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The Relation between the level of RDW and Permanent non valvular AF

Rahimeh Eskandarian, Mahboobeh Darban* and Anita Nejati

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Abstract

Introduction & Objective: Atrial fibrillation is the most common cardiac arrhythmia associated with increased risk of stroke, and can even cause death. A number of studies has reported the distribution of red blood cell distribution width as an independent factor in the prediction of the onset or outcome of the disease. The aim of this study was to determine the relationship between AF and RDW .

Materials and Methods: In this cross-sectional analytical study, 50 patients with symptomatic permanent non-valvular AF hospitalized in the heart disease department of Semnan during a one-year period (2015 to 2016) and 50 non-afflicted patients were selected easily at convenience. Then, the completion of the study checklist included RDW related information was done by the researcher at the time of the morning and at the bedside of the hospitalized patient.

Results: The mean ± standard deviation of RDW values in patients with the permanent non-valvular AF was significantly higher than control group (14.74 ± 1.43 versus 13.96 ± 1.11 and P = 0.003). 30% of the afflicted patients and 14% of the control group had abnormal RDW values (more than 15%). Afflicted men had significantly higher RDW values than those of control group (14.72 ± 1.66 vs. 13.77± 0.82 and P = 0.017); however, for women, there was no any significant difference (14.75 ± 1.22 vs. 14.12 ± 1.32% and P = 0.80).

Conclusion: In general, the results of this study showed that RDW values were higher in patients with the permanent non-valvular atrial fibrillation.

Keywords: Atrial fibrillation, Red blood cell distribution width, Hospitalized patients.

Rahimeh Eskandarian

Associate Author Cardiologist Department of Internal Medicine, Semnan University of Medical Sciences, Semnan, Iran.

Mahboobeh Darban*

Assistant Professor Pulmonologist Department of Internal Medicine, Semnan University of Medical Sciences, Semnan, Iran.

Anita Nejati

General Physician Department of Internal Medicine, Semnan University of Medical Sciences, Iran.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia that is associated with an increased risk of other diseases, such as stroke, and can even cause death in humans (Sarıkaya et al., 2014); AF is nearly one of the major causes of hospitalization and serious health risks, and its costs can cause irreversible damages to the health of any society (Kannie & Benjamin, 2008; Vardas & Mavrakis, 2006); in the meta-analysis performed by Tamariz et al. (2014), AF is mentioned as the most important cause of mortality and morbidity in patients (Tamariz et al., 2014); therefore, the prediction of its creation or exacerbation is necessary and needs to evaluate various Laboratory Indices. The inflammatory mechanisms play a role in the development and stability of AF, as some evidence has been reported for it (Guo, Lip & Apostolakis, 2012); the results of various studies have referred to the association of different inflammatory factors such as C-reactive protein (CRP), Tumor necrosis factor-α, TNFα, interleukins 2, 6, and 8, and the monocyte chemo attractant protein (MCP) with AF incidence or prognosis (Sarıkaya et al., 2014; Patel et al., 2010). However, recently, various researchers have investigated the relationship between AF and other indices, because the factors mentioned above are often expensive and costly, and in routine evaluations, examining them is not possible; therefore, it seems necessary to use an index to evaluate the incidence and outcome of AF patients, which, in addition to the low cost, it is also easy to achieve, because the characteristics of screening tests rely on the instrumental simplicity; one of the indices that is investigated recently and the studies conducted on its association with AF are few and often controversial, is the Red blood cell distribution width (RDW) (Sarıkaya et al., 2014; Gurses et al., 2015; Liu et al., 2014). RDW is defined as a quantitative criterion of the size change of red blood cell (RBC) environment, which is available in conventional blood tests (Sarıkaya et al., 2014) and in addition to detection of anemia (Gurses et al., 2015), it can be used as an indicator of inflammation, in the incidence and outcome of patients (Patel et al., 2010). An important point that distinguishes this factor from other inflammatory markers is that RDW, in addition to low cost of testing, often displays chronic inflammation and high levels of oxidative stress (Evans & Jehle, 1991; Weiss & Goodnough, 2005; Ferrucci et al., 2005); the reason for this is that flaring up the inflammatory mechanisms by activating cytokines delays the maturity of erythropoietin-dependent RBCs and, by increasing immature erythrocytes in the blood, increases RDW (Uyarel et al., 2012; Ozcan et al., 2013; Emans et al., 2013). Therefore, given the

