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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Assessment of the relationship between red cell distribution width and cardiac syndrome X

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Abstract

Background: Cardiac syndrome X (CSX) is characterised by angina-like chest pain, a positive stress test, and normal coronary arteries. Increased red cell distribution width (RDW) level may be indicative of an underlying inflammatory state.

Aim: To investigate RDW level in patients with CSX and compare patients having coronary artery disease (CAD) and normal subjects.

Methods: 245 subjects (79 patients with CSX, 81 patients with CAD, and 85 controls) were enrolled in the study. The CSX group consisted of patients with anginal chest pain, ischaemia on noninvasive stress test and a normal coronary angiogram. CAD was defined as ≥ 50% stenosis in at least one coronary artery. The control group was selected from the patients with anginal symptoms but a normal stress test and a normal coronary angiogram. RDW measurements among the three groups were compared.

Results: Baseline clinical and biochemical characteristics were not different among the three groups. There were no statistically significant differences in RDW levels between the CSX and CAD groups ($p = 0.17$). RDW measurements in both the CSX and CAD groups were found to be significantly higher than the control group ($p < 0.01$).

Conclusions: We discovered that patients with CSX and CAD have significantly higher RDW measurements compared to controls. The relationship between CSX and higher RDW level suggests that endothelial dysfunction may also contribute to the etiopathogenesis of the CSX phenomenon as it does with CAD.

Key words: cardiac syndrome X, red cell distribution width, endothelial dysfunction

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INTRODUCTION

Cardiac syndrome X (CSX) is a clinical entity that needs to be distinguished from angina pectoris due to typical obstructive coronary heart disease. It has three characteristic features: angina or angina-like chest pain with exertion; ST segment depression on treadmill exercise testing or pathological thallium scan and normal coronary arteriography; and no spontaneous or inducible epicardial coronary artery spasm on ergonovine or acetylcholine provocation [1]. It has been reported that despite normal coronary vessels, these patients have electrocardiographic as well as metabolic evidence of myocardial ischaemia. In addition, noncardiac causes of chest pain such as oesophageal disorders or psychiatric conditions like panic disorder should be ruled out before making a CSX diagnosis. Although the exact mechanisms leading to CSX are not yet clear, silent atherosclerosis and endothelial vasomotor dysfunction have been suggested as possible responsible factors.

Red cell distribution width (RDW), a measurement of variability and size of erythrocytes, can be easily measured during routine complete blood counts [2]. Increased RDW, independent of haemoglobin values, has been demonstrated

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to be associated with negative clinical outcomes in patients with heart failure, previous myocardial infarction, and stable coronary artery disease (CAD) [3, 4]. The association of RDW with adverse outcomes in cardiovascular diseases has not been fully understood. Inflammation may bring about changes in red blood cell maturation by disturbing the red cell membrane, leading to increased RDW [5]. A strong correlation between RDW and inflammatory markers including C-reactive protein (CRP) and sedimentation rate has also been reported [6]. Increased RDW may arise from an underlying inflammatory state that is associated with adverse outcomes [6]. To the best of our knowledge, there is no study in the literature regarding the assessment of RDW in patients with CSX. Therefore, the aim of our study was to evaluate the levels of RDW in patients with CSX and to compare patients with CAD and normal control subjects.

METHODS

Patients

A total of 2,125 patients undergoing diagnostic coronary angiography between June 2010 and October 2011 in a tertiary referral centre were examined retrospectively. Of these, 245 patients were enrolled into the current study and they were divided into three groups. The CSX group consisted of 79 subjects (38 men, mean age 49.3 ± 5.2 years). The diagnosis of CSX was based on the presence of a typical exercise-induced angina pectoris associated either with a transient ischaemic ST segment depression (≥ 1 mm) during the treadmill exercise test (46 patients) or reversible perfusion defect on myocardial perfusion scintigraphy (33 patients) with angiographically normal coronary arteries in the absence of coronary artery spasm (determined by hyperventilation maneouvre). The CAD group consisted of 81 subjects (39 men, mean age 48.6 ± 5.2 years) with CAD, which was defined as ≥ 50% stenosis in at least one epicardial coronary artery. The control group consisted of 85 age and sex-matched individuals (41 men, mean age 48.1 ± 6.2 years) with anginal chest pain but a normal coronary angiography, without any sign of inducible ischaemia on myocardial perfusion scintigraphy or treadmill exercise test. The Institutional Ethics Committee approved the study protocol and the study was conducted in accordance with the Declaration of Helsinki. All subjects were evaluated with a detailed medical history, physical examination and biochemical analysis. Special emphasis was put on cardiovascular risk factors and comorbid conditions. All subjects were questioned for any cardiovascular drug use, smoking habit and alcohol consumption, and underwent transthoracic echocardiography for analysis of structural heart disease. Image acquisition was performed in the left lateral decubitus position using a Vingmed System Vivid 7 (GE Vingmed Ultrasound, Horten, Norway) with a standard two-dimensional transducer. Blood samples were analysed with respect to concentrations of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides (Beckman Coulter Syncron LX 20, Beckman Coulter, Brea, CA, USA).

