

Red cell distribution width and inflammatory markers in patients with angiographically confirmed coronary artery disease

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Abstract

Lipid accumulation and inflammation in the vessel wall play the most important roles in atherosclerosis and perpetuate atherosclerotic plaque development. Mediators of inflammation as fibrinogen and interleukin 6 (IL-6) may contribute to the exacerbation of atherosclerosis. Red cell distribution width (RDW) is a strong predictor of cardiovascular events. The aim of the present study was to compare RDW, serum levels of fibrinogen and IL-6 in patients with angiographically confirmed coronary artery disease according to the disease extension. We enrolled 201 patients with angiographically confirmed coronary artery disease that were divided in three groups by the extent of the atherosclerotic lesion of the coronary arteries: 126 patients with monovascular affection (group A: mean age 59.1 ± 9.84 years), 42 with bivascular affection (group B: mean age 59.1 ± 9.65 years) and 33 with trivascular affection (group C: mean age 64.0 ± 8.81 years). We measured RDW, fibrinogen and IL-6 levels in all patients. We obtained significantly increased mean values of fibrinogen and IL-6 in trivascular compared to bivascular, monovascular and control groups (all $p < 0.001$). We also obtained significantly increased mean values of RDW in trivascular group compared to bivascular, monovascular and control groups (all $p < 0.001$). A significant correlation between IL-6 and RDW ($r = 0.485$, $p < 0.001$) was found. Our study showed that increased levels of RDW, fibrinogen and IL-6 are associated with severe extension of angiographically confirmed coronary artery disease. The correlation between IL-6 and RDW values explains that high levels of RDW could reflect an underlying inflammatory state causing anisocytosis.

Keywords: atherosclerosis, fibrinogen, interleukin 6

Introduction

Over the last years, as atherogenesis has been the object of extended research it has become more clear that chronic inflammation is at the root of atherosclerosis

and its complication [1]. Endothelial dysfunction and inflammation plays an important pathogenic role in the development of atherosclerosis.

Inflammation biomarkers as fibrinogen, hs-CRP and IL-6 are providing independent prognostic information, improving the ability to identify patients with high cardiovascular risk. Plasma fibrinogen is an independent risk factor for coronary, cerebral and peripheral artery disease [2].

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Table 1. Baseline characteristics of the patients in the four groups.

Parameters	TRI group (n=33)	BI group (n=42)	MONO Group (n=126)	CON Group (n=41)
Age (years)	64.0±8.81	59.1±9.65	59.1±9.84	56.3±5.20
Sex M/F (%)	85/15	62/38	69/31	44/56

IL-6 is a cytokine that regulates humoral and cellular responses and plays a central role in inflammation and tissue injury. It is associated with higher all-cause mortality, unstable angina, left ventricular dysfunction, diabetes and its complications, hypertension, obesity and several types of cancer [3] [4]. It seems that the interaction of proinflammatory cytokine IL-6, the main regulator of fibrinogen synthesis, with the renin-angiotensin system represents an important pathogenetic mechanism in the development of the atherosclerotic process.

Red blood cell distribution width (RDW) is a measure of the size variability of circulating erythrocytes and a parameter that is routinely reported as part of a complete blood count. Higher RDW values indicate greater heterogeneity in the size of circulating erythrocytes. RDW is recognized as an independent predictor of outcome in patients with established cardiovascular disease, observation made initially in cases of heart failure [5]. As well as the inflammation markers, RDW have been shown to predict adverse outcomes in patients with heart failure, stable coronary artery disease, stroke and acute myocardial infarction. Elevated RDW may reflect a state of inflammation and high oxidative stress linked to endothelial dysfunction [6].

The aim of this study was to compare RDW and inflammatory markers - fibrinogen and Il-6 in patients with angiographically proved coronary artery disease.

Materials and Methods

This prospective study included 201 consecutive patients with angiographically confirmed coronary artery disease (CAD) that were divided in three groups considering the presence of vascular affection: 126 patients with monovascular disease (MONO group), 42 patients with bivascular disease (BI group) and 33 patients with trivascular disease (TRI group). CAD was classified by its extent (number of major coronary vessels affected by at least one stenosis of 50% or more). The three groups were compared with a control group of 41 subjects that had no coronary artery disease confirmed angiographically.

