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Research Article

Whole Blood Viscosity as a Neglected Parameter May Predict Higher Coronary Atherosclerotic Burden in Patients with First Diagnosis of Acute Coronary Syndrome

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Abstract

Objective: Blood viscosity is associated with the risk of cardiovascular events and plays a role in the pathophysiology of atherosclerosis [1,2]. Endothelial shear stress (ESS) have been proposed as novel risk markers for acute coronary syndromes [3]. SYNTAX score, an angiographic scoring system, defines the grade and complexity of coronary artery disease (CAD). We aimed to evaluate the relationship between whole blood viscosity and severity of CAD according to the SYNTAX score in patients with first diagnosis of acute coronary syndrome.

Methods: A total of 356 subjects were included into the study, of whom 236 underwent coronary angiography (CA) with the first diagnosis of Acute Coronary Syndrome (ACS) and 120 had normal coronary arteries detected in CA. Patients with ACS were divided into 2 groups: low SYNTAX score (<23) (129 patients) and high SYNTAX score (≥ 23) (107 patients).

Results: The ACS patients with a high SYNTAX score had a higher WBC values for both LSR and HSR (58 ± 17.1 and 17.2 ± 1.2, respectively) compared to the ACS patients with a low SYNTAX score 48.2 ± 15.5 and 16.7 ± 1.1, respectively) and the control group (35.2 ± 13.7 and 16.0 ± 1.1, respectively). There was also a positive correlation between SYNTAX score and WBV for both LSR ($\beta = 0.333$, $p < 0.001$) and HSR ($\beta = 0.347$, $p < 0.001$). Higher values of WBV for both LSR and HSR (OR = 1.003; 95% CI: 0.997 - 1.017; $p < 0.001$ and OR = 1.517; 95% CI: 1.431 - 1.923; $p < 0.001$, respectively) were independent predictor for a high SYNTAX score in the ACS patients after multiple linear regression analysis.

Conclusion: WBV values for both LSR and HSR were higher in the high SYNTAX group than in the low SYNTAX group in patients with ACS. A higher WBV indicating increased ESS could have a role in the pathogenesis of atherosclerotic burden in patients with first diagnosis of ACS.

Keywords: *Acute Coronary Syndrome; Whole Blood Viscosity; SYNTAX Score*

Introduction

Blood viscosity is associated with the risk of cardiovascular events and plays a role in the pathophysiology of atherosclerosis [1,2]. Endothelial shear stress (ESS) and its determinants have been assumed as novel risk markers for acute coronary syndromes [3]. Hemorheologic alterations, which increase shear stress, can trigger rupture of the atherosclerotic plaque, thrombus aggregation and lead to deterioration in microvascular circulation [3-5].

As a primary indicator of shear stress, blood viscosity has not been utilized as a common practice in the cardiovascular evaluation despite having close relationship with multiple cardiovascular diseases [6]. In addition, hyperviscosity has similar important pathophysiologic effects on cardiovascular system with conventional risk factors such as hypertension, hypercholesterolemia, diabetes mellitus, male gender, cigarette smoking [7].

Measuring WBV as a routine may be too difficult because of not having standardized methods, the must of sophisticated devices and rare research data [8]. But, a validated equation can be used to calculate WBV by using hematocrit (HCT) and total plasma protein levels (TP) for low and high shear rate [9]. Calculating an estimated value about WBV with this basic formula, can provide clinicians a new tool for bedside evaluation of patients. According to De Simone., *et al.* [9,20], WBV could be extrapolated from its major determinants, which are red blood cells and total plasma protein. The first study extrapolating viscometer derived whole blood viscosity from total protein and hematocrit level. These extrapolation formulas have been used in formerly performed studies in different populations but have not been studied at firstly diagnosed ACS patients [10-15].

SYNTAX (The anatomical synergy between percutaneous coronary intervention (PCI) with taxus and cardiac surgery) score, which is an angiographic scoring system, represents the grade and complexity of coronary artery disease (CAD). Various publications showed that patients with a relatively high SYNTAX score have poor outcomes and that the score independently predicts major advanced cardiovascular events (MACE) for percutaneous coronary intervention (PCI) [16].

