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Association between red blood cell distribution width and aortic valve sclerosis

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Abstract

RDW is a simple and inexpensive parameter, which reflects the degree of anisocytosis. Evidence from recent studies indicates that anisocytosis is common in most of the cardiovascular diseases and is related to their prognosis. Relation between red blood cell distribution width (RDW) levels and aortic valve sclerosis (AVSc) has not been investigated so far. Our aim is to investigate the relation between RDW and AVSc. This is a single center, retrospective cohort study. A total of 250 patients, 136 patients (mean age 65.4±7.7 years) with AVSc and 114 patients (mean age 68.5±6.8 years) as control group were enrolled. The serum RDW levels of two groups were compared. RDW levels were higher and statistically significant in patients with aortic sclerosis compared to the control group [14.1 (12.4-19 .1) vs 14.0 (11.7-17.1) p=0.044]. In multivariate regression analysis, high levels of RDW were associated with aortic sclerosis (OR=1.474, p=0.005), while hs-CRP was excluded from the analysis. To the best of our knowledge, this is the first study to demonstrate the correlation between RDW and Aortic valve sclerosis. Exploring the causes of RDW increment may contribute to our knowledge about pathogenesis of aortic sclerosis and our treatment strategies.

Keywords: Aortic valve sclerosis, Red blood cell Distribution Width (RDW), Atherosclerosis.

Introduction

Aortic valve sclerosis (AVSc) is a progressive disease characterized by calcification and thickening of aortic valve in the absence of ventricular outflow obstruction. It is common in the elderly, affecting 21 to 26 percent of adults over 65 years old and prevalence is as high as 37% over 75 years and 48% over 85 years [1-3].

AVSc is diagnosed via echocardiography by viewing focal thickening of the aortic valve, characteristically in the leaflet center with sparing of commissures. Valvular hemodynamics are in normal ranges and forward flow velocity across the valve is less than 2.5 m/s [4].

Prospective clinical studies suggest that AVSc gradually progresses to clinically significant aortic stenosis in many patients within 6 to 8 years, which is a clinical condition that carries poor prognosis and high mortality rates unless treated surgically [5-6]. The presence of AVSc has been shown to be associated with an increased risk of cardiovascular events such as angina pectoris, myocardial infarction, congestive heart failure, stroke, and cardiovascular death, although there is no demonstrable obstruction in blood flow across the aortic valve [7]. And this relation was definitely independent from the common clinical risk factors associated with both AVSc and atherosclerosis including age, blood pressure, serum lipid levels, and smoking status. Furthermore; in the Cardiovascular Health Study; after almost 5 years follow up of more than 5000 adults over the age of 65, AVSc was found to be associated with a 40% increased risk of myocardial infarction and 50% increased risk of cardiovascular death in the individuals with no preexisting diagnosis of coronary artery disease (CAD) [7].

Red blood cell distribution width (RDW) is a parameter of complete blood count (CBC) used in the differential diagnosis of anemia and is briefly the numerical measure of the variation of circulating erythrocyte volume. Besides that, RDW is a measure which is an independent and potent predictor of unfavourable outcomes in general population [8]. Highly significant associations have been described between RDW values and all-cause, non-cardiac and cardiac mortality in patients with CAD, acute and chronic heart failure, peripheral artery disease, stroke, pulmonary embolism and pulmonary arterial hypertension [8-14]. Association

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between progressive increase in RDW and unfavourable outcomes was detected in a medium sized study with patients who have undergone transcatheter aortic valve implantation (TAVI) [15]. Higher baseline (RDW ≥ 15.5%) and increasing levels of RDW by the time, was significantly associated to an increased mortality risk after TAVI procedure [15]. According to our knowledge there is no previous report concerning any relationship between AVSc and RDW levels. In this study our aim is to investigate the relation between RDW and AVSc.

Materials and Methods

This was a single center retrospective cohort study. We retrospectively collected data from 530 subjects who underwent coronary angiography for any indication at our clinic, between January 2011 and June 2013. We excluded 280 subjects based on criteria described below, and enrolled 250 subjects. Echocardiography reports were reviewed for the presence of AVSc. The study population was divided into 2 groups according to presence or absence of AVSc via echocardiographic examinations. The subjects having AVSc are consisted of 136 patients (98 females and 38 males; mean age, 68.5±6.8 years). Patients without AVSc (77 females and 37 males; mean age, 65.4±7.7 years) were assigned as control group.

