The Relationship Between Nitrate-Induced Headache and -Blood Viscosity: An Observational Prospective Study

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Abstract: Nitrates are one of the most prescribed medications in the treatment of angina pectoris today. Headache is the most common side effect of nitrates, and there is limited prospective data on the determinants of this effect. Our aim in this study is to open a foresight window for clinicians in clinical practice by explaining the possible relationship between nitrate-induced headache and whole-blood viscosity (WBV). After coronary revascularization treatment, 869 patients with angina who were prescribed nitrate preparations were divided into groups according to the development of headache or not and categorized according to the 4-grade scale level. Those who had no headache during nitrate use were graded as grade 0, those who felt mild headache were grade 1, those who felt moderate headache were grade 2, and those who described severe headache were graded as grade 3. The groups were compared according to WBV values. A total of 869 participants were included in the study. Most patients (82.1%) experienced some level of headache. Headache severity correlated with both WBV at high shear rate (r = 0.657; $P < 0.001$) and WBV at low shear rate (r = 0.687; $P < 0.001$). In multivariate analysis, WBV was determined as an independent predictor of headache experience. WBV predicted nitrate-induced headache with 75% sensitivity and 75% specificity at high shear rate and 77% sensitivity and 77% specificity at low shear rate. WBV seems to be one of the major determinants for nitrate-induced headache. WBV may be a guide for initiating alternative antianginal drugs without prescribing nitrates to the patient to increase patient compliance.

Key Words: nitrate-induced headache, whole-blood viscosity, high shear rate, low shear rate

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INTRODUCTION

Nitrates are vasodilator agents that are frequently used as antianginal in coronary artery disease.[1] They show these effects mainly nonselectively through the nitric oxide (NO)–cyclic guanosine monophosphate (cGMP) axis.[2] The biggest side effect of these drugs is the headache that develops after use, and this headache negatively affects the quality of life of some patients by seriously disrupting drug use compliance.[3] Nitrates are thought to cause headache by mediating changes in cerebrovascular tone, and generally, the symptoms of nitrate-induced headache are similar to the pain during acute attacks of migraine.[4] As a matter of fact, according to the dominant opinion of migraine pain, it is suggested that the vasodilation caused by the disorder in the NO–cGMP axis in the cerebral vessels causes headache by stimulating the nociceptors.[5] The main evidence for this hypothesis comes from clinical studies investigating the acute effects of intravenous administration of NO donors, such as glyceryl trinitrate.[6] Acute administration of glyceryl trinitrate significantly increases pain intensity in migraine patients.[4,5] Therefore, understanding the mechanism of migraine headache will help to understand the mechanism of nitrate-induced headache (NIH). The fact that nitrates do not show the same severity of side effects in every patient and that some vasodilator agents reduce migrainoid pain suggests that the vasodilation hypothesis is insufficient to explain such pain.[7–9] One study failed to demonstrate in vivo cerebral and meningeal vasodilation in patients during migraine headache.[10] However, the role of small cerebral vessels was not excluded in this study. This is relevant because small cerebral vessels are involved in blood flow changes that occur during a migraine attack.[11]

It is known that increased blood viscosity causes cerebral blood flow dysregulation and induces headache.[12] Indeed, patients often complain of headache in cases of excessive blood viscosity, such as polycythemia vera, essential thrombocytosis, and secondary polycythemia.[13,14] Blood viscosity plays its most important role in microcirculation, where it contributes significantly to peripheral resistance and can cause red blood cell aggregation in capillary and postcapillary venules.[15] Clinical observations that migraine is associated

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Informed consent was obtained from all individual participants included in the study.

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

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with cerebral small vessel diseases suggest that impaired tissue perfusion at the microvascular level is one of the triggering factors for migraine pain.[16] Although different hypotheses have been put forward for this deterioration, the main reason has not been fully understood.[17] The effects of nitrates on cerebral blood flow in microvascular level with a migraine-like mechanism may explain the relationship between increased blood viscosity and NIH. Until now, the possible relationship between NIH and whole-blood viscosity (WBV) has not been investigated. In this study, we aimed to investigate the possible relationship between NIH and WBV.