Aim of the Study

This study aimed to evaluate the relationship between WBV and the severity of CAD according to the SYNTAX score in patients with first diagnosis of ACS.

Methods

Patient selection and study design

Consecutive patients with first-time ACS who underwent urgent coronary angiography (CA) and 120 randomly chosen patients with normal coronary artery detected in CA in the Department of Cardiology in the Turkiye Yuksek Ihtisas Education and Research Hospital were enrolled into the study. For this analysis, patients with known CAD (history of previous myocardial infarction, prior stent placement, or bypass grafting) were excluded in order to have a more homogeneous study group. The study protocol was reviewed and approved by the institutional ethics committee in accordance with the Declaration of Helsinki. All patients gave informed consent.

469 consecutive patients admitted to the emergency department with the diagnosis of ACS from November 2015 to December 2016 were included into the study. Of these, 236 patients (59%) had an admission for ACS as a first time. Among those cases, 213 patients with previous CAD and coronary angiography and 20 patients with only medical treatment without diagnostic coronary angiography were excluded from the study. Patients with previous coronary artery bypass grafting (CABG) were also excluded from the study, since SYNTAX score is suitable only for patients with native coronary artery lesions.

Patients were stratified into 3 groups: low SYNTAX score (< 23), high SYNTAX score (≥23) and patient with normal CA.

Patients with available demographic data, procedural details and CAD severity were analyzed. Other risk factors for CAD and demographic parameters (age, gender and body mass index (BMI) at the time of enrollment into the study were evaluated by history-taking and physical examination results. The CAD risk factor profile comprised of history of cigarette smoking, dyslipidemia (low-density lipoprotein cholesterol ≥70 mg/dL; 1.8 mmol/L), family history of CAD (first degree relatives before the age of 55 years in men and 65 years in women) and hypertension (systolic blood pressure≥140 mm Hg, diastolic blood pressure ≥90 mm Hg and/or on antihypertensive treatment).

Peripheral venous blood was drawn from an antecubital vein on admission and on the first morning after admission. Admission glucose level, fasting blood glucose, baseline creatinine lipid profile, troponin I, C-reactive protein and other biochemical parameters were measured using Standard methods. WBV was calculated with a validated formula for both low shear rate (LSR) (0.5 sec-1) and high-shear rate (HSR) (208 sec-1) by using hematocrit and total plasma protein concentration [9].

High shear rate: WBV (208 sec-1) = (0.12× HCT) + 0.17 (TP -2.07)

Low shear rate: WBV (0.5 sec-1) = (1.89× HCT) + 3.76 (TP -78.42)

Patients with normal CA were selected from those to whom was performed CA as a result of a positive stress test (exercise stress test or myocardial perfusion scintigraphy test) or clinically high suspicion of CAD (e.g. patients with strong family history of CAD or early death with or without associated risk factors and patients with unexplained chest pain after careful clinical and laboratory evaluation if there was strong suspicion of ischemic heart disease). Normal coronary arteries were defined as no visible disease or luminal irregularity (less than 50%)by judging visually on CA.

Acute coronary syndrome included non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). After a diagnosis of ACS, coronary angiography was performed on the same day using standard Judkins techniques or radial approach. During cardiac catheterization, nitroglycerin was used in all patients suspected of having coronary spasm. Each coronary artery was displayed on at least 2 different planes. All the coronary angiograms were recorded on compact disks (DICOM format). Percutaneous coronary intervention (PCI) procedures were performed using standard techniques. Coronary artery disease was defined on the quantitative coronary angiography as a coronary stenosis ≥ 50% luminal diameter narrowing. According to baseline CA, the SYNTAX score was calculated for all patients by two experienced interventional cardiologists unaware of the patients' clinical or laboratory results. SYNTAX score was determined for all coronary lesions with > 50% diameter stenosis in a vessel > 1.5 mm based on SYNTAX score calculator 2.1 (www.syntaxscore.com). Patients with ACS were divided into 2 groups: low SYNTAX score (< 23) (129 patients) and high SYNTAX score (≥ 23) (107 patients).

