Red Cell Distribution Width Has a Predictable Value for Differentiation of Provoked and Unprovoked Venous Thromboembolism

Sehmus Ertop¹ · Muammer Bilici² · Huseyin Engin³ · Cagatay Buyukuysal⁴ · Muzeyyen Arslaner¹ · Bilal Toka² · Ishak Ozel Tekin⁵

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Abstract Venous thromboembolism (VTE) is generally classified as provoked or unprovoked. This dichotomy is important for following patients, mortality rate, prognosis and whether more efficient therapy is needed. In VTE patients, during initial diagnosis, it is not known exactly whether red cell distribution width (RDW) have a predictable value for this differentiation and pathogenesis. In this study, 298 patients with VTE and 197 control subjects were included. Patients with VTE were defined as provoked or unprovoked with respect to physical examination findings and laboratory values. Changes in RDW were tested between VTE patients and control subjects, provoked and unprovoked VTE patients, and separately with control subjects. RDW was found to be high in provoked and unprovoked groups compared with control group ($p < 0.001$, $p = 0.003$ respectively). RDW was significantly high in provoked VTE patients group compared with unprovoked patients ($p < 0.001$) and a cut-off value was found to be 13.6 %. In ROC analysis, sensitivity was

90.19 % and specificity was 82 % (95 % CI 85.4–93.8 % and 95 % CI 72.3–89.6 % respectively). RDW could be used as a simple, costeffective and a reliable test independent of age in differentiation of provoked and unprovoked VTE. In order to better understand its role, prospective large homogenized population studies in different regions are necessary.

Keywords Red cell distribution width · Venous thromboembolism · Differentiation of VTE

Introduction

Venous thromboembolism (VTE) is a common disease with serious short and long-term complications, and a potentially fatal outcome [1]. The annual incidence is approximately 1–3 per 1000 adults in developed countries [2]. Recent studies such as COPER and EMPEROR have shown that some important prognostic risk factors

✉ Sehmus Ertop
drsertop@yahoo.com

Muammer Bilici
drmbilici@hotmail.com

Huseyin Engin
bulengin@yahoo.com

Cagatay Buyukuysal
cbuyukuysal@gmail.com

Muzeyyen Arslaner
m_beydogan@hotmail.com

Bilal Toka
bilaltoka@hotmail.com

Ishak Ozel Tekin
ishaktek@yahoo.com

¹ Department of Hematology, Bulent Ecevit University School of Medicine, 67600 Zonguldak, Turkey

² Department of Internal Medicine, Bulent Ecevit University School of Medicine, Zonguldak, Turkey

³ Department of Oncology, Bulent Ecevit University School of Medicine, Zonguldak, Turkey

⁴ Department of Biostatistic, Bulent Ecevit University School of Medicine, Zonguldak, Turkey

⁵ Department of Immunology, Bulent Ecevit University School of Medicine, Zonguldak, Turkey

associated with death from pulmonary embolism (17 %) were age (over 70 years), cancer, congestive heart failures, chronic obstructive pulmonary disease, systemic arterial hypotension, tachypnea and the mortality rate directly attributable to pulmonary embolism was only 1 % [3, 4]. These prognostic risk factors are often used to identify provoked VTE [5]. Consequently identification of VTE as provoked and unprovoked is very important both for prognosis and more efficient therapy during the follow up patients or optimally adapted the treatment to the risk of the fatal outcome [6]. The red blood cell (RBC) distribution width (RDW) is a measurement of the size of RBC, thus “width” referring to width of distribution curve and not the width of cells as well as index of heterogeneity of RBC (i.e. anisocytosis). It is routinely assessed as part of a standard complete blood count (CBC) and is used for classification of anemia [7, 8]. RDW has been associated with VTE and it is a predictor of first event of VTE [9], but it is still unclear whether anisocytosis might be the cause or a simple epiphenomenon of an underlying disease as in provoked VTE or both [10]. Moreover in VTE patients during the initial diagnosis, it is not known exactly whether RDW have a predictable value to differentiate between provoked and unprovoked VTE. So in this study we aimed to determine if RDW have any predictable value in differentiation and pathogenesis of provoked and unprovoked VTE.

