical, laboratory and echocardiographic characteristics of patient groups without and with left ventricular remodeling

	LV reverse remodeling group	LV non-reverse remodeling group	p
Age, years (mean ± SD)	56±9.9	58±11	0.108
Male, %	78.4%	80.7%	0.617
Arterial hypertension, %	43.9	42.9	0.858
Diabetes Mellitus, %	17.3	39.1	**<0.001**
Smoking, %	66.2	50.3	**0.006**
Hyperlipidemia, (%)	41	39.8	0.825
Family history of ischemic heart disease, %	21.6	21.1	0.922
History of myocardial infarction, (%)	13.7	9.9	0.315
History of PCI, (%)	12.9	9.3	0.316
History of CABG operation, %	0.7	3.7	0.085
ASA using, %	11.5	14.9	0.388
Clopidogrel using, %	1.4	0.6	0.478
Oral antidiabetic using, %	14.4	18.6	0.322
Beta-blockers using, %	8.6	10.6	0.574
Statins using, %	22.3	18.6	0.431
ACE inhibitors using, %	16.5	20.5	0.381
Ca channel blockers using, %	5.8	5	0.762
Killip classification 3-4, %	2.8	11.2	**0.042**
ST segment resolution (0-30), %	7.9	11.8	**0.002**
Three vessel disease, %	14.4	10.6	0.254
Infarct related artery, %			
LDA	46.8	45.3	
CX	17.5	16.3	0.956
RCA	35	37.2	
TIMI risk score 3%	90.6	77.6	**0.009**
Door-balloon time (mean ± SD)	29.5±5.4	30±6	0.889
Systolic blood pressure, mmHg (mean ± SD)	131±28	128±32	0.521
Diastolic blood pressure, mmHg (mean ± SD)	78±18	74±19	0.088
Heart rate, pulse/min (mean ± SD)	76±16	76±19	0.917
WBC 10^3/mL (mean ± SD)	12.2±3.1	12±4	0.905
Hemoglobin, g/dL (mean ± SD)	13.5±1.9	13.4±2	0.568
RDW (mean ± SD)	15.4±2.4	17.8±3.6	**<0.001**
Platelets 10^3/mL (mean ± SD)	264.6±66	259±58.5	0.361
Creatinine (mean ± SD)	0.9±0.3	1.0±0.5	0.119
Glucose, mg/dL (mean ± SD)	143±69	161±90	**0.040**
Total cholesterol, mg/dL (mean ± SD)	179±38	176±40	0.527
LDL-cholesterol, mg/dL (mean ± SD)	114±34	112±37	0.660
HDL-cholesterol, mg/dL (mean ± SD)	39±12	39±12	0.637
Triglyceride, mg/dL (mean ± SD)	145±105	138±73	0.522
LV-EF (basal), % (mean ± SD)	46.8±7.3	46.6±7.6	0.796
LV-EF (3rd month), % (mean ± SD)	53.9±7.8	45.6±9	**<0.001**

CABG: Coronary artery bypass grafting, ACE: Angiotensin converting enzyme WBC: White blood cell, PCI: Percutaneous coronary intervention, RDW: Red blood cell distribution width, LDL: Low-density lipoprotein, HDL: High density lipoprotein, LV-EF: Left ventricular ejection fraction, CX: Circumflex, RCA: Right coronary artery, LDA: Left anterior descending artery, SD: Standard deviation, TIMI: Thrombolysis in myocardial infarction, ASA: Acetylsalicylic acit
*: p≤0.05, **: p≤0.01

dysfunction. The mechanism underlying LV dysfunction, the most important factor determining the prognosis in the period after myocardial infarction, is LV remodeling[20]. The association between LV reverse remodeling and improvement in clinical outcomes was first demonstrated

Figure 1. The ROC curve of the RDW in prediction of LV non-reverse remodeling

ROC: Receiver operating characteristic, RDW: Red blood cell distribution width, LV: Left ventricular

Table 2. Independent variables detected in the logistic regression analysis in the prediction of left ventricular non-reverse remodeling

	OR (95% CI)	p
Diabetes Mellitus	3.4 (1.7-6.7)	0.001
Smoking	0.7 (0.4-1.2)	0.241
History of CABG operation	11.9 (1.2-13.2)	0.031
Killip Classification	1.4 (0.6-3)	0.319
RDW	1.30 (1.20-1.43)	<0.001
Diastolic blood pressure	0.99 (0.97-1.0)	0.165
Glucose	0.99 (0.99-1.0)	0.498
ST Segment resolution	0.514 (0.29-0.90)	0.021
TIMI	0.39 (0.18-0.87)	0.023

CABG: Coronary artery bypass grafting; RDW: Red blood cell distribution width; TIMI: Thrombolysis in Myocardial Infarction, OR: Odds ratio, CI: Confidenceinterval

by Pfeffer et al.[21], who determined that angiotensin-converting enzyme inhibition improved survival after AMI by providing LV reverse remodeling. Additionally, a multicenter trial by Daubert et al.[19] similarly showed the association among increase of EF, reverse LV remodeling and mortality. Furthermore, the level of LV remodeling was determined to be correlated with the risk of death and HF events in the Echo sub-study analysis of the VALIANT study[22]. This value of EF change was determined to be correlated with reduced mortality in similar patients with reduced EF[23]. In our study, LV reverse remodeling was defined as improved systolic function with an increase of 5% and higher in EF from the baseline to follow-up 3 months later.