Reproducibility

To define intra-observer variability, 15 patients were randomly selected from the study group. Measurements were repeated under the same basal conditions and reproducibility of the SYNTAX score by CA was assessed according to the coefficient of variation between measurements.

Intra-observer variability was 6.1% for SYNTAX score.

Statistical Analysis

Data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, Il, USA). Continuous variables were reported as mean ± SD and categorical variables were reported as percentages and counts. The Student's t-test was used for comparisons of normally distributed variables and the Mann-Whitney U test was used for nonnormally distributed variables if 2 groups existed. Oneway analysis of variance was used to compare normally distributed variables between 3 groups. Tukey's test was used for post-hoc analysis. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate.

Pearson's correlation coefficients were used to assess the strength of relationship between continuous variables and Spearman correlation analysis was performed for non-continuous and categorical variables. Major clinical factors and predictors of SYNTAX score ≥ 23 as displayed in table 1 were used in univariate and multiple linear regression analysis. In all analyses, a p value of < 0.05 was considered to be statistically significant and the confidence interval was 95%.

Results

Baseline clinical characteristics and laboratory parameters of the study population are shown in table 1. There was no significant difference in the terms of the sex, hyperlipidemia, diabetes mellitus, hypertension, ACS subtype and smoking between the groups (Table 1).

The ACS patients with a high SYNTAX score (score ≥23) had higher WBV values for both LSR and HSR (58 ± 17.1 and 17.2 ± 1.2, respectively) compared to the ACS patients with a low SYNTAX score (score < 23) (48.2 ± 15.5 and 16.7 ± 1.1, respectively) and the control group (35.2 ± 13.7and 16.0 ± 1.1, respectively). WBV values were statistically significantly different between all groups ($p < 0.001$). In addition, there were significant differences between the high SYNTAX score group and control group ($p < 0.001$ for both LSR and HSR), low SYNTAX score group and control group ($p < 0.001$ for both LSR and HSR) and high SYNTAX score group and low SYNTAX score group ($p < 0.004$ for LSR and $p < 0.003$ for HSR). As demonstrated in table 3, correlation analysis demonstrated a significant positive correlation between the SYNTAX score and WBV for both LSR ($\beta = 0.333$, $p < 0.001$) and HSR ($\beta = 0.347$, $p < 0.001$).

We performed univariate and multiple linear regression analyses for the predictors of SYNTAX ≥ 23 score as demonstrated in table 1 and table 2. In univariate regression analysis, age [odds ratio (OR) = 1.032; 95% confidence interval (CI): 1.012 - 1.052; $p < 0.001$], BMI (OR = 1.114; 95% CI: 1.041 - 1.191; $p = 0.050$), Diabetes Mellitus (OR = 1.721; 95% CI: 1.057 - 2.801; $p = 0.029$), glucose (OR = 1.007; 95% CI: 1.004 - 1.011; $p = 0.043$), Hematocrit (OR = 1.107; 95% CI: 1.056 - 1.160; $p = 0.031$), CRP (OR = 1.014; 95% CI: 1.004 - 1.024; $p = 0.049$) and total protein (OR = 1.794; 95% CI: 1.162 - 2.271; $p = 0.020$) were associated with a higher SYNTAX score. Higher values of WBV for both LSR and HSR (OR = 1.003; 95% CI: 0.997 - 1.017; $p < 0.001$ and OR = 1.517; 95% CI: 1.431 - 1.923; $p < 0.001$, respectively) were independent predictor for a high SYNTAX score in the ACS patients after multiple linear regression analysis.

