Relationship between Nitrate-Induced Headache and Coronary Artery Lesion Complexity

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Abstract

Objective: The aim of the present study was to investigate the association between nitrate-induced headache (NIH) and the complexity of coronary artery lesions in patients with stable coronary artery disease (CAD). *Subjects and Methods:* Two hundred and seventy-five patients with anginal chest pain who underwent coronary angiography were enrolled in the present study. NIH was defined as the presence of headache due to nitrate treatment (isosorbide mononitrate 40 mg) after excluding confounding factors. Coronary artery lesion complexity was assessed by the SYNTAX score (SXscore) using a dedicated computer software system. *Results:* The mean SXscore was lower in the patients with NIH than in patients without NIH (7.3 ± 5.2 vs. 14.4 ± 8.5, respectively; p < 0.001). Additionally, patients with NIH had a lower rate of multivessel disease compared with those without NIH (the mean number of diseased vessels was 1.5 ± 0.7 and 2.0 ± 07, respectively; p < 0.001). In multivariate analysis, increasing age (p = 0.02) and headache (p = 0.001) were found to be in-dependent determinants of SXscore. *Conclusion:* The present study demonstrated an independent inverse association between NIH and SXscore. The NIH could provide important predictive information about coronary artery lesion complexity in patients with stable CAD.

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Introduction

The SYNTAX score (SXscore), which was developed based on the coronary anatomy and lesion characteristics, is an angiographic scoring system that represents lesion complexity [1–3]. The SXscore is not only used to quantify coronary lesion complexity but also to predict major adverse cardiac events after percutaneous coronary revascularization in patients with multivessel and/or left main coronary artery disease (CAD) [4–6].

Nitrates, which lead to vasodilation in arteries and veins, are used to relieve angina pectoris in patients with coronary disease [7]. The most frequently encountered side effect of nitrates is headache, which may be linked to vasodilation of the cerebral arteries due to direct activation of the nitric oxide-cyclic guanosine monophosphate

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

	Patients with NIH (76 patients)	Patients without NIH (114 patients)	p
Age, years	61±9.7	64±8.6	0.06
Gender, male, n (%)	58 (76.3)	79 (69.3)	0.2
Hypertension, n (%)	45 (59.2)	59 (51.8)	0.3
Diabetes mellitus, n (%)	19 (25)	32 (28)	0.6
Dyslipidemia, n (%)	30 (39.5)	47 (41.2)	0.8
Smoking, n (%)	30 (39.5)	37 (32.5)	0.3
BMI	28.03±3.18	27.76±2.41	0.1
Glucose, mg/dl	104.2±28.4	124±56.4	0.045
Creatinine, mg/dl	0.93±0.2	0.95±0.2	0.2
LDL, mg/dl	143±32	154±38	0.05
Triglycerides, mg/dl	184±66	173±74	0.3
HDL, mg/dl	38.52±7.73	37.8±5.61	0.6
ACE or ARB, n (%)	27 (35)	47 (41)	0.4
β-Blockers, n (%)	20 (26)	28 (24)	0.7
Calcium channel blockers, n (%)	18 (23)	22 (19)	0.5
Cholesterol-lowering drugs, n (%)	15 (19)	26 (22)	0.6
ASA, n (%)	19 (25)	34 (29)	0.4
Single-vessel disease, n (%)	45 (59.2)	29 (25.4)	<0.001
Two-vessel disease, n (%)	20 (26.4)	52 (45.6)	0.007
Three-vessel disease, n (%)	11 (14.4)	33 (28.9)	0.02
Mean number of diseased vessels	1.5±0.7	2.0±0.7	<0.001
SXscore	7.3±5.2	14.4±8.5	<0.001

BMI = Body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein; ACE/ARB = angiotensin-converting enzyme/angiotensin receptor blocker; ASA = acetylsalicylic acid.

pathway [8]. There exists an inverse relationship between nitrate response and atherosclerosis. A large number [9, 10] of studies have shown that vasodilator response of the arterial smooth muscles to exogenous nitric oxide is significantly reduced in patients with atherosclerosis. In addition, nitrate-induced headache (NIH) episodes are more frequent in patients with normal coronary arteries than in patients with obstructive CAD [11–13]. However, there is no information about the relationship between NIH and coronary artery atherosclerotic burden and lesion complexity. Accordingly, the aim of the present study was to investigate the association between NIH and coronary artery lesion complexity assessed by SXscore in patients with stable CAD.