Exclusion criteria were defined as refusal to participate in the study, hypertension, presence of anaemia, diabetes mellitus, left ventricular dysfunction (left ventricular ejection fraction < 50%) and hypertrophy, acute coronary syndromes (unstable angina pectoris and myocardial infarction), valvular heart disease, congenital heart disease, any abnormality in thyroid function tests, renal or hepatic dysfunction (creatinine > 1.2 mg/dL, aspartate aminotransferase and alanine transaminase more than twice the upper limit of normal, respectively), inflammatory diseases and any medication that could potentially interfere with the measurement of RDW.

Cardiac catheterisation

Coronary angiograms were performed with a femoral approach using the Judkins technique without the use of nitroglycerin, adenosine or a calcium channel blocker. All patients in the study population underwent elective coronary artery angiography using Siemens Axiom Artis DFC (Siemens Medical Solutions, Erlangen, Germany) following appropriate patient preparation. All angiograms were evaluated by two experienced physicians who were blinded to the study. Coronary angiograms were judged with regard to smooth appearance, luminal wall irregularities, epicardial local or diffuse calibre reduction and stenosis. Coronary arteries were classified as normal on the basis of visual assessment of the absence of any luminal irregularities. To exclude the possibility of coronary artery vasospasm, during coronary arteriography, patients with normal coronary artery underwent a hyperventilation test, which was performed by asking the patients to breathe quickly and deeply for five minutes.

Biochemical measurements

Blood samples were withdrawn without stasis, on the morning of the day before coronary angiography and following a fasting period of 12 hours. We analysed the blood samples of all groups after 2 h of venipuncture using an automatic blood counter (Sysmex SE 9500, Roche). In all groups, we measured RDW in a blood sample collected in tripotassium EDTA (7.2 mg) tubes. Glucose, creatinine, and lipid profile were determined by standard methods. Haematological parameters, including haemoglobin, white blood cell count, and platelet count were also analysed by standard methods.

Statistical analysis

Continuous variables were given as mean ± standard deviation and categorical variables were defined as percentages. Data was tested for normal distribution using the Kolmogorov-Smirnov test. To compare continuous variables, a one-way analysis of variance test or a Kruskal-Wallis test was used as appropriate. When a significant difference was observed between

Table 1. Baseline clinical and biochemical characteristics of the study groups

	CSX group (n = 79)	CAD group (n = 81)	Control group (n = 85)	P
Age [years]	49.3 ± 5.2	48.6 ± 5.2	48.1 ± 6.2	NS
Gender (male)	38 (48%)	39 (48%)	41 (48%)	NS
Active smokers	26.1%	25.5%	27.2%	NS
Alcohol consumption	11.1%	10.8%	10.4%	NS
BMI [kg/m^2]	26.9 ± 6.5	25.1 ± 5.8	27.2 ± 6.0	NS
Fasting glucose [mg/dL]	93 ± 9	93 ± 12	92 ± 6	NS
LDL-cholesterol [mg/dL]	117.0 ± 28.1	113.0 ± 33.3	114.7 ± 22.9	NS
HDL-cholesterol [mg/dL]	43.1± 9.1	40.9 ± 6.9	41.3 ± 7.1	NS
Triglycerides [mg/dL]	148.6 ± 56.8	150.6 ± 71.9	146.8 ± 58.8	NS
Creatinine [mg/dL]	1.02 ± 0.13	0.97 ± 0.22	0.96 ± 0.17	NS
Urea [mg/dL]	32.8 ± 5.0	34.9 ± 8.8	33.1 ± 8.2	NS

CSX — coronary syndrome X; CAD — coronary artery disease; BMI — body mass index; LDL — low density lipoprotein; HDL — high density lipoprotein; Values are mean ± SD

Table 2. Comparison of the RDW and other parameters among the study groups

	CSX group (n = 79)	CAD group (n = 81)	Control group (n = 85)	P
Haemoglobin [g/dL]	13.5 ± 1.5	13.1 ± 1.3	13.3 ± 1.1	NS
MCV [fL]	86 ± 6	85 ± 5	84 ± 7	NS
WBC [/mm^3]	6.900 ± 2.420	7.100 ± 1.890	6.800 ± 2.200	NS
Platelet [10^3/mm^3]	255 ± 59	252 ± 63	262 ± 49	NS
RDW [%]	13.8 ± 0.6	14.0 ± 0.7	13.4 ± 0.5	< 0.01

