Whole Blood Viscosity Estimated by de Simone's Formula in Patients with Aortic Stenosis

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Abstract

Objectives. Whole blood viscosity (WBV) may promote endothelial shear stress, endothelial inflammation, and vascular remodeling, and can accelerate the atherosclerotic process. We aimed to evaluate the relationship between WBV and Aortic Stenosis (AS). Methods. The study population included 209 participants of which 49 patients with severe AS, 98 patients with mild-to-moderate AS and 62 patients as control. The WBV calculated with a formula from Hct and total plasma protein (TP) for wall shear stress. WBV was cal-culated for both low shear rate (LSR) (0.5 s–1) and high shear rate (HSR) (208 s–1) from Hct and TP protein concentration using a validated formula. Results. WBV values were significantly higher for HSR ($p = 0.001$) and for LSR ($p=0.002$) in severe aortic stenosis group than mild-to-moderate aortic stenosis group. HSR and LSR were correlated with mean systolic transaortic gradient ($p<0.001$ and $p<0.001$, respectively). WBV for both LSR and HSR were found to be independent predictors for the aortic stenosis severity ($\beta=0.265$;$p=0.034$ and $\beta=0.237$;$p=0.049$, respectively). Hypertension independently associated with the aortic stenosis severity ($p<0.05$). Conclusion. We found a significant relationship between WBV and AS

INTRODUCTION

Aortic stenosis (AS) is one of the most common valvular diseases in the western world.[1] Aortic stenosis is a progressive chronic disease such as atherosclerosis and is characterized by mechanical stress, lipid accumulation, endothelial damage, calcification and as a result ,inflammation.[2-4] As a result of wall stress, endothelial damage occurs and lipid and inflammatory cells infiltrate the valve. [5]The center of the valve cusp has the greatest mechanical stress and is more frequently involved than the commissures.

Increased blood viscosity can be one plausible biological mechanism through which increases in haematocrit and fibrinogen may promote ischaemic heart disease and stroke.[6] Hematocrit, total plasma protein, erythrocyte aggregation, and erythrocyte deformability can affect whole blood viscosity (WBV).[7] Recent studies have shown that elevated WBV may promote endothelial shear stress, endothelial inflammation, and vascular remodeling, and can accelerate the atherosclerotic process.[8] The inflammatory, calcific and fibrotic pathogenesis in both atherosclerosis and AS are similar. Thus, we aimed to evaluate the relationship between whole blood viscosity and AS.

METHODS

Between June 2015 and July 2018, a total of 147 consecutive patients with AS and 62 healthy subjects were enrolled into the study. The patients with AS were divided into two groups as mild-to-moderate (n=98) and severe AS (n=49). All participants were evaluated by echocardiography. Patients with severe valvular heart disease other than AS, history of rheumatic fever, bicuspid and prosthetic valves, decompensated heart failure, malignancy, renal or hepatic dysfunction, acute or chronic infection or inflammatory condition, hematologic diseases including anemia, chronic obstructive pulmonary disease were excluded. Baseline

demographic and clinical characteristics were reviewed. Hypertension was defined as documentation of a systolic blood pressure of [?]140 mmHg and/or a diastolic blood pressure of [?]90 mmHg in at least two measurements or active use of any antihypertensive agent. Diabetes mellitus was diagnosed as a fasting plasma glucose level over 126 mg/dl or glucose level over 200 mg/dl at any measurement or active use of an antidiabetic agent. The study was in compliance with the principles outlined in the Declaration of Helsinki and approved by local ethics committe.

Echocardiography

Echocardiographic evaluation was performed by using a VIVID 7 Dimension Cardiovascular Ultrasound System (Vingmed-General Electric, Horten, Norway) with a 3.5 MHz transducer. Echocardiographic examination was performed in the left lateral decubitus position. Parasternal long- and short-axis views and apical views were used as standart imaging windows. Ejection fraction was calculated by using modified Simpson method. Septal wall thickness, left atrial diameter, end systolic and end diastolic dimensions were measured from parasternal long-axis view. Aortic jet velocity was calculated by Doppler echocardiography. Aortic stenosis was defined as mild if mean systolic transaortic gradient is less than 25 mmHg or jet velocity is less than 3.0 m/s, moderate if mean systolic transaortic gradient is between 25 mmHg and 40 mmHg or jet velocity is between 3.0 m/s and 4.0 m/s and severe if mean systolic transaortic gradient is greater than 40 mmHg or jet velocity is greater than 4.0 m/s [9]. All echocardiographic examinations were performed by an experienced cardiologist.

Laboratory Measurements

Blood samples were obtained from the antecubital vein after a fasting period of 12 hours. Coulter Counter LH Series (Beckman coulter Inc, Hialeah, Florida) was used for complete blood count (CBC) analysis. All hematological parameters were evaluated using an automated chemistry analyzer (Abbott Aeroset, USA) using commercially available kits (Abbott, USA).

Calculation of whole blood viscosity

The WBV calculated with a formula from Hct and total plasma protein (TP) for wall shear stress. WBV was calculated for both low shear rate (LSR) (0.5 s^{-1}) and high shear rate(HSR) (208 s^{-1}) from Hct and TP protein concentration using a validated formula.[10]

HSR: WBV (208 s^{-1}) = (0.12 × Hct) + 0.17 (TP – 2.07).