chronicity of the changes in AF in the individual, it is not surprising that the sensitivity of RDW is higher in relation to AF than most inflammatory indices that only show transient inflammation (Sarıkaya et al., 2014); although the exact relationship between them has not yet been fully elaborated (Liu et al., 2014); however, a number of studies have described the role of oxidative stress to be effective in the development and progress of AF, and have mentioned RDW as an independent and effective factor in prediction, development or outcome of this disease (Korantzopoulos & Liu, 2015; Hwang et al., 2011; Adamsson Eryd et al., 2014). In the Cohort studies, Adamsson Eryd et al in Sweden in 2013 examined the association between RDW and AF prevalence; the results of this study showed that during the follow up period of 13.6 years, 1894 people (53% Male) were diagnosed with AF. The risk ratio for patients with high RDW from the outset was reported to be 1.33 for the AF outbreak. The authors of this study concluded that high RDW values are associated with an increase in AF prevalence, which is independent of other confounding variables (Liu et al., 2014). Tong Liu et al in China in 2014 studied the relationship between RDW and AF in non-valvular attacks; the results of this study showed that RDW levels significantly increased in patients with AF, more than the other group; the blood parameters including RBCs, hemoglobin, serum creatinine, uric acid and fasting blood glucose did not show any significant relationship between the two groups. The authors of the study concluded that RDW, as an available indicator, was very suitable for predicting AF or exacerbation of AF in these patients (Liu et al., 2014). In contrast, Balta et al., in a Letter to the Editor, have pointed out that RDW has only been approved as an indicator for the detection of anemia, and should not be used as an inflammatory measure to predict the creation or outcome of AF in these patients, because more accurate and specialized inflammatory markers can be used in this regard (Balta et al., 2014). Therefore, according to the conducted searches, the studies on the relationship between atrial fibrillation and RDW not only are rare in the world, but also in few studies that have been conducted, this relationship is controversial; also, relying on the fact that the exact pathophysiology of the relationship between AF and RDW is still ambiguous and the need for more studies, especially descriptive ones, seems necessary (Gurses et al., 2015), this study, conducted in 2015-2016, aimed to determine the relationship between atrial fibrillation and the distribution of red blood cells in patients referring to the heart disease department of Kosar in Semnan.

Materials and Method

After confirmation of the preliminary plan at the research council of the Kosar Hospital of Semnan, and after receiving of the Moral Code from the Moral Committee of the University, the written consents for accepting the participation in this study was given to the individuals; after presenting the description and significance of this study and giving a full description of the process of carrying out this project, they were completed and confirmed by them. It is worth noting that when completing the checklists, the descriptions and significance of the study were fully explained to the research units. The statistical population included all patients with congenital conditions in the heart disease department of Semnan Kosar Hospital in a one-year interval (from the time of approval of the plan to one year later):

A. Case group statistic population: Patients with permanent non-valvular atrial fibrillation

B. The statistical population of the control group: other patients with congenital conditions in the heart disease department of Kosar Hospital of Semnan

According to the inclusion and exclusion criteria for participation in study, 50 patients with symptomatic permanent non-valvular AF (confirmed by a specialized cardiologist) were selected by diagnostic methods such as an examination (symptoms like Heart palpitations, decreased energy and excessive fatigue, dizziness, chest discomfort and respiratory depression), and ECG findings (confirmed by ECG in the atrial fibrillation, without an electrical stimulation wave of the atrium (P)) and 50 Non-AF patients.

