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Brief Communication

Increased Dilator Response to Nitrate and Decreased Flow-Mediated Dilatation in Migraineurs

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Background.—It has been known that in a migraine attack intracranial and extracranial arteries on the headache side dilate and when the migraine attack has subsided, the intracranial arteries show segmental narrowing. We hypothesized that patients with migraine had an underlying systemic vasomotion abnormality and there might be an increased nitrate-mediated vasodilatory response in the brachial artery of migraineurs. Accordingly we aimed to measure endothelium dependent and independent functions of brachial artery in migraineurs and healthy subjects.

Materials and Methods.—Twenty-four patients who fulfilled the diagnostic criteria of migraine were enrolled in the study. Twenty-six age- and sex-matched healthy control subjects comprised the control group. Flow-mediated dilatation and nitrate-mediated dilatation were measured in all patients and control subjects by means of brachial artery ultrasonography.

Results.—Flow-mediated dilatation of patients with migraine was significantly lower than that of control subjects ($7.6 \pm 3.7\%$ vs $10.4 \pm 3.5\%$, respectively, $P = .008$). However, nitrate-mediated dilatation in migraineurs was significantly higher than that of nonmigraineurs (25% vs 14%, respectively, $P < .001$).

Conclusion.—We have shown that migraineurs have decreased endothelium dependent function whereas increased nitrate-mediated response in their brachial artery. It can be suggested that the mechanism underlying migraine may be a diffuse vascular vasomotion abnormalities and migraine may be a local manifestation of systemic vascular abnormality rather than a primary cerebral phenomenon.

Key words: migraine headache, endothelial function, flow-mediated dilatation, endothelium

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Migraine is a common neurovascular disorder characterized by attacks of severe headache, autonomic and neurological symptoms. It is well known that the meninges and large cerebral vessels are the predominant pain sensing structures in the cranium.[1,2] Migraine headache may originate from dilatation of the large cranial vessels and duramater, which are innervated by the trigeminal nerve as part of the trigeminovascular system.[3-5]

The brachial artery ultrasound test for flow-mediated endothelial-dependent vasodilatory function (FMD), described by Celermajer et al,[6] include administration of sublingual nitrates to examine the vasodilating effect of an exogenous source of nitric oxide (NO). The capacity of blood vessels to respond to physical and chemical stimuli in the lumen confers the ability to self regulate tone and to adjust blood flow and distribution in response to changes in the local environment. Many blood vessels respond to an increase in flow, or more precisely shear stress, by dilating. This phenomenon is designated flow-mediated dilatation

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(FMD). A principal mediator of FMD is endothelium derived NO.[6-8]

Cerebral hypoperfusion has been documented during the migraine attack with aura and spreading depression phase of the migraine.[9,10] It has also been proposed that NO may be involved in the pathophysiology of spontaneous headache attack such as migraine.[11-13] In a migraine attack intracranial and extracranial arteries on the headache side dilate and when the migraine attack has subsided, the intracranial arteries show segmental narrowing.[14,15] An association between migraine and some vascular disorders such as vasospastic angina and Raynoud's phenomenon has been reported.[16,17] Recently we have shown that migraineurs have impaired endothelium dependent function compared with control subjects.[18] We hypothesized that patients with migraine had an underlying systemic vasomotion abnormality and there might be an increased nitrate-mediated vasodilatory response in the brachial artery of migraineurs. Accordingly we aimed to measure both endothelium dependent and independent functions of brachial artery in migraineurs by means of an ultrasonographic study.

MATERIALS AND METHODS

Study Population.—Twenty-four patients who fulfilled the diagnostic criteria of migraine were enrolled in the study between January 2004 and June 2004. Diagnosis of migraine was made according to International Headache Society Criteria.[19] Patients who had hypertension (known hypertension treated with antihypertensive drugs, 2 or more blood pressure recordings greater than 140/90 mmHg), coronary artery disease (angiographically proven coronary lesions >50%, or documented myocardial infarction, angina pectoris, previous percutaneous coronary intervention or coronary artery bypass grafting), diabetes mellitus (known diabetes treated with diet or drugs or both; or either a fasting serum glucose of more than 126 mg/dL), or infectious disease were not included in the study. Hypercholesterolemia was defined as known treated hypercholesterolemia or fasting or nonfasting serum cholesterol concentrations higher than 240 mg/dL and current cigarette smoking was defined as active smoking within the past 12 months.[20,21] FMD was not measured during the menstrual phase in female patients. Twenty-six age- and sex-matched control subjects without known coronary artery disease, infectious disease, or diabetes mellitus comprised the control group. None of them had family history of migraine. Control subjects were recruited from the hospital staff after performing a questionnaire. All vasoactive medications and NSAIDs were withheld for at least 4 half-lives. For the FMD of the brachial artery, patients fasted for 12 hours before the study. Caffeine intake and cigarette smoking were also prohibited for 12 hours before the evaluation. Patients with migraine with aura were not included in the study. Patient with oligomenorrhea, polymenorrhea, polycystic ovary disease, and morbid obesity (BMI > 35) were not included in the study. Hospital ethic committee approved the study protocol and all patients gave informed consent.

