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Whole Blood Viscosity Predicts Amputation in Patients With Lower Extremity Peripheral Arterial Disease

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Objective: This study aims to find the relationship between whole blood viscosity (WBV) and amputation events occurring within 1 year of patients with lower extremity peripheral arterial (LEPAD) disease who cannot be revascularized by surgical or percutaneous methods.

Materials and Methods: The study retrospectively examined the data of 261 LEPAD patients with critical limb ischemia. WBV values of the patients were found with a formulation obtained from the total protein and hematocrit values in the blood samples (Simone's formula).

Results: Amputation developed in 51 (19.6%) patients. Hemoglobin, hematocrit, white blood cell count, neutrophil, platelet, WBV at high shear rate (HSR) (16.58±2.13 vs. 15.74±1.47, p<0.001) and WBV at low shear rate (LSR) of patients with amputation (100.15±14.97 vs. 92.84±13.39, p=0.002) value was found to be higher. As a result of multivariate regression analysis, WBV at HSR (OR: 1.096 95%CI (1.067-1.182), p=0.002) and WBV at LSR (OR: 6.481 95%CI (4.102-9.486), p<0.001) were found to be independent risk factors indicating the development of amputation. As a result of the receiver operating characteristics curve analysis, the cut-off value showing amputation for WBV at HSR is 16.34 (69% sensitivity, 68.6% specificity, and area under the curve (AUC): 0.728(0.532-0.823), p=0.005), a cut-off value indicating amputation for WBV at LSR is 97.48 (71.5%) sensitivity, specificity of 70.2% and AUC: 0.736(0.551-0.842), p=0.003).

Conclusions: According to the shear rate, both WBV values were found predictive of amputation in patients with critical limb ischemia who could not be revascularized.

Key Words: *Whole blood viscosity, peripheral artery disease, critical limb ischemia, amputation*

Alt Ekstremite Periferik Arter Hastalığı Olan Hastalarda Tam Kan Viskozitesi Amputasyonu Ön Gördürebilmektedir

Amaç: Bu çalışmada amaç; alt ekstremite periferik arter hastalığı olan ve cerrahi ya da perkütan yöntemlerle revaskülarize edilemeyen hastaların 1 yıl içerisinde gelişen amputasyon olaylarının tam kan vizkozitesi (TKV) ile ilişkisini bulmaktır.

Gereç ve Yöntem: Çalışma kritik ekstremite iskemisi olan 261 tane AE-PAH hastasının verileri retrospektif olarak incelenerek yapılmıştır. Hastaların TKV değerleri alınan kan örneklerindeki total protein ve hematokrit değerlerinden elde edilen bir formülasyon ile bulunmuştur. Analiz için SPSS 23.0 programı kullanılmıştır.

Bulgular: 51 (19.6%) hastada amputasyon gelişmiştir. Amputasyon gelişen hastaların hemoglobin, hematokrit, beyaz kan hücresi sayısı, nötrofil, platelet, yüksek kesme oranında (YKO) TKV (16.58±2.13 vs. 15.74±1.47, p<0.001) ve düşük kesme oranında (DKO) TKV (100.15±14.97 vs. 92.84±13.39, p=0.002) değeri daha yüksek bulunmuştur. Çoklu regresyon analizi sonucunda YKOTKV (OR: 1.096 95%CI (1.067-1.182), p=0.002) ve DKOTKV (OR: 6.481 95%CI (4.102-9.486), p<0.001) amputasyon gelişimini gösteren bağımsız risk faktörleri olarak bulunmuştur. Yapılan alıcı işlem karakteristikleri eğrisi analizi sonucunda YKOTKV için amputasyonu gösteren kesme değeri 16.34 (%69 sensitivite, %68.6 spesifite ve eğri altında kalan alan (EAA): 0.728(0.532-0.823), p=0.005), DKOTKV için amputasyonu gösteren kesme değeri 97.48 (%71.5 sensitivite, %70.2 spesifite ve EAA: 0.736(0.551-0.842), p=0.003) olarak bulunmuştur.