The inclusion criteria for participating in the study included patients aged 20 years and older and full satisfaction with participation in the study. Individuals who met the criteria known in other studies as RDW disturbing factors were excluded from the study as outcome disruptors; these factors are included:

Iron deficiency anemia and the anemia that disturbs RDW values (hemoglobin values of less than 12 g/dl for women and less than 13 g/dl for men), congenital heart diseases, valvular diseases, Thyroid dysfunction, Liver disorders, Recent blood transfusion, Alcohol consumption, Recent infection, Serum creatinine level more than 1.20 mg/dl, Diabetes, Self-immune deficiency, Contraindications for treatment with anti-coagulant, thrombosis in the left atrium, left ventricular drainage fraction of less than 50%, and left ventricular diameters greater than 55 mm. Meanwhile, people with known deficits of vitamin B12 and folic acid deficiency were excluded.

After sampling at convenience (from the time of the start of the project until reaching the desired sample volume), the questionnaire was completed by the researcher at the time of the morning and at the bedside of the admitted patient. The information about the underlying diseases and the medical history was also extracted from the file or summaries of available files. In line with the objectives of this study, thyroid-stimulating hormone (TSH), complete blood count (CBC), blood iron level, creatinine, uric acid, aspartate aminotransferase (AST) and alanine aminotransferase (alanine aminotransferase = ALT) were measured and analyzed by sending blood samples to the laboratory.

Each unit at the beginning of the study was examined once in terms of RDW level; from each unit of study, 2 milliliters of blood were taken from the left brachial vein and with a medium syringe with blueberries of 10 milliliters and transferred to EDTA K3 diluent tubes. The resulting sample was given to the cellar counter (sysmexxs 800I made by Japan, purchased by the advanced

electronic company and the mindray BC 300 made in China) purchased by Framatb Company). After combining the sample, 20 Landa was sucked by means of a nozzle, analyzed by RINS and LYSE isoton solutions, and RDW values were recorded. Measuring the length of the patient's height by means of a tape measure mounted on the wall, without shoe and hat: the legs sticking together and the heels, hips, shoulders, and post-head contacted with the wall (with a precision of one centimeter, in meters, at the Kosar Hospital, by a medical student); measuring the patient's weight with a scale of 100 grams, without shoes and heavy clothing, was done at the Kosar Hospital (by a medical student); the ECG using an electrocardiogram card available in the department was done as 12 full leads (by a medical student).

Findings

The mean ± standard deviation of RDW values in patients with permanent non-valvular atrial fibrillation was 14.74 ± 1.43 and in control group was 13.96 ± 1.11, which was of a significant difference (0.003 = P). The distribution of the RDW values of the two groups has been shown in the table 1 and in Figure 1. The lowest and highest RDW values in patients with the permanent non-valvular atrial fibrillation were 12.20% and 20%, and 12.20% and 18.70% in the control group, respectively.

Table 1: distribution of red blood cell width (percentage) of patients with permanent non-valvular atrial fibrillation and control group

distribution of red blood cell width (percentage)	Group under study			
	with permanent non-valvular atrial fibrillation		control group	
	Number	Percentage	Number	Percentage
Normal: ≤ 15	35	70.0	43	86.0
Abnormal: > 15	15	30.0	7	14.0
Total	50	100	50	100

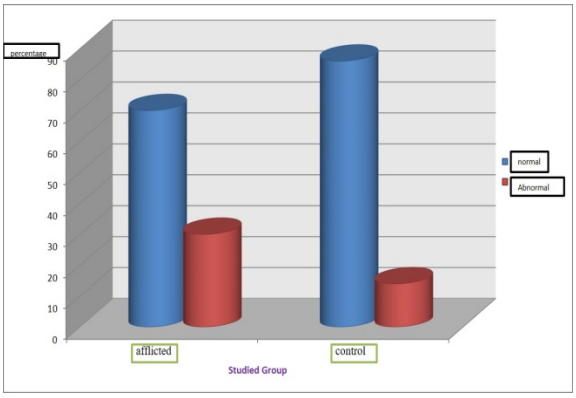

Fig. 1: Frequency of red blood cell width (RDW) in patients with permanent non-valvular atrial fibrillation and control group. Percentage, normal, abnormal, afflicted, control, group under study