Patients with complete data on the medical records were included. The exclusion criteria were: i) the presence of important CAD, ii) history of heart valve surgery or percutaneous coronary intervention (PCI), iii) congenital bicuspid aortic valve, iv) rheumatic heart disease, v) congestive heart failure, vi) chronic kidney disease, vii) vitamin B12, folate or iron deficiency or taking medication for these reasons, viii) acute or chronic inflammatory disease, ix) active infection, x) body mass index (BMI) >40 or <18.5. CAD is defined by history of previous myocardial infarction or greater than or equal to 50% narrowing of at least one coronary artery as detected by angiography, or previous revascularization to coronary arteries.

Patients' demographic data (age, sex, height, weight and BMI), angiographic findings and echocardiographic measurements, clinical history (hypertension (HT), diabetes, dyslipidemia, CAD, heart failure, smoking, medications), laboratory results on admission (hemogram parameters, RDW, high sensitivity C-reactive protein (hs-CRP), fasting glucose, lipid profile and creatinine) were all derived from electronic health records and patient files. Creatinine clearance was used as an estimate of the glomerular filtration rate of the patients and was calculated using Cockcroft-Gault formula [16].

Transthoracic echocardiography was performed using commercially available systems Vivid 7 (GE, Horten, Norway) and Philips iE33 using 2.5-3.5 MHz transducers. In our clinic, all echocardiographic measures are obtained according to recommendations of American Society of Echocardiography Guidelines [17.18]. Patients reported with poor echogenicity were excluded in this study. AVSc is defined echocardiographicaly as the presence of irregularly increased echogenicity and thickening of aortic leaflets, with no outflow obstruction, as documented by a maximum transvalvular jet velocity of < 2.5 m/sec [2. 4].

Thickening with restricted systolic opening of the valve leaflets and with peak instantaneous trans-aortic jet velocity of > 2.5 m/sec was diagnosed as aortic stenosis and excluded from the study. End-systolic left atrium diameter and end-diastolic left ventricle wall thickness were obtained from parasternal long axis, presence of mitral annular calcification and diastolic dysfunction were noted. Presence of diastolic dysfunction was evaluated according to mitral inflow velocity pattern and early filling wave deceleration time. The study was approved by local ethical committee. Given the retrospective, chart review study design, obtaining an informed consent was not deemed required.

Statistical analysis

Data were analyzed in SPSS for Windows 11.5 Program. Normality distribution of nonlinear variables was assessed by Kolmogorov Smirnov test. For comparison, Student t test, chi-square test, and Mann-Whitney U test were used as appropriate. For correlations, Pearson's and Spearman's correlation tests were used. Results are expressed as the mean ± standard deviation (SD), median (min-max) and percent. Multivariable logistic regression analyses were used to determine the independent associations of RDW and aortic sclerosis. The multivariate models adjusted for the variables that were of statistical significance in the univariate and bivariate analyses for each of the endpoints of interest. Odd's values and 95% confidence intervals for each variable are calculated. Statistical significance was assumed when the p-value was less than 0.05.

Results

Of 250 patients, 136 (54.4%) had aortic valve sclerosis. The demographic characteristics are summarized in table 1.

The AVSc and non AVSc groups were similar in most characteristics with some exceptions. AVSc group was younger (65.4 ± 7.7 vs 68.5 ± 6.8, p<0.001) and average height of AVSc group was lower than the control group (p= 0.036). Hypertension and ACE-I use was higher in the AVSc group (p<0.001). Patients were categorized according to their BMI groups (BMI 18.5 - 24.9 kg/m²: normal group, 25 - 29.9 kg/m²: overweight group and > 30 kg/m²: obese group). The distribution of BMI categories were similar among two groups. (p= 0.186).