Sonuç: Kesme oranlarına göre her iki TKV değeri de kritik ekstremite iskemisi olan ve revaskülarize edilemeyen hastalarda amputasyon gelişimini öngördüren değerler olarak bulunmuşlardır.

***Anahtar Kelimeler*:** *Tam kan vizkozitesi, periferik arter hastalığı, kritik ekstremite iskemisi, amputasyon*

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Introduction

Peripheral arterial disease (PAD) is a relatively common chronic disease characterized by decreased blood flow due to the narrowing of the vessel lumen and subsequently reduced oxygen delivery to tissues And lower extremity (LE) PAD is the most common form in daily practice. LEPAD can vary from asymptomatic to critical limb-threatening ischemia (CLTI), which is the most challenging situation to manage medically in patients with PAD and can cause extremity loss. CLTI is by definition, ischemic pain at rest with or without tissue loss and has been shown in the literature to occur in 11% of PAD patients (1). Mortality in CLTI patients is higher than any other occlusive cardiovascular disease, including symptomatic coronary artery disease. While annual mortality in CLTI patients varies between 10% and 40%, 5-year mortality exceeds 50% (2-4). In addition to this increased mortality, 6-month extremity loss in CLTI patients can be seen at rates ranging from 10% to 40% (5-7). Although amputation rates have decreased in these patients with newly developed treatment techniques, it is crucial to identify CLTI patients who may undergo amputation, especially in patients who do not have a revascularization option, in terms of providing increased awareness and improvements in wound care (4, 8).

Although revascularization is the primary treatment option in treating CLTI, some patients are unsuitable for revascularization due to anatomical and physiological reasons (9). In addition to medical treatment, treatment options such as lumbar sympathectomy, spinal cord stimulation, hemodilution and intermittent pneumatic compression have been recommended for these patients (9-11). Indeed, Kim et al. showed that hemodilution therapy reduces major amputation in CLTI patients without a revascularization option (10). The physiological rationale of hemodilution therapy is that despite the decrease in hemoglobin level, the reduction in blood viscosity increases tissue perfusion (12). Although the hemoglobin level, which is essential for oxygen delivery to the tissue, decreases in this treatment option, the improvement in blood viscosity increases tissue oxygenation, suggesting that blood viscosity is an important clinical determinant in CLTI patients. Besides, the effectiveness of whole blood viscosity (WBV) as an important predictor in different cardiovascular diseases has been shown in the literature (13, 14). Based on this, we planned to investigate whether whole blood viscosity predicts amputation in CLTI patients unsuitable for revascularization.

Materials and Methods

Research and Publication Ethics: Ethics committee approval was received from the ethics committee of the University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey (Date number: 14.05.2018, number: 50/16). The work was carried out in accordance with the principles of the Helsinki Declaration.

For this retrospective study, 684 patients who underwent invasive lower extremity peripheral angiography diagnosed with LEPAD CLTI between September 2016 and November 2021 were screened. A total of 261 patients who met the criteria of being technically unsuitable for revascularization or having previously experienced an unsuccessful revascularization procedure and having pain at rest (Rutherford grade 2-3) were included in the study. Patients with a body mass index (BMI) below 18 kg/m2, acute arterial disease, major tissue loss, liver failure, kidney disease, acute or chronic infection, chronic inflammatory disease, hematological disease, heart failure, oncological disease, use the anticoagulant treatment for any reason and patients whose follow-up data cannot be accessed from hospital records were excluded from the study. In the formula used by De Simone et al. to calculate WBV, since it is recommended to use patients with plasma total protein values of 5.4–9.5 g/100 mL and values of 32-53% for HCT, patients with values outside these ranges were also excluded from the study (15, 16). The patients included in the study were divided into two groups as amputated and not amputated within one year.