It is well known that the inflammatory process plays a crucial role in LV reverse remodeling following AMI that causes the activation of an inflammatory response[24]. The association of RDW with inflammatory processes has also been demonstrated in previous studies[25]. Furthermore, there is growing evidence that RDW is associated with HF, metabolic syndrome and poor prognosis of coronary artery disease[26-29]. In this study, we found that RDW, one of the simple and inexpensive inflammatory biomarkers in clinical practice, was independently associated with
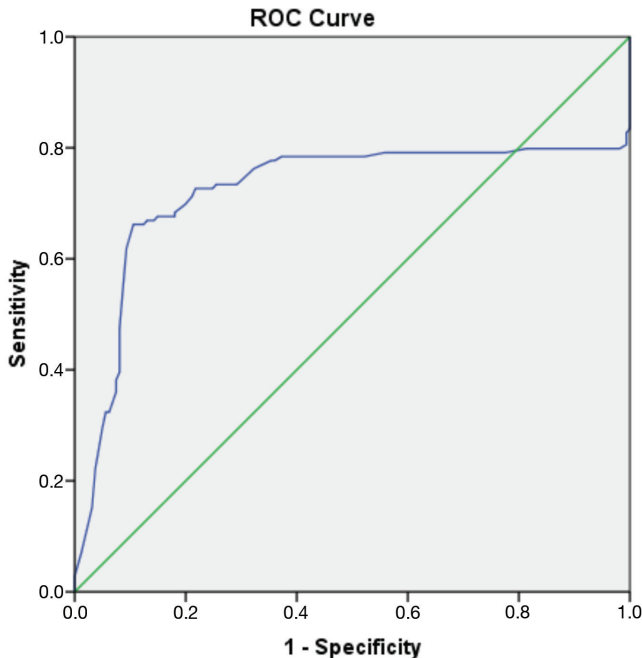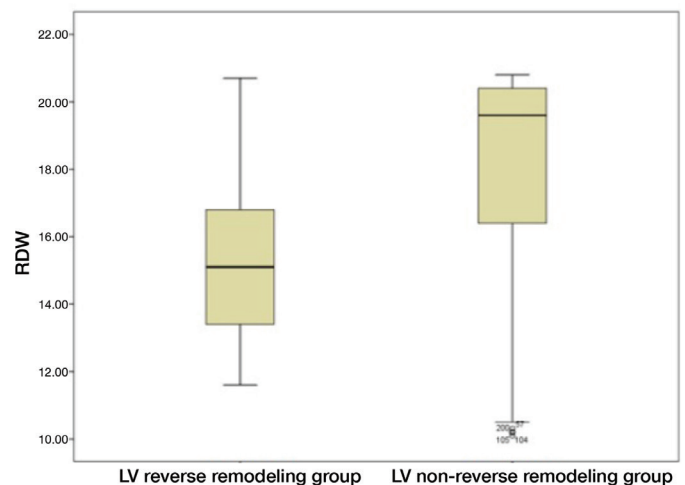

Figure 2. The mean RDW value was higher in the LV non-reverse remodeling group than in the LV reverse remodeling group (17.8±3.6 vs 15.4±2.4, p<0.00)

RDW: Red blood cell distribution width, LV: Left ventricular

LV reverse remodeling. According to the review of Fertin et al.[30], numerous circulating biomarkers such as white blood cell, neutrophil lymphocyte ratio, C-reactive protein, brain natriuretic peptide, atrial natriuretic peptide, neopterin and aldosterone have been reported as independent predictive markers in LV reverse remodeling after AMI. It is possible to say that our results are consistent with the literature when we consider that most of the biomarkers and RDW are related to inflammatory processes. This is thought to be a possible mechanism in explaining the RDW and LV reverse remodeling relationship.

Another possible mechanism for explaining the association of RDW and LV reverse remodeling is focused on the structure of membranous cholesterol on erythrocytes. Membranous cholesterol on erythrocytes is a source of atherosclerotic nuclei, and it is being discussed that erythrocyte membrane cholesterol levels may be a new marker in the diagnosis of acute coronary syndrome[30]. Tziakas et al.[31] demonstrated that RDW and erythrocyte membrane cholesterol levels were correlated with each other. These data show that RDW levels may be used to demonstrate plaque instability.

We also found that the presence of DM, CABG operation history, ST segment depression rate after PPCI and TIMI flow class could be used in STEMI patients, as well as baseline RDW level as a predictor of LV reverse remodeling[32]. It is possible to state that these data were in accordance with the literature. Moreover, our study found that smoking, ST segment resolution and glucose levels were associated with LV reverse remodeling development in our patient population.

Study Limitations

The most important limitation of our study was that it was retrospective, and it may be stated that providing more accurate data is an obstacle. Additionally, the number of patients included in the study was limited, and the echocardiography controls performed 3 months after the hospitalization of patients may lead to resultant variability due to the short follow-up period. The current data have shown that there may be improvement over a period of one year after AMI. Additionally, the short- and long-term morbidity and mortality rates of the patients were not evaluated, and the relationship of the results with survival was not mentioned. The use of echocardiography in evaluation of LV reverse remodeling and healing was also a major limitation. Today's gold standard imaging method for assessing LV function is cardiac MR imaging. It should be noted that echocardiographic imaging at this point may lead to incorrect results.

Conclusion

Measuring initial RDW levels may be useful for predicting LV reverse remodeling in patients with STEMI who are treated with PPCI. RDW may be helpful in making adverse cardiovascular event risk assessments of patients as an objective value that can be measured simply and quickly. Studies with a larger sample size are needed to plan to further investigate serum RDW levels in LV reverse remodeling after AMI.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Trials Ethics Committee of Atatürk University (decision no and date: 4/17 and 02.06.2015).

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: P.D.G., Design: P.D.G., K.K., E.A., Data Collection or Processing: P.D.G., R.D., K.K., Analysis or Interpretation: E.A., A.U., Literature Search: P.D.G., R.D., Writing: E.A., R.D.

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