METHODS

Study Population

Patients who had angina symptoms despite being revascularized due to coronary artery disease between June 2020 and July 2022 and were prescribed isosorbide mononitrate, an antianginal nitrate derivative, were enrolled in the study consecutively. Those with a history of chronic headache and migraine, uncontrolled arterial hypertension, a history of analgesic drug or nitrate use in the past 3 months, a history of head trauma in the past 6 months and a history of cerebrovascular event or intracranial surgery were excluded from the study. Patients were categorized and grouped according to a standard, categorical, patient-rated, four-grade headache pain assessment (four-grade scale), where grade 0 indicates the absence of headache, grade 1 indicates mild pain, grade 2 indicates moderate pain, and grade 3 indicates severe pain experience. Overall, 155 patients were categorized in grade 0, 199 patients in grade 1, 357 patients in grade 2, and 158 patients in grade 3 groups. Written consent was obtained from all subjects participating in the study, and the study was approved by the hospital ethics committee.

Nitrate Treatment and Assessment of Headache

Oral 50 mg of isosorbide mononitrate was prescribed to all patients experiencing angina pectoris. In patients who were prescribed oral isosorbide mononitrate, in their outpatient clinic controls 1 week later, it was recorded whether they experienced headache after the start of drug use, and if they developed headache, how severe they felt was recorded by grading according to the four-grade scale. Headache quality was 83% migraineoid and 17% pressure/squeeze type. Nitrate-induced headache was defined as a headache occurring 0.5–6 hours after receiving oral isosorbide mononitrate on at least 2 consecutive days after excluding confounding factors.[18]

Biochemical Measurements and Definitions

Laboratory tests for fasting blood glucose, lipid profile, creatinine levels, complete blood count, and total protein (TP) were performed by standard methods using commercial laboratory kits. WBV values were obtained using serum hematocrit (HcT) and total protein (TP) concentration at both the high shear rate (HSR = 208/s^{-1}) and the low shear rate (LSR = 0.5/s^{-1}). WBV at HSR (208/s^{-1}) was calculated using the formula (0.12 × HcT) + 0.17 (TP – 2.07) and WBV at LSR (0.5/s^{-1}) was calculated with using the formula (1.89 × HcT) + 3.76 (TP – 78.42), where HcT is presented as a percentage and TP as concentration in grams per deciliter.[19]

Hypertension was defined as a systolic blood pressure of ≥140 mm Hg, a diastolic blood pressure of ≥90 mm Hg, or current treatment by any antihypertensive drug. The diagnosis of diabetes mellitus was based on the history of diabetes mellitus or following criteria: fasting plasma glucose >126 mg/dL, HbA1c > 6.5% (48 mmol/mol), and a random plasma glucose >200 mg/dL. Dyslipidemia was defined as the presence of one of the 4 parameters: (1) total cholesterol >200 mg/dL, (2) low-density lipoprotein cholesterol >130 mg/dL, (3) high-density lipoprotein cholesterol <40 mg/dL for male patients and <50 mg/dL for female patients, and (4) triglyceride >150 mg/dL or history of statin use. Glomerular filtration rate was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation formula: glomerular filtration rate = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1) − 1.209 × 0.993 age × 1.018 [if female] _ 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for women and 0.9 for men, α is −0.329 for women and −0.411 for men, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. Body mass index was calculated as weight (kg)/height^2 (m^2). Patients who currently smoke or have recently quit smoking was considered a smoker. Coronary atherosclerotic burden was evaluated with the SYNTAX score.

Statistical Analysis

Statistical Program for Social Sciences 26 (IBM SPSS, Chicago, IL) was used for all statistical calculations. Kolmogorov–Smirnov test was used to determine whether the data fit the normal distribution. Continuous variables that fit the normal distribution were expressed as mean ± SD, and those that did not fit the normal distribution were expressed as median with interquartile range. Comparisons between the groups were analyzed using 1-way analysis of variance. Univariate and multivariate regression analyses were performed to determine the independent predictors of NIH. Receiver operating characteristic curve analysis was performed to determine the predictors of NIH. The optimal cutoff value was calculated from the point of maximum sensitivity and specificity. Two-tailed *P*-values of <0.05 were considered to be statistically significant. All data are reported in accordance with STROBE requirements.

Ethical Approval

The study was performed according to the recommendations set forth by the Declaration of Helsinki on biomedical research involving human subjects. The study was approved by the Ethics Committee of the Harran University Faculty of Medicine.