Flow-Mediated Dilatation.—FMD of the brachial artery was determined using a high-resolution B-mode ultrasonographic system (ATL Ultrasound, HDI 5000, Bothell, WA, USA) with a linear transducer mid-frequency of 7.5 MHz, using the technique described by Celermajer et al.[6] Briefly, each subject was requested to lie at rest for 10 minutes before the procedure began and the first scan at rest was then taken. This was followed by inflation pneumatic tourniquet of the standard sphygmomanometer (Erka BP Apparatus, Germany) placed around forearm to a pressure of 300 mmHg followed by deflation after 4.5 minutes. The second scan was taken 30 seconds before and 90 seconds after cuff deflation. Fifteen minutes were then allowed for vessel recovery and a further scan at rest was then recorded. Sublingual nitroglycerin (0.4 mg) was administered and 3 to 4 minutes later the last scan was performed. Electrocardiography was monitored continuously throughout the study. All measurements were made at end diastole incident on the R wave on a continuously recorded electrocardiogram. The cardiac cycles were analyzed for each scan and the measurements were averaged. Flow-mediated dilatation and nitrate-mediated dilatation were expressed as the change in poststimulus (flow- and nitrate-mediated) diameter as percentage of the baseline diameter. All scans were recorded on S-VHS videotape for offline analysis. All migraineurs were asked for the occurrence of headache after sublingual administration

either in hospital follow-up or by home call. All measurements were performed during pain-free period in migraineurs. And none of them had migraine attack 24 hours preceding the test. Female patients who were in menstrual phase did not undergo ultrasonographic evaluation. These patients were allowed to undergo ultrasonographic evaluation either in luteal or follicular phase. All measurements were performed by a single cardiologist blinded to clinical data. The intraobserver variability for repeated measurements of brachial arterial diameter at rest was detected to be less than 2% both for flow- and nitrate-mediated dilatation.

Statistical Analysis.—Categorical variables were expressed as percentage and numerical variables as mean ± SD. For categorical data, χ^2 and Fisher's exact *t* test were used. Unpaired *t* test was used to compare the numerical variables and the flow-mediated dilatation in migraineurs and nonmigraineurs. Statistical significance was defined as a *P* value of less than .05.

RESULTS

Baseline characteristics of migraineurs are presented in Table. Mean age of the patients was 31 ± 8 years in migraineurs (range: 18 to 42 years, 21 female, 3 male) and 32 ± 6 years in nonmigraineurs (range: 17 to 40 years, 22 female and 4 male). There were not statistically significant differences between migraineurs and control subject in respect to systolic (109 ± 13 mmHg vs 115 ± 13 mmHg) and diastolic (70 ± 7 mmHg vs 70 ± 7 mmHg) blood pressure, heart rate (74 ± 5 beats/min vs 76 ± 7 beats/min), body mass index (24 ± 3 vs 24 ± 3), smoking status (7/24 vs 10/26), and presence of hypercholesterolemia (7/24 vs 9 / 26) ($P >$ .05 for all, Table). Flow-mediated dilatation of patients with migraine was significantly lower than that of control subjects (7.6 ± 3.7% vs 10.4 ± 3.5%, respectively, $P = .008$). However, nitrate-mediated dilatation in migraineurs was significantly higher than that of nonmigraineurs (25% vs 14%, respectively, $P < .001$, Fig. 1). Fifteen of the migraine patients experienced a delayed headache 2 to 4 hours after administration of sublingual nitrate. Migraine-like delayed headache after administration of sublingual nitrate occurred in 15 migraineurs (63%) and delayed headache occurred in 5 nonmigraineurs (19%) ($P = .019$).

