

Red cell distribution width, other hematological parameters and atherogenic index of plasma in patients with clopidogrel and aspirin resistance

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ABSTRACT

Objectives. Chronic inflammation might favour platelet hyperactivity, which leads to inter-individual variability in antiplatelet resistance. The aim of this study was to test the hypothesis that there is a relationship between some hematological parameters reported as measures of systemic inflammation, the atherogenic index of plasma (AIP), and antiplatelet responsiveness. **Methods.** This retrospective study included patients receiving aspirin (100 mg) and clopidogrel (75 mg) daily before and after stenting. Platelet inhibition was assessed using the VerifyNow P2Y12 point-of-care test. Resistance to antiplatelet therapy was defined as P2Y12 reactivity exceeding 240 units (for clopidogrel) or aspirin reaction units exceeding 550 units (for aspirin). The AIP was calculated as the logarithm of triglyceride/high density lipoprotein cholesterol. The white blood cell (WBC), platelet (P), neutrophil (N), and lymphocyte (L) counts, red cell distribution width (RDW), hemoglobin (Hb), plateletcrit, mean platelet volume (MPV), platelet distribution width, and N/L and P/L ratios were evaluated. **Results.** Of 232 patients (73% male; median age, 63 years; range, 38-87 years), 52 (22%) were aspirin resistant and 82 (35%) were clopidogrel resistant; 7.7% were both aspirin and clopidogrel resistant. Median RDW levels were significantly higher (14.4% [interquartile rate (IQR) 3] vs. 13.9% [IQR 1.3]; $p=0.01$) and Hb levels significantly lower (12.0 ± 1.6 g/dL vs. 13.2 ± 1.7 g/dL; $p<0.001$) in the clopidogrel-resistant patients than in the clopidogrel responders. WBC, AIP, MPV, N/L, and P/L ratios were not statistically significant ($p>0.05$). Multivariate logistic regression showed that Hb (odds ratio [OR]=0.73; 95% confidence interval [CI], 0.60-0.88; $p=0.001$) and RDW (OR=1.26; 95% CI, 1.02-1.55; $p=0.02$) were independent predictors of clopidogrel resistance. **Conclusions.** Both RDW and Hb were independent variables associated with clopidogrel resistance, but antiplatelet resistance cannot be predicted based on other hematological parameters or AIP.

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Keywords: Red cell distribution width; hematological parameters; atherogenic index of plasma; systemic inflammation; clopidogrel resistance

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Introduction

Antiplatelet therapy is mandatory during and after percutaneous coronary intervention (PCI) for the prevention of acute stent thrombosis. To reduce the risk of stent thrombosis, dual antiplatelet therapy is currently recommended for PCI patients [1].

Stent thrombosis is more frequent when platelet inhibition by aspirin and clopidogrel is inadequate [2]. Clopidogrel and aspirin use different pathways to inhibit platelet aggregation. A combination of these drugs provides an additive effect over those of either agent alone [3]. There is wide inter-individual variability in the inhibitory effect of these drugs on platelet aggregation, some individuals exhibit a reduced or even absent antiplatelet response, and this is called antiplatelet drug resistance.

Inflammation and haemostasis are pathophysiologic processes that affect each other. Platelets influence various aspects of the inflammatory process, including interactions with leucocytes and the vascular endothelium. Recently, a number of studies have shown that chronic inflammation might favour platelet hyperactivity, which leads to inter-individual variability in antiplatelet resistance [4-6].

Mean platelet volume (MPV), platelet distribution width (PDW), red cell distribution width (RDW), neutrophil-to-lymphocyte (N/L) ratio are simple markers that indicate chronic inflammation [7]. The platelet-to-lymphocyte (P/L) ratio is an indicator of the balance between inflammation and thrombosis which is more advantageous than platelet or lymphocyte counts alone.

The atherogenic index of plasma (AIP) calculated as log triglyceride (TG)/high density lipoprotein cholesterol (HDL-C) has been universally used by practitioners as a significant predictor of atherosclerosis [8]. Plasma TG and HDL-C are basically opposite in direction with respect to measures of oxidative stress/systemic low-grade inflammation. Recently its shown that hypertriglyceridemia affects antiplatelet response [9].

We aimed to test the hypothesis that there is a relationship between inflammation-related haematological parameters, AIP and antiplatelet resistance. We also evaluated the relationship between RDW, MPV, N/L ratio, and P/L ratio, and (AIP) and antiplatelet responsiveness.

