Predictive Value of Nitrate-Induced Headache on Atherosclerotic Burden in Patients with Stable Coronary Artery Disease

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ABSTRACT

Introduction: Nitrates, which lead to vasodilation in vessels, is one of the cornerstone drugs of antianginal therapy. The most frequently encountered side effect of nitrates is headache, which is linked to vasodilation of the cerebral arteries. Vasodilator response to nitrates is significantly reduced in patients with atherosclerosis. The aim of present study was to assess the relationship between nitrate-induced headache (NIH) and systemic and coronary atherosclerotic burden in patients with stable coronary artery disease.

Patients and Methods: Overall, 40 patients with NIH (group I: 61.2 ± 8.56 years, 32 males) and 62 patients without headache (group II: 63.5 ± 8.45 years, 41 males) were included in the study. Systemic atherosclerotic burden was evaluated by carotid intima-media thickness (CIMT) and cardio-ankle vascular index (CAVI). Coronary atherosclerotic burden was assessed by the Gensini score.

Results: CIMT and CAVI were significantly greater in group II than in group I (0.8 ± 0.20 vs. 0.6 ± 0.20 and 9.5 ± 1.0 vs. 8.4 ± 1.2, respectively; p< 0.001). The Gensini score was also higher in group II than in group I [median 32 (16.7-45.2) vs 12.5 (5.2-19.2); p< 0.001]. In multivariate analysis, headache was found as an independent determinant of CIMT, CAVI, and Gensini score (p< 0.001).

Conclusion: Patients with NIH had a low level systemic and coronary atherosclerotic burden, evaluated by CIMT, CAVI, and Gensini score, compared with those without NIH.

Key Words: Nitrates; headache; atherosclerosis

Kararlı Koroner Arter Hastalığı Olan Hastalarda Nitratların Oluşturduğu Baş Ağrısının Aterosklerotik Yükü Öngörmedeki Değeri

ÖZET

Giriş: Damarlarda genişlemeye yol açan nitratlar antianginal tedavinin köşetaşı ilaçlarından biridir. Nitratların en sık karşılaşılan yan etkisi beyin arterlerinin genişlemesi ile bağlantılı oluşan baş ağrısıdır. Nitratlara karşı damar genişletici cevap aterosklerozlu hastalarda anlamlı olarak azalmıştır. Bu çalışmanın amacı kararlı koroner arter hastalığı olan hastalarda nitratların indüklediği baş ağrısı (NİB) ile sistemik ve koroner aterosklerotik yük arasındaki ilişkiyi belirlemektir.

Hastalar ve Yöntem: NİB olan kırk hasta (grup I: 61.2 ± 8.56 yıl, 32 erkek) ve NİB olmayan atmış iki hasta (63.5 ± 8.45 yıl, 41 erkek) çalışmaya kaydedildi. Sistemik aterosklerotik yük karotis intima-media kalınlığı (KİMK) ve kalp-ayak bileği damar indeksi (KADİ) ile değerlendirildi. Koroner aterosklerotik yük, Gensini skoru ile değerlendirildi.

Bulgular: KİMK ve KADİ grup ll'de grup I'e göre anlamlı olarak daha büyüktü. (0.8 ± 0.20 karşı 0.6 ± 0.20 ve 9.5 ± 1.00 karşı 8.4 ± 1.20 p< 0.001, sırasıyla). Gensini skoruda grup ll'de grup l'den daha yüksekti. [ortanca 32 (16.7-45.2) karşı 12.5 (5.2-19.2) p< 0.001]. Multivariate analizde baş ağrısı KİMK, KADİ ve Gensini skorunun bağımsız belirleyicisi olarak bulundu (p< 0.001).

Sonuç: NİB olan hastalar NİB olmayanlarla karşılaştırıldığında KİMK, KADİ ve Gensini skoru ile belirlenmiş düşük seviyede sistemik ve koroner ateroskleroz yüke sahiptir.

Anahtar Kelimeler: Nitrat; baş ağrısı; ateroskleroz

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Submitted: 05.10.2015
Accepted: 12.10.2015

INTRODUCTION

A number of methods have been applied for non-invasive and invasive assessments of atherosclerotic burden and cardiovascular risk. These include cardio-ankle vascular index (CAVI), carotid intima-media thickness (CIMT), and Gensini score. CAVI, which represents overall stiffness of the artery from the origin of the aorta to the ankle, is closely related to many atherosclerotic diseases such as coronary artery disease and carotid atherosclerosis[1]. Similarly, CIMT is widely accepted as a surrogate marker for systemic atherosclerosis[2]. The Gensini score, which is calculated based on the localization of stenotic coronary artery segments and the degree of their lumenstenos, reflects the severity of coronary lesions [3].