CSX — coronary syndrome X; CAD — coronary artery disease; MCV — mean corpuscular volume; WBC — white blood cell; RDW — red cell distribution width; Values are mean ± SD

the three groups post hoc (Tukey test or Mann-Whitney U) was used for the determination of difference between couples. To compare categorical variables, χ^2 test was used. Statistical significance was defined as $p < 0.05$. Statistical Package for the Social Sciences statistical software package version 15 for Windows (Statistical Package for the Social Sciences, Chicago, IL, USA) was used for statistical analyses.

RESULTS

The main characteristics of the study population are set out in Table 1. There was no statistically significant difference between the three groups with respect to age, sex, smoking, alcohol consumption, body mass index, lipid profiles, or fasting levels of glucose (Table 1). The medications were statistically similar among the groups. Haematological parameters including haemoglobin, white blood cell, and platelet count were not statistically significantly different between the three groups (Table 2). There were no statistically significant differences in RDW measurements between the CSX group and the CAD group ($p = 0.17$) (Fig. 1). However, RDW was found to be significantly higher in both the CSX and CAD groups compared to that of the control group ($p < 0.01$) (Fig. 1).

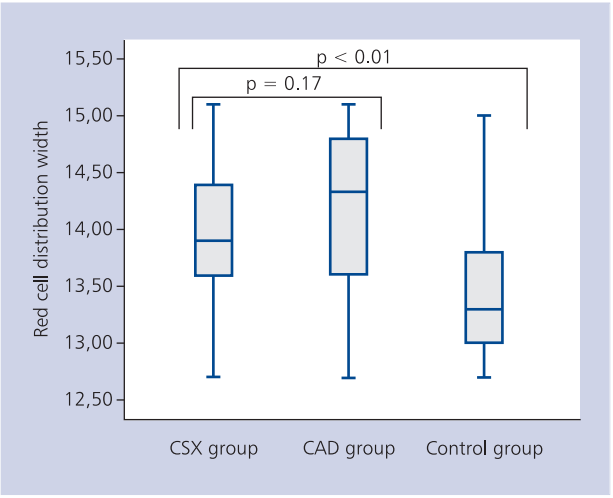

Figure 1. Red cell distribution width (RDW) levels in patients among the three groups. There were no statistically significant differences in RDW among the cardiac syndrome X (CSX) group and the coronary artery disease (CAD) group ($p = 0.17$). RDW was significantly increased in patients in both the CSX group and the CAD group, compared to the control group ($p < 0.01$)

The calculated overall intra-assay coefficient of variation was 2.2%, and the calculated overall inter-assay coefficient of variation was 2.5%.

DISCUSSION

In the present study, we have demonstrated that RDW values are significantly higher in both CSX and CAD groups, compared to those of control subjects. These results may indicate that elevated serum RDW levels may be associated with the ongoing inflammation in the pathophysiology of CSX. RDW could simply be a by-stander of the increased inflammation process, without direct pathophysiological connection with CAD or CSX.