RESULTS

Basic demographic, clinical, and biochemical characteristics of the study population are given in Table 1. When the grade 0 group was taken as a reference, there was no

TABLE 1. Baseline Characteristics and Outcomes of Patients Classified by 4GS Level

	4GS Level (n = 869)				
Variables	**Grade 0 (No Headache), n = 155**	**Grade 1 (Mild Pain), n = 199**	**Grade 2 (Moderate Pain), n = 357**	**Grade 3 (Severe Pain), n = 158**	***P***
Demographic characteristics and medical history					
Age, y	65.6 ± 6.2	65.7 ± 6.3	65.6 ± 6.3	64.8 ± 6.0	0.554
Gender, male (%)	97 (62.6)	131 (65.8)	217 (60.7)	101 (63.9)	0.195
BMI (kg/m^2)	26.4 ± 3.5	26.3 ± 3.2	26.7 ± 3.4	26.5 ± 3.3	0.473
Diabetes mellitus (%)	65 (41.9)	73 (36.7)	131 (36.7)	55 (34.8)	0.587
Hypertension (%)	112 (72.3)	149 (74.9)	265 (74.2)	126 (79.7)	0.451
Dyslipidemia (%)	125 (80.6)	165 (82.9)	286 (80.1)	125 (79.1)	0.103
Smoking (%)	90 (58.1)	113 (56.7)	189 (52.9)	91 (57.5)	0.543
Cardiovascular measurements					
LVEF (%)	51.4 ± 8.8	49.2 ± 9.3	50.5 ± 9.1	49.4 ± 8.8	0.268
SBP (mm Hg)	136.8 ± 18	134.3 ± 25	135.2 ± 21.6	133.9 ± 23.8	0.224
DBP (mm Hg)	72.4 ± 10.9	70.4 ± 13.6	71.2 ± 11.8	71.6 ± 12.3	0.312
Heart rate (beats per minute)	77.3 ± 14.3	76.3 ± 11.8	75.8 ± 13.3	77.2 ± 15.6	0.189
SYNTAX score	13.6 (11.8–14.3)	14.2 (13.2–15.1)	14.5 (12.5–15.4)	14.6 (10.8–13.3)	0.154
Laboratory results					
FPG (mg/dL)	166.0 ± 89.5	155.0 ± 83.2	147.0 ± 83.5	161.3 ± 74.7	0.568
Creatinine (mg/dL)	1.01 (0.84–1.18)	0.92 (0.84–0.99)	0.89 (0.79–0.98)	0.88 (0.83–0.93)	0.052
Uric acid (mg/dL)	6.0 ± 1.5	5.0 ± 1.6	5.0 ± 1.4	5.5 ± 1.8	0.180
Albumin (mg/dL)	4.0 ± 0.4	4.0 ± 0.4	4.1 ± 0.4	4.3 ± 0.5	0.031
Fibrinogen (mg/dL)	410.8 ± 91.9	409.3 ± 81.4	412.3 ± 94.4	435.9 ± 91.3	0.010
Total protein (g/L)	59.9 ± 6.1	64.0 ± 4.7	67.6 ± 3.5	71.3 ± 3.3	<0.001
Hemoglobin (mg/dL)	13.4 ± 3.5	13.2 ± 2.4	14.7 ± 8.0	15.0 ± 1.96	<0.001
HcT (%)	40.9 ± 5.8	40.7 ± 4.4	42.6 ± 4.6	47.3 ± 6.0	<0.001
Triglycerides (mg/dL)	171.0 (141.7–200.3)	149.0 (129.5–168.6)	173.8 (156.2–191.3)	177.0 (144.6–209.4)	0.924
TC (mg/dL)	173.2 ± 42.1	170.1± 40.8	175.6 ± 45.7	186.5 ± 46.7	0.063
HDL-C (mg/dL)	36.8 (34.1–39.5)	37.1 (32.6–41.6)	38.6 (35.0–42.2)	38.0 (35.7–40.4)	0.754
LDL-C (mg/dL)	104.1 ± 34.2	109.2 ± 34.2	105.2 ± 35.6	113.1 ± 35.4	0.096
HbA1c (%)	7.1 ± 2.2	6.5 ± 2.0	6.7 ± 1.9	7.0 ± 2.1	0.816
CRP (mg/dL)	2.65 (0.83–4.47)	1.95 (0.90–3.00)	2.23 (1.27–3.19)	2.46 (0.26–4.65)	0.928
e-GFR (mL/min)	78.5 (75.0–81.9)	81.7 (79.1–84.4)	82.3 (80.5–84.2)	83.5 (80.8–86.1)	0.093
WBC (×1000/mm^3)	10.2 (9.2–11.1)	9.4 (8.8–10.0)	9.7 (9.3–10.2)	11.5 (10.5–12.5)	0.103
Lymphocyte (×1000/mm^3)	1.95 (1.81–2.09)	2.08 (1.90–2.26)	2.13 (1.92–2.34	2.15 (1.98–2.32)	0.627
Monocytes (×1000/mm^3)	0.63 (0.59–0.68)	0.66 (0.59–0.73)	0.70 (0.63–0.76)	0.77 (0.69–0.85)	0.103
Neutrophil, (×1000/mm^3)	7.13 (6.49–7.77)	6.90 (6.28–7.51)	6.71 (6.35–7.08)	7.55 (6.90–8.21)	0.149
Platelet count (×1000/mm^3)	264.3 ± 81.1	247.1 ± 70.8	263.3 ± 87.1	270.8 ± 96.6	0.053
RDW, fL	12.70 ± 1.41	12.99 ± 1.65	12.79 ± 1.48	12.90 ± 1.56	0.571
MPV, fL	8.02 ± 1.21	8.26 ± 1.45	8.14 ± 1.31	7.85 ± 1.21	0.556
Total bilirubin (mg/dL)	0.68 (0.62–0.73)	0.76 (0.68–0.84)	0.71 (0.66–0.75)	0.74 (0.68–0.80)	0.335
Phosphorus (mg/dL)	3.34 ± 0.95	3.12 ± 0.84	3.31 ± 0.92	3.42 ± 1.15	0.106
Calcium (mg/dL)	9.04 ± 0.60	8.87 ± 0.94	8.91 ± 0.81	9.20 ± 0.56	0.125
Medical therapy					
Antiplatelet (%)	155 (100)	199 (100)	357 (100)	158 (100)	0.999
B-blocker	144 (92.9)	178 (89.4)	331 (92.7)	146 (92.4)	0.875
Statin (%)	142 (91.6)	181 (90.9)	329 (92.1)	147 (93.0)	0.813
CCB (dihydropyridine derivative) (%)	81 (52.2)	113 (56.7)	168 (47.0)	86 (54.4)	0.214
ACEI or ARB (%)	97 (62.5)	136 (68.3)	213 (59.6)	102 (64.5)	0.452
Oral antidiabetic (%)	51 (32.9)	62 (31.1)	112 (31.3)	49 (31.0)	0.622
WBV measurements					
WBV at LSR, 0.5 s^{-1}	8.1 (11.9 to −29.3)	25.6 (28.1 to −23.0)	37.9 (36.5–39.4)	65.2 (62.1–68.3)	<0.001
WBV at HSR, 208 s^{-1}	14.76 ± 1.18	15.61 ± 0.83	16.10 ± 0.70	17.59 ± 1.14	<0.001

