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Coronary Artery Disease

The Relationship between Blood Viscosity and Isolated Coronary Artery Ectasia

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Background: It is unclear whether isolated coronary artery ectasia (iCAE) is associated with whole blood viscosity (WBV). In the present study, we investigated WBV in coronary artery ectasia (CAE) patients.

Method: Seventy-eight patients with iCAE and 83 controls with normal coronary arteries were selected from 12290 patients who underwent coronary angiography between January 2014 and December 2017. WBV was calculated with a validated equation from hematocrit and total plasma protein levels for a low (LSR) and high (HSR) shear rate.

Results: Baseline demographic characteristics and medical history of the groups were similar. The mean level of C-reactive protein (2.1 ± 0.53 vs. 1.93 ± 0.44; $p = 0.042$) and total protein (7.2 ± 0.3 vs. 7.0 ± 0.6; $p = 0.009$) were significantly higher in the iCAE group than in the control subjects. Both HSR (4.57 ± 0.6 vs. 3.9 ± 0.7; $p < 0.001$) and LSR (33.5 ± 9.6 vs. 25.1 ± 9.2; $p < 0.001$) levels were significantly higher in the iCAE group than in the control group. In ROC analysis, a cut-off value of 4.19 WBV for HSR had an 80.8% sensitivity and 72.3% specificity [area under the curve (AUC): 0.779, 95% CI 70.6-85.1; $p < 0.001$] and a cut-off value of 27.5 WBV for LSR had an 80.1% sensitivity and 72.3% specificity for predicting iCAE (AUC: 0.788, 95% CI 71.4-86.2; $p < 0.001$). In multivariate analysis, both LSR ($p < 0.001$, OR 1.10, 95% CI 1.05-1.15) and HSR ($p < 0.001$, OR 4.60, 95% CI 2.33-9.09) were independent predictors for the presence of iCAE.

Conclusions: In the present study, we determined that in WBV, both HSR and LSR were significantly higher in the iCAE group than in the control subjects, and that this may be a possible cause of iCAE.

Key Words: Atherosclerosis • Coronary artery ectasia • Whole blood viscosity

INTRODUCTION

Coronary artery ectasia (CAE) is a clinical entity characterized by localized or diffuse dilatation of the coronary arteries with a diameter greater than 1.5 times that of adjacent segments. The prevalence of CAE has been reported to be 1.2% to 4.9% in various studies.[1,2] Although the exact mechanism leading to CAE is not clear, atherosclerosis, endothelial dysfunction, and vasculitis have been suggested as possible factors.[2,3] Atherosclerosis is linked to aneurysm formation through a process of inflammation. Prior studies have demonstrated that elevation of inflammatory markers is significantly increased in patients with CAE.[4-12] In approximately half of all cases, CAE occurs due to atherosclerosis, but in a minority of cases, CAE is observed in the absence of a significant atherosclerotic lesion and is called "isolated CAE" (iCAE). Blood viscosity is the intrinsic resistance of blood to flow in the vessels. The major determinants of blood viscosity are plasma viscosity, hematocrit, red cell deformation, and aggregation.[13,14] Previous studies have shown that any alteration in hemorheological factors can play a central role during atherosclerotic processes.[13,14] In addition, many studies have shown an association between blood viscosity and conventional risk factors for atherosclerosis such as male gender, smoking, diabetes mellitus,

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hypercholesterolemia and blood pressure.[14] Whole blood viscosity (WBV) can be calculated with a validated equation from hematocrit and plasma total protein levels (TP) for low and high shear rates with routine laboratory measurements.

We hypothesized that increased WBV may be associated with iCAE. Therefore, in the present study, we aimed to compare WBV values of patients with iCAE and control subjects.

METHODS

Patients

Between January 2014 and December 2017, 381 (3.1%) patients with CAE were selected from among 12290 patients who underwent elective diagnostic coronary angiography (CAG) for typical angina pectoris or significant myocardial ischemia in noninvasive stress tests at our center. After applying the exclusion criteria (see below), the remaining 78 (0.61%) iCAE patients were classified into the iCAE group. During the same period of the study, 83 age- and gender-matched controls with normal coronary arteries were consecutively selected. The exclusion criteria were as follows: acute coronary syndrome, significant left ventricular hypertrophy (septal thickness ≥ 13 mm), severe valvular disease, acute decompensated heart failure, left ventricular ejection fraction < 40%, acute or chronic infectious diseases, previously known inflammatory/autoimmune disorders or oncological diseases.