The exclusion criteria from the study were: patients with anemia (according to WHO is defined as hemoglobin <12g/dl in women and <13g/dl in men, abnormal ferritin level), excessive alcohol intake, myocardial infarction in the last 4 weeks, diabetes mellitus, renal failure or serum creatinine level over 1.5 mg/dL and neoplastic or hepatic disease.

Traditional risk factors such as age, gender, hypertension, smoking, diabetes and family history of coronary artery disease were assessed through questionnaires.

After informed consent was obtained, clinical evaluation included blood pressure measurement, physical examination, chest radiograph, 12-lead electrocardiogram.

Table 2. Biochemical parameters in the four groups.

Parameters	TRI group (n=33)	BI group (n=42)	MONO Group (n=126)	CON Group (n=41)
Fibrinogen (mg/dl)	364.4 ± 10.25	357.3 ± 15.85	352.9 ± 14.38	299±12.42
IL-6 (pg/ml)	13.1 ± 2.72	10.8 ± 2.54	9.9 ± 1.56	5.6 ± 1.06
RDW (%)	14.9 ± 0.93 %	14.5 ± 0.78 %	14.1± 1.01 %	11.3±1.29 %

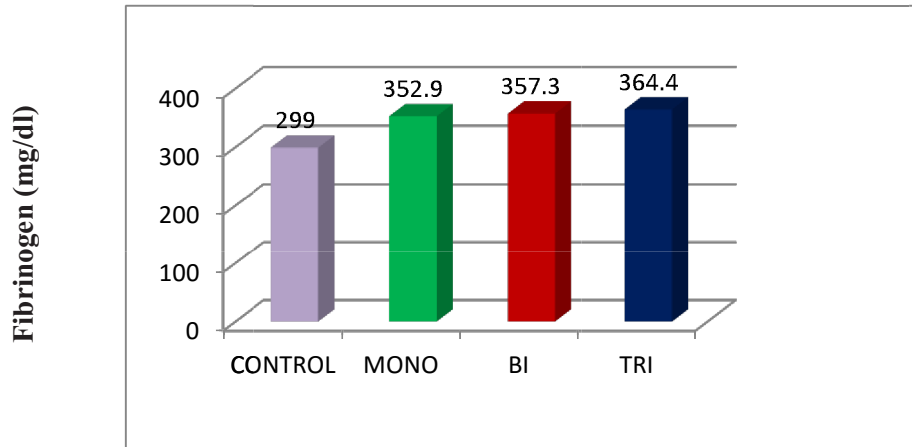


Figure 1. Distribution of mean fibrinogen levels (mg/dl) in the four groups studied.

While on their usual diet, a venous blood sample was drawn from an antecubital vein in all subjects after an overnight fast to determine RDW.

Fibrinogen was measured by Dimension RxL Max (Dade Behring Inc., USA), using a nephelometric research assay.

IL-6 levels were measured using an immunoenzymatic assay.

Continuous variables were expressed as means \pm SD. The relationship between RDW and IL-6 was tested for all four groups, Pearson's rank bivariate correlation tests were performed. Statistical significance was defined as two-sided $p < 0.05$. All statistical analyses were performed using Excel Microsoft Office 2007.

The procedures followed were in accordance with the ethical standards of the Hospital Ethics Committee and with the Helsinki Declaration of 1975, as revised in 2000.

Results

The baseline characteristics of the subject are summarized in Table 1 and the studied biochemical parameters values are included in Table 2.

We obtained statistically significant differences when we compared the mean fibrinogen levels between MONO group and control group ($p < 0.001$), between