Values are presented as mean ± SD, n (%), or median (IQR) unless otherwise stated.

ACEIs, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; CCB, calcium channel blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; FPG, fasting plasma glucose; e-GFR, estimated glomerular filtration rate; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MPV, mean platelet volume; RDW, red cell distribution width; WBC, white blood cell; IQR, interquartile range; 4GS, four-grade scale.

significant difference between the groups in demographics, medical history, cardiovascular measurements, and medical therapy ($P > 0.05$, for all). Albumin, fibrinogen, total protein, hemoglobin, and HcT values were significantly higher in the group describing severe pain (grade 3) compared with the groups describing no headache (grade 0) or mild to moderate pain (grade 1–2) ($P < 0.05$, for all). WBV was significantly higher in grade 1 than in grade 0, grade 2 compared with grade 1, and grade 3 compared with grade 2 at both HSR and LSR ($P < 0.001$, for all) (Figs. 1A, B). NIH development and severity increased as the cutoff values of WBV increased at both high shear rate (WBV at HSR) and low shear rate (WBV at LSR) (Figs. 2A, B). Headache severity correlated with both WBV at HSR (r = 0.657; $P < 0.001$) and WBV at LSR (r = 0.687; $P < 0.001$) (Figs. 3A, B). When multivariate regression analysis was performed to identify independent predictors of NIH development, WBV at HSR (odds ratio: 0.299; 95% confidence interval [CI], 0.098–0.0910; $P = 0.034$) and WBV at LSR (odds ratio: 1.135; 95% CI, 1.075–1.199; $P < 0.001$) were found to be independent predictors of NIH development (Table 2). When the values of WBV to predict NIH at HSR and LSR were evaluated by receiver operating characteristic curve analysis: receiver operating characteristic curve analysis showed that the best cutoff value of the WBV at HSR (15.5 s^{-1}) to predict the NIH was 75% sensitivity and 75% specificity (area under the curve, 0.830; 95% CI, 0.789–0.871; $P < 0.001$) and WBV at LSR (23.5 s^{-1}) to predict the NIH was 77% sensitivity and 77% specificity (area under the curve, 0.837; 95% CI, 0.796–0.878; $P < 0.001$) (Fig. 4).