The patients' blood results before the procedure were obtained from the hospital automation system, and the biochemistry and whole blood count values required for analysis were recorded. The complete blood test was evaluated using an automatic hematology analyzer (Symex XN-550 analyzer, Symex, Kobe, Japan) and biochemical tests using standard biochemical methods with Beckman Coulter LH 780 device (Beckman Coulter Inc., Brea, New York, USA). WBV values were calculated using Simone's formula, using hematocrit (HTC) and total protein (TP) concentration for both high shear rate (HSR=208 s^{-1}) and low shear rate (LSR=0.5 s^{-1}). For HSR, WBV (208 s^{-1}) = (0.12 × HTC) + 0.17 (TP-2.07), for LSR, WBV (0.5 s^{-1}) = (1.89×HTC) + 3.76 (TP-78.42) formulas were used. HTC is in %, TP is in g/l and WBV is whole blood viscosity in centipoise (cP) (15,16).

Statistical Analysis: Categorical data are presented as numbers and percentages. All the variables were examined with the Kolmogorov–Smirnov test for normality and the Levene test for homogeneity of variances before significance tests were used and normally distributed homogeneous data were used with the t-test in independent groups. The Mann–Whitney U test was used to evaluate the difference in the parameters that did not show normal distribution. For non-parametric data analysis, the chi-square test was used. Multivariate and univariate logistic regression was done to analyze the defined risk factors for amputation development and determine independent risk factors. Receiver operating characteristic (ROC) analysis was drove to estimate the optimal cut-off value of WBV at HSR, WBV at LSR, and HCT in indicating amputation. Sensitivity, specificity, and area under the curve (AUC) values were calculated. The significance level was accepted p<0.05 2- sided for all statistical analyses. All data was analyzed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA) for Windows.

Results

261 patients were included in the study. 193 (73.9%) of the patients were male. Amputation occurred in 51 (19.6%) of the patients included in the study. There was no difference between the demographic characteristics of the patients. As a result of laboratory analysis, hemoglobin, hematocrit, white blood cell (WBC), neutrophil, platelet, WBV at HSR, and WBV at LSR values of amputated patients were found to be higher than those of non-amputee patients (Table 1). On the contrary, total protein levels were found to be lower in amputated patients (6.73±1.02 vs. 6.99±0.80, p=0.027).

Table 1. Basal demographic and laboratory characteristics of the patients according to amputation status

Demographics	**Amputees, n=51**	**Non-amputees, n=210**	**p**
Age (years), mean (SD)	66.1±10.2	64.5±9,4	0.371
Male gender n (%)	33(66.0)	160(76.2)	0.098
Smoking n (%)	29(56.9)	108(51.7)	0.306
Dyslipidemia n (%)	22(43.1)	113(53.8)	0.113
DM n (%)	28(54.9)	117(55.7)	0.274
HT n (%)	35(68.6)	116(55.2)	0.066
CAD n (%)	13(25.5)	61(29.2)	0.368
Laboratory parameters			
Hemoglobin (g/dL)	12.15±2.39	13.22±2.57	**0.004**
Hematocrit (%)	35.71±6.65	39.11±7.67	**0.002**
WBC (10^3 /μL)	9.61±3.43	8.40±1.91	**0.019**
Neutrophil (10^3 /μL)	6.57±3.18	5.61±1.72	**0.043**
Platelets (mm^3)	306.62±42.53	271.2±34.16	**0.030**
Total protein (g/dL)	6.73±1.02	6.99±0.80	**0.027**
Albumin (g/dL)	3.57 ± 0.32	3.68±0.72	0.513
LDL-C (mg/dL)	126.21±38.13	122.38±41.07	0.565
HDL-C (mg/dL)	38.86±11.26	38.95±13.57	0.963
Triglycerides (mg/dL)	166.46±52.44	159.78±49.69	0.651
Creatinine (mg/dL)	1.34±0.76	1.29±0.86	0.086
BUN (mg/dL)	51.01±23.98	46.86±22.78	0.514
Glucose (mg/dL)	143.61±65.68	134.27±54.34	0.137
WBV at HSR	16.58±2.13	15.74±1.47	**<0.001**
WBV at LSR	100.15±14.97	92.84±13.39	**0.002**

DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, WBC: White blood cell, RDW: red cell distribution width LDL: Low-density lipoprotein, HDL: high-density Lipoprotein, WBV: Whole blood viscosity, HSR: High shear rate, LSR: Low shear rate.

