

# Nitroglycerin-Induced Headache is Associated With Mild Coronary Artery Disease in Patients With Chest Pain

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## ABSTRACT

**Background and Objectives:** We hypothesized that patients with nitroglycerin-induced headache had preserved systemic vasomotion and there might be an increased nitroglycerin-mediated dilation (NMD) response in the brachial artery. The aim of this study is to evaluate whether nitroglycerin (NTG)-induced headache is associated with the level of the NMD and flow-mediated dilation (FMD) or the severity of coronary artery disease (CAD). **Subjects and Methods:** The study included 87 patients (Group I: mean age:  $54.8 \pm 9.5$  years, 46 males) with headache and new onset chest pain, and 109 patients (Group II: mean age:  $57.4 \pm 8.9$  years, 67 males) without headache and with new onset of chest pain. Patients were excluded from this study if they had a history of chronic headache, long term nitrates use and coronary artery procedures. Coronary angiography was performed within one month after administering nitroglycerin for the usual clinical indications. **Results:** The clinical characteristics did not differ between the two groups. The NMD was significantly higher in Group I than in Group II ( $23.0 \pm 7.5\%$  vs.  $18.5 \pm 8.6\%$ , respectively,  $p < 0.001$ ). The FMD was significantly higher in Group I than in Group II ( $9.0 \pm 4.1\%$  vs.  $7.5 \pm 4.3\%$ , respectively,  $p = 0.007$ ). On multiple regression analysis, NTG-induced headache was a predictor of CAD {odds ratio (OR), 0.04, 95% confidence interval (CI), 0.02-0.11;  $p < 0.001$ , respectively}. **Conclusion:** We have shown that the vasodilator response to NTG and FMD are increased in the patients with NTG-induced headache. More NTG-induced headache developed in the patients with normal coronary arteries or minimal CAD than in the patients with obstructive CAD. This finding might be helpful as additional information for evaluating the patients with chest pain syndrome. (Korean Circ J 2008;38:524-528)

**KEY WORDS:** Endothelium vascular; Nitrates; Coronary arteries.

## Introduction

Nitroglycerin (NTG) was discovered in 1847 by Ascanio Sobrero in Turin, following the work with Theophile-Jules Pelouze. Sobrero first noted the 'violent headache' produced by minute quantities of NTG on the tongue.<sup>1)</sup> NTG acts directly at the level of the arterial smooth muscle cells and it produces an endothelium-independent dilation response.<sup>2)</sup> Headache is currently the most prominent side effect of nitrate therapy in patients with

chest pain. Much work has been published regarding the role of increased nitric oxide (NO) in migraine subjects during acute migraine attacks.<sup>3,4)</sup> In a migraine attack, the intracranial arteries on the headache side dilate and when the migraine attack has subsided, they return to baseline values.<sup>5,6)</sup> Besides, when an exogenous source of NO is developed by administering sublingual nitrates for examining the vasodilating effect, the capacity of blood vessels to respond to physical and chemical stimuli in the lumen confers the ability for the blood vessels to self regulate tone and to adjust the blood flow and distribution in response to changes in the local environment. Many blood vessels respond to an increase in flow, or more precisely an increase in shear stress, by dilating. This phenomenon is designated as flow-mediated dilation (FMD) and nitroglycerin-mediated dilation (NMD). Accordingly, we hypothesized that NO may play a key role in migraine and patients with NTG-induced headache have a pre-

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served smooth muscle function and there might be an increased NMD response in the brachial artery.

Therefore, the aim of this study is to evaluate whether NTG-induced headache is associated with the level of NMD, FMD or the severity of coronary artery disease (CAD).

## Subjects and Methods

### Study population

This study included 87 patients (Group I: mean age:  $54.8 \pm 9.5$  years, 46 males) with NTG-induced headache, and 109 patients (Group II: mean age:  $57.4 \pm 8.9$  years, 67 males) without NTG-induced headache and with new onset of chest pain. Patients were excluded from this study if they had a history of chronic headache, long term nitrate use or they had undergone coronary artery procedures. Coronary angiography was performed within one month after NTG administration with the usual clinical indications.