DISCUSSION

In this study, we found that nitrate-induced headache was more common in individuals with high WBV. This may provide a prediction for clinicians in nitrate selection to increase patient compliance in patients to be started antianginal.

Nitrates are frequently used as antianginal in daily practice.[1] They show these effects by vasodilation through the NO-cGMP axis, but they exert their effects not only on the coronary arteries but also on the cerebral arteries and veins.[2] The adverse effects of nitrate use are also due to these nonselective properties.[3] The most common side effect after nitrate use is headache, and this headache is mostly of the migraineoid type.[3,4,18] The fact that the NO-cGMP pathway is one of the main pathophysiological mechanisms in the pathophysiology of migraine explains the similarity between NIH and migraine pain.[20,21] Therefore, understanding the pathophysiology of migraine will help to understand the pathophysiology of NIH.[6] The etiology of migraine is not completely clear; however, there is a group of views suggesting that the pain in migraine is related to the stimulation of nociceptors as a result of vasodilation of the great cerebral arteries.[6] Studies investigating NO donors, indications of increased pain, when administered acutely have been suggested to support this hypothesis.[21] This hypothesis is paradoxical because dilatation of the large cerebral arteries alone is not recommended in studies examining the net change in cerebral blood flow in migraine patients. There is increasing evidence that lowering the oxygen pressure in inhaled air (through enrichment with carbon dioxide) can provide relief in migraine pain through an autoregulatory mechanism.[7,8] Carbon dioxide is a potent cerebral vasodilator; therefore, considering the mechanism of pain amplification caused by the administration of NO donors such as nitrate, it contradicts the interpretation of studies trying to explain NIH or migraine pain only by vasodilation of the large cerebral arteries. Rather, it has been proposed that with dilation of the great arteries, there is vasoconstriction downstream of the cerebral microcirculation, raising the notion of an alternative causation.[17,22]

One of the major determinants of cerebral blood flow is blood viscosity, and studies have shown that cerebral blood flow regulation has a dominant role in primary headaches such as migraine.[23–26] Whole blood is a non-newtonian fluid, which means that the viscosity of the blood depends on the shear rate. At LSR of whole-blood viscosity (WBV at LSR), blood cells aggregate, resulting in a sharp increase in blood viscosity, whereas at higher shear rate (WBV at HSR), blood cells disaggregate, deform, and align in the direction of flow.[15] The main important determinants of blood viscosity are HcT, presence of macromolecules in the medium, temperature, and deformability of red blood cells, especially at HSR. Blood viscosity plays its most important role in microcirculation, where it contributes significantly to peripheral resistance and can cause red blood cell aggregation in capillary and postcapillary venules.[15] Blood viscosity plays an important role on tissue perfusion.[27,28] This effect is predominantly at the microvascular level. In cases where the blood viscosity is excessively increased, the development of headache is due to the deterioration of tissue perfusion at the capillary and postcapillary levels, which triggers nociceptors.[12–14]

In our study, we found more NIH development in those with high WBV. This effect may be due to reflex vasoconstriction in the microvascular bed as a result of vasodilation of the large cerebral arteries,[17,22] further accentuating the effect of blood viscosity, which is of critical importance for blood flow. Because nitrates cause reflex vasoconstriction at the microvascular level, impair tissue perfusion, and stimulate nociceptors, we can say that blood viscosity, which has a stable hemorheological status under normal conditions, differentiates its hemorheological properties after nitrate use and shows a significant interaction in blood flow mechanics. The

TABLE 2. Multivariate Logistic Regression Analysis for Determining the Independent Predictors of the NIH

Variables	β	SE	OR (95% CI)	*P*
Age	0.000	0.018	1.000 (0.967–1.035)	0.981
Male gender	0.027	0.235	1.028 (0.648–1.630)	0.907
Hypertension	0.057	0.249	1.058 (0.650–1.725)	0.819
Diabetes mellitus	−0.098	0.223	0.906 (0.586–1.402)	0.658
Dyslipidemia	0.316	0.271	1.372 (0.806–2.335)	0.244
WBV at LSR	0.127	0.028	1.135 (1.075–1.199)	<0.001
WBV at HSR	−1.207	0.568	0.299 (0.098–0.0910)	0.034

OR, odds ratio; SE, standard error.