A detailed medical history of the study population was obtained from the medical records and was recorded on forms that were prepared for each patient. All routine laboratory parameters before CAG were recorded from the digital system of the hospital. Hypertension was considered to be present if the systolic blood pressure was ≥ 140 mmHg or if the diastolic blood pressure was ≥ 90 mmHg or both; or if the individual was taking anti-hypertension medication. Diabetes mellitus was defined as the use of anti-diabetic medication or fasting glucose level ≥ 126 mg/dL in at least two measurements, or HbA1c ≥ 6.5%. For each patient, body mass index (BMI) was calculated as weight (kg) divided by height $(m)^2$. BMI was categorized as normal (≤ 25 kg/m^2), overweight (25-30 kg/m^2) or obese (> 30 kg/m^2). The patients who smoked at least one cigarette a day for at least 1 year were defined as smokers. A family history of coronary artery disease was diagnosed by considering the patients' first-degree male relatives < 55 years of age or female relatives < 65 years of age with coronary artery disease. Hypercholesterolemia was defined as low-density lipoprotein (LDL)-cholesterol ≥ 130 mg/dL or the use of lipid-lowering drugs. The study protocol was reviewed and approved by the Institutional Ethics Committee in accordance with the Declaration of Helsinki.

Angiographic evaluation

All patients underwent elective CAG by an experienced cardiologist using the standard Judkins technique with a femoral or radial approach. Images were recorded in digital format and stored for later analysis. Evaluations were performed visually by two experienced cardiologists blinded to each other's findings. Coronary ectasia was defined as coronary arteries with luminal dilatation exceeding 1.5-fold the adjacent normal coronary segment without significant coronary stenosis in this study according to a previous study[1] If there was no adjacent segment, the mean diameters of the control patients were used for the related segment.[1,2] If the coronary arteries had a normal appearance or no atherosclerotic plaque with ≥ 25% stenosis, they were regarded as being normal. The patients with concomitant obstructive and ectatic lesions were not included in the study. CAE was defined as focal when involving one segment and as diffuse when involving two or more segments in a major coronary artery, and as severe when diffused (≥ 2 segments) in ≥ 2 vessels.

Blood sampling and laboratory assays

Peripheral blood samples were collected via the antecubital vein after a 12-hour overnight fast. Serum glucose, creatinine and lipid profile were determined by standard methods. Whole blood counts were made in a blood sample collected in dipotassium ethylenediaminetetraacetic acid tubes with an automated hematology analyzer (XE-1200 Sysmex, Kobe, Japan). The neutrophil to lymphocyte ratio (NLR) was calculated using the absolute count method. C-reactive protein (CRP) was measured by the turbidimetric method (Toshiba ACCUTE TBA-40FR; Toshiba Medical Systems, Tokyo, Japan). Other

biochemical tests were performed using original kits with an Olympus autoanalyzer (Olympus, Japan).

Extrapolation of whole blood viscosity

WBV was calculated for both low shear rate (LSR) (0.5 sec-1) and high shear rate (HSR) (208 sec-1) from hematocrit and total plasma protein concentrations using the validated formula:[14]

HSR: WBV (208 sec-1) = (0.12 × HCT) + (0.17 TP) – 2.07
LSR: WBV (0.5 sec-1) = (1.89 × HCT) + (3.76 TP) – 78.42

Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD), and categorical variables were expressed as the number of patients and percentages. The variables were investigated using the Kolmogorov-Smirnov analytic method to determine whether or not they were normally distributed. The Student's *t*-test was performed for normally distributed variables with the Mann Whitney U test for non-normally distributed variables. The chi-square test or Fisher's exact test was used for categorical variables. Logistic regression analysis was performed to determine independent correlates of iCAE. A stepwise model with the backward selection method was used, and p values of < 0.1 were selected for inclusion in the next step. Results were tabulated as odds ratio (OR) and 95% confidence interval (CI). To evaluate the usefulness of WBV for iCAE, receiver operating characteristic (ROC) curve analysis was used. A p value < 0.05 was considered to be statistically significant. Intraclass correlation coefficients and Bland & Altman methods were used for inter-observer correlation analysis. The data were analyzed using SPSS statistical software version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The baseline characteristics and laboratory findings of the study groups are summarized in Table 1 and 2. There were no significant differences between the two groups in terms of baseline demographic characteristics and medical history. Although hemoglobin (14.6 ± 1.7 g/ dL vs. 13.8 ± 1.7 g/dL; p = 0.082) and hematocrit (43.5% ± 4.9 vs. 41.6% ± 5.9; p = 0.067) levels were slightly higher in the iCAE group than the control

