Thrombosis Research 136 (2015) 590–594

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Association between red cell distribution width and risk of venous thromboembolism

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ARTICLE INFO

Article history:
Received 13 May 2015
Received in revised form 30 June 2015
Accepted 22 July 2015
Available online 26 July 2015

Keywords:
Red cell distribution width
Venous thromboembolism
Thrombophilia
Risk factors
Biological markers

ABSTRACT

Background: An association between high red cell distribution width (RDW) and venous thromboembolism (VTE) has been observed. However, it is not known whether this association differs within various manifestations of VTE, nor if there is an interaction between RDW and thrombophilia abnormalities on the risk of VTE.
Aims: To investigate whether RDW is a marker of the risk of VTE; to identify subgroups of patients in which the association between RDW and VTE is stronger; to investigate a possible interaction between RDW and thrombophilia abnormalities.
Methods: Case–control study on 730 patients with a first objectively-confirmed VTE episode (300 unprovoked and 430 provoked) consecutively referred to our Center between 2007 and 2013, and 352 healthy controls. Blood was taken for a thrombophilia work-up and a complete blood count, including RDW, at least three months after VTE.
Results: Individuals with RDW above the 90th percentile (>14.6%) had a 2.5-fold increased risk of VTE compared to those with RDW ≤90th percentile, independently of age, sex, body mass index, other hematological variables and renal function (adjusted odds ratio: 2.52 [95%CI:1.42-4.47]). The risk was similar for unprovoked and provoked VTE, and slightly higher in patients with pulmonary embolism (adjusted odds ratio 3.19 [95%CI:1.68-6.09]) than in those with deep vein thrombosis alone (2.29 [95%CI:1.22-4.30]). No interaction between high RDW and thrombophilia abnormalities on the risk of VTE was observed.
Conclusion: Our findings confirm RDW as an independent and easily available marker for stratification of the risk of VTE.

1. Introduction

Venous thromboembolism (VTE) is the third most common cardiovascular disease. It occurs in approximately 1 per 1000 persons per year, with a case-fatality rate up to 25% at 1 year [1]. Several acquired and genetic risk factors for VTE have been identified so far [2,3], but the causes of VTE remain unexplained in approximately 40% of cases [4].

The red blood cell distribution width (RDW), usually part of the standard complete blood count of a routine hematology laboratory test, is a measurement of the size variation of circulating red blood cells and an index of their heterogeneity [5]. Together with the mean corpuscular volume (MCV), RDW is used as a predictor of an underlying anemia [6], being increased in iron-deficiency and megaloblastic anemias and normal in thalassemia and macrocytic anemias from other causes. Recently, several studies demonstrated that RDW is a good predictor of cardiovascular mortality and morbidity [7–13]. A variety of conditions may determine a significant variation of the red blood cell size, generating a high RDW (anisocytosis), whereas a low RDW indicates a uniform size of red blood cells. For instance, high RDW was independently associated with declining glomerular filtration rate, suggesting an inverse association between RDW and renal function [14,15]. Inflammation is also strongly related to ineffective erythropoiesis [16], and some studies showed that inflammatory cytokines, such as tumour necrosis factor (TNF)-α and interleukin (IL)-6, inhibit red blood cell maturation, thus promoting anisocytosis [17,18]. Both renal impairment and inflammation have been associated with an increased risk of VTE [19,20]. To date, there are only few studies addressing the relationship between RDW and VTE. One [21] suggested RDW as a predictor of worse outcome and early mortality after a first episode of acute

Abbreviations: VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; RDW, red blood cell distribution width; MCV, mean corpuscular volume; TNF, tumour necrosis factor; IL, interleukin; CRP, C Reactive Protein; SD, standard deviation; OR, odds ratio; CI, confidence interval; P_{90}, 90th percentile.

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http://dx.doi.org/10.1016/j.thromres.2015.07.020
0049-3848/

pulmonary embolism. Two other case–control studies [22,23] and one population-based cohort study [24] consistently reported a 2 to 3-fold increased risk of VTE in individuals with high RDW. Since RDW is an easily available parameter, valuable confirmation of the aforementioned studies is warranted to better stratify the risk of VTE.

The primary aim of this case–control study was to assess whether RDW is associated with an increased risk of VTE. Secondary aims were to verify whether this association is different according to the etiology (unprovoked *vs* provoked) and severity (i.e., presence or absence of pulmonary embolism) of VTE, and to evaluate the possible interaction between RDW and thrombophilia on the risk of VTE.