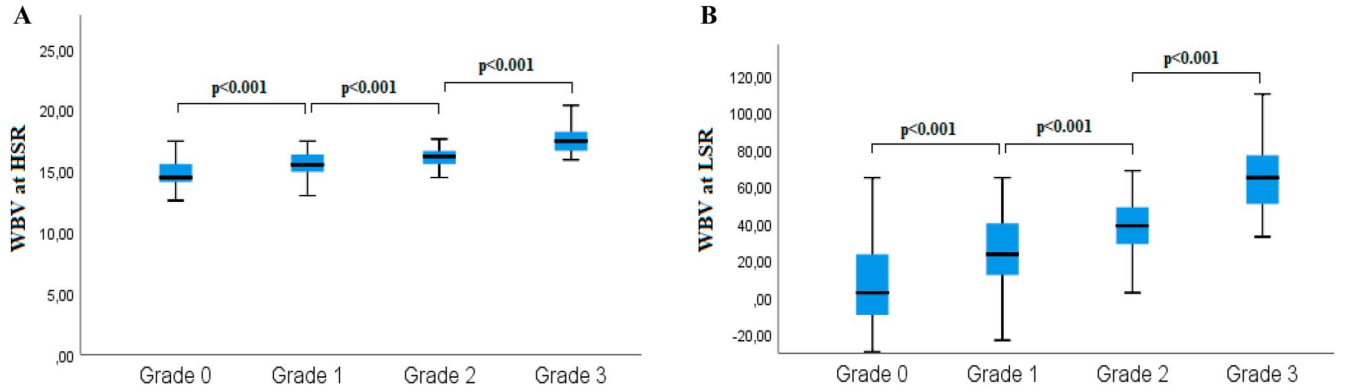

FIGURE 1. Distribution of WBV at HSR (A) and WBV at LSR (B) according to standard categorical 4GS of headache development during follow-up of patients using isosorbide mononitrate. Grade 0 indicates no pain, grade 1 indicates mild pain, grade 2 indicates moderate pain, and grade 3 indicates severe pain. 4GS, 4-grade scale.

increased incidence of headache in individuals with pathologically increased blood viscosity, supporting our postulation.[13,14] We think that the deterioration of the Fåhræus–Lindqvist effect, which is the determinant of the basic hemorheological properties of microvascular flow, after nitrate intake in individuals with high blood viscosity, may be one of the major determinants that can explain our hypothesis. The Fåhræus–Lindquist effect is one of the main factors affecting blood viscosity at the microvascular level.[29–35] The Fåhraeus–Lindqvist effect is a hemodynamic phenomenon that describes how the viscosity of blood changes with the diameter of the vessel through which it passes. In particular, there is a decrease in viscosity as the vessel diameter decreases. This is because the erythrocytes move toward the center of the vessel and leave only plasma near the vessel wall.[31] Because the cell-free layer is poor in red cell, its effective viscosity is lower than that of whole blood.[31] Therefore, this layer acts to reduce flow resistance within the capillary.[31] This has the net effect that the effective viscosity is less than that for whole blood.[31] This effect begins to appear when the vessel diameter is below 1.5 mm.[33] This effect is very pronounced in vessels as thin as capillaries, and its viscosity is half that of the great vessels. The Fåhræus–Lindquist effect creates a free-flowing singular and independent formation of erythrocytes as they pass through these vessels. Thanks to this effect, erythrocytes flow in a single line within the microvessels instead of in a random motion. Thus, the viscous resistance in the blood itself is reduced.[29–35] Diameter-related dynamic changes in blood viscosity, thanks to the Fåhræus–Lindqvist effect, help to ensure the hemorheological hemostasis of the blood under normal conditions, and it is highly possible that nitrates cause this diameter change in the microvessels, disrupting the physiological effect of the Fåhræus–Lindqvist effect and having a side effect such as headache.[29] In addition, red blood cell–plasma coupling problems, which are caused by high plasma proteins that contribute significantly to plasma viscosity, may be aggravated after nitrate use and may contribute to the side effect of headache, which deteriorates the viscosity-reducing effect of the Fåhræus–Lindqvist effect and is more pronounced with nitrate at higher blood viscosity.[36]