LSR: WBV (0.5 s^{-1}) = (1.89 × Hct) + 3.76 (TP – 78.42).

Statistical Analysis

The SPSS 21.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous variables were shown as mean ± standard deviation or median (interquartile range) and categorical variables were given as number and percentages. In order to test normality of distribution, Kolmogorov-Smirnov test was used. One-Way ANOVA test was used to show the differences between the groups in continuous numeric parameters with normal distribution. Tukey's test was used for the post-hoc analysis. Kruskal-Wallis test was used for comparison of more than two groups without normally distributed and if there was statistical signifigancy, the Mann-Whitney U test was used for nonpaired groups. Differences between treatment groups for the categorical variables were analyzed using the chi-square test. Spearman correlation analysis were performed to examine the relationship between WBV values and mean systolic transaortic gradient. Linear regression analysis was used to examine the association between AS severity and other variables. Variables with a p value of < 0.1 in univariate logistic regression analysis were included in a multivariate linear regression model. A 2-tailed $P < 0.05$ was considered significant.

RESULTS

The baseline characteristics and laboratory findings of the study groups are given in Table 1. The study groups were similar in regard to various baseline parameters except for age, hypertension, coronary artery

disease, albumin, total cholesterol level, lower high-density lipoprotein cholesterol level, hemoglobin level, hematocrit ($p < 0.05$). Also, left ventricular ejection fraction, left ventricle mass, left ventricular end diastolic and end sistolic diameter, left atrial diameter and interventricular septum thickness were significantly different between study groups ($p<0.05$).

WBV values were significantly higher for HSR (17.3 ± 1.0 vs. 17.2 ± 1.1, $p = 0.001$) and for LSR (62.0 ± 18.4 vs. 61.6 ± 23.2, $p=0.002$) in severe aortic stenosis group than mild-to-moderate aortic stenosis group. Also, HSR and LSR were correlated with mean systolic transaortic gradient ($r=0.449$, $p<0.001$ and $r=0.428$, $p<0.001$, respectively).

WBV for both LSR and HSR were found to be independent predictors for the aortic stenosis severity ($\beta=0.265$;$p=0.034$ and $\beta=0.237$;$p=0.049$, respectively). Also, hypertension independently associated with the aortic stenosis severity ($p<0.05$) (Table 2).

DISCUSSION

In this trial, we found a significant and independent relationship between WBV and AS. To the best of our knowledge, this is the first study to determine the association between WBV and AS. We found that WBV was significantly higher in patients with severe AS than control subjects and patients with mild-to-moderate AS. Also, WBV had significant positive correlation with maximum, mean aortic gradient. Besides, we found that WBV was also independently associated with the presence of AS.

Lipid accumulation, calcification and inflammation is related with progressive aortic stenosis.[11,12]Valvular endothelial deterioration consists on aortic valve due mechanical stress, followed by emigration of inflammatory cells such as T-lymphocytes and macrophages and deposition of low-density lipoprotein, lipoprotein A, with oxidation of lipoprotein[13-15].

Several inflammator mediators and complex such as vascular endothelial growth factor-A (VEGF-A) and transforming growth factor-β (TGF-β), interleukins (IL-1b, IL-6, IL-8), tumor necrosis factor-α (TNF-α) have been reported in AS [16]. These mediators can stimulate fibrosis and participate the progression of AS [17].

Aortic stenosis and atherosclerosis have similar risk factors such as diabetes, lipids, hypertension, and renal failure[18,19]. Inflammation plays an active role both in progression of atherosclerosis[20] and AS[13]. Increased blood viscosity can be a decisive of coronary artery disease, either indirectly because of its relation with hypertension, a major coronary risk factor, or because of its amplification of the resistance produced by a given degree of coronary artery narrowing, with adverse effects on clinical manifestations of coronary disease and on maximal myocardial oxygen delivery.[10]

WBV is an important prognostic factor of endothelial shear stress. WBV plays a substantial role in the formation and progression of the atherosclerotic process not only alone and by also interacting other certain cardiovascular risk factors such as hypertension and diabetes mellitus[10] The association of WBV have been arised in cardiovascular diseases. Several studies showed that WBV estimated by the de Simone formula was found to be associated with occurrence of MAC, and coronary collateral circulation in patients with chronic total occlusion, ST-elevation myocardial infarction, and coronary slow-flow phenomenon.[21-23]Sercelik et al. demonstrated that WBV was independently associated with aortic valve sclerosis in 209 patients.[24] They suggest that higher WBV can be an indicator of AVS due to increased AV resistance.[24]

In light of these studies, WBV is associated with inflammation and atherosclerotic process, there can be a role for WBV in patients with AS. In our study, we demonstrated that WBV was significantly higher in patients with AS. It can be suggested that shear stress may have an important role in the process of AS.

There are some limitations of this study. First, it was a retrospective study. We could not evaluate the association between admission WBV and clinical conditions such as symptoms and the New York Heart Association (NYHA) Functional Classification of the patients. Further prospective studies are needed to clarify if WBV predicts outcome in patients with AS. In addition, we did not evaluate other cytokines or

inflammatory markers such as fibrinogen. All biochemical data were based on a single measurement, and direct measurements of blood viscosity with a viscometer were not done.

CONCLUSION

In conclusion, we found a significant relationship between WBV and AS. WBV was an independent predictor of AS. Besides, WBV was correlated inflammatory markers such as NLR and CRP.

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