Oral nitrates hold prominent roles in the management of angina pectoris in coronary artery disease. They provide antianginal effects as well as vasodilatation of veins and systemic and coronary arteries[4]. These vasodilator effects on the arterial smooth muscle are reduced in patients with atherosclerosis[5]. Nitrate-induced headache (NIH) is the most common side effect and occurs because of vasodilation in the cerebral arteries[6]. There is scarce data about the relationships between NIH and atherosclerosis markers. The aim of this study was to investigate the associations between NIH and atherosclerosis markers, assessed using CAVI, CIMT, and Gensini score.

PATIENTS and METHODS

Study Population

This cross-sectional, prospective, and observational study was conducted from October 2014 to January 2015. Overall, 150 patients undergoing coronary angiography because of anginal chest pain and evidence of documented myocardial ischemia via exercise treadmill or myocardial scintigraphy were enrolled consecutively. Any patient who underwent a previous percutaneous coronary intervention or coronary artery bypass graft operation or had acute coronary syndrome, known peripheral artery disease, intermittent claudication, any peripheral artery revascularization, acute or chronic heart failure, moderate to significant valvular disease, or renal or liver disease were excluded. In addition, any patient who had a history of chronic headache and migraine, uncontrolled arterial hypertension, analgesic drug use, or nitrate use was excluded from the study.

Assessment of CAVI

CAVI was measured in the morning with a VaSera VS-1000 CAVI instrument (Fukuda Denshi Co. Ltd., Tokyo). All measurements were obtained before coronary angiography and nitrate prescription. Briefly, cuffs were applied to the bilateral upper arms and ankles while the subject was in the supine position. Electrography, phonocardiography, and pressures and waveforms of brachial and ankle arteries were measured. Then, CAVI was automatically calculated by the device.

Assessment of CIMT

CIMT measurement was performed in the right common carotid arteries using gray scale B-mode imaging ultrasonography (Esaote Mylab equipped with a 7.5-MHz linear imaging transducer probe). Subjects were placed in the supine position, and their heads were tilted slightly to the left. We scanned the common carotid artery from the carotid bifurcation to the proximal portion as far as possible in three longitudinal sections. Then, CIMT was evaluated as the distance between the lumen intima interface and the media-adventitia interface from these portions. The average of the three CIMT measurements was used for analyses.

Coronary Angiography and Gensini Score

Coronary angiography was performed by the Judkins technique. Each angiogram was analyzed independently by two experienced interventional cardiologists who were blinded to the patient clinical data. In cases of disagreement, the decision of a third observer was obtained, and the final decision was made by consensus. Coronary artery severity was assessed by the Gensini score. The Gensini score is computed by assigning a severity score to each coronary stenosis according to the degree of luminal stenosis and its importance based on position. More specifically, reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion were given a Gensini score of 1, 2, 4, 8, 16, and 32, respectively. This score is multiplied by a factor accounting for the importance of the lesion location in the coronary arterial tree, such as 2.5 for proximal LAD and 1 for proximal RCA. The severity of the disease is expressed as the sum of the scores for individual lesions[3].

Assessment of NIH

Forty milligrams of isosorbide mononitrate (ISMN) were prescribed to all patients at least 3 days prior to coronary angiography. Then, patients were questioned about the presence of headache before coronary angiography. NIH was defined as the presence of headache occurring 0.5-3 h after receiving oral ISMN for at least two consecutive days, according to the literature[7].

Statistical Analysis

Categorical variables were expressed as percentage values. Continuous variables that have normal distribution were assessed using Kolmogorov-Smirnov test. Variables that have normal distribution were expressed as mean ± standard deviation and those that do not have normal distribution were expressed as median and 25-75th percentiles. Student's t-test and Mann-Whitney U test were used when appropriate. The relationship between atherosclerotic burden indicators, including CAVI, CIMT, Gensini score, and other continuous variables, was assessed by either Pearson or Spearman correlation analysis when appropriate. To determine the independent variables of CAVI, CIMT, and Gensini score, a linear regression model was used for each indicator. Initially, the continuous parameters that have a significance univariate relationship with CAVI, CIMT, and Gensini score were detected by correlation analysis ($p < 0.1$). Later, the categorical variables that have differences for CAVI, CIMT, and Gensini score were established. Finally, each of the regression models was created using these variables. A p-value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) statistical software (SPSS 13.0, IL, USA).

RESULTS

The demographic and clinical characteristics of patients are summarized in Table 1. Initially, 150 consecutive patients were enrolled. However, 16 patients refused coronary angiography, and 32 patients had normal coronary arteries. Thus, 102 patients with coronary artery disease were included. Patients were divided into two groups according to the presence of NIH. Group 1 included patients with NIH, and group 2 included patients without NIH. There were no significant differences between the groups in terms of sex, risk factors, blood pressure, or medications. However, CIMT, CAVI, and Gensini score were significantly higher in group 2 than in group 1 ($p< 0.001$; Table 1).