In conditions of hyperviscosity such as multiple myeloma, Waldenström's macroglobulinemia, and inflammatory and connective tissue disorders, erythrocytes tend to form rolls instead of free-flowing individual and independent red blood cells in the microvessels, which restricts blood flow in the microvessels, and this limitation of blood flow due to hyperviscosity in cerebral microvessels often presents itself as

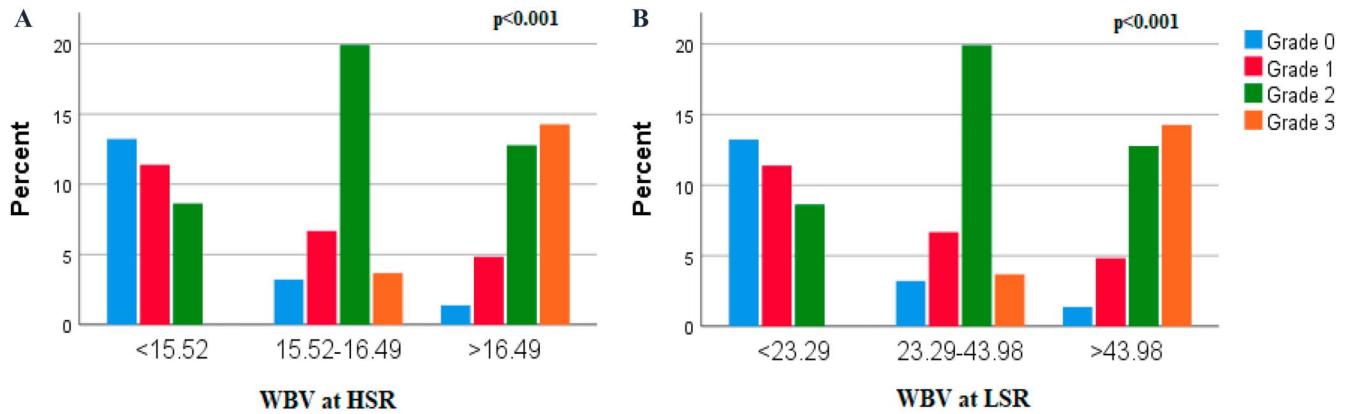

FIGURE 2. Frequency of headache groups (grade 0–3) according to different cutoff values for WBV at HSR (A) and WBV at LSR (B).

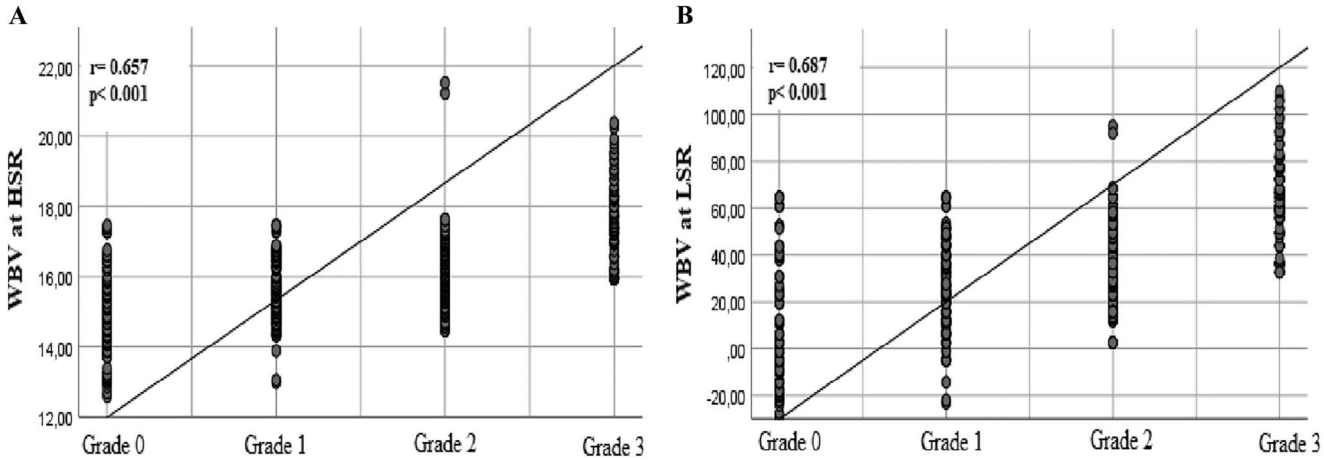

FIGURE 3. Correlation of headache severity with WBV at HSR (A) and WBV at LSR (B).

headache.[12–14,37–39] As a matter of fact, we attribute the more frequent headache side effects of nitrates at higher blood viscosity to the fact that the Fåhræus–Lindqvist effect, which is a physiological viscosity-reducing effect, is impaired by nitrates and has a similar effect to hyperviscosity syndromes.