The mean ± standard deviation of RDW values in women with permanent non-valvular atrial fibrillation was 14.75 ± 1.22% and in the women of control group was 14.12 ± 1.32%, which was statistically different (p=0.08%). The mean ± standard deviation of RDW values in men with permanent non-valvular atrial fibrillation was 14.72 ± 1.66% and in the men of control group (13.77 ± 0.82), which was of a significant difference (p=0.017).

Discussion and Conclusion:

The results of the data analysis showed that the level of RDW values in patients with the permanent non-valvular atrial fibrillation was significantly more than that of the control group (14.74 ± 1.43 versus 13.96 ± 1.11 and P = 0.003). Also, 30% of patients with the permanent non-valvular atrial fibrillation had abnormal RDW values (more than 15%), which is approximately 2 times more than the control group (14% had abnormal RDW values). Due to the small number of sample size, the comparison was not valuable for age, body mass index and cigarette smoking, and therefore the RDW values in the two groups were limited to the gender of individuals; although the RDW values in women Patients with the permanent non-valvular atrial fibrillation were more than women in the control group, there was no statistically significant difference (14.75 ± 1.22 vs. 14.12 ± 1.32 and P = 0.080) while men with the permanent non-valvular atrial fibrillation had RDW values significantly higher than the men in control group (14.72 ± 1.66 versus 13.77 ± 0.82 and p=0.017).

In a study published in China in 2014, with the aim of examining the relationship between RDW and non-valvular AF, the results showed that RDW levels were significantly higher in AF patients than in control group (Non-AF) (12.71 ± 0.9% vs. 12.45 ± 0.6%); the authors of this study concluded that RDW, as an available indicator, is very suitable for predicting the creation or intensification of AF in these patients, (Liu et al., 2014); similar to this study, in the present study, the results showed that the patients with permanent non-valvular atrial fibrillation significantly have RDW values more than individuals of the control group. In another study in Turkey, the relationship between increasing RDW and non-valvular AF was investigated; the results showed that RDW level in AF patients was significantly higher than that of the control group (non-afflicted individuals) (13% versus 12.6% and P = 0.01), which was similar to the results of our study; the results of logistic regression analysis also showed that RDW acts as an independent factor in the prevalence and prediction of AF patients; therefore, the authors of the study concluded that RDW, as a low-cost and available indicator, is very suitable for predicting the creation or intensification of AF (Güngör et al., 2014). According to the results of this study and similar studies, although there is a high degree of consensus in increasing the RDW values in patients with atrial fibrillation, the cause and effect relationship between these two variables is not yet fully determined. In other words, the principle of whether the increase of RDW values is related to the incidence of non-valvular AF, or that the non-valvular AF has increased the RDW values, is in the midst of ambiguity; a more precise study requires more extensive surveys and a larger sample size. Meanwhile, some studies have been conducted showing that the risk ratio for patients with high RDW from the outset was greater for the incidence of AF than those for whom the baseline RDW was reported to be normal; For example, Adamsson Eryd et