Patients and Methods

Study Population

Between December 2008 and February 2012, the hospital files from the archive of patients with an event of VTE admitted to Emergency Department of Bulent Ecevit University Hospital within 24 h after the onset of symptoms were screened retrospectively to determine RDW. The inclusion criteria were age between 18 and 80 years and a documented diagnosis of VTE. Clinical data detailing VTE and both comorbid conditions and contributing risk factors such as smoking, coal miners, hypertension, diabetes mellitus, pregnancy, post-partum, oral contraceptive therapy, spinal cord injury, major surgery, multiple trauma, hip fracture, congestive heart or respiratory failure, obesity, prolonged immobility, malignancy, infection for VTE have been recorded using clinical progress notes of the responsible physician and results of laboratory tests. In case of recurrent VTE, only the first VTE event was included if possible (sixty seven patients had recurrent VTE). Twenty seven patients who had any defined hematological diseases (iron deficiency anemia, sickle cell anemia, leukemia, lymphoma and myeloma) were

excluded from the study. After excluding patients the main study group consisted of 298 patients with VTE. The control group consisted of 197 healthy subjects. The control group was formed of subjects consecutively admitted to the hospital for routine check-up or students who had no history of VTE and any other conditions. The registry was approved by the Local Ethics Committee of Bulent Ecevit University, Zonguldak, Turkey (2013-132-31/12).

Diagnosis of VTE

A diagnosis of VTE was based on a combination of a D-dimer assay (using a D-dimer cutoff of 243 ng/mL) with both clinical assessment of risk factors and physical findings [11]. The diagnosis of venous thromboembolism was confirmed by Doppler ultrasonography, computed tomography (CT) venography, magnetic resonance imaging (MRI) venography and scintigraphic evaluation [12]. Overall, doppler ultrasound test was performed in 260 patients with DVT or PE. Pulmonary embolism (PE) was diagnosed either by contrast mediated multi-detector spiral computerized tomography or ventilation-perfusion lung (VQ) scanning (3mCi Tc-99mMAA) in 221 patients (167 and 54 of them were evaluated by CT and VQ scan, respectively). Ventilation lung scanning was performed using 10mCi Tc-99m pertechnetate aerosol by Mo-99/Tc-99m generator. In total, 38 patients were evaluated with MRI or CT in other unusual sites of VTE.

Differentiation of Provoked and Unprovoked VTE

VTE is considered as provoked if it is related to one of following risk factors: immobilization for longer than 3 days, travelling more than 6 h, surgical intervention within the previous 4 weeks, acute and chronic inflammatory diseases, active malignant disease at the time of VTE manifestations or diagnosed cancer within 6 months after VTE events, oral contraceptive use, pregnancy and child-birth within post-partum period (6 weeks) for females, acute or chronic medical illnesses such as congestive heart failure, renal failure and infections. If none of above-mentioned criteria are present, VTE is considered unprovoked. In our study, 84 patients do not have risk factors that are defined above (28.1 %) and 214 patients have at least one of these factors or more (71.9 %).

Laboratory Tests

Initial CBC results that were obtained during the first admission in the emergency department or after being accepted to the specific clinics were used in the study. Peripheral venous blood samples were drawn from antecubital vein using standard operational procedure.