Variables	ACS SYNTAX score ≥23 (n = 107)	ACS SYNTAX score <23 (n = 129)	NCA (n = 120)	P value*	P value$^{\alpha}$	P value$^{\beta}$	P value$^{\gamma}$
Age, years	61.6 ± 11.7	57.9 ± 12.0	56.2 ± 11.7	<0.001	0.020	<0.001	0.246
BMI, kg/m^2	27.7 ± 3.5	27.4 ± 3.6	25.4 ± 2.3	<0.001	0.588	<0.001	<0.001
Male, n (%)	79 (73.8)	64 (72.9)	75 (62.5)	0.110	-	-	-
Hyperlipidemia, n (%)	24 (22.4)	23(17.8)	19 (15.8)	0.389			
Diabetes Mellitus, n (%)	39 (36.4)	39 (30.5)	23 (19.2)	0.013	0.332	0.004	0.040
Hypertension, n (%)	44 (41.1)	57 (44.2)	40 (33.3)	0.201	0.637	0.227	0.080
Smoking, n (%)	41 (38.3)	59 (45.7)	41 (34.2)	0.167	-	-	-
Multi-vessel disease, n (%)	41 (52.6)	16 (14)	0 (0)	-	<0.001	-	-
ACS subtype				-	-		
NSTEMI (%)	57 (47.2)	49 (45.8)	0 (0)		0.805		
STEMI (%)	58 (54.2)	72 (55.8)	0 (0)		0.805	-	-
Stent implantation, n (%)	68 (63.6)	114 (88.4)	0 (0)	-	<0.001	-	-
Decision for CABG, n (%)	38(35.5)	12 (9.3)	0 (0)	-	<0.001	-	-

Glucose, mg/dL	155.21 ± 84.9	144.8 ± 67.4	98.8 ± 33.3	<0.001	0.319	<0.001	<0.001
Creatinine, mg/dL	1.97 ± 8.3	1.0 ± 0.34	0.99 ± 0.12	0.213	-	-	-
Total cholesterol, mg/dL	203 ± 42.0	189.5 ± 50	165.8 ± 43.1	<0.001	0.030	<0.001	<0.001
LDL-C, mg/dL	131.7 ± 35.4	123.5 ± 35.0	100.2 ± 30.1	<0.001	0.120	<0.001	<0.001
HDL-C, mg/dL	45.1 ± 10.7	43.4 ± 10.1	45 ± 13.7	0.306	-	-	-
Hemoglobin, g/dL	15.2 ± 1.8	14.8 ± 1.6	14.4 ± 1.3	0.71		-	-
Hematocrit (%)	45.7 ± 5.5	44.4 ± 4.7	41.5 ± 4.9	<0.001	0.06	<0.001	0.030
WBC,10^3/mm^3	11.2 ± 2.7	11.1 ± 2.9	10.3 ± 2.5	0.117	-	-	-
Platelet, 10^3/mm^3	236.7 ± 70.9	238.1 ± 61.4	238.2 ± 66.5	0.982	-	-	-
Neutrophil, 10^3/mm^3	8.27 ± 3.5	8.45 ± 5.5	7.8 ± 6.6	0.690	-	-	-
Lymphocyte,10^3/mm^3	2.1 ± 1.2	2.5 ± 1.3	2.4 ± 1.1	0.035	0.017	0.043	0.528
CRP,mg/L	19.1 (44)	11 (21)	4 (9)	<0.001	0.089	<0.001	0.001
LVEF, %	44.6 ± 10.1	48.9 ± 8.9	60.6 ± 6.9	-	0.001	-	-
Total protein (g/l)	70.8 ± 7	68.9 ± 5.0	66.9 ±5.1	<0.001	0.014	<0.001	0.002
Peak troponin-T, ng/mL	5.3 (14.5)	4.6 (12.3)	-	0.744	-	-	-
SYNTAX score	29.1 ± 5.3	15.1± 5.1	0 ± 0	-	<0.001		
WBV at LSR	58 ± 17.1	48.2 ± 15.5	35.2 ± 13.7	<0.001	0.004	<0.001	<0.001
WBV at HSR	17.2 ± 1.2	16.7 ± 1.1	16.0 ± 1.1	<0.001	0.003	<0.001	<0.001

Table 1: *Baseline characteristics and laboratory parameters of the study groups (n = 356).*

*Data are given as mean ± SD, n (%) or median (lower-upper limit). BMI: Body Mass Index; CABG: Coronary Artery Bypass Grafting; CRP: C-Reactive Protein; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; LVEF: Left Ventricular Ejection Fraction; NCA: Normal Coronary Artery; NSTEMI: Non ST-Segment Elevation Myocardial Infarction; MI: Myocardial Infarction; STEMI: ST-Segment Elevation Myocardial Infarction; SYNTAX: The Anatomical Synergy between Percutaneous Coronary Intervention (PCI) with Taxus and Cardiac Surgery; WBC: White Blood Cell; WBV at HSR: Whole Blood Viscosity at High Shear Rate; WBV at LSR: Whole Blood Viscosity at Low Shear Rate. * p value between all groups.*

$^{\alpha}$ p value between NSTEMI SYNTAX score ≥ 23 and NSTEMI SYNTAX score < 23 groups.