Table 2. Regression analysis results in predictive factors for amputation

	Univariable Analysis		**Multivariable Analysis**	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Hemoglobin	0.979(0.966-0.993)	**0.004**	0.985(0.970-1.002)	0.069
Hematocrit	0.932(0.890-0.977)	**0.003**	0.891(0.765-1.237)	0.349
WBC	1.149(1.025-1.258)	**0.020**	0.804(0.543-1.191)	0.276
Neutrophil	1.138(1.002-1.257)	**0.047**	1.038(0.682-1.580)	0.862
Platelet	1.003(1.001-1.006)	**0.033**	1.003(1.001-1.006)	0.038
Total protein	0.614(0.404-0.932)	**0.024**	0.833(0.522-1.329)	0.443
WBV at HSR	1.083(1.059–1.137)	**0.001**	1.096(1.067-1.182)	**0.002**
WBV at LSR	6.362(3.605–9.208)	**<0.001**	6.481(4.102-9.486)	**<0.001**

WBC: White Blood Cell, WBV: Whole blood viscosity, HSR: High shear rate, LSR: Low shear rate.

Multivariate and univariate logistic regression analyzes were performed to investigate the predictive factors for amputation. Hemoglobin, hematocrit, WBC, neutrophil, platelet, total protein, WBV at HSR, and WBV at LSR were found to be good predictor factors for amputation (p=0.004, p=0.003, p=0.020, p=0.047, p=0.033, p=0.024), p=0.001, p<0.001, respectively). When all the factors that were affected the amputation by multivariate regression analysis were examined, WBV at HSR (OR (95%CI) 1.096(1.067-1.182), p=0.002) and WBV at LSR (OR (%95CI) 6.481(4.102-9.486), p<0.001) were determined as independent risk factors for amputation (Table 2).

ROC curve analysis for WBV at HSR and WBV at LSR showed that the ideal cut-off values of WBV at HSR and WBV at LSR as a predictor of amputation was 16.34 (69.0 % sensitivity and 68.8% specificity) for WBV at HSR and 97.48 (71.5% sensitivity and 70.2% specificity) for WBV at LSR. The AUC for WBV at HSR was found to be 0.728 (95% CI 0.532-0.823; p=0.005), and the AUC for WBV at LSR was found to be 0.736 (95% CI 0.551-0.842; p=0.003) (Figure 1) (Table 3).

Table 3. Receiver operating characteristic curve analysis results for amputation

Risk Factor	AUC (95%)	Cut- Off	p	Sensitivity (%)	Specificity (%)
Hematocrit	0.629(0.504-0.713)	37.65	**0.004**	58.6	66.9
Total Protein	0.577(0.476-0.677)	***	0.089	***	***
WBV at HSR	0.728(0.532-0.823)	16.34	**0.005**	69.0	68.8
WBV at LSR	0.736(0.551-0.842)	97.48	**0.003**	71.5	70.2

WBV: Whole blood viscosity, HSR: High shear rate, LSR: Low shear rate, AUC: area under the curve