Echocardiographic measures of patients and control groups are listed in table 2. Mean aortic valve jet velocity of patient group was 2.0 m/sec while it was 1.35 m/sec in control group. Ascending aorta diameter and presence of aortic regurgitation were similar in the two groups. Mean left ventricle ejection fraction was 60% in both groups. Mitral annular calcification, LVH (p<0.001) and diastolic dysfunction prevalence (p= 0.002) were higher in the patient group.

Laboratory findings of subjects are listed in table 3. Mean platelet volume and hemoglobin levels were lower in AVSc group (p= 0.032 and 0.020). Hs-CRP levels were higher in AVSc group (p= 0.003). RDW levels were also higher in AVSc group compared to non-AVSc group (p= 0.044). In the box plot analysis, larger range for RDW was observed in AVSc group. Number of the higher RDW levels pointed over the 50th percentile and pointed far over the 75th percentile in AVSc group were conspicuously more than those in non-AVSc group (figure 1).

Table 1. Demographic and Clinical Characteristic of Patients Groups

Variables	Control(n:114)	AVSc(n:136)	p value
Age (years)	68.5 ± 6.8	65.4 ± 7.7	<0.001
Sex			0.438
Female	77(%67.5)	98 (%72.1)	
Male	37 (%32.5)	38 (%27.9)	
Height (cm)	161.4±9.5	158.9±9.3	0.036
Weight (kg)	79.7±10.2	81.6±13.8	0.221
Body Mass Indexclass:			0.186
Normal Weight	7 (%6.1)	12 (%8.8)	
Overweight	43 (%37.7)	37 (%27.2)	
Obese	64 (%56.2)	87 (%64.0)	
Smoking	35 (%30.7)	30 (%22.1)	0.121
Hyperlipidemia	57 (%50.0)	79 (%58.1)	0.201
DiabetesMellitus	32 (%28.1)	44 (%32.6)	0.440
Hypertension	83 (%72.8)	122 (%89.7)	<0.001
Beta Blocker	39 (%34.2)	46 (%34.1)	0.982
ACE-INH	47 (%41.2)	90 (%66.2)	<0.001
Aspirin	41 (%36.0)	54 (%39.7)	0.544
Statin	31 (%27.2)	32 (%23.5)	0.506

ACE-INH: Angiotensin converting enzyme inhibitors, AVSc: aortic valve sclerosis

Table 2. Echocardiographic Findings

Variables	Control(n:114)	AVSc(n:136)	p value
Ejection Fraction	60.0 (47.0-69.0)	60.0 (45.0-65.0)	<0.001
Left Atrium Diameter	3.7 (3.2-5.0)	4.0 (3.0-5.2)	<0.001
Ascending Aorta Diameter	3.5 (2.6-4.7)	3.5 (2.9-4.2)	0742
Aortic Velocity	1.35 (0.80-1.70)	2.00 (1.80-2.30)	<0.001
Aortic Regurgitation	45 (%39.5)	51 (%37.8)	0.784
Mitral Annular Calcification	15 (%13.2)	50 (%36.8)	<0.001
Left Ventricle Hypertrophy	19 (%16.7)	78 (%54.7)	<0.001
Diastolic Dysfunction	61 (%53.5)	98 (%72.1)	0.002
Pulmonary Hypertension	30 (%26.3)	49 (%36.0)	0.100

Table 3. Laboratory Findings

Variables	Control(n:114)	AVSc(n:136)	p value
White Blood Cell	7.4 (3.8-15.2)	7.1 (3.4-12.8)	0.434
Platelet	249.5 (90.0-711.0)	244.0 (35.0-406.0)	0.591
MPV	8.2 (6.1-11.4)	8.0 (6.5-11.5)	0.032
Hemoglobin	13.7±1.1	13.3±1.0	0.020
MCV	88.4 (72.8-100.0)	87.5 (63.5-98.6)	0.170
RDW	14.0 (11.7-17.1)	14.1 (12.4-19.1)	0.044
Hs-CRP	1.44 (0.46-11.40)	2.33 (0.53-14.10)	0.003
LDL	112.0 (50.0-202.0)	121.5 (55.0-234.0)	0.029
HDL	45.0 (17.0-71.0)	45.5 (13.0-75.0)	0.395
Triglyceride	148.0 (45.0-412.0)	134.0 (30.0-422.0)	0.811
Total Cholesterol	187.0 (105.2-300.2)	200.9 (103.6-305.2)	0.035
Total Cholesterol/HDL	4.27 (2.24-15.73)	4.30 (2.42-13.71)	0.549
LDL/HDL	2.53 (0.99-11.35)	2.64 (1.27-10.31)	0.330
Urea	36.0 (23.0-97.0)	35.5 (21.0-96.0)	0.929
Creatinine	0.96 (0.58-1.42)	0.94 (0.57-1.42)	0.459
GFR	73.6 (58.5-145.5)	79.4 (48.8-168.5)	0.060