Methods

This study complies with the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Committee. This retrospective analysis was based on computerized databases in our Hospital's cardiovascular center. All study participants were hospitalized as acute coronary patients from the emergency department and were scheduled to undergo planned PCI for other coronary vessels. In addition, all patients were undergoing elective PCI, and all medical records for the cases from January to December 2015 were reviewed.

Based on medical records, patients aged >18 years and receiving 75 mg daily doses of clopidogrel, combined with 100 mg aspirin daily during 10 days to one month prior to elective PCI, were selected. Peripheral venous blood samples were obtained from subjects prior to the next dose of clopidogrel and aspirin on elective PCI day for study.

Patients with severe anaemia, thrombocytopenia, myelodysplastic syndrome, coagulopathy and recent blood transfusion, history of stroke or central nervous system damage, recent major surgery, or chronic renal insufficiency requiring dialysis were excluded.

Throughout the study, the quality of test results was validated by daily internal quality control procedures and participation in an external quality assessment scheme.

Platelet Aggregation Assays

Platelet response to aspirin and clopidogrel (P2Y₁₂) was performed with the Verifynow point-of-care system (Accumetrics Inc., San Diego, CA) based on turbidimetric-based optical changes measurement in whole blood as platelets aggregate. Specific cartridges for the aspirin and P2Y₁₂ pathway were used, and the degree of aggregation was quantified by a corresponding increase in light transmission and is reported as aspirin reaction units (ARU) and P2Y₁₂ reaction units (PRU), respectively. In the literature, a value of ≥ 550 ARU indicates aspirin resistance, and clopidogrel resistance is indicated as PRU ≥ 240 [10].

Atherogenic Index

The levels of total cholesterol (T Chol), TG and HDL-C were determined using commercially available assay kits (Abbott Diagnostics, Abbott Park, IL) with an Architect C16000 auto-analyser (Abbott Diagnostics). AIP is calculated as previously described [8].

Complete Blood Cell Count

Samples were analysed in an automated haematology analysis system (Coulter LH-780 haematology analyser, Beckman Coulter Inc., Fullerton, CA) that measures platelet size and platelet count using aperture-impedance technology. The WBC, P, N and L counts, RDW, MPV and PDW were recorded, and the N/L and P/L ratios were calculated from these parameters. Patients with elevated WBC counts (>11,000/mL) and any inflammatory, infective, or malignant diseases were excluded from the study.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 21.0 for Windows (SPSS Inc., Chicago, IL). Data are expressed as median (interquartile range) or mean±SD after normality test. The Shapiro–Wilk test was used to determine the normality of the evaluated variables. After evaluating the normality, statistically significant differences between parameters with Gaussian distributions were tested by a Student's t-test; variables with a non-Gaussian distribution were compared using the Mann-Whitney U test. Variables (PRU, ARU, T Chol, N/L and P/L ratios, MPV, RDW) were evaluated using the Spearman correlation coefficients. Logistic regression analysis of the relationship between clopidogrel resistance and the

variables were analysed. Statistical significance was set at $p<0.05$.

Results

A total of 232 patients (73% male, median age, 63 years) were included in the analysis. The patients were divided into two groups according to aspirin and clopidogrel response. According to our criteria, a total of 52 patients (22%) were aspirin-resistant and 82 patients (35%) were clopidogrel-resistant (Tables 1 and 2). Approximately 7.7% of the patients were both aspirin-resistant and clopidogrel-resistant.

The median ARU for the responder group was 471 (interquartile range [IQR] 80), and 590 ARU (IQR 72) for aspirin-resistants. The median PRU for the responder group was 173 (IQR 100), and for the resistant group, it was 289 (IQR 46).

Median RDW levels were significantly higher (14.4% [interquartile rate (IQR) 3] vs. 13.9% [IQR 1.3]; $p=0.01$) and Hb levels significantly lower (12.0 ± 1.6 g/dL vs. 13.2 ± 1.7 g/dL; $p<0.001$) in the clopidogrel-resistant patients than in the clopidogrel responders. However; WBC, AIP, MPV, N/L, and P/L ratios were not statistically significant ($p>0.05$). Our correlation analysis indicated that clopidogrel resistance as PRU was positively correlated with

Table 1. Demographic and laboratory parameters in patients (n=232)