DISCUSSION

The main finding of our study is that migraineurs have decreased endothelium-dependent vasodilatation and increased nitrate-mediated dilatation in the brachial artery. We have recently demonstrated in a larger series that migraineurs have less endothelium-dependent vasodilatation capacity compared with nonmigraineurs.[18] It has been suggested that NO is involved in the pain mechanisms of both types of migraine, namely with and without aura. In sufferers of migraine with aura, nitroglycerin induces the same headache response as in sufferers of migraine without aura, but with no aura symptoms.[22] Transcranial

Table—Baseline Characteristics of Migraineurs and Nonmigraineurs

	Migraineurs	Nonmigraineurs	*P* Value
Age (years)	31 ± 8	32 ± 6	.55
Gender (male/female)	3/24	3/26	.52
Heart rate (beats/min)	74 ± 5	76 ± 7	.16
Systolic blood pressure (mmHg)	109 ± 13	115 ± 13	.54
Diastolic blood pressure (mmHg)	70 ± 7	70 ± 7	.96
Smoking	7/24 (29%)	10/26 (38%)	.49
Hypercholesterolemia (>200 mg/dL)	7/24 (29%)	9/26 (35%)	.68
Body mass index	24 ± 3.4	24 ± 2.8	.97
Baseline brachial artery diameter (mm)	3.31 ± 0.50	3.31 ± 0.54	.92
Flow-mediated dilatation (%)	7.6 ± 3.7	10.4 ± 3.5	.008
Nitrate-mediated dilatation (%)	24 ± 6	16 ± 5	<.001

Doppler studies of middle cerebral artery blood velocity in migraine without aura have reported controversial results.[23,24] Zwetsloot et al[23] have found no difference between blood velocity at the headache and nonheadache sides nor between blood velocity during and outside attacks. Thompson et al[14] reported unilateral decrease in the middle cerebral artery velocity; on the contrary Zanette et al[24] reported a tendency to bilateral increase. The considerable variability in TCD measurements and other methodological aspects may have been involved in this discrepancy. Furthermore, the clinical features of studied attack might have differed. Additionally the timing of measurements in relation to onset of attacks may have been a crucial factor.[25]

In a migraine attack intracranial arteries on the headache side dilate and when the migraine attack has subsided, they return to baseline values.[14,15] It has been suggested that NO may play a pivotal role in the initiation and maintenance of migraine headache.[26] An increased headache response could reflect a greater general sensitivity to pain, or it could be due to increased physiological sensitivity to NO. Nitric oxide has been implicated in the development of the pain of some types of headache, especially migraine and cluster headache.[27] Administration of nitroglycerin to migraineurs and nonmigraineurs induces a different pattern of response. The nitric oxide donor glyceryl trinitrate and some other organic nitrates and nitrites induce an immediate vascular headache in nearly all subjects and a delayed migraine-like headache in migraineurs.[28,29] In susceptible subjects, glyceryl trinitrate reliably triggers a cluster headache-like pain.[30] The occurrence of the delayed migraine-like headache following nitroglycerin administration is considered specific and enables the diagnosis of migraine. The delayed migraine-like headache cannot be simply ascribed to a cause exclusively targeting drug-induced vasodilatation, since the half-life of nitroglycerin in the blood compartment is in the order of 3 to 4 minutes.[31]

Nitric oxide acts directly at the level of the arterial smooth muscle cells and produces an endothelium-independent dilatation response. Nitrate-mediated dilatation (NMD) has therefore been used as a control test for the FMD measurement to ensure that a decreased FMD capacity observed is truly a consequence of endothelial dysfunction and not a reflection of underlying smooth muscle dysfunction.[32] We have found that, in contrast to decreased endothelium-dependent functions, migraineurs have overdilatory response to nitrate compared with nonmigraineurs. The baseline endothelial dysfunction may underlie in the pathogenesis of increased NMD. This overdilatory response may correlate with the increased cerebral artery dilatation during migraine attack. Infusion of the NO donor nitroglycerin has shown to cause greater dilatation of the middle cerebral artery in migraineurs compared with nonmigraineurs. It has been proposed NO supersensitivity might play a major role in migraine pathophysiology.[33] Sances et al[34] have reported that nitrate provocation test is an easy, safe, and reliable method that offers high diagnostic accuracy, and as a result will prove helpful in supporting and confirming the diagnosis of migraine without aura. However, reliability of nitrate provocation test is less satisfactory with a low sensitivity and diagnostic accuracy.