In an experimental study, it has been shown that dietary nitrate can decrease blood viscosity by suppressing hepatic erythropoiesis and lowering HcT.[40] This may contribute to the development of headache tolerance in the long-term use of nitrates, and these results support a causal relationship between NIH and WBV.

Considering these physiological mechanisms, it can be interpreted that nitrate use may cause microvascular vasoconstriction, similar to the pathophysiology of migraine, and this may impair the Fåhræus–Lindquist effect in individuals with high blood viscosity, making blood flow difficult at the microvascular level and triggering headache in a way that mimics the physiological characteristics of pathologically high blood viscosity. In summary, considering all these interactions, we suggest that nitrates trigger headache in a way that mimics the physiological properties of high blood viscosity.

Limitations

Our study had some limitations. First, our patient population was relatively small. Second, we did not have a healthy control group. Finally, the headache experiences of

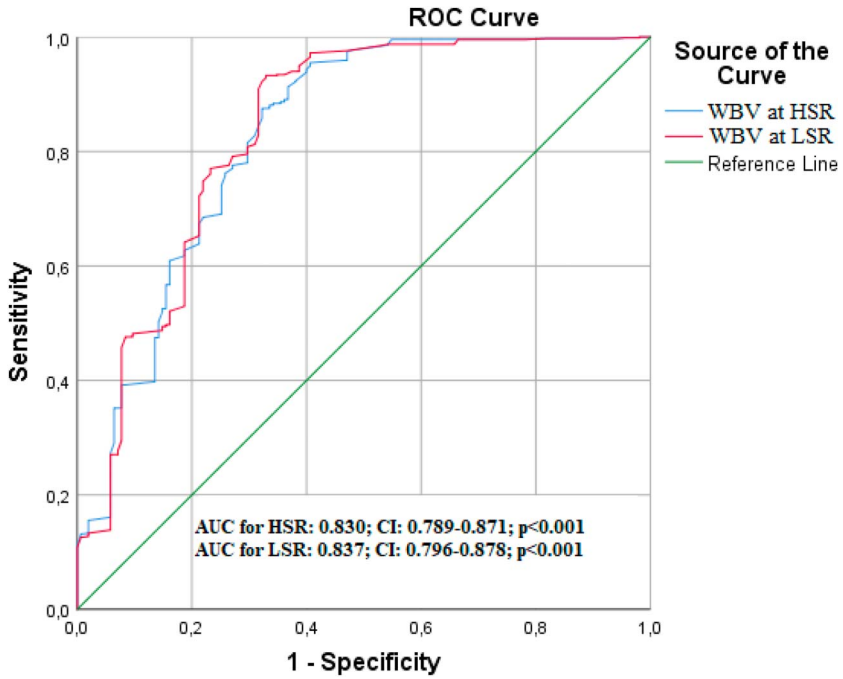

FIGURE 4. ROC curve analysis showed that the best cutoff value of the WBV at HSR to predict the NIH was 75% sensitivity and 75% specificity (AUC, 0.830; 95% CI, 0.789–0.871; $P < 0.001$) and WBV at LSR to predict the NIH was 77% sensitivity and 77% specificity (AUC, 0.837; 95% CI, 0.796–0.878; $P < 0.001$). AUC, area under the curve; ROC, receiver operating characteristic.

the patients were recorded according to the qualitative values they felt, which may have affected the results of the study.

CONCLUSIONS

In our study, we found that individuals with high blood viscosity experienced more NIH, and we found that they experienced more severe headache as blood viscosity increased. This can explain us that nitrate use causes different levels of symptoms in each patient. In summary, we suggest that nitrates trigger headache in a way that mimics the physiological properties of high blood viscosity. In addition, WBV can be a guide for clinicians in the selection of antianginal drugs to increase patient compliance. Larger randomized clinical studies are needed to confirm the results of this study.

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