Hemoglobin (Hgb), Hematocrit values (Htc), Mean Corpuscular Volume (MCV), red cell distribution width (RDW) and Mean Platelet Volume (MPV) were obtained from the automated complete blood count using a Coulter LH780 Hematology Analyzer (Beckman Coulter Inc. Brea., CA, USA). Hematology analyzer was calibrated yearly. The internal and external controls were applicated everyday by the recommendation of manufacturer. In our laboratory, the normal values are as follows: RDW (%): 11.5–15.0, Hb: 12–18 % gr, Hct: 37–52 %, MCV: 80–100 fl, MPV: 7.4–10.4 fl. For detecting Factor V Leiden and prothrombin 20120 gene (Factor II) mutations, the following procedures were used. Genomic DNA was extracted from peripheral blood leucocytes (200 µl of total blood) by using a Macherey–Nagel (MN) Nucleospin blood[®] DNA extraction kit (cat. no. 740.951.250) according to the manufacturer's instructions. FV G1691A, FV G1091C and FII G20210A gene mutations were detected by Dr. Zeydanli[®] Type I PCR System (Ankara, Turkey) based TaqMan[®] 5' nuclease assay method in ABI 7500 (Applied Biosystems, Foster City, CA, USA). PCR reaction was performed according to the manufacturer's instructions. The reactions were started at 95 °C for 10 min, followed by 32 cycles of 95 °C for 15 s and 60 °C for 1 min.

Statistical Analyses

SPSS 19.0 was used for statistical analysis. Continuous variables are given with mean, median, standard deviation, minimum and maximum values; qualitative variables are given with frequency and percentage. Shapiro–Wilk Test was used for testing normal distribution. Mann–Whitney

U test was used for two group comparisons and Kruskal–Wallis test for 3+ group comparisons for non-normal data. Analysis of covariance has been used to test the main and interaction effects of age on continuous dependent variables. Pearson Chi-square test was used for crosstab comparisons. ROC analysis was used to determine a cut off value for RDW to discriminate patients as provoked and unprovoked. The results were given with sensitivity and specificity. For all statistical comparisons *p* value below 0.05 was assumed statistically significant.

Results

A total of 298 consecutive patients and 197 control subjects were included in the study; of which 136 (45.6 %) were male with median age 54 (18–80) years and 162 (54.4 %) were female with median age 53 (20–80) years. Control subjects, of which 87 (44.2 %) were male with median age 30 (19–56) years and 110 (55.8 %) were female with median age 31(18–43) years. Patients were divided into two groups; provoked and unprovoked according to whether patients have risk factors or not. All VTE in provoked and unprovoked patients and control subjects characteristics are shown in Table 1. In VTE patients, age was significantly higher than control subjects [54 (18–80) vs 30 (18–56) *p* < 0.001] and provoked VTE patients were older than unprovoked VTE patients [58 (20–80) vs 40 (18–76) *p* < 0.001]. DVT of legs was diagnosed in 104 (34.8 %) patients, PE in 221(74.1 %), other unusual sites of DVT in 38 (12.7 %) whereas 65 (21.8 %) had both DVT and PE. PE was more common among patients with provoked VTE (64.2 vs 78.0 % *p* = 0.015), whereas the opposite was true

Table 1 Characteristics of VTE patients and control subjects

	VTE patients (n = 298)	Control subjects (n = 197)	<i>p</i>	Unprovoked (n = 84)	Provoked (n = 214)	<i>p</i>
Age	54 (18–80) ^a	30 (18–56) ^a	<0.001*	40 (18–76) ^a	58 (20–80) ^a	<0.001*
Gender	n (%)	n (%)		n (%)	n (%)	
Male	136 (45.6)	87 (44.2)	0.747	48 (57.1)	88 (41.1)	0.012*
Female	162 (54.4)	110 (55.8)		36 (42.9)	126 (58.9)	
PE	221 (74.1)			54 (64.2)	167 (78.0)	0.015*
DVT of leg	104 (34.8)			37 (44.0)	67 (31.3)	0.038*
DVT of other site	38 (12.7)			16 (19.0)	22 (10.2)	0.065
PE + DVT	65 (21.8)			23 (27.3)	42 (19.6)	0.192
FV Leiden	99 (33.2)	13 (6.5)	<0.001*	43 (51.2)	56 (26.1)	<0.001*
PT II	29 (9.7)	6 (3.0)	0.008*	13 (15.4)	16 (7.4)	0.060
FV Leiden + PT II	8 (2.6)			4 (4.7)	4 (1.8)	0.227