al in Sweden in 2013 investigated the relationship between RDW and AF outbreak and concluded that during the follow-up period of 13.6 years, the risk ratio for AF in Patients who had high RDW at the beginning, were 1.33 times more than those who have normal RDW values. Therefore, the authors of the study concluded that high RDW levels are associated with increasing incidence of AF, which was independent of other confounding variables (Liu et al., 2014); a number of studies also found that RDW values were more effective in AF relapse or intensification, and contrary to other studies, the relationship between more RDW values in the incidence of AF was not found; for example, in a study in Turkey in 2015 aimed at investigating the relationship between RDW and the outcome of AF patients, the results showed that the individuals with higher RDW values were more likely to have recurrence or exacerbation of AF (14.30 ± 0.9 vs. $13.0 \pm 52.93\%$ and $P < 0.001$); they also reported that RDW, as an independent factor, has been proposed in the prediction of recurrence or exacerbation of AF in these patients (Gurses et al., 2015); while Balta et al in an article (Letter to the Editor), in response to the study of Adamsson Eryd (Liu et al., 2014), pointed out that RDW was only approved as an indicator for the diagnosis of anemia and should not be considered as an inflammatory measure to predict the creation or outcome of AF in these patients. Because more accurate and specialized inflammatory markers can be used in this regard (Balta et al., 2014); although the existing contradictions can be due to differences in the methods for checking high RDW values, the difference in the size of statistical samples, the lack of control group in a number of studies, the type of study, the difference between laboratory methods and the multiplicity of devices, the treatment or non-treatment of patients, and the differences in diagnostic criteria, as well as the different types of AF in several studies, but it is important to note that there is a high correlation between abnormal RDW values with the permanent non-valvular AF in our study and a considerable number of similar studies (Sarıkaya et al., 2014; Korantzopoulos & Liu, 2015; Hwang et al., 2011; Adamsson Eryd et al., 2014), which should be justified in a reasonable way; While the exact relationship between them has not yet been fully elucidated (Liu et al., 2014), a number of studies have described the effective role of oxidative stress in the development and progress of AF, and considered RDW as an independent and effective factor in the prediction of the onset or outcome of the disease (Korantzopoulos & Liu, 2015; Hwang et al., 2011; Adamsson Eryd et al., 2014); because RDW, as an indicator of inflammation (Patel et al., 2010), often displays chronic inflammation and high levels of oxidative stress (Evans & Jehle, 1991; Weiss & Goodnough, 2005; Ferrucci, 2005); the reason for this is that the flare-up of inflammatory mechanisms, by activating cytokines, delays the maturation of the erythropoietin-dependent RBCs and increased RDW by increasing erythrocytes in the blood; therefore, due to the chronicity of changes in AF in the person, it is not surprising that the RDW sensitivity is significantly higher in atrial fibrillation than most of inflammatory indications that only show transient inflammation (Sarıkaya et al., 2014); thus, it is expected that there is a significant relationship between the RDW changes and the diseases like Cardiovascular diseases, cancers, anemia, chronic kidney disease, diabetes, hypertension and stroke, and the results show that the high the severity of the disease and the worse the Patients' prognostic, the high the RDW values of the patient (Patel et al., 2010). Various studies report that the various inflammatory indicators such as C-reactive protein (CRP), red blood cell sedimentation rate (ESR), interleukin 6, interleukin 1 beta, and tumor necrosis factor-alpha have an important role in RDW changes in patients with the chronic diseases, including atrial fibrillation; because these inflammatory factors, along with pro-inflammatory cytokines, can stop the maturity of red blood cells and, on the other hand, reduce the half-life of these cells in circulation and, as a result, increase RDW (Jo et al., 2013); however, this needs more examinations. Other studies have suggested the role of oxidative stress and inflammatory materials in reducing the number of red blood cells (Kiefer & Snyder, 2000; Weiss & Goodnough, 2005). Another argument could be that in the diseases in which the level of oxidative stress is high, such as Down syndrome, lupus abnormalities, and dialysis patients (Kobayashi et al., 2003), RDW values have been higher than ordinary people; however, due to the very confounding factors affecting RDW values, this claim will require more studies and control of the intervening causes. Another justification can be the analysis of data from the large study of third NHANES, which indicates that the reduction of serum levels of oxidative stress and inflammatory factors with carotenoids, selenium and vitamin E, is associated significantly with reduced RDW values (Patel et al., 2009). Also, the study of third NHANES showed that RDW has a significant and direct relationship with WBC in addition to CRP (Patel et al., 2009).

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