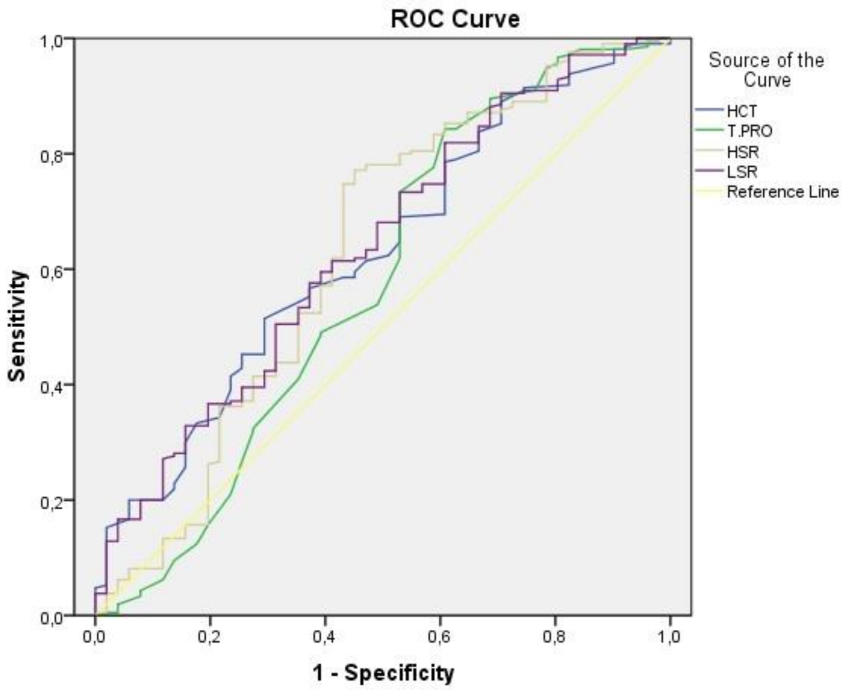

Figure 1. Receiver operating characteristic curve analysis table for amputation

Discussion

Our study showed that WBV at both shear rates was significantly higher in those undergoing amputation in patients with LEPAD who did not have the option of revascularization. Our study also showed that WBV is a strong independent risk factor for amputation in the same patient group.

Although the primary treatment recommended for CLTI patients is revascularization, different treatment protocols have been proposed for patients who cannot be revascularized due to various reasons. One of them is the hemodilution method. It is thought that the main effect of the hemodilution therapy is the positive effect on the plasma viscosity and the increased flow in the micro-vessels (12, 17, 18). As a matter of fact, it has been shown in the literature that WBV is improved with hemodilution therapy. Kim et al. (10) showed that despite the decrease in hemoglobin levels with hemodilution therapy in patients with CLTI, the tissue oxygen delivery index increased due to improved WBV, which was reflected in positive clinical results. Considering all of the above, it is seen that WBV is the treatment target that has an essential place in physiopathogenesis in patients with LEPAD. Especially in patients with multiple, long collateralized vascular obstructions, such as CLTI patients, WBV is an important factor determining endothelial shear stress, thus increasing its clinical importance in this patient group (19).

In addition to the above, the atherosclerosis process is significantly influenced by hemorheological factors has been shown in the literature that increased blood viscosity plays a vital role in the atherosclerotic process by causing intravascular stasis and endothelial dysfunction (20). A high degree of blood viscosity causes turbulent blood flow that exacerbates endothelial disruption and impairs endothelial integrity and function (21-23). Apart from the atherosclerotic process, endothelial shear stress also affects atherosclerotic plaque rupture and thrombosis formation (24, 25). As the main determinant of endothelial shear stress, WBV has an important role in this physiopathological pathway. As a matter of fact, Erdogan et al. showed that WBV was significantly higher in patients presenting with acute arterial occlusion compared to the control group (26).

Viscometers such as falling-ball, capillary, and rotational viscometers are used for viscosity measurements (27). However, access to these methods is limited in daily clinical practice. The formula we used in our study, defined by Simone, provides important data on WBV through total protein level and complete blood count, which we commonly use in routine practice. With the formula described by Simone, estimated WBV values can be obtained at different shear rates (15). Compared to the viscometer-measured analysis, the estimated WBV values calculated with the formula described by Simone demonstrated a smaller degree of error (15).

Limitations of this study, first, the study is a single-center and retrospective study which may cause selection bias. Secondly, platelet and erythrocyte aggregability and rigidity, which may influence blood viscosity, were not assessed. And lastly, blood viscosity was not directly measured in the study. Even though other studies have proven the validity of the extrapolation method, we employed in this study, investigating the correlation between estimated WBV and blood viscosity measured directly with a viscometer could increase the effectiveness of our study.

In our study, we showed that WBV calculated using simple laboratory tests predicts amputation in LEPAD patients who do not have the option of revascularization. Considering that the population in our study has no option for revascularization, the value of WBV as a predictor of amputation in these patients is vital for identifying high-risk patients and managing their treatment.

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