We used the NTG-induced headache diagnostic criteria by the International Headache Society (IHS): A. Headache with at least one of the following characteristics and fulfilling criteria C and D: 1) a bilateral 2) fronto-temporal location 3) a pulsating quality 4) aggravated by physical activity, B. Absorption of a NO donor, C. Headache develops within 10 minutes after absorption of the NO donor, D. The headache resolves within 1 hour after the release of NO has ended.<sup>7)</sup> The two groups were well matched with respect to age, gender and the body mass index. The FMD, NMD and the inflammatory and coagulation markers were measured early in the morning following overnight fasting for more than 12 hours.

### Ultrasound measurements

The FMD of the brachial artery, as the non-invasive parameter of endothelial function, was measured according to the previously described guidelines. All the studies were performed in the morning before coronary angiography. An eight MHz high resolution lineal vascular ultrasound transducer was used to image the brachial artery longitudinally just above the antecubital fossa (Acuson 512, USA). A tourniquet that measured blood pressure was placed on the lower arm in order to create shear stress that was induced by reactive hyperemia. After obtaining the baseline measurements of the brachial artery diameter, the blood pressure cuff was inflated to at least 50 mmHg above the systolic blood pressure to occlude arterial flow for 5 minutes. Subsequent deflation of the cuff induces a brief high flow state through the brachial artery (reactive hyperemia) to accommodate the dilated resistance vessels. The resulting increase in shear stress causes the brachial artery to dilate. The brachial artery was continuously imaged for the first 2 minutes of reactive hyperemia.

The flow-mediated dilatory response was used as a measure of the endothelial dependent dilation. After 10 minutes of rest to reestablish the baseline condition, 0.6 mg of NTG was administered sublingually. The brachial artery was continuously imaged for 10 minutes to measure the peak diameter. NMD was used as a measure of the endothelial independent dilation. All the patients were asked about the NTG-induced headache after sublingual administration. In this study, the intra-and inter-observer variabilities for the repeated measurements of the resting arterial diameter were very excellent ( $r=0.997$ ,  $p<0.001$ ,  $r=0.997$ ,  $p<0.001$ , respectively).

### Diagnosis and coronary angiography

Diagnostic coronary angiography was performed using the percutaneous femoral approach. Coronary artery disease was defined as 50% or greater narrowing of the coronary artery.

### Laboratory measurements

From the blood samples, we measured the erythrocyte sedimentation rate (ESR), the white blood cell (WBC) count and the high-sensitivity C-reactive protein (hs-CRP) and homocysteine levels to examine the inflammatory activity, and the fibrinogen level was assessed to examine the coagulation system. Blood samples were non-traumatically taken by venipuncture in the morning before angiography from patients after they'd fasted for >12 hours. hs-CRP was measured by the immunoturbidimetric CRP-Latex (II) assay with using Olympus AU 5400. The measurements of fibrinogen and fibrin degradation products (FDP) were performed via chromogenic assay (Sysmex, CA1500, USA).

### Statistical analysis

The data for the categorical variables is expressed as both the number and the percentage of patients. For the continuous variables, the data is expressed as means  $\pm$  SDs. Independent sample t-tests were used to compare variables between the two groups. Comparison between different groups was made using the chi-squared test for categorical variables. Multivariate logistic regression analysis was performed to identify the independent predictors of CAD. A  $p<0.05$  was considered indicative of statistical significance. All statistical calculations were performed using a commercially available statistical package for social science (SPSS, version 15.0, USA).

## Results

### Baseline patient characteristics

The clinical characteristics, including the risk factors of the study population, are shown in Table 1. No significant differences in age, gender and the risk factors were observed between the subgroups.