Using univariate correlation analysis, there were significant relationships between age and CIMT, CAVI, and Gensini score. Additionally, there was a significant correlation between LDL and Gensini score. However, creatinine, triglyceride, and HDL were not correlated with CIMT, CAVI, or Gensini score (Table 2). In addition, there was a significant relationship between DM and CAVI, but no significant relationships between other categorical variables such as gender, HT, and smoking and CIMT, CAVI, and Gensini score were observed (Table 3). Using multivariate analysis, headache was found to be an independent determinant of CIMT [β -0.129; 95% confidence interval (CI) -0.205 to -0.052; $p< 0.001$], CAVI (β -0.818; 95% CI -1.278 to -0.358; $p< 0.001$) and Gensini score (β -0.348; 95% CI -0.502 to -0.194; $p< 0.001$; Table 4).

DISCUSSION

In this study, we compared the levels of systemic and coronary atherosclerotic burdens evaluated by CIMT, CAVI, and Gensini score in patients with and without NIH. All of these measures were higher among patients without NIH than those with it.

Nitrates have been used as antianginal agents in the treatment of patients with coronary artery disease for more than 100 years[8]. The therapeutic effect of these drugs is based on their vasodilatation effects mediated by the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) pathway located in the endothelium layer. The vasodilatation of veins and systemic and coronary arteries provides the same favorable hemodynamic effects on the circulatory system, such as decreases in pulmonary and systemic vascular resistances, ventricular preload, and myocardial wall stress and increases in myocardial blood flow[9,10]. However, vasodilatation of the cerebral arteries causes headache, the most common adverse reaction of taking nitrates[11,12]. The relationship between nitrates and vasodilation of cerebral arteries was assessed in some studies[13-15]. Using magnetic resonance angiography, Hansen et al. found dilatation of the middle cerebral artery after infusion of glyceryl trinitrate in healthy volunteers[13]. Dahl et al. evaluated the effect of nitroglycerine on cerebral circulation using SPECT[14]. Bednarczyk et al. assessed brain-blood flow using positron emission tomography and

Table 1. Comparison of baseline demographic properties of the study population

	Group 1 (headache) (40 patients)				Group 2 (No headache) (62 patients)				p
	n (%)	Mean ± SS	Median	25-75th quartiles	n (%)	Mean ± SS	Median	25-75th quartiles	
Age *		61.2 ± 8.56				63.5 ± 8.45			0.071
Gender, male	32 (80.0)				41 (66.1)				0.129
Hypertension	25 (62.5)				40 (64.5)				0.836
Diabetes	10 (25.0)				16 (25.8)				0.327
Dyslipidemia	20 (50.0)				36 (58.1)				0.073
Smoking	20 (50.0)				24 (38.7)				0.261
Glucose **			98.5	90-115.3			101	90.8-120.8	0.393
LDL **			137	112-160			144	124-190.8	0.053
Triglyceride**			156	119-220.8			142	97.8-193.3	0.147
HDL**		38.5 ± 7.72				37.8 ± 5.61			0.631
Creatinine **			0.9	0.8-1.0			1	0.7-1	0.673
CIMT (mm)		0.6 ± 0.20				0.8 ± 0.20			< 0.001
CAVI		8.4 ± 1.20				9.5 ± 1.00			< 0.001
Gensini score			12.5	5.2-19.2			32	16.7-45.2	< 0.001

LDL: Low-density lipoprotein; CIMT: Carotid intima-media thickness; CAVI: Cardio-ankle vascular index; Continuous values are expressed as years (*) and mg/dL (**).

Table 2. Univariate correlation analysis between continuous variables and atherosclerotic burden indicators

	CIMT		CAVI		Gensini score	
	r	p	r	p	r	p
Age	0.292	0.003	0.381	< 0.001	0.205	0.039
LDL	-0.115	0.251	0.147	0.141	0.218	0.028
Triglyceride	-0.070	0.482	0.049	0.623	0.018	0.856
HDL	0.065	0.525	0.156	0.434	0.023	0.724
Creatinine	0.067	0.502	0.045	0.655	0.101	0.311

CIMT: Carotid intima-media thickness; CAVI: Cardio-ankle vascular index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

Table 3. Univariate relationship between nominal demographic features and atherosclerotic burden indicators