$^{\beta}$ p value between NSTEMI SYNTAX score ≥ 23 and NCA groups.

$^{\gamma}$ p value between NSTEMI SYNTAX score < 23 groups and NCA groups groups.

	Univariable		Multivariable	
Variables	**Beta (95% CI)**	**P value**	**Beta (95% CI)**	**P value**
Age	1.032 (1.012 - 1.052)	0.001	1.028 (1.001 - 1.056)	0.043
BMI	1.114 (1.041 - 1.191)	0.050	0.979 (0.896 - 1.069)	0.631
Diabetes Mellitus	1.721 (1.057 - 2.801)	0.029	1.055 (0.516 - 2.157)	0.434
Glucose	1.007 (1.004 - 1.011)	0.043	1.002 (0.997 - 1.006)	0.428
Total cholesterol	1.002 (0.997 - 1.007)	0.420	-	-
LDL-C	1.004 (0.999 - 1.010)	0.141	-	-
Hematocrit	1.107 (1.056 - 1.160)	0.031	1.080 (1.016 - 1.148)	0.078
Lymphocyte	0.758 (0.608 - 0.944)	0.160	-	-
CRP	1.014 (1.004 - 1.024)	0.049	1.001 (0.991 - 1.011)	0.858
Total protein	1.794 (1.162 - 2.271)	0.020	1.889 (1.117 - 2.011)	0.057
WBV at LSR	1.025 (1.015 - 1.035)	< 0.001	1.003 (0.997 - 1.017)	< 0.001
WBV at HSR	1.693 (1.388 - 2.066)	< 0.001	1.517 (1.431 - 1.923)	< 0.001

Table 2: *Multivariate linear regression analysis showing the predictors for the SYNTAX score.*
BMI: Body Mass Index; CRP: C-Reactive Protein; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; WBV at HSR: Whole Blood Viscosity at High Shear Rate; WBV at LSR: Whole Blood Viscosity at Low Shear Rate.

Variables	r value	p value
WBV at LSR	0.333	< 0.001
WBV at HSR	0.347	<0.001

Table 3: *Pearson analysis of SYNTAX score with hemorheological parameters.*
WBV at HSR: Whole Blood Viscosity at High Shear Rate; WBV at LSR: Whole Blood Viscosity at Low Shear Rate.

Discussion

To the best of our knowledge, this is the preliminary study demonstrating the usefulness of WBV in predicting coronary artery severity in patients with first diagnosis of ACS. This parameter also provides the clinicians an easily avaiable and cheap tool to predict coronary artery severity in patients with first diagnosis of ACS. The present study demonstrated that in patients with ACS, coronary atherosclerosis was more advanced in patiens with higher WBV and higher WBV was an independent risk factor for patient with first diagnosed ACS. SYNTAX score showed a positive correlation with WBV.

According to previous studies, hemorheological changes increasing ESS could be as potential triggers for the rupture of atherosclerotic plaque, aggregated thrombus formation and may lead to deterioration in microvascular circulation [3,5]. As the principal determinant of ESS, WBV has a critical role for normally functioning endothelium. The terms of 'Poiseuille flow' proposes that elevated viscosity leads to the blood not to flow steadily and aggravates turbulent blood flow, causing the endothelial injury and disruption of the integrity of the endothelium and its function [17,18]. In addition to this term, the impact of the blood viscosity on blood flow have got new aspects and provided a new perspective to this entity. The effect of hemorheologic factors on blood flow are nonlinear, with a biphasic shape. Based on this nonlinear relation, a moderate increase in viscosity leads endothelium to release vasodilatator substances including NO, promoting blood flow. But,this phenomenon to the elevation of blood viscosity can be observed in the functionally normal endothelium. However, in