### Laboratory findings

The comparison of the biochemical markers is summarized in Table 2. The laboratory findings of hs-CRP, fibrinogen and homocysteine were not different between the subgroups. The levels of total-cholesterol (TC) were significantly increased in Group I compared to Group II ( $197.9 \pm 42.7$  mg/dL vs.  $184.4 \pm 41.8$  mg/dL, respectively,  $p=0.027$ ). The levels of high density lipoprotein-cholesterol (HDL-C) were significantly increased in Group I compared to Group II ( $52.5 \pm 10.7$  mg/dL vs.  $48.9 \pm 12.9$

**Table 1.** Baseline clinical characteristics

	Group I (n=87)	Group II (n=109)	p
Age (years)	$54.8 \pm 9.5$	$57.4 \pm 8.9$	0.051
Gender (%)			0.835
Male	46 (52.9)	67 (61.5)	
Female	41 (47.1)	42 (38.5)	
Body mass index (kg/m <sup>2</sup> )	$25.3 \pm 3.2$	$24.7 \pm 2.5$	0.190
Risk factors (%)			
Smoking	30 (34.4)	34 (31.1)	0.648
Hyperlipidemia	11 (12.6)	19 (17.4)	0.427
Hypertension	26 (29.8)	41 (37.6)	0.290
Diabetes mellitus	13 (14.9)	15 (13.7)	0.840
Family history	1 (1.1)	4 (3.6)	0.385

**Table 2.** Comparison of the biochemical markers

	Group I (n=87)	Group II (n=109)	p
WBC count (/mm <sup>3</sup> )	$6980.8 \pm 2345.7$	$6712.5 \pm 2004.8$	0.391
Monocyte count ( $10 \times 3/\text{mm}^3$ )	$512.4 \pm 268.9$	$559.7 \pm 278.1$	0.567
hs-CRP (mg/dL)	$3.4 \pm 28.7$	$2.7 \pm 25.6$	0.856
Fibrinogen (mg/dL)	$258.5 \pm 77.7$	$255.7 \pm 76.5$	0.809
Homocysteine ( $\mu\text{mol/L}$ )	$7.3 \pm 3.6$	$8.1 \pm 4.2$	0.165
HbA1C (%)	$5.8 \pm 1.1$	$5.8 \pm 0.9$	0.950
TC (mg/dL)	$197.9 \pm 42.7$	$184.4 \pm 41.8$	0.027
HDL-C (mg/dL)	$52.5 \pm 10.7$	$48.9 \pm 12.9$	0.039
LDL-C (mg/dL)	$139.1 \pm 53.6$	$125.0 \pm 37.8$	0.033
TG (mg/dL)	$95.0 \pm 60.1$	$103.4 \pm 57.7$	0.326

WBC: white blood cell, hs-CRP: high sensitivity C-reactive protein, TC: total cholesterol, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, TG: triglyceride

mg/dL, respectively,  $p=0.039$ ). The levels of low density lipoprotein-cholesterol (LDL-C) were significantly increased in Group I compared to Group II ( $139.1 \pm 53.6$  mg/dL vs.  $125.0 \pm 37.8$  mg/dL, respectively,  $p=0.033$ ).

### Nitroglycerin-mediated dilation, flow-mediated dilation and the brachial basal flow diameter

The NMD was significantly higher in Group I than in Group II ( $23.0 \pm 7.5\%$  vs.  $18.5 \pm 8.6\%$ , respectively,  $p<0.001$ ). The FMD was significantly higher in Group I than in Group II ( $9.0 \pm 4.1\%$  vs.  $7.5 \pm 4.3\%$ , respectively,  $p=0.007$ ) (Fig. 1). There was no significant difference in the brachial basal flow diameter between the 2 groups (Table 3).

### Outbreak of nitroglycerin-induced headache in patients with or without coronary artery disease

One hundred eighteen patients had normal coronary arteries or minimal coronary artery disease. Seventy eight patients had obstructive CAD with greater than 50% luminal diameter narrowing in one or more of the left or right coronary arteries or their major branches. For the patients with normal coronary arteries or minimal CAD, 67.8% had headache caused by sublingual NTG. For the patients with obstructive CAD, only 8.0% had headache after NTG use ( $p<0.001$ ) (Fig. 2). On multivariate regression analysis, NTG-induced headache was a predictor of CAD {odds ratio (OR), 0.04, 95% confidence interval (CI), 0.02-0.11:  $p<0.001$ , respectively} (Table 4).