	CIMT		CAVI		Gensini score	
	Mean ± SD	p	Mean ± SD	p	Mean ± SD	p
Gender						
Female	0.7 ± 0.20	0.377	9.1 ± 1.27	0.932	31.5 ± 23.40	0.182
Male	0.7 ± 0.19		9.1 ± 1.32		25.2 ± 20.34	
HT						
Yes	0.7 ± 0.20	0.076	9.1 ± 1.26	0.557	27.8 ± 23.35	0.642
No	0.6 ± 0.19		9.0 ± 0.32		25.7 ± 17.42	
DM						
Yes	0.7 ± 0.22	0.234	9.6 ±1.09	< 0.001	25.7 ± 22.95	0.624
No	0.7 ± 0.18		8.7 ± 1.29		27.8 ± 20.40	
Smoking						
Yes	0.7 ± 0.22	0.333	8.8 ± 1.41	0.083	22.2 ± 18.22	0.048
No	0.7 ± 0.17		9.3 ± 1.14		30.6 ± 22.90	
Headache						
Yes	0.6 ± 0.18	< 0.001	8.4 ± 1.27	< 0.001	16.6 ± 17.69	< 0.001
No	0.7 ± 0.19		9.5 ± 1.08		33.7 ± 20.89	

CIMT: Carotid intima-media thickness; CAVI: Cardio-ankle vascular index; HT: Hypertension; DM: Diabetes mellitus.

Table 4. The results of multivariate analysis between atherosclerotic burden indicators and other variables

	β	t	95% CI		p
CIMT					
Age	0.004	1.917	0.000	0.009	0.058
HT	0.053	1.351	-0.025	0.130	0.180
Headache	-0.129	-3.328	-0.205	-0.052	< 0.001
CAVI					
Age	0.038	2.877	0.012	0.064	0.005
DM	0.554	2.429	0.101	1.006	0.017
Smoking	-0.016	-0.707	-0.602	0.286	0.2481
Headache	-0.818	-3.530	-1.278	-0.358	< 0.001
Gensini score					
Age	0.004	0.833	-0.005	0.012	0.407
LDL	0.001	1.366	-0.001	0.003	0.175
Smoking	-0.046	-0.614	-0.195	0.103	0.540
Headache	-0.348	-4.482	-0.502	-0.194	< 0.001

CIMT: Carotid-intima media thickness; CAVI: Cardio-ankle vascular index; HT: Hypertension; DM: Diabetes mellitus; LDL: Low-density lipoprotein; CI: Confidence interval.

transcranial Doppler in the nitroglycerin model of migraine[15]. Previous studies reported that the vasodilator response of arterial smooth muscles to nitrates is impaired in patients with atherosclerosis[16]. Lai et al. evaluated the vasodilator response of the carotid artery to nitrates using high-resolution ultrasonography and demonstrated that dilation was impaired in early-stage atherosclerosis. In addition, they found that the carotid vascular elasticity induced by nitrates was lessened in patients with severe coronary artery disease[17].

Some studies suggesting the clinical importance of NIH have recently been published in the literature. Hsi et al. reported that glyceryl trinitrate causes significantly more frequent headache episodes in patients with normal coronary arteries than in those with obstructive coronary artery disease[18]. This finding was confirmed using glyceryl trinitrate by Cho et al., who also showed that patients with NIH had smaller CIMTs and lower heart-carotid pulse wave velocities than those without NIH[19]. These results were consistent with our study. In contrast to our research, these two studies evaluated headache episodes in patients with and without coronary artery disease. The relationship between coronary atherosclerotic burden and NIH was not investigated. We also evaluated coronary atherosclerotic burden using the Gensini score, suggesting the diffusiveness and severity of coronary disease[(3)]. In our study, patients with NIH had lower Gensini scores than those without NIH.

Clinical Implications

This study demonstrated a significant relationship between NIH and atherosclerotic burden in both coronary and systemic arteries evaluated by the Gensini score, CAVI, and CIMT. The results may have potential clinical importance. Initially, systemic atherosclerotic burden is higher among patients without NIH than those with it. Therefore, it has been assumed that these patients have an increased risk of major adverse cardiovascular events such as stroke. Later, it is the coronary atherosclerotic burden that is higher among those without NIH. Thus, it has been thought that patients without NIH may have more serious coronary disease than those with it. Therefore, more aggressive risk stratification and treatment may be applied to patients with NIH.

Study Limitations

The number of patients is relatively small. In addition, our study design was cross sectional; thus, it does not allow conclusions regarding pathophysiological mechanisms.

CONCLUSION

We demonstrated that systemic and coronary atherosclerotic burden was lower in patients with NIH than in those without it. The absence of NIH may be an additional marker for identifying increased coronary and systemic atherosclerotic burden in patients with stable coronary artery disease.

CONFLICT of INTEREST

There are no conflict of interest for all authors.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: HE, GK, LK, ŞÇ
Analysis/Interpretation: HE, LK, İGÇ, ŞÇ
Data acquisition: HE, GK, LK, İGÇ
Writing: HE, GK, ŞÇ, İGÇ
Critical revision: ŞÇ
Final Approval: All of authors

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