AVSc: aortic valve sclerosis, MPV: mean platelet volume, MCV: mean corpuscular volume, RDW: red blood cell disrtribution width, Hs-CRP: high sensitivity C-reactive protein, LDL: low density lipoprotein, HDL: high density lipoprotein, GFR: glomerular filtration rate

In multivariate regression analysis of the clinical and laboratory parameters which were related to AVSc, all the parameters except HT and Hs-CRP, lose their significance (table 4). When hs-CRP was put out of repeated regression analysis (table 5), as well as hypertension, higher RDW levels were statistically significantly associated with AVSc prevalence independent from other risk factors (OR: 1.474, 95% CI:1.126-1.931, p=0.005).

Table 4. Multivariate Logistic Regression Analysis of Risk Factors Associated with AVSc after Adjustment for Other Risk Factors

Variables	Odd'sratio	%95 CI		p value
		Lower Limit	Upper Limit	
Height	0.981	0.952	1.010	0.194
HT	3.001	1.447	6.226	0.003
MPV	0.703	0.518	0.956	0.054
HGB	0.808	0.622	1.050	0.111
RDW	1.266	0.930	1.723	0.146
LDL	1.007	0.999	1.015	0.061
Hs-CRP	1.147	1.024	1.284	0.017

CI: confidence interval, HT: hypertension, MPV: mean platelet volüme, HGB: hemoglobin, RDW: red blood cell disrtribution width, LDL: low density lipoprotein, Hs-CRP: high sensitivity C-reactive protein

Table 5. Multivariate Logistic Regression Analysis of Risk Factors Associated with AVSc after Adjustment for Other Risk Factors (Hs-CRP Left out of the Model)

Variables	Odd'sratio	%95 CI		p value
		Lower Limit	Upper Limit	
Height	0.979	0.951	1.008	0.150
HT	3.161	1.529	6.532	0.002
MPV	0.752	0.560	1.009	0.057
HGB	0.836	0.648	1.080	0.170
RDW	1.474	1.126	1.931	0.005
LDL	1.007	1.000	1.015	0.055

CI: confidence interval, HT: hypertension, MPV: mean platelet volume, HGB: hemoglobin, RDW: red blood cell disrtribution width, LDL: low density lipoprotein

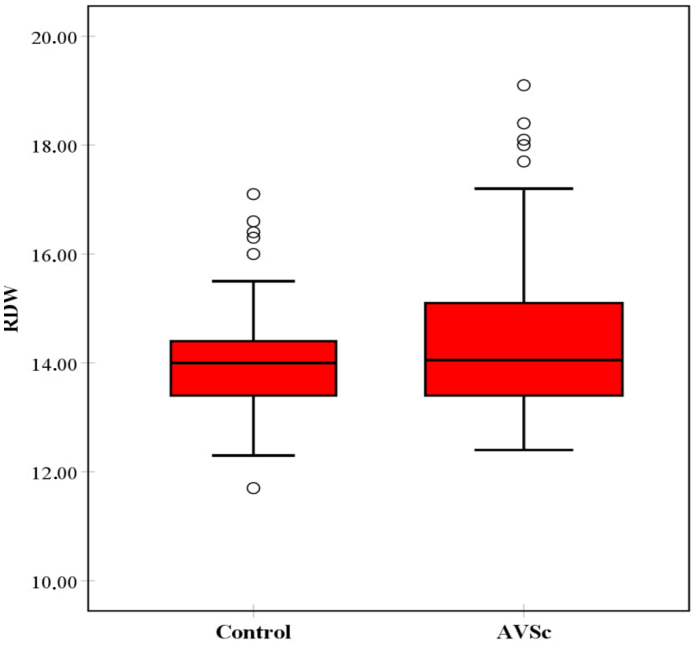

Figure 1. Box plots of the RDW Levels in AVSc and Control Groups. Means and interquartile ranges are depicted. Whiskers represent minimum and maximum values