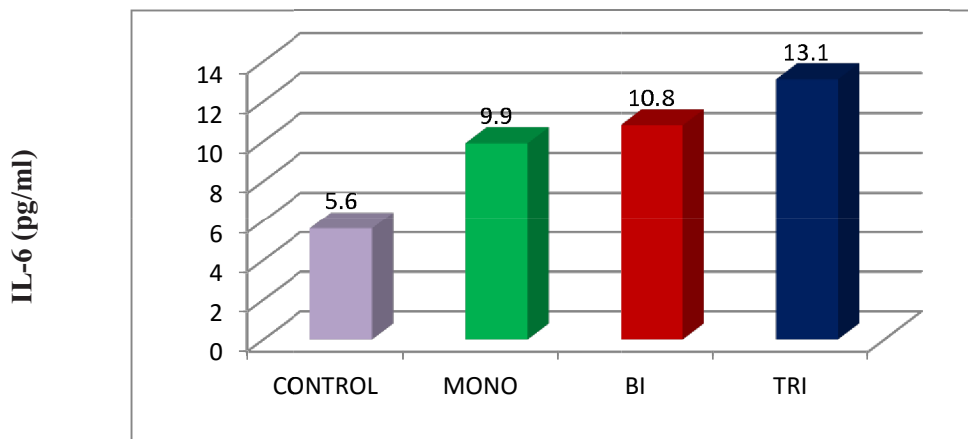


Figure 2. Distribution of mean IL-6 (pg/ml) in the four groups studied.

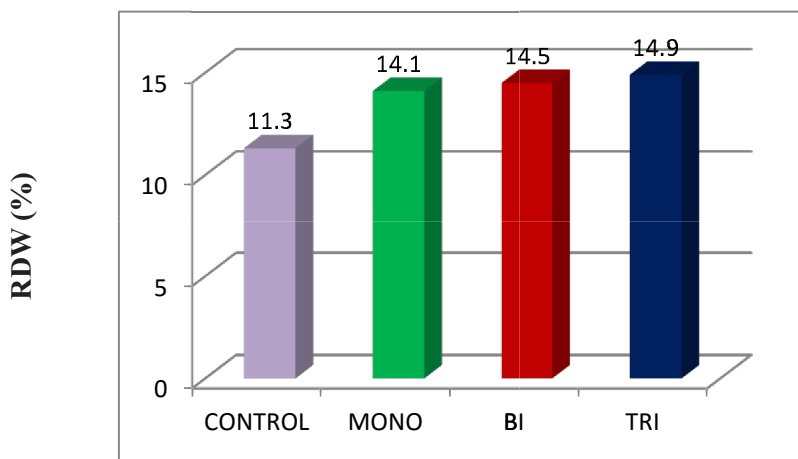


Figure 3. Distribution of mean RDW (%) in the four groups studied.

the BI group and control group ($p < 0.001$) and between TRI group and control group ($p < 0.001$). Also, we obtained statistically significant differences between mean values of fibrinogen between TRI and MONO groups ($p < 0.001$), TRI and BI ($p = 0.048$) and between BI and MONO groups ($p = 0.027$) (Fig. 1).

There were statistically significant differences when we compared the mean IL-6 values between MONO group ($p < 0.001$), BI group ($p < 0.001$), TRI group and CONTROL group ($p < 0.001$) (Fig. 2). The highest IL-6 values were obtained in the trivascular coronary artery disease group.

We obtained statistically significant higher RDW values in TRI, BI and MONO groups compared to control group ($p < 0.001$). Statistically significant differences between mean values of RDW were obtained when we compared TRI with MONO groups ($p < 0.001$), TRI with BI ($p = 0.048$) and BI with MONO groups ($p = 0.027$) (Fig. 3), higher values being obtain in the groups with multiple coronary artery stenosis.

Finally, we observed a significantly correlation between RDW, plasma levels of fibrinogen ($r=0.392$, $p<0.001$) (Fig. 4) and plasma levels of IL-6 ($r=0.485$, $p<0.001$) (Fig. 5).