Table 1. Baseline characteristics of the study population

Parameters	Ectasia group (n = 78)	Control group (n = 83)	p
Age	52.7 ± 11	50.7 ± 9.5	0.230
Gender (male), n (%)	59 (75.6)	58 (769.9)	0.412
BMI (kg/m^2)	27.4 ± 4.1	25.7 ± 3.7	0.217
Diabetes mellitus, n (%)	19 (24.4)	17 (20.5)	0.555
Hypertension, n (%)	24 (30.8)	23 (27.7)	0.670
Hyperlipidemia, n (%)	10 (12.8)	14 (16.9)	0.471
Smoking, n (%)	19 (24.4)	24 (28.9)	0.514
LVEF	64 ± 5.3	65 ± 4.1	0.617
SBP (mmHg)	126 ± 14	119 ± 8	0.589
DBP (mmHg)	86 ± 8	82 ± 7	0.358
Heart rate (beat/m)	71 ± 11	69 ± 8	0.411
Aspirin	11 (14.1)	10	0.698
Beta-blockers	17 (21.8)	14	0.428
Statins	7 (8.9)	11	0.386
ACEIs or ARBs	16 (20.5)	11	0.217
Calcium antagonists	7 (8.9)	6	0.684

ACE, angiotensin-converting enzyme; BMI, body mass index; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Table 2. Baseline laboratory parameters of the study population

Parameters	Ectasia group (n = 78)	Control group (n = 83)	p
Hemoglobin, g/dL	14.6 ± 1.7	13.8 ± 1.7	0.082
Hematocrit, %	43.5 ± 4.9	41.6 ± 5.9	0.067
Platelets, ×10^3/μl	254 ± 69	267 ± 72	0.260
Neutrophils, ×10^3/μl	2.48 ± 0.24	2.51 ± 0.37	0.547
Lymphocytes, ×10^3/μl	1.44 ± 0.17	1.43 ± 0.45	0.953
CRP	2.1 ± 0.53	1.93 ± 0.44	0.042
NLR	2.48 ± 0.24	2.51 ± 0.37	0.547
Urea, mg/dl	7.2 ± 0.3	7.1 ± 0.6	0.121
Serum creatinine, mg/dL	0.93 ± 0.4	1.05 ± 0.6	0.150
Total protein, g/L	7.2 ± 0.3	7.0 ± 0.6	0.009
Serum albumin, mg/dL	4.4 ± 0.5	4.3 ± 0.5	0.495
Total cholesterol, mg/dL	190 ± 43	188 ± 35	0.759
LDL cholesterol, mg/dL	114 ± 32	104 ± 31	0.064
HDL cholesterol, mg/dL	39 ± 10	38 ± 6.2	0.605
Triglycerides, mg/dL	220 ± 43	193 ± 58	0.132
WBV at HSR	4.57 ± 0.6	3.9 ± 0.7	< 0.001
WBV at LSR	33.5 ± 9.6	25.1 ± 9.2	< 0.001

CRP, C-reactive protein; HDL, high-density lipoprotein; HSR, high shear rate; LDL, low-density lipoprotein; LSR, low shear rate; NLR, neutrophil to lymphocyte ratio; WBV, whole blood viscosity.

group, the differences were not statistically significant. The mean levels of CRP (2.1 ± 0.53 vs. 1.93 ± 0.44; p = 0.042) and total protein (7.2 ± 0.3 vs. 7.0 ± 0.6; p = 0.009) were significantly higher in the iCAE group than in the control subjects. In addition, there was no significant difference between the two groups in terms of NLR, as a marker of inflammation (Table 2). In the iCAE group, WBV values were significantly higher both for HSR (4.57 ± 0.6 vs. 3.9 ± 0.7; p < 0.001) and LSR (33.5 ± 9.6 vs. 25.1 ± 9.2; p < 0.001) compared to the control group (Table 2). In ROC analysis, a cut-off value of 4.19 WBV for HSR had am 80.8% sensitivity and 72.3% specificity for predicting iCAE [area under the curve (AUC): 0.779, 95% CI 70.62-85.14; p < 0.001] and a cut-off value of 27.5 WBV for LSR had an 80.1% sensitivity and 72.3% specificity for predicting iCAE (AUC: 0.788, 95% CI 71.4-86.2; p < 0.001) (Figure 1). In multivariate analysis, both LSR and HSR were independent predictors for the presence of iCAE (WBV at HSR: p < 0.001, OR 4.60, 95% CI 2.33-9.09; WBV at LSR: p < 0.001, OR 1.10, 95% CI 1.05-1.15) (Table 3).