Subjects and Methods

Patient Selection
The study population consisted of patients who were admitted to the Outpatient Cardiology Clinic due to chest pain from June 2014 to October 2014. Two hundred and seventy-five patients who

had symptoms of angina and evidence of ischemia demonstrated by noninvasive testing such as exercise treadmill test or myocardial scintigraphy were enrolled in the study consecutively. Eighty-five patients were excluded from the study: 32 who refused coronary angiography and 53 who had normal coronary arteries or minimal coronary disease where SXscore could not be calculated, who had known CAD, previous percutaneous coronary intervention or coronary artery bypass grafting, a history of chronic headache and migraine, uncontrolled arterial hypertension, and those receiving analgesic drugs and nitrates before the enrollment. Thus, 190 patients with obstructive CAD were included in the final statistical analysis of the study. The patients were divided into two groups according to the presence or absence of NIH (76 patients with NIH and 114 patients without NIH). Baseline demographic and angiographic characteristics of the patients with and without NIH are presented in table 1. Patients with a systolic blood pressure of >140 mm Hg and/or those with diastolic blood pressure of >90 mm Hg or those using antihypertensive drugs were considered hypertensive; patients with a fasting glucose level of >126 mg/dl or those with a 2-hour postprandial blood glucose level of ≥200 mg/dl and/or those receiving oral hypoglycemic agents or insulin (to lower blood glucose levels) were considered to have diabetes mellitus. Smoking status was defined as being a current smoker or ex-smoker. (Hypercholesterolemia was defined as a total cholesterol level of >200 mg/dl or use of medications.) Body mass index was

calculated as weight (kg) divided by the square of height (m^2). The study protocol was approved by the Institution's Ethics Committee and written informed consent was obtained from the patients.

Nitrate Treatment and Assessment of Headache

Acetylsalicylic acid, beta-blockers, cholesterol-lowering drugs, and nitrate were prescribed to patients according to the recommendations of the current guidelines. Isosorbide mononitrate 40 mg was prescribed to all patients. Coronary angiography was performed after a mean of 5 ± 2 days. The presence or absence of headache in the patients receiving oral isosorbide mononitrate was recorded before coronary angiography. NIH was defined as a headache occurring 0.5–3 h after receiving oral isosorbide mononitrate on at least 2 consecutive days, as described previously [14].

Determination of Coronary Atherosclerosis Complexity

All coronary angiographies were performed using the Judkins technique. Two experienced interventional cardiologists (H.E. and G.K.), both of whom were blinded to the patients' data, evaluated each angiogram independently. If there was disagreement, a final decision was obtained by consensus with a third cardiologist's assessment. Coronary atherosclerotic burden was evaluated by semiquantitative (number of diseased coronary arteries) and quantitative (SXscore) methods. Severe CAD was defined as a 50% or greater luminal narrowing in one or more of the left or right coronary arteries or in their major branches. Total SXscore was calculated by summing the separate score of each coronary lesion causing ≥50% stenosis in vessels with a diameter of ≥1.5 mm, which was obtained using the SXscore algorithm [3].

Statistical Analysis

Statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS Inc., Chicago, Ill., USA) statistical software version 13.0. Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as percentages. Normal distribution of the variables was assessed using the Kolmogorov-Smirnov test and histogram. The unpaired t test and the Mann-Whitney U test were used for continuous variables, where appropriate; χ^2 and Fisher's exact tests were used for categorical variables. The relationship between SXscore and other parameters was analyzed by univariate correlation analysis. Multiple regression analysis was performed to determine the relationship between independent variables and SXscore. Categorical variables which showed a difference for the SXscore and continuous variables which showed a correlation ($p < 0.1$) with the SXscore were included in the multiple analysis. Logarithmic transformation was performed for nonnormally distributed continuous variables. A p value of less than 0.05 was considered statistically significant.