the atherosclerotic process involving endothelial dysfunction, the augmented shear stress does not lead to the additional production of vasodilators by biochemical mechanotransduction and elevated WBV shows damaging effects on this process [19]. As another acknowledged mechanism about the relation of increased WBV and atherosclerotic events, in-patients with increased blood viscosity, both leukocytes and platelets locate with higher concentrations near the artery wall purposely for adhesion and activation. These disrupted flow situations accelarate the infiltration of atherogenic molecules including cholesterol particles and fibrinogen into the wall of vessel [20].

Some studies have also revealed a relationship between hemorheological parameters and atherosclerotic process of the carotid and coronary arteries [21,22]. WBV has a prognostic significance in cardiovascular diseases. In Edinburgh Artery Study, WBV was a strong and reliable predictor of incident cardiovascular events and stroke at least as other well-established risk factors such as diastolic blood pressure, LDL cholesterol and cigarette smoking in random population [1].

The main factors including plasma viscosity, hematocrit, red blood cell (RBC) deformability and aggregation determine WBV. WBV and plasma viscosity have positive correlation with low-density lipoprotein, cholesterol, triglycerides, uric acid, von Willebrand factor and C-reactive protein whereas these parameters are negatively associated with high-density lipoprotein [23-25]. Any change in any of the variables adressed above alters the plasma viscosity [26]. Various therapies such as lipid-lowering drugs, apheresis and streptokinase have positive effects by decreasing the plasma viscosity, RBC aggregation and improving RBC deformability [27-29]. The RBC deformability provides oxygen delivery and determines the cell survival span in the circulation. So it is very vital [30].

At the different shear rates, how much the parameters affect WBV changes because they reflect distinct physiologic hemodynamic situations. High shear rates indicate higher velocity blood flow regimes in large arteries at the peak of systole, whereas low shear rate indicates flow conditions at end–diastole [31,32]. That's why, the shear rate that WBV was evaluated for should be kept in mind.

Acute coronary syndrome (ACS) consists of both STEMI and NSTEMI and unstable angina. The common pathological process leading to mycardial infarction is thrombus formation on top of a complex atheromatous plaque, resulting in partial or complete blockade of the coronary artery and myocyte necrosis. Whereas patients with unstable angina have no myocyte necrosis and is defined as ischaemia at rest or on minimal exertion [33]. Intensive medical therapy and invasive procedures was shown to decrease the morbidity and mortality of patients with ACS [34], however, the severity of CAD in CA is the leading determinant in chosing the most useful treatment strategy.

On the grounds of CA, SYNTAX score is used to grade CAD complexity by considering the number of lesions and their functional and anatomic components including location, presence of bifurcations, tortuosity, total occlusions, collaterals, thrombus and calcification. It is helpful for physicians to decide the optimal revascularization strategies especially among patients with complex CAD. A high SYNTAX score reflects a more complex disease and is an indicator of a therapeutic compelling. Patients with a high SYNTAX score have been reported to have more major adverse cardiac or cerebrovascular events [35-37]. The patients with a high SYNTAX (≥ 23) score in this study population had higher WBV values than both low SYNTAX (< 23) score and normal CA group.

Conclusion

In conclusion, we found that the coronary atherosclerosis burden was more advanced in patients with higher WBV values at first presentation of ACS. This simple and costless formula to estimate WBV by using hematocrit and total protein level provides physicians a new tool to predict advanced coronary atherosclerosis at patients with first diagnosis of ACS.

Limitations

Our study should be interpreted with some limitations. As the main limitation of our study, the viscometer measurement of blood viscosity and hemorheological parameters were not obtained to validate the WBV. Although this formula has been validated and used in several studies, the validation of the extrapolation formula should be investigated extensively in larger prospective studies.

The present study is a cross-sectional study with a relatively small sample size. We did not have follow-up MACE data. Therefore, our results should be verified in multi-center prospective longitudinal studies with a larger sample size. The limitations of this study should be considered when interpreting the results.

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