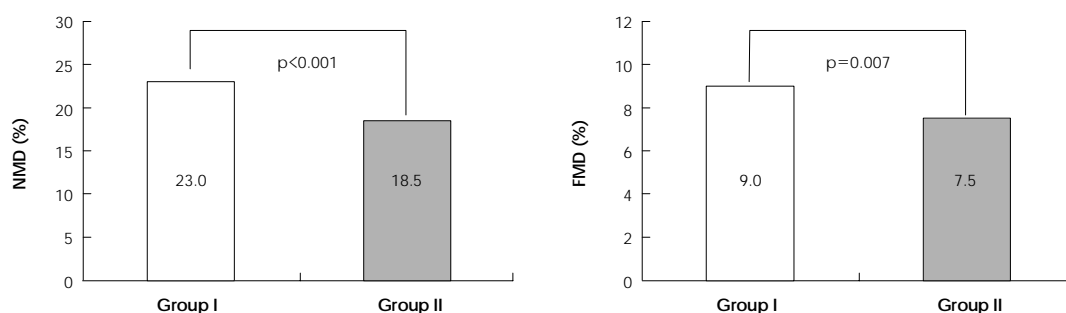
## Discussion

Although vascular, neurogenic, and inflammatory theories have been proposed as the pathomechanism of mi-

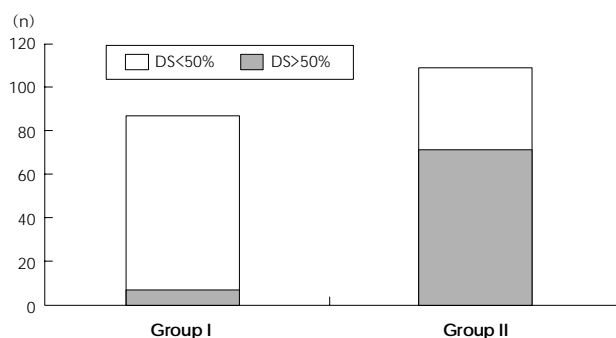
**Table 3.** Flow-mediated dilation, nitroglycerin-mediated dilation and the brachial basal flow diameter

	Group I (n=87)	Group II (n=109)	p
Brachial basal diameter (mm)	$3.8 \pm 0.6$	$4.8 \pm 0.7$	0.063
FMD (%)	$9.0 \pm 4.1$	$7.5 \pm 4.3$	0.007
NMD (%)	$23.0 \pm 7.5$	$18.5 \pm 8.6$	<0.001

FMD: flow-mediated dilation, NMD: nitroglycerin-mediated dilation



**Fig. 1.** The nitroglycerin-mediated dilation (NMD) and flow-mediated dilation (FMD). The NMD and FMD were significantly increased in the patients with NTG-induced headache (Group I) compared to the patients without NTG-induced headache (Group II).



**Fig. 2.** The incidence of NTG-induced headache. It was more frequent in the patients without significant coronary artery stenosis than in the patients with coronary artery disease. DS: diameter stenosis, NTG: nitroglycerin.

**Table 4.** Predictors of coronary artery disease by multivariate regression analysis

	OR	95% CI	p
Age	1.03	0.96-1.10	0.311
Male sex	0.71	0.48-6.09	0.406
Nitroglycerin-induced headache	0.04	0.02-0.11	<0.001
Flow-mediated dilation	0.91	0.78-1.06	0.271
Nitroglycerin-mediated dilation	1.00	0.94-1.06	0.927
Total cholesterol (mg/dL)	0.98	0.95-1.01	0.209
High density lipoprotein-cholesterol (mg/dL)	0.97	48.9 ± 12.9	0.432
Low density lipoprotein-cholesterol (mg/dL)	1.00	125.0 ± 37.8	0.403
Triglyceride (mg/dL)	1.00	0.99-1.02	0.230