PE Pulmonary thromboembolism, DVT deep vein thrombosis, FV *leiden* factor V *leiden*, PT II prothrombin gen II

* Statistically significant (*p* < 0.05)

^a Median (min–max)

Table 2 Comorbid illnesses and risk factors in VTE patients

	Provoked (n = 214) n (%)	Unprovoked (n = 84) n (%)	<i>p</i>
Coal miners	38 (17.7)	11 (13.0)	0.422
D. Mellitus	36 (16.8)	9 (10.7)	0.252
Smoking			
Yes	34 (15.8)	15 (17.8)	0.914
Ex Smoker	45 (21.2)	17 (20.2)	
No	135 (63)	52 (61.9)	
Hypertension	62 (28.9)	14 (16.6)	0.041*
Risk factors			
Pregnancy	1 (0.4)	–	
Post-partum	3 (1.4)	–	
HRT	16 (7.4)	–	
Surgery	21 (9.8)	–	
Trauma	17 (7.9)	–	
Immobilization	46 (21.4)	–	
Cancer	21 (5.6)	–	
Infection	101 (27.1)	–	
COPD	67 (18.0)	–	
Heart failure	79 (21.2)	–	

HRT Hormone replacement therapy, *COPD* chronic obstructive pulmonary disease

* Statistically significant ($p < 0.05$)

Table 3 Comparison of CBC results of VTE patients, control subjects and provoked/unprovoked VTE patients

	VTE patients (n = 298) median (min–max)	Control subjects (n = 197) median (min–max)	<i>p</i>	Unprovoked (n = 84/28.1 %) median (min–max)	Provoked (n = 214/71.9 %) median (min–max)	<i>p</i>
Hgb (gr/dl)	13.0 (7.8–16.5)	13.2 (9.9–17.0)	0.077			
Htc (%)	38.3 (22.9–51.0)	38.6 (29.1–49.0)	0.782			
MCV (fl)	87.3 (77.4–103.9)	88.0 (80.1–97.1)	0.177			
RDW	14.5 (11.2–24.2)	12.8 (10.7–14.9)	<0.001*	12.9 (11.2–16.4)	15.2 (12.0–24.2)	<0.001* 0.003**

* *p* values for statistical significances between provoked VTE patients and both unprovoked VTE patients and control subjects ($p < 0.05$)

** *p* value for statistical significance between unprovoked VTE patients and control subjects ($p < 0.05$)

for DVT of leg (44.0 vs 31.3 % $p = 0.038$). Genetic factors were more common among patients with unprovoked VTE when compared to those with provoked VTE for Factor V Leiden and Prothrombin II gene mutation (51.2 vs 26.1 % $p < 0.001$ and 15 vs 7.4 % $p = 0.008$, respectively). In our study, co-morbid illnesses and risk factors for provoked VTE are shown in Table 2. With regards to smoking and diabetes mellitus, there was no difference between two groups, but hypertension was high in the provoked VTE, probably due to old age ($p = 0.914$, $p = 0.252$ and $p < 0.005$, respectively). All VTE patients were compared with control subjects in terms of RDW, Htc, Hgb and MCV, the details of which are shown in Table 3. RDW was significantly high in VTE patients more

than control subjects [14.5 (11.2–24.2) vs 12.8 (10.7–14.9) $p < 0.001$]. Between these two groups there were no difference in terms of Hb, Hct and MCV ($p = 0.077$, $p = 0.782$, and $p = 0.177$, respectively). MPV was higher in control group than the patients with VTE ($p < 0.001$). Although, there was no significant difference between unprovoked and provoked patients regarding MPV ($p = 0.162$). Between unprovoked and provoked patients, RDW was markedly elevated in provoked VTE compared with unprovoked VTE [15.2 (12.0–24.2) vs 12.9 (11.2–16.4) $p < 0.001$]. When provoked and unprovoked VTE patients were separately compared with control subjects (Table 3), in unprovoked patients RDW levels were higher [12.9 (11.2–16.4) vs 12.8 (10.7–14.9), $p = 0.003$]