Parameters	Aspirin responder	Aspirin resistant	<i>p</i>
Age	63 (15)	64 (12)	
Number of patients	180	52	
Female/male	43/137	20/32	
Baseline laboratory results			
PRU	206 (125)	219 (187)	
ARU	471(80)	590(72)	
Hb (g/dL)	12.7±1.9	13.0±1.4	0.831
RDW (%)	14.2 (1.6)	14.0 (1.1)	0.078
Platelet ($10^3/\mu\text{L}$)	235 (88)	241 (80)	0.451
MPV (fL)	8.6±1.0	8.3±1.0	0.089
PCT	0.20 ±0.06	0.20±0.04	0.706
PDW (%)	16.8±0.6	16.7 ±0.6	0.290
WBC ($10^3/\mu\text{L}$)	8.5(2.8)	8.2 (2.4)	0.235
N/L ratio	2.6±1.4	2.5±1.4	0.299
P/L ratio	117±48	120±48	0.418
T Chol (mg/dL)	182±48	200±49	0.062
Triglycerides (mg/dL)	145 (107)	162 (140)	0.287
HDL (mg/dL)	40 (12)	43 (14)	0.591
LDL (mg/dL)	104±39	118±41	0.055
Atherogenic index	0.16±0.30	0.21±0.30	0.362

Data are expressed as median (interquartile range) or mean±SD after normality test. PRU=P2Y12 reactivity unit, ARU=aspirin reaction units, N/L=neutrophile/lymphocyte, P/L=platelet/lymphocyte, MPV=mean platelet volume, PCT=plateletcrit, PDW=platelet distribution width, WBC=white blood cell, T Chol=total cholesterol, HDL=high density lipoprotein, LDL=low density lipoprotein LDL

Table 2. Demographic and laboratory parameters in patients (n=232)

Parameters	Clopidogrel responder	Clopidogrel resistant	<i>p</i>
Age	62 (15)	65 (15)	
Number of patients	150	82	
Female/male	29/121	34/48	
Baseline laboratory results			
PRU	173 (100)	289 (46)	
ARU	495 (120)	509 (83)	
Hb (g/dL)	13.2±1.7	12.0±1.6*	<0.001
RDW (%)	13.9 (1.3)	14.4 (3)*	0.001
Platelet (10 ³ /μL)	240 (89)	235 (67)	0.337
MPV (fL)	8.5±1.0	8.5±0.9	0.857
PCT	0.20±0.06	0.23±0.05	0.309
PDW (%)	16.8 ±0.6	16.8 ±0.6	0.557
WBC (10 ³ /μL)	8.6 (2.3)	8.0 (1.9)	0.056
N/L	2.6±1.1	2.5±1.3	0.747
P/L	118±47	121±45	0.323
T Chol (mg/dL)	191±46	178±53	0.840
Triglycerides (mg/dL)	150 (120)	175 (85)	0.632
HDL (mg/dL)	40 (12)	43 (14)	0.075
LDL (mg/dL)	110±40	102±41	0.078
Atherogenic index	0.18±0.31	0.15±0.29	0.480

Data are expressed as median (interquartile range) or mean±SD after normality test. PRU=P2Y12 reactivity unit, ARU=aspirin reaction units, N/L=neutrophile/lymphocyte, P/L=platelet/lymphocyte, MPV=mean platelet volume, PCT=plateletcrit, PDW=platelet distribution width, WBC=white blood cell, T Chol=total cholesterol, HDL=high density lipoprotein, LDL=low density lipoprotein LDL, **p*<0.05

RDW (*r*=0.297, *p*<0.001), and that aspirin resistance as ARU was negatively correlated with RDW (*r*= -0.149, *p*=0.023); whereas *r* values point to a poor correlation between variables. Hb was negatively correlated with PRU (*r*= -0.35, *p*<0.001) and RDW (*r*= -0.41, *p*<0.001). None of the other correlations were statistically significant (Table 3).

In univariate logistic regression analysis; Hb, RDW, and WBC were predictors of clopidogrel resistance (Table 3). In multivariate logistic regression analysis, Hb (odds ratio [OR]=0.73; 95% confidence interval [CI], 0.60-0.88; *p*=0.001) and RDW (OR=1.26; 95% CI, 1.02-1.55; *p*=0.02) were independent predictors of clopidogrel resistance (Table 4). None of the variables we evaluated was a risk factor for aspirin resistance.

Discussion

This is the first study showing that high RDW is a significant and independent predictor of resistance to clopidogrel and that there is a negative correlation between RDW and PRU.

There are a number of studies indicating that RDW has been influenced by inflammation and oxidative stress, and a strong correlation between RDW and inflammatory markers, C-reactive protein, and sedimentation rate has been observed [11-13]. We found that inflammation-related CBC parameters were similar between the groups; however, this was not in agreement with our working hypothesis. We did not find a correlation between RDW and inflammation markers, N and WBC counts, N/L ratio, or MPV.

Table 3. Correlation between variables in all patients (n=232).