2. Methods

2.1. Study Population

The study was carried out at the Thrombosis Center of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan. Cases were consecutive patients referred to the Center from 2007 to 2013 for a symptomatic objectively-confirmed first episode of VTE (i.e., deep vein thrombosis of the lower limbs [DVT] or pulmonary embolism [PE]). DVT was diagnosed by compression ultrasound or venography, and PE by ventilation/perfusion lung scan or spiral CT scan. VTE episodes were considered unprovoked if they occurred in the absence of transient risk factors (surgery, prolonged immobilization, trauma, pregnancy, puerperium, oral contraceptive use). Clinical and demographic data were collected by interview. Controls were partners or friends of VTE patients referred to the Center in the same time period for a thrombophilia work-up. Previous episodes of thrombosis were excluded by a validated questionnaire [25]. Individuals with overt cancer or autoimmune diseases were excluded from the study. The study was approved by the Hospital Institutional Review Board, and all patients and controls signed the informed consent before inclusion in the study.

2.2. Laboratory Tests

Blood samples were collected in vacuum tubes with EDTA as anticoagulant for automated complete blood count. For the thrombophilia screening, additional samples were collected into vacuum tubes containing 3.2% sodium citrate (Vacuette Premium tubes, Greiner Bio-One, Kremsmünster, Austria) and centrifuged within 15 min at 20 °C for 20 min at 2880 ×*g*. The plasma obtained was aliquoted and snap-frozen in liquid nitrogen, and then stored at −80 °C until analysis. Serum creatinine and C-Reactive Protein (CRP) were also measured. Creatinine clearance was calculated as a measure of renal function, following the Cockroft-Gault formula. All samples were collected at least 3 months after VTE, in order to avoid changes in biological parameters related to the event.

RDW is calculated by the automated coulter by dividing the standard deviation of the red blood cell volume (MCV) by the mean MCV, then multiplying the result by 100 in order to express it as a percentage (RDW% = [standard deviation MCV / mean MCV] × 100) [5]. The RDW normal reference range may vary widely according to the analytical technique used for measuring the erythrocyte volume [26]. With our automated coulter (Sysmex XE2100, Dasit Diagnostica), the lower and upper limit of the normal laboratory reference range are 11.5% and 14.5%, respectively. The coefficient of variability (CV%) for RDW is 3.0%.

Thrombophilia testing included DNA analysis for factor V Leiden and G20210A polymorphism in the prothrombin gene [27,28], functional assay for plasma factor VIII, functional and immunoassays (when required) for plasma antithrombin, protein C and protein S [29], antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-β_2 glycoprotein I antibodies) [30], fasting and post-methionine load homocysteine [31].

2.3. Statistical Analysis

All analyses were performed with the statistical software SPSS (release 20.0, IBM SPSS Statistics for Windows, IBM Corp., Armonk,

Table 1
Demographic and clinical characteristics of the study population.

	All patients (n = 730)	Unprovoked VTE (n = 300)	Provoked VTE (n = 430)	Controls (n = 352)
Demographic and clinical characteristics				
Age, yrs	48.2 (15.9)	53.9 (15.5)	44.4 (15.2)	42.1 (13.1)
Male sex, N (%)	374 (51)	206 (69)	168 (39)	136 (39)
Body Mass Index, Kg/m^2	25.6 (4.8)	26.4 (5.1)	25.1 (4.6)	24.2 (4.5)
Creatinine clearance, mL/min	0.92 (0.39)	0.97 (0.5)	0.88 (0.27)	0.86 (0.17)
Hemoglobin, g/dL	13.8 (1.6)	14.3 (1.6)	13.6 (1.5)	13.9 (1.4)
Mean Corpuscular Volume, fL	87.3 (6.2)	87.8 (5.8)	86.9 (6.4)	86.7 (6.7)
C reactive protein, mg/dL	0.43 (2.27)	0.39 (0.89)	0.46 (2.93)	0.23 (0.39)
VTE subtypes				
DVT only, N (%)	454 (62)	192 (64)	262 (61)	-
PE (with or without DVT), N (%)	276 (38)	108 (36)	168 (39)	-
*Risk factors for VTE, N (%)**				
Pregnancy**	-	-	12 (12)	-
Oral contraceptives†	-	-	161 (64)	-
Surgery	-	-	99 (23)	-
Immobilization	-	-	104 (24)	-
Thrombophilia, N (%)‡				
None				
AT, PC or PS deficiency	94 (13)	35 (12)	59 (14)	6 (1.7)
Factor V Leiden	89 (12)	37 (12.3)	52 (12)	13 (3.7)
Prothrombin G20210A	100 (14)	33 (11)	67 (16)	5 (1.4)
Antiphospholipid antibodies	29 (4)	17 (6)	12 (3)	4 (1.1)
Hyperhomocysteinemia	142 (19)	55 (18)	87 (20)	23 (6.5)
High factor VIII levels	100 (14)	37 (12)	63 (15)	15 (4.3)

Continuous variables are indicated as mean with SD between brackets.
VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; AT: antithrombin; PC: protein C; PS: protein S. *Some patients had more than one risk factor.
** Percentage calculated on women not taking oral contraceptives.
† Percentage calculated on non-pregnant women.
‡ Some patients had more than one thrombophilia marker.