Fig. 1 ROC curve showing the Cut off value for RDW between provoked and unprovoked groups, RDW limit determined as >13.6 with a 90.19 (85.4–93.8) sensitivity and 82.14 (72.3–89.6) specificity

but they were still within normal RDW ranges and provoked VTE patients have significantly elevated RDW than control subjects [15.2 (12.0–24.2) vs 12.8 (10.7–14.9), $p < 0.001$]. This indicates the high RDW levels may be due to both VTE itself as in unprovoked VTE and associated risk factors in addition to VTE itself as in provoked VTE. The receiver operating characteristic (ROC) analysis showed the best cut-off value is 13.6 % for RDW with 90.19 sensitivity (95 % CI 85.4–93.8 %) and 82 % specificity (95 % CI 72.3–89.6 %) for predicting differentiation of provoked and unprovoked VTE (Fig. 1). When the effect of age has been neglected, there was no difference detected both in control group and VTE cases and provoked and unprovoked groups. This shows RDW difference is a predictable factor independent of age.

Discussion

This was a retrospective study to elucidate that RDW has a predictable value on differentiation of provoked and unprovoked VTE and its effect on VTE pathogenesis. This study showed that high RDW levels are related to both provoked and unprovoked VTE but more significant in provoked VTE patients. Additionally, this study showed that anisocytosis is both a cause and a simple epiphenomenon due to underlying diseases.

Increased RDW levels are seen not only in classical hematological diseases but also might be associated with cardiovascular disease and heart failure [13, 14], stroke [15], diabetes associated complications [16], malignancy [17], peripheral artery disease, pulmonary arterial

hypertension [18] and VTE. The mechanism underlying the relationship between RDW and VTE is still unclear. VTE is a venous disease with red thrombus in contrast to coronary artery disease which is a separate arterial disease with white platelet plaque. In VTE, RBCs play a pro-thrombotic role in blood coagulation by increasing blood viscosity and forcing platelets toward the vessel wall. Therefore venous thrombosis begins with the aggregation of RBCs, fibrin and platelets [19, 20]. RBCs are constituents of blood clots and thrombin formed in vivo. Incorporation of RBCs into a fibrin clot affects clot structure and mechanical properties. Moreover, RBCs are involved actively in thrombin generation, unlike platelets, by producing thrombin through the meizothrombin pathway, which has consequences in the context of clot formation and stabilization [21]. As a result, impaired blood flow and increased viscosity lead to stasis in venous vessels. In a study performed by Patel et al. [22] it was shown that greater variation in RBC volumes (increased RDW) is associated with decreased RBC deformability, which can impair blood flow through the microcirculation and even though the cells may be deformed while passing through the clot. In our study; all VTE patients had high RDW levels compared with control subjects ($p < 0.001$) similar to other studies. Patients were divided into two groups as provoked and unprovoked depending on their clinical data. When unprovoked VTE patients were compared with control subjects, RDW levels were higher in unprovoked VTE than in control subjects ($p = 0.003$) but were still in normal reference ranges. However, this minute but important changes in RDW might also reveal the occurrence of VTE due to, small structural differences of RBCs may have a large influence on pathophysiology. RBCs triggered variability in the fibrin network structure, individual fiber characteristics, and overall clot viscoelasticity compared to the absence of cells as well [23]. In unprovoked VTE, these findings elucidate the reason why it has high RDW levels even in normal reference ranges and whether this condition is due to VTE itself. So, for the next step, we compared provoked VTE and control subjects and found that RDW was higher in provoked VTE than control subjects ($p < 0.001$). In several studies, it was shown that increased RDW levels were seen in heart failure, chronic renal insufficiency, systemic inflammation, COPD, malignancies and with diabetes mellitus complications [13–18]. The vast majority of these risk factors have been associated with provoked VTE. The patients who have these diseases, in addition to this effect of VTE itself, they have some risk factors that also lead to elevated RDW. In unprovoked VTE, elevation of RDW is caused by VTE itself whereas in provoked VTE this condition is not only due to VTE itself but also due to other concomitant risk factors. In provoked VTE, increased RDW is both a result and a cause. Maybe