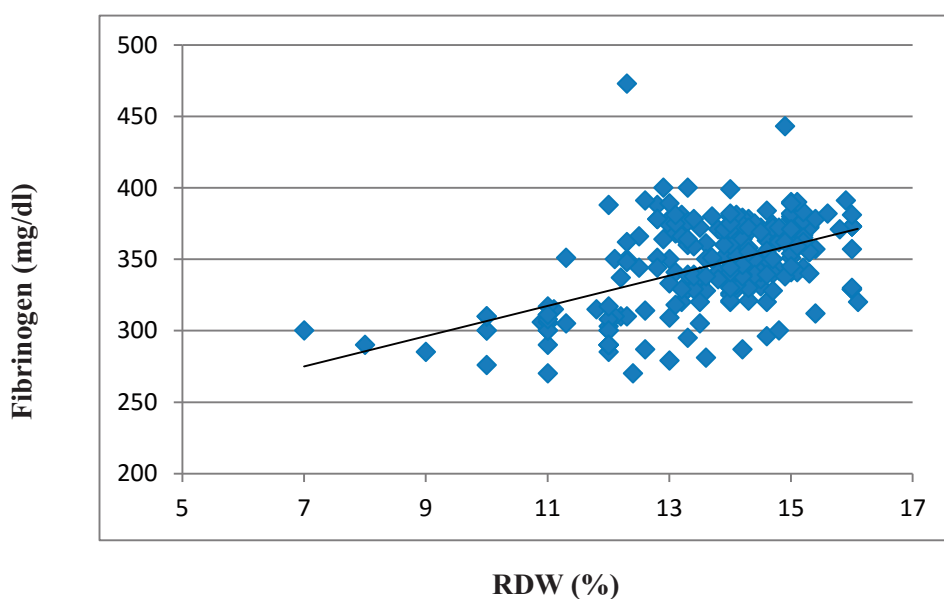


Figure 4. Correlation between fibrinogen and RDW.

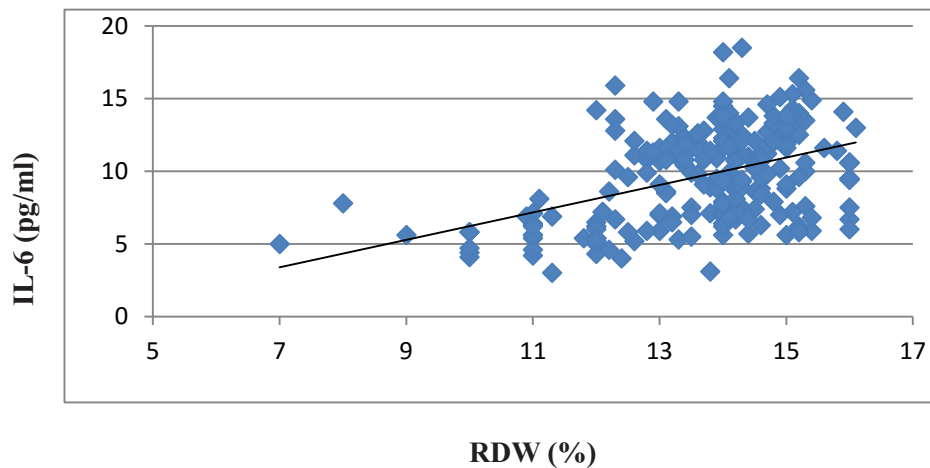


Figure 5. Correlation between IL-6 and RDW.

Discussion

Our study showed that both inflammatory parameters (fibrinogen, IL-6) in patients with angiographically confirmed coronary artery disease were increased in extended coronary artery affection. According to other studies [1], IL-6 values were significantly increased in patients with severe CAD, IL-6 representing an important factor in the development of atherosclerotic lesions and endothelial dysfunction in this patients.

We observed that RDW is also correlated with the extend of CAD in concordance with previous studies that showed that RDW was independently associated with the severity of CAD in patients with acute myocardial infarction [7].

An association between plasma levels of fibrinogen and RDW, and also between plasma levels of IL-6 and RDW was obtained in patients with coronary artery disease, observation in concordance with previous studies in patients with heart failure [8]. In present, it is well know that atherosclerosis is a chronic inflammatory disease and varied causative cytokines such as IL-6 are released in its process [9]. RDW increased values in patients with severe CAD might be secondary to altered iron availability and erythropoetic activity caused by the inflammation.

The limitations of our study consist in the fact that being a cross-sectional study other studies are required to conclude that RDW analysis should be performed routinely. It would be have been also useful studing the link between RDW and other markers of inflammation.

Conclusion

Our study showed that increased levels of fibrinogen, IL-6 and RDW are associated with severe extension of angiographically confirmed coronary artery disease. The correlation between inflammation markers and RDW shows that high levels of RDW may reflect an underlying inflammatory state causing anisocytosis.

We consider that given the fact that RDW measurement can be done in every lab that can measure hemoglobin concentrations, and its measurement is strikingly cost-effective, thus RDW might became a valuable parameter in assessing inflammation status.

Abbreviations

IL-6-interleukin 6

RDW-red cell distribution width

Hs-CRP-high sensitivity C reactive protein

CVD-cardiovascular disease

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