Discussion

Our results demonstrated a positive relation between RDW and AVSc. According to our best knowledge this is the first study investigating the relationship between RDW and AVSc. In this study we compared serum RDW levels of AVSc patients with patients with no aortic valve disease or rheumatoid valvular heart disease. Our results revealed a positive association between higher RDW levels and AVSc such as similar association demonstrated between RDW and atherosclerotic heart disease in previous studies.

Aortic valve sclerosis is focal thickening and calcification of the aortic valve without obstruction in ventricular outflow and highly frequent in elderly. At seven years mean follow up, progression to severe aortic stenosis is reported up to 6% of cases. Sclerotic lesions of the aortic valve and atherosclerosis have histopathological and epidemiological similarities. Endothelial damage caused by mechanical stress and/or other cardiovascular risk factors are liable factors for initiation of the pathophysiologic processes. Association between AVSc and ageing, HT, HL, DM and smoking is revealed in some epidemiologic studies [19-21]. Moreover, AVSc is related to a 50% increase in cardiovascular mortality and MI risk in population over the age of 65 [7]. It has been demonstrated that AVSc is significantly associated with

coronary atherosclerosis, carotid and peripheral arterial diseases. Sclerotic lesions of aortic valve have many histopathological and epidemiological similarities to atherosclerosis. The results obtained from studies investigating the pathogenesis of calcific aortic valve disease support that it is a chronic progressive disease with chronic inflammation, lipoprotein deposition and leaflet calcification. Moreover numerous studies are under way to elicit physiopathology of this progressive disease.

RDW is calculated by dividing the standard deviation of erythrocytes volume by MCV and the result is expressed as a percentage. Elevated RDW levels indicate the increase of heterogeneity and variation in size of Red Blood Cells which is conventionally referred as anisocytosis. Recent studies have demonstrated that higher RDW levels, even within the normal reference ranges, were associated with unfavorable clinical outcomes in patients with CAD, heart failure, pulmonary hypertension, diabetes mellitus, and stroke independent of hemoglobin values [8-14]. While the precise pathophysiological mechanism of this relationship is not fully clarified, ageing, chronic inflammation, malnutrition, and anemia are liable underlying factors. Once that RDW is a widely available measure as a parameter of the complete blood count and this implies no extra charge, in contrast to other novel markers, the importance of RDW in diagnosis and prognostic estimation of cardiovascular diseases should not be overlooked.

Our results demonstrate a positive relationship between higher RDW levels and AVSc presence. In our study, when demographic characteristics of the subjects were compared, AVSc group was younger than non AVSc group (68.5±6.8 vs 65.4±7.7 and $p<0.001$). AVSc is a clinical condition that increases with age. This conflicting finding could be as a result of our small patient population and also might be explained by clinical conditions like hypertension and inflammation which have stronger impacts on AVSc pathogenesis than the degenerative process related to ageing. Sverdlov et al found that patients with AVSc had higher BMI levels compared to control group (28.5±5.1 vs 26.7±4.2, p 0.019) in a study with 253 patients [21] unlike our study, in which there was not a significant difference in BMIs of two groups. Nevertheless both studies are limited by small sample sizes and it will be more reasonable to set any association between BMI and AVSc, after demographic studies with larger patient populations are conducted. Compatible with the previous studies, mean height of AVSc subjects was shorter than the control group in this study [24]. Mechanism of the inverse relation between height and AVSc is not clear, besides this, it is known that, hemodynamic and shear stress effects related to the length of the peripheral vasculature result in endothelial damage, and are likely to initiate early aortic lesions.