this coexistence can have a synergy and elevated RDW levels more than expected. When RDW levels were compared between provoked and unprovoked groups, we observed that provoked groups have higher RDW levels than unprovoked group ($p < 0.001$). The difference in two groups for RDW was used for ROC analysis to find a cut-off value. The ROC analysis showed that the best cut-off value is 13.6 % for RDW and it has a predictive value for differentiation. In studies performed by Rezende et al. [24], Cay et al. [25], and Ozsu et al. [26], they found that high RDW level was associated with VTE and it was also an independent risk factor for mortality and VTE diagnosis. Zorlu et al. [27] found that RDW seems to aid in the risk stratification of patients with acute PE with RDW >14.6 . These studies found that a high RDW level was an independent predictor for early PE-related mortality and other DVT associated risk factors but cannot exclude the possibility that anisocytosis was the result of thrombotic event itself. The present study has not consisted long-term follow up of VTE patients regarding impact of RDW on mortality. In our study, we found that increased RDW levels were not only due to VTE itself but also as a result of concomitant risk factors and the latter was more significant. These results are important and elucidate either differentiation or pathogenesis of VTE. In addition, death from VTE is associated with concomitant risk factors rather than VTE itself and this coexistence may create a synergy for worsening prognosis and mortality rate. In our study, unlike developed countries, the most common risk factors for VTE were acute and chronic medical illnesses including especially activation of chronic obstructive pulmonary disease (COPD), probably due to the fact that our region is a coal mine region and the incidence of COPD in coal mine workers is high because of pneumoconiosis [28]. In another study from RIETE registry, they found that COPD patients presenting with PE have an increased risk for PE recurrence and fatal PE compared with those presenting with DVT alone and more efficient therapy is needed in this subtype of patients [29]. Uhm et al. [30] from Korea performed to compare clinical and imaging parameters and prognosis of provoked and unprovoked acute PE patients and they found that provoked PE with irreversible risk factors has a poor prognosis for all-cause mortality and recurrent PE than unprovoked PE and provoked PE with reversible risk factors. Ellingsen et al. [31] suggested that high RDW is a risk factor of incident VTE, and that RDW is a predictor of all-cause mortality in VTE patients. All of these studies show that VTE treatment needs to be rearranged according to associated risk factors. Identification of these associated risk factors may effectively be done with advanced and costly procedures; however RDW, as a simple and cheap test, can be used for this purpose to gain similar results as effectively as others.

Conclusion

In VTE patients, high RDW levels may be due to both VTE itself and associated risk factors, but it is more prevalent in provoked VTE patients. Increased RDW levels are likely to be caused by provoked VTE. How close it is to normal will determine whether it will be unprovoked VTE. This dichotomy is important for following patients, mortality rate, prognosis, recurrence and whether more efficient therapy is needed. Therefore RDW which may be obtained in a CBC result from all patients on bedside on the first sight can be used as a simple, cheap, and reliable test, independent of age, for the differentiation of provoked and unprovoked VTE. In order to define its role better, prospective large homogenized population studies from different geographical regions are necessary.

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Compliance with Ethical Standards

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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