DISCUSSION

In this study, we showed that higher WBV was a risk factor for iCAE. To the best of our knowledge, this is the first report to demonstrate a relationship between WBV and iCAE.

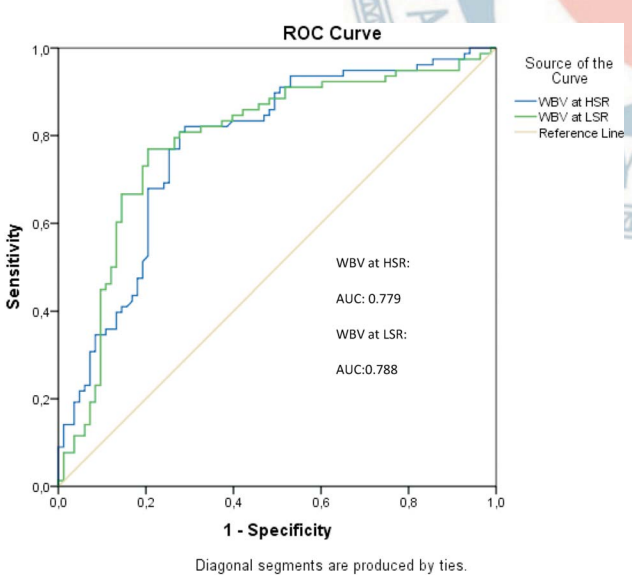

Figure 1. *ROC curve analysis showing the predictive cut-off value of WBV at a high shear rate (blue line) and low shear rate (green line) for isolated coronary artery ectasia. AUC, area under the curve; HSR, high shear rate; LSR, low shear rate; ROC, receiver operating characteristic; WBV, whole blood viscosity.*

The underlying pathological mechanism of CAE is not completely understood. Although a definitive link between atherosclerosis and iCAE has not been confirmed, it has been suggested that iCAE is a variant of coronary artery disease, and atherosclerosis is thought to be the major cause of CAE.[1,15-19] The role of inflammation in the initiation and progression of coronary atherosclerosis is well known.[18,20,21] Atherosclerosis is linked to aneurysm formation through a process of inflammation, extending into the tunica media, which eventually causes degeneration of the cystic media.[22] Prior studies have demonstrated that the elevation of inflammatory markers such as plasma soluble adhesion molecules, leukocytes, adiponectin, lipoprotein-associated phospholipase-A2, C-reactive protein, plasminogen activator inhibitor-1, IL-1, TNF-alfa and IL-10 are significantly in-

Table 3. The effects of variables on MAC in univariate and multivariate logistic regression analysis

Parameters	OR	95% CI	p
Age	1.019	0.998-1.050	0.229
BMI (kg/m^2)	1.025	0.991-0.1041	0.224
Hemoglobin, g/dL	1.178	0.978-1.418	0.084
Hematocrit, %	1.055	0.996-1.118	0.069
CRP	2.039	1.009-4.118	0.047
NLR	0.733	0.265-2.023	0.548
Urea, mg/dl	1.700	0.945-1.014	0.282
Creatinine, mg/dL	0.505	0.167-1.530	0.227
Total protein, g/L	2.502	1.235-5.068	0.011
LDL cholesterol, mg/dL	1.010	0.999-1.021	0.066
Triglycerides, mg/dL	1.003	0.999-1.006	0.138
WBV at HSR	5.314	2.779-10.160	< 0.001
WBV at LSR	1.105	1.059-1.152	< 0.001
Model-1			
CRP	1.709	0.704-4.149	0.237
LDL cholesterol, mg/dL	1.003	0.991-1.016	0.593
WBV at HSR	4.522	2.269-9.011	< 0.001
Model-2			
CRP	2.039	0.566-3.065	0.552
LDL cholesterol, mg/dL	1.006	0.994-1.018	0.337
WBV at LSR	1.083	1.038-1.131	< 0.001