Mitral annular calcification (MAC) and AVSc have similar risk factors and both are accepted as atherosclerosis risk factors. In our study, MAC and AVSc were associated independent from other factors ($p<0.001$). Among the other atherosclerosis risk factors, hypertension and high hs-CRP levels were the only clinical conditions which were significantly associated with AVSc ($p<0.001$).

Relationship between HT and AVSc was shown in previous studies [19]. Jithesh, et al. observed that inflammatory markers like hs-CRP and RDW levels were higher in the hypertensive patients compared to healthy ones [22]. So, it is not surprising that in our study, in multivariate analysis, higher RDW values were associated with AVSc independent of all other risk factors except hs-CRP (p 0.005) and HT. Hs-CRP is one of the most sensitive indicators of inflammation. Role of inflammation and oxidative stress on pathogenesis of AVSc is well known. Relation between CRP and calcific aortic valve disease was documented in previous studies [23-25]. In a study designed by Imai et al, baseline CRP levels of patients with severe Aortic Stenosis were significantly higher than of patients with mild or moderate Aortic stenosis [23]. Sanchez et al revealed that lower levels of CRP were associated with slower progression rates of the aortic valve disease [25]. Both results give rise to make inference about the predictive value of CRP for the prognosis of aortic stenosis. In our study mean hs-CRP level was higher in the AVSc group in a statistically significant manner. The relation between RDW and AVSc lost its significance when hs-CRP was involved in regression analysis, thus supports power of the role of inflammation in AVSc pathogenesis. Apart from our study, studies that shows high RDW and high CRP level association in cardiovascular diseases are also present in the literature [26,27] . Moreover; RDW has been a strong predictor of all-cause mortality in population cohorts. Veeranna et al revealed RDW but not hs-CRP was associated with coronary heart disease mortality independent of traditional risk factors in an 8513 patients cohort with no preexisting CVD [28]. The results of these studies support that the pathophysiologic mechanisms involved in the increase of RDW may affect the outcome in patients with chronic cardiovascular diseases.

The precise mechanisms underlying the relation between RDW and AVSc remain unknown in this stage. One suggested hypothesis is that factors changing erythrocyte homeostasis like inflammation and oxidative stress may play a role. It is widely accepted that inflammation causes secondary ineffective erythropoiesis. Inflammation disrupts iron metabolism and suppresses response of erythroblasts to erythropoietin, so impairs erythroid maturation and accelerates reticulocyte passage into the peripheral circulation, and after all, results in increased RDW. Lippi et al showed a correlation between RDW levels with hs-CRP and Erythrocyte Sedimentation Rate by conducting a large-scale cohort study, suggesting that RDW can be used as an inflammatory marker [27]. Circulating neurohumoral mediators also induce erythropoiesis and result in higher RDW values. Sympathetic system and renin-angiotensin system can also increase RDW levels by stimulating Erythropoietin secretion [29]. Chronic inflammation and neurohumoral activation can cause both increase in RDW levels and sclerocalcific changes of aortic valve. Thus, it seems to be more rational to consider RDW and AVSc as the epiphenomenon of the same underlying biological and metabolic pathologies rather than trying to establish a causal relationship. The anisocytosis researchs may provide a better understanding of pathophysiology.

Limitations

There are some weaknesses of our study. Since it is a retrospective study, some positive or negative factors might be overlooked, such as; markers of inflammation other than hs-CRP that may affect RDW were not involved, so their relationship could not be evaluated. Another major limitation of this study was the small size of the cohort. Additionally, in this study, only subjects with AVSc - recognized as first stage of calcific aortic valve disease -

are conducted.

Conclusion

Our results are consistent with the hypothesis that RDW levels are directly related to sclerotic lesions of the aortic valve. While HT and hs-CRP seem to remain as the pivotal factors in relation with AVSc, the direct relation between RDW and AVSc should not be ignored. It wouldn't be inaccurate to state that RDW is a feasible tool that may give a suspicion about AVSc, since it is a standard parameter of widely used CBC studies. Further large-scale studies with different stages of the aortic disease and controlled for other inflammatory parameters are needed to support the association between higher RDW levels and AVSc.

Competing interests
We declare that we have no conflict of interest.

Financial Disclosure
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Ethical approval
The study was approved by local ethical committee.

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