The pathophysiology of CSX has not been clearly identified yet, although multiple abnormalities including abnormal coronary flow reserve, insulin resistance, abnormal autonomic control, enhanced sodium hydrogen exchange activity, abnormal cardiac sensitivity, and microvascular spasm have been reported [7]. Previous studies have demonstrated that elevated levels of inflammatory molecules are markers of atherosclerotic disease activity and also indicate an increased risk for the progression of atherosclerosis [8]. Inflammation has been shown to be associated with endothelial dysfunction in patients with CSX. Increased concentrations of circulating CRP concentrations correlate with vascular abnormalities in CSX patients [9, 10]. The most persuasive explanation is that the pathophysiology of CSX includes generalised endothelial dysfunction, inflammation, and progression of atherosclerosis. Abnormal coronary arteries with atheromatous plaques and intimal thickening have been observed by intravascular ultrasonographic studies in patients with CSX [11, 12]. High sensitivity-CRP and white blood cell count were higher in patients with CSX than in control subjects [13]. RDW reflects variability in the size of circulating red cells (anisocytosis) and is routinely reported by automated laboratory equipment used to perform complete blood counts. Heterogeneity of red blood cell sizes is associated with worse clinical outcomes even in the absence of anaemia and these conditions may be related to inflammation [14]. Inflammatory cytokines may cause increased heterogeneity of erythrocyte maturation and impairment [13]. In experimental studies, inflammatory cytokines have been found to suppress the maturation of erythrocytes, so immature erythrocytes enter into the circulation and increase RDW [15]. Moreover, the sympathetic system and renin–angiotensin system stimulate the release of erythropoietin which may in turn increase RDW. As a result, both inflammation and neurohumoural activation can cause increased RDW that may further contribute to the atherosclerotic process [16]. The relationship between RDW and CSX is not fully understood. Systemic factors affecting erythrocyte homeostasis, such as inflammation and oxidative stress, probably play a role in the pathogenesis of CSX. Inflammation has been found to be associated with endothelial dysfunction in patients with CSX and increased concentrations of circulating CRP correlate with vascular abnormalities in CSX patients [9, 10]. In addition, the possibility that inflammatory mechanisms might contribute to endothelial activation and dysfunction in CSX has been suggested by Tousoulis et al. [17], who found increased blood levels of VCAM-1 and ICAM-1, adhesion molecules that are synthesised by activated endothelial cells in response to inflammatory stimuli in patients with CSX. Inflammation may cause changes in red blood cell maturation by disturbing the red cell membrane, leading to increased RDW [5]. Lippi et al. [6] demonstrated a strong graded association of RDW with high sensitivity-CRP and erythrocyte sedimentation rate. Although we did not examine CRP levels, we suggest that increased RDW may denote increased inflammation in patients with CSX and in CAD patients.

Limitations of the study

The major limitation of our study was the comparatively small size of the study population. Another limitation was the possibility of any underlying coronary artery spasm in patients with CSX, which was ruled out by a hyperventilation test despite the superiority of the ergonovine test. Also, we did not analyse markers of inflammation such as CRP in the current study, although the role of inlammation has been previously reported in these patients. Finally, we did not have the opportunity to perform intravascular ultrasound in spite of the fact that intravascular ultrasound provides more precise values about the presence and distribution of atherosclerosis in vessel lumen and throughout the wall.

CONCLUSIONS

Our findings suggest that higher RDW levels are observed more frequently in patients with CSX and CAD compared to a control group. We conclude that higher RDW levels, especially in patients with CSX, may be related to increased vascular inflammation. However, large-scale prospective clinical studies are needed to prove this hypothesis.

Conflict of interest: *none declared*

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Ocena zależności między szerokością rozkładu objętości krwinek czerwonych a sercowym zespołem X

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Streszczenie

Wstęp: Sercowy zespół X (CSX) charakteryzuje się występowaniem bólów dławicowych, dodatnim wynikiem próby wysiłkowej i prawidłowym obrazem naczyń wieńcowych. Zwiększona szerokość rozkładu objętości krwinek czerwonych (RDW) może wskazywać na obecność stanu zapalnego.

Cel: Niniejsze badanie przeprowadzono w celu określenia RDW u chorych z CSX i porównania jej z wartościami tego parametru uzyskanymi u pacjentów z chorobą wieńcową (CAD) i u osób zdrowych.

Metody: Do badania włączono 245 osób (79 chorych z CSX, 81 chorych z CAD i 85 osób zdrowych stanowiących grupę kontrolną). Do grupy CSX przydzielono pacjentów z bólem dławicowym, cechami niedokrwienia w nieinwazyjnym teście wysiłkowym i prawidłowym angiogramem tętnic wieńcowych; CAD zdefiniowano jako zwężenie o ≥ 50% w co najmniej 1 tętnicy wieńcowej. Grupę kontrolną stanowili pacjenci z objawami dławicowymi, u których uzyskano prawidłowe wyniki próby wysiłkowej i nie stwierdzono zmian w koronarografii. We wszystkich trzech grupach przeprowadzono ocenę RDW.

Wyniki: Wyjściowo kliniczne i biochemiczne parametry nie różniły się między grupami. Nie zanotowano statystycznie istotnych różnic w wartościach RDW między grupami CSX i CAD ($p = 0,17$). Wartości RDW w grupach CSX i CAD były znamiennie większe niż w grupie kontrolnej ($p < 0,01$).

Wnioski: W badaniu wykazano po raz pierwszy, że RDW jest istotnie większa u chorych z CSX i CAD niż u osób zdrowych. Zależność między CSX i zwiększoną RDW sugeruje, że dysfunkcja śródbłonka może się przyczyniać nie tylko do rozwoju CAD, ale również odgrywać znaczącą rolę w etiopatogenezie CSX.

Słowa kluczowe: zespół sercowy X, szerokość rozkładu krwinek czerwonych, dysfunkcja śródbłonka

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