Results

Baseline Properties

Baseline demographics, and laboratory and medication features of the study population are given in table 1. Age, gender, hypertension, diabetes mellitus, dyslipidemia, smoking, and body mass index were similar in pa-
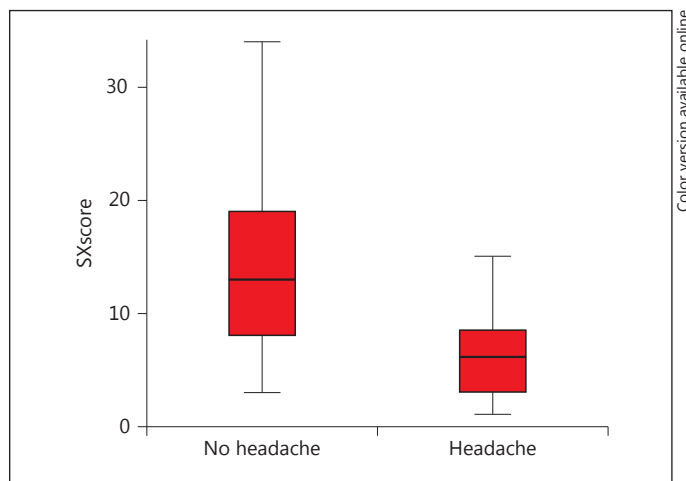
Fig. 1. Comparison of the mean SXscore in patients with and without NIH.

Table 2. Results of multiple linear regression analysis between SXscore and other variables

	Beta	t	95% CI	p
Age	0.228	3.505	0.004 to 0.13	0.02
Gender	−0.081	−1.263	−0.148 to 0.032	0.32
LDL	0.107	1.723	0.000 to 0.002	0.09
Headache	−0.399	−6.274	−0.352 to −0.183	0.001

CI = Confidence interval; LDL = low-density lipoprotein.

tients with NIH and in those without NIH. In laboratory findings there were no differences except for blood glucose level (104.2 ± 28.4 vs. 124 ± 56.4; p = 0.045). In addition there was a tendency for significance in low-density lipoprotein (143 ± 32 vs. 154 ± 38; p = 0.05). Also medications of both groups were similar.

Coronary Angiographic Findings

The number of patients with single-vessel disease was higher among patients with NIH than without NIH [45 (59.2%) vs. 29 (25.4%); p < 0.001] and the number of patients with three-vessel disease, the mean number of diseased vessels and the mean SXscore were lower in the patients with NIH than in those without NIH [11 (14.4%) vs. 33 (28.9%), p = 0.02; 1.5 ± 0.7 vs. 2.0 ± 0.7, p < 0.001, and 7.3 ± 5.2 vs. 14.4 ± 8.5, p < 0.001, respectively; fig. 1].

Multivariate analysis demonstrated that increasing age and headache were independent determinants of SXscore (table 2). In addition, patients with CAD (76, 40%) had
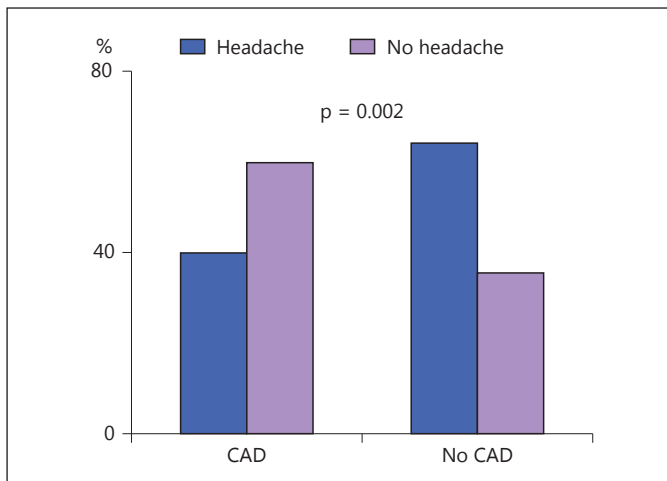
Erkan/Kırış/Korkmaz/Ağaç/Çavuşoğlu/
Dursun/Yılmaz/Aslan/Kırcı/Çelik

Fig. 2. Comparison of the frequency of headache in patients with and without severe CAD; the rate of patients without headache significantly differed between patients with and without severe CAD (p = 0.002).

less headache than patients with normal coronary arteries or minimal CAD (34, 64.2%) and the difference was statistically significant (p = 0.002, fig. 2).