		T Chol	Atherogenic index	N/L ratio	P /L ratio	MPV	RDW
PRU	<i>r</i>	-0.08	-0.06	-0.09	-0.01	0.07	0.30
	<i>p</i>	0.273	0.443	0.443	0.935	0.322	<0.001*
ARU	<i>r</i>	0.11	0.10	-0.09	0.01	-0.09	-0.15
	<i>p</i>	0.109	0.184	0.160	0.871	0.194	0.023*

* Correlation is significant at the .05 level (2-tailed). PRU=P2Y12 reactivity unit, ARU=aspirin reaction units, T Chol=total cholesterol, N/L=neutrophile/lymphocyte ratio, P/L=platelet /lymphocyte ratio, MPV=mean platelet volume, RDW=red cell distribution width

Table 4. Evaluation of parameters tested for their ability to predict the clopidogrel resistance using univariate and multivariate logistic regression analysis

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Hb	0.65 (0.55-0.78)	<0.001*	0.73 (0.60-0.88)	0.001*
RDW	1.40 (1.17-1.68)	<0.001*	1.26 (1.02-1.55)	0.020*
WBC	1.15 (1.01-1.28)	0.056	1.14 (0.99-1.39)	0.060
N/L ratio	1.01(0.82-1.25)	0.860		
P/L ratio	1.002 (0.99-1.008)	0.550		
PLT	0.99 (0.99-1.002)	0.320		
MPV	1.02 (0.78-1.33)	0.850		
AIP	0.75(0.28-1.96)	0.550		
LDL	0.99 (0.98-1.002)	0.190		

Hb=hemoglobin, RDW=red cell distribution width, WBC=white blood cell, LDL=low density lipoprotein, N/L=neutrophile/lymphocyte, P/L=platelet/lymphocyte ratio, MPV=mean platelet volume, AIP=atherogenic index of plasma, **p*<0.05

Oxidative stress may be another underlying biological mechanism that may lead to increased RDW. High oxidative stress contributes to elevated RDW by reducing RBC survival, increasing the release of large premature red blood cells into the peripheral circulation and increasing the fragility of red blood cells and affecting red cell lifespan [14]. Oxidative stress can enhance platelet aggregation to clopidogrel responsiveness in coronary artery disease patients [15]. Moreover, a recent study showed that patients under clopidogrel therapy showed different expressions of proteins involved in oxidative stress [16]. Because we did not look at the oxidative parameters, we cannot comment on if the RDW is related to the oxidant status in clopidogrel-resistants in our study group.

Tziakas *et al.* [17] described a link between RDW and lipidic composition of erythrocyte membranes. The stability of erythrocytes may be maximal within an optimal range of membrane fluidity [18]. Increases in erythrocyte membrane cholesterol levels are responsible for the deterioration of cell deformability, which affects the lifespans of circulating erythrocytes, and this results in elevated RDW values [13, 17, 18]. However, we did not find a correlation between AIP, T cholesterol, and RDW in our patients, which is in agreement with Vaya *et al.* [13]'s study. They also did not observe a correlation between RDW and T cholesterol, HDL-C, LDL cholesterol, or TG in a healthy Mediterranean population [13]. They found that RDW is associated with inflammatory markers but not with an unfavourable lipid profile.

Aspirin's effect on platelet aggregation is subject to inter-individual and intra-individual variability, which can be attributed to multifactorial reasons [20-22]. MPV, PDW, or PCT values were not different between groups, similar to Nada [21]'s study, which

observed that diabetic patients receiving aspirin or clopidogrel did not show significant differences in MPV when compared with controls [19]. Hyperglycaemia may decrease the effectiveness of antiplatelet therapy by increasing reactive oxidant species and lead to aspirin resistance by binding to thromboxane receptors, whereas hypercholesterolaemia may blunt aspirin's effect on thrombin [23, 24]. Genetics also play a role in patient response to aspirin as polymorphisms of platelets membranes postulated to cause aspirin resistance. However, we could not find the variables we evaluated as a risk factor of ASA resistance.

The Limitations of the Study

There are some limitations of this study. First of all, this is a single-centre, retrospective case-control study in which the selected population may not reflect the whole cohort. A lack of CRP, erythrocyte sedimentation rate and interleukin levels as inflammatory markers is another limitation of this study. Finally, we selected the VerifyNow method for ASA and clopidogrel resistance measurements, but there are other methods of measuring antiplatelet resistance that were not chosen for this study.

Conclusions

Antiplatelet resistance cannot be predicted based on other haematological parameters or AIP. However, this result should be verified in well-designed, large-scale studies on antiplatelet therapy resistance.

Conflict of interest

The authors disclosed no conflict of interest during

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