Since we have shown both decreased endothelium-dependent function and increased nitrate-mediated response of migraineurs compared with nonmigraineurs in the brachial artery, the pathogenesis underlying migraine might have some components related with systemic vascular abnormality. In

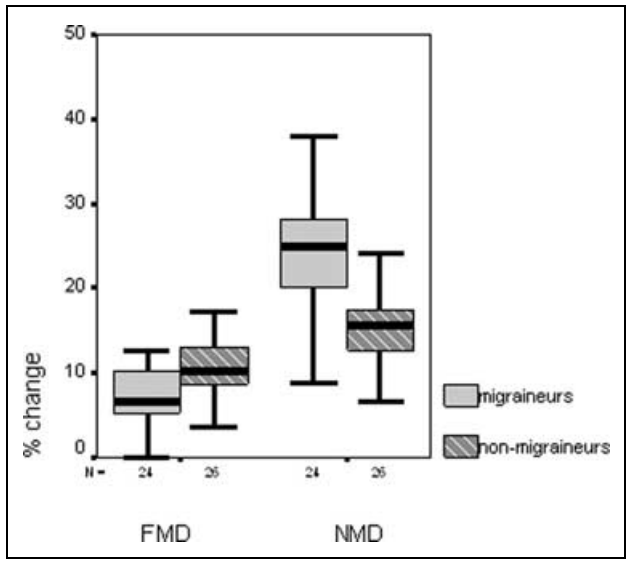

Fig 1.—Each box represents mean ± SD of flow- and nitrate-mediated dilatation in migraineurs and nonmigraineurs.

accordance with this suggestion there are some reports demonstrating a possible association with migraine and some other vascular disorders. Prevalence of migraine has been found to be higher in patients with vasospastic angina than in control subjects in Japanese population.[35] Miller et al[16] reported that the prevalence of migraine was 26% in 62 patients with variant angina, which was higher than in a coronary control group (6%) and non-coronary control group (10%). The prevalence of Raynoud's phenomenon was 24% in patients with variant angina, which was higher than in coronary control group (5%) and non-coronary control group (3%). Smithy et al[17] have reported that in patients with primary Raynaud phenomenon, there is a higher personal history of migraine than in controls (32.6% vs 7.2%; $P<0.0001$). The high prevalence of migraine suggests that primary Raynaud phenomenon is part of a more widespread disorder of vascular tone.[17] Regarding the association between migraine, Raynaud's phenomenon, and vasospastic angina, it can be suggested that there is at least a common pathway underlying these vascular disorders and each of them might be considered as a local manifestation of systemic vascular abnormality. On the contrary, Thedskov et al[36] reported comparable nitrate-mediated dilatation in migraineurs and nonmigraineurs subjects. However, the number of patients in whom vascular study was performed was relatively low (8 patients) compared with our study population. Additionally, range of patients' age (22–61) was relatively large, which might further necessitate to compare cardiovascular risk factors such as smoking, hypercholesterolemia, and diabetes mellitus. Since we did not consider the headache attack frequency and frequent medication use in the analysis, it might affect the vascular data if only patients with frequent attacks (and with subsequent frequent use of vasoactive medication) were included despite the cessation of medications.

Furthermore, similar to the findings observed in our study, decreased endothelium-dependent and increased nitrate-mediated responses have been observed in patients with vasospastic angina. Kugiyama et al[37] have reported that flow-dependent coronary dilatation is impaired in spasm arteries, partly due to a deficiency in endothelial nitric oxide bioactivity, which in turn may contribute to the increase in coronary tone during physiologic stimuli in patients with coronary spastic angina. It has been demonstrated that spastic arteries have greater dilator response to nitroglycerin,[38] a phenomenon that is compatible with previous studies.[39-42] However, the increased dilator response of spastic coronary arteries to nitroglycerin is not common to all vasodilators. It has been suggested that more constricted arteries would dilate more in response to nitroglycerin either by increase in conversion of NO activity, or guanylate cyclase activity or increase in cGMP activity in effector system of smooth muscle cells.[38] Physiologic stimuli, such as exercise and exposure to cold, which increase coronary blood flow, have been shown to dilate coronary arteries in normal patients[42,43] but cause coronary constriction in patients with coronary spastic angina.[44-47] Similar stimuli such as exercise, fatigue, stress, weather conditions are known to be a trigger of migraine attack.

Although the increased nitrate-mediated response was observed within 4 to 5 minutes after administration of sublingual nitrate, delayed headache occurred 2 to 4 hours after the administration, in accordance with the previous literature. It has been also demonstrated that migraine response appeared 3 to 10 hours after administration of NO.[48] So it is reasonable to expect another mechanism or mechanisms during this time period.

In conclusion, we have shown that migraineurs have decreased endothelium-dependent function in contrast to increased nitrate-mediated response in their brachial artery compared with control subjects. With the support of further clinical studies it can be suggested that the mechanism underlying migraine may be diffuse vascular vasomotion abnormalities and migraine may be a local manifestation of systemic vascular abnormality rather than a primary cerebral phenomenon.

Conflict of Interest: None

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