Discussion

In this study, we found an independent relationship between NIH and coronary artery lesion complexity evaluated by SXscore. Additionally, NIH occurred more frequently in patients with normal coronary arteries than in those with obstructive CAD. Equally important, the number of patients with single-vessel disease was higher among patients with NIH than among those without NIH. In contrast, the number of patients with three-vessel disease and the mean number of diseased vessels were lower in patients with NIH than in those without NIH in the present study.

Nitrates play a prominent role in the management of angina pectoris in CAD. The nitrates provide an antianginal effect with vasodilation in veins, and systemic and coronary arteries [15]. In addition, nitrates lead to vasodilation in intracranial arteries in humans [16, 17]. As a consequence of vasodilation of the intracranial arteries, cerebral blood flow increases and vascular-type headache is triggered [18]. In atherosclerosis, this vasodilator effect of nitrates is impaired [19]. Because of these findings, a possible relationship between NIH and atherosclerosis had been suggested [11]. Hsi et al. [11] demonstrated that nitrates caused more frequent headache episodes in pa-

tients with normal coronary arteries than in those with obstructive CAD, and our results are consistent with this explanation because in our study population, NIH developed more frequently in patients with normal coronary arteries than in those with obstructive CAD. Furthermore, in our study the finding that NIH developed more frequently in patients with single- than in those with multiple-vessel disease confirmed the findings of Cho et al. [12], who had reported that NIH was associated with mild (nonobstructive) CAD in patients with chest pain.

In an another study, an inverse association between NIH and surrogate systemic atherosclerosis markers was demonstrated in patients with chest pain [13]. Coronary atherosclerosis is a variant of systemic atherosclerotic disease and there is a significant relationship between coronary artery lesion complexity and systemic atherosclerotic burden [20]. Identifying patients with complex coronary lesions may be important to obtain prognostic information, decision of appropriate revascularization procedure, and for prevention and treatment of complications in percutaneous coronary intervention [6, 21–24]. Therefore, some noninvasive methods were proposed to predict the SXscore in patients who have atherosclerosis [25, 26]. In this study, we also demonstrated that NIH as a noninvasive indicator could provide predictive information about SXscore in patients with stable CAD. The previously mentioned studies only demonstrated the relation between NIH and qualitative CAD (presence or absence and obstructive or nonobstructive). Moreover, as the main difference from our study, neither of them investigated the relationship between NIH and coronary atherosclerotic burden taking into account the number of diseased vessels and lesion properties such as bifurcation or trifurcation, lesion length, severe calcification, and chronic total occlusion etc. Considering these results, we are of the opinion that patients with less pain in response to nitrate treatment have a high atherosclerotic burden and increased coronary artery lesion complexity. Therefore, patients with typical anginal chest pain and risk factors for CAD and without NIH may have excessive CAD and may be at increased risk of major adverse events. Thus, a more careful clinical evaluation should be performed in such patients.

Major limitations of the present study included: (a) the relatively moderate patient population; (b) lack of a questionnaire to grade headache severity – SXscore may be different between patients with severe and with mild or no headache, and (c) the cross-sectional design of the study. Thus, conclusions regarding pathophysiological mechanisms could not be drawn.

Conclusion

An independent association between NIH and SX-score was demonstrated in the present study. In patients with CAD, assessment of headache response to nitrate treatment could provide valuable information in terms of the presence, extent and complexity of coronary artery lesions regardless of the relief of angina symptoms. Further studies on the clinical significance of this association are needed.

Disclosure Statement

The authors have no conflicts of interest to reveal.

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