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; HSR, high shear rate; LDL, low-density lipoprotein; LSR, low shear rate; NLR, neutrophil to lymphocyte ratio; OR, odds ratio; WBV, whole blood viscosity.

creased in patients with CAE.[4-12] In addition, NLR ratio, as a marker of inflammation, has been associated with atherosclerosis and CAE.[20,23] Blood NLR reflects systemic inflammation well; it is cost effective, easily available and can be calculated quickly. Thus, previous studies have provided strong evidence for the role of inflammation in CAE and also atherosclerosis.[24] Conversely, other previous studies have reported no significant differences between iCAE and control group in terms of NLR. This difference may be due to differences between inclusion and exclusion criteria of the studies. Although, CRP was a significant predictor of iCAE in univariate analysis, it lost significance in multivariate analysis. Even though, our results show that inflammation is not a risk factor for iCAE, it is difficult to make a definite conclusion. As in previous studies, we believe that if we had evaluated a more sensitive inflammatory marker such as hsCRP or an interleukin it would be possible to show a relationship inflammation and iCAE.

Blood viscosity is the intrinsic resistance of blood to flow in vessels. Its major determinants are the volume fraction of red blood cells (hematocrit), plasma viscosity (which is determined mainly by plasma fibrinogen, other biologically reactant globulins, and lipoproteins), red cell deformation (under high flow/shear conditions), and red cell aggregation (under low flow/shear conditions). Epidemiological studies have shown the association between blood viscosity and conventional atherosclerotic risk factors such as male gender, blood pressure, cigarette smoking, and plasma lipids. The impact of blood viscosity on cardiovascular homeostasis remains incompletely understood. Blood viscosity abnormalities were associated with decreased tissue perfusion and with the development of atherosclerosis. Many previous studies have shown that increased blood viscosity is associated with hypertension, peripheral vascular disease, diabetes mellitus, coronary artery disease, and it has also been proposed that it might act synergistically with atherosclerosis and microvascular dysfunction in determining an increase in vascular resistance associated with a decrease in capillary perfusion.[25-29] In the West of Scotland Coronary Prevention Study that enrolled 6595 patients, it was shown that plasma and WBV were associated with an increased prevalence of cardiovascular risk factors and coronary and peripheral atherosclerosis.[30] In addition, in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, WBV was positively related to the Framingham Risk Score in the subjects aged 70 years.[31] As a result, it has long been proposed that blood viscosity should be considered to be a cardiovascular risk factor.

Although the exact mechanism leading to iCAE is not fully understood, many studies have suggested atherosclerosis. At the same time, many previous studies have shown that WBV is also associated with atherosclerosis and proposed that it should be considered to be a cardiovascular risk factor. The present study indicates that WBV both for HSR and LSR was significantly higher in the patients with iCAE than in the control subjects. This result supports the hypothesis that atherosclerosis causes iCAE.

Limitations

Our study has several limitations. The most important limitation of the study is the absence of a direct measurement of WBV. Even so, the formula that we used in the present study has been validated in large studies and has been shown to provide a valid alternative in setting the direct measurement of viscosity. The other important limitation is that because of the retrospective nature of the study, we could not evaluate inflammatory markers that might be associated with iCAE. However, we evaluated NLR ratio and CRP as a marker of inflammation, and they showed a relationship between atherosclerosis and iCAE. The other limitation is that it is single center study with a small sample size. Finally, inherent to the cross-sectional design of the study, the prognostic relationship between WBV and future adverse cardiac events cannot be addressed in the iCAE population. The prognostic importance of WBV in iCAE patients should be evaluated in another prospective study with a larger sample size.

CONCLUSIONS

To the best of our knowledge, this is the first study in to show an association between iCAE and WBV. In the present study, we determined that in WBV, both HSR and LSR were significantly higher in the iCAE group than in the control subjects, and that this may be a possible cause of iCAE.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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AUTHORSHIP CONTRIBUTIONS

YÇ and ES: concept and design of the study, SK and MÇ: contributed to critical revision of the manuscript and statistical analysis, MY: involved in the collection and analysis of data, İVD: literature research and critical reviewer. All authors discussed the results and contributed to the final manuscript.

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