Adjusted for the body mass index, the smoking status, diabetes mellitus and the family history. OR: odds ratio, CI: confidence interval

graine, any single theory is not enough to explain all the clinical manifestations of migraine.<sup>8-10</sup> Accumulating evidence on NO's involvement in migraine headache has been reported based on the NO-cGMP pathway. There are three hypotheses that can possibly explain the involvement of NO in migraine. First, activation of the NO-cGMP pathway causes migraine attacks in migraineurs. Second, drugs that are effective for the treatment of migraine exert their activity by inhibiting one or more steps in the NO-cGMP pathway or by antagonizing the effects of the products of this pathway. Third, substances that can cause a migraine attack work by stimulating one or more steps in the NO-cGMP pathway or by exerting effects that are agonistic to those effects in this pathway. The possible mechanisms for NO to cause migraine are by dilation of the cerebral and extracerebral blood vessels and this is due to the changes of the cerebrovascular regulation following the spread of cortical depression, by the direct effect of the perivascular sensory nerves and so on.<sup>11-14</sup>

In this study, the patients with NTG-induced headache were more likely to have an unfavorable lipid profile than those patients without NTG-induced headache. An increased lipid profile in migraine suffers has been re-

ported to be a cardiovascular risk factor.<sup>15</sup> Nitrates can dilate the epicardial coronary arteries and collateral vessels in patients with obstructive CAD.<sup>16,17</sup> It has been suggested that nitrates selectively dilate the coronary arteries to a larger extent than the cerebral arterioles in the patients with obstructive CAD. The prevalence of carotid atheromatous plaque was highly correlated with the prevalence of CAD and the carotid vascular elasticity that was induced with use of NTG was decreased in patients with severe CAD.<sup>18</sup>

Therefore, NTG might cause less frequent headache in patients with atherosclerosis because of the impaired cerebral arterial dilation. This finding may support our theory that NTG causes less frequent headache in patients with atherosclerosis because of the impaired cerebral arterial dilation. The vascular endothelium has been reported to be a multifunctional organ whose integrity is essential for normal vascular physiology. The loss of adequate endothelial cell function is most widely quantified by assessing the FMD and NMD. Especially, the dilatory response to NTG is used as a measure of endothelium independent vasodilation. The vasodilator response to NTG is impaired in the brachial artery of patients with CAD and this is consistent with the functional abnormalities of smooth muscle dilation in adults with atherosclerosis.<sup>19,20</sup> In addition, a decreased FMD in CAD patients has also been reported. There is strong, growing evidence that endothelial function abnormalities are present before the development of angiographically evident coronary atherosclerosis in patients with coronary risk factors.<sup>21-24</sup> The main finding of our study is that patients with NTG-induced headache have an increased NMD and FMD in their brachial arteries. NTG-induced headache is also associated with mild coronary artery disease. This study shows, for the first time, the correlation of endothelial function with NTG-induced headache in patients suffering with chest pain.

The present study has limitations. The sample size was relatively modest, so a further study is need with a larger number of subjects. Further studies are also needed to establish the true mechanism of NTG-induced headache in patients with chest pain, to investigate the other markers of endothelial dysfunction and to examine the potential role of smooth muscle function as an aid to stratifying the risk of patients with NTG-induced headache.

Several previous clinical and hemodynamic studies that used nitrate have been published in Korea,<sup>25-30</sup> however, the clinical impact and mechanisms of have not been exactly determined. This study highlighted the importance of endothelial function for the development of coronary disease in Korean patients with NTG-induced headache. Further studies should be considered to ascertain the role of NTG-induced headache in patients with mild coronary artery stenosis and vasospasm.

## Conclusion

The present study has shown that NTG-induced headache is associated with an increased NMD and FMD in patients with chest pain. More NTG-induced headache developed in the patients who had normal coronary arteries or minimal CAD than in the patients with obstructive CAD. The presence of NTG-induced headache might be helpful as additional information when evaluating the patients with chest pain syndrome.

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