Decreased endothelium-dependent vasodilatation in patients with migraine: a new aspect to vascular pathophysiology of migraine

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Background **Migraine is a common neurovascular disorder characterized by attacks of severe headache, autonomic and neurological symptoms. We hypothesized that patients with migraine had abnormal endothelial function. The vascular theory of migraine assumes that the major pathophysiological events that initiate the migraine attack occur in the perivascular nerves of the major cerebral vessels. Accordingly, we aimed to measure endothelium-dependent vasodilatation in migraineurs by means of flow-mediated dilatation, which reflects endothelium-dependent vasodilatation capacity.**

Materials and methods **Forty-five patients who fulfilled the diagnostic criteria for migraine and 45 age and sex-matched healthy participants were enrolled in the study. Flow-mediated dilatation of the brachial artery was determined using a high-resolution B-mode ultrasonographic system. Flow-mediated vasodilatation was expressed as the change in post-stimulus diameter as a percentage of the baseline diameter.**

Results **Mean ages of the patients were 33 ± 10 years in migraineurs (range: 18–52 years, 36 female, 9 male) and 33 ± 9 years in non-migraineurs (range: 17–50 years, 36 female and 9 male). Flow-mediated dilatation of patients with migraine is significantly lower than that of the controls (8.02 ± 4.095% vs. 10.72 ± 3.52%, respectively, $P = 0.001$).**

Conclusion **We have shown that migraineurs have decreased endothelium-dependent vasodilatation capacity compared with non-migraineurs. Migraine may be a local manifestation of systemic vascular vasomotion abnormalities.** *Coron Artery Dis* **17:29–33 © 2006 Lippincott Williams & Wilkins.**

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Introduction

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 (FMD). A principal mediator of FMD is endothelium-derived nitric oxide (NO) [1–4]. Although the precise mechanism is not fully understood, activation of ion channels, endothelial NO synthase and subsequent generation of NO appears to account for FMD [5,6].

Migraine is a common neurovascular disorder characterized by attacks of severe headache, autonomic and neurological symptoms. Neuronal and vascular hypotheses have been suggested to define the mechanism of migraine. The vascular theory of migraine assumes that the major pathophysiological events that initiate the migraine attack occur in the perivascular nerves of the major cerebral vessels. Migraine headache may originate from dilatation of the large cranial vessels and dura mater, which are innervated by the trigeminal nerve as part of the trigeminovascular system [7–12]. On the other hand, cerebral hypoperfusion preceding migraine headache has been observed using neuronal imaging techniques [13–15]. Previously, an important association has been shown between some vasospastic disorders (Raynaud's phenomenon and variant angina) and migraine [16–18]. We hypothesized that patients with migraine could have abnormal endothelial function, which might cause a propensity to the prodromal phase of migraine in which vasoconstriction occurs. Accordingly, we aimed to measure endothelium-dependent vasodilatation in migraineurs by means of FMD, which reflects endothelium-dependent vasodilatation capacity.

Materials and methods

Study population

Forty-five patients who fulfilled the diagnostic criteria for migraine were enrolled in the study. Diagnosis of

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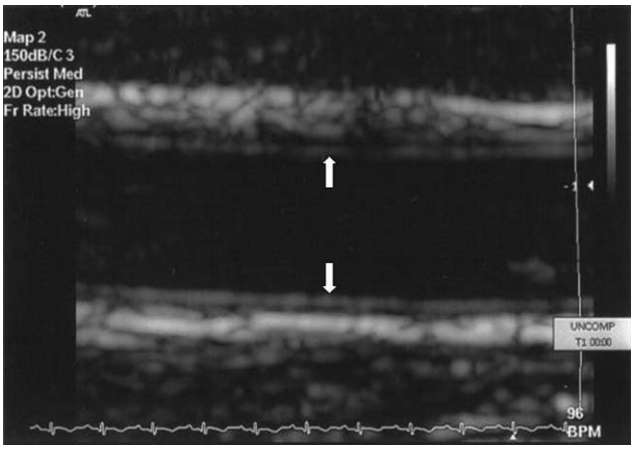
migraine was made according to the International Headache Society Criteria [19]. Patients who had hypertension (known hypertension treated with antihypertensive drugs, two or more blood pressure recordings greater than 140/90 mm Hg), coronary artery disease (angiographically proven coronary lesions $>50\%$, 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. FMD was not measured during the menstrual phase in female patients. Patients with oligomenorrhea, polymenorrhea, polycystic ovary disease and morbid obesity (body mass index >35) were not included in the study. Forty-five age and sex-matched controls without known coronary artery disease, infectious disease, hypertension or diabetes mellitus comprised the control group. Patients with migraine with aura were not included in the study. Hypercholesterolemia was defined as known treated hypercholesterolemia or fasting or non-fasting serum cholesterol concentrations higher than 200 mg/dl, and current cigarette smoking was defined as active smoking within the past 12 months. All vasoactive medications were withheld for at least four half-lives. The hospital Ethics 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, Washington, USA) with a linear transducer mid-frequency of 7.5 MHz by an experienced ultrasonographer blinded to the clinical details of the individual case, using the technique described by Celermajer *et al.* [3]. The ultrasound examination was performed between 10:00 and 12:00h. Briefly, each study participant was requested to lie at rest for 10 min 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, Kallmeyer Medizintechnik GmbH & Co. KG, Bad Toelz, Germany) placed around the forearm to a pressure of 300 mmHg and followed by deflation after 4.5 min. The second scan was taken 30 s before and 90 s after cuff deflation. The diameter of the brachial artery was measured from longitudinal images in which the lumen–intima interface is visualized on the near (anterior) and far (posterior) walls in all images (Fig. 1). All measurements of the brachial artery internal diameter were performed at end diastole (timed by the R wave); the four consecutive measurements obtained through the consecutive cardiac cycles were averaged out and recorded. FMD was expressed as the change in poststimulus diameter as a percentage of the baseline diameter. All measurements were performed during pain-free period in migraineurs. Pregnant women and female patients who were in the menstrual phase did not undergo ultrasonographic evaluation. These patients were allowed to undergo ultrasonographic evaluation in either the luteal or follicular phase.

Fig. 1



Ultrasound image of the brachial artery (longitudinally). Arrows show the anterior and posterior intima–lumen interface.

Statistical analysis

Categorical variables were expressed as percentages and numerical variables as mean ± SD. For categorical data, χ^2 and Fisher's exact *t*-test were used. After showing a normal distribution using the Kolmogorov–Simirnov test, an unpaired *t*-test was used to compare the FMD in migraineurs and non-migraineurs. Statistical significance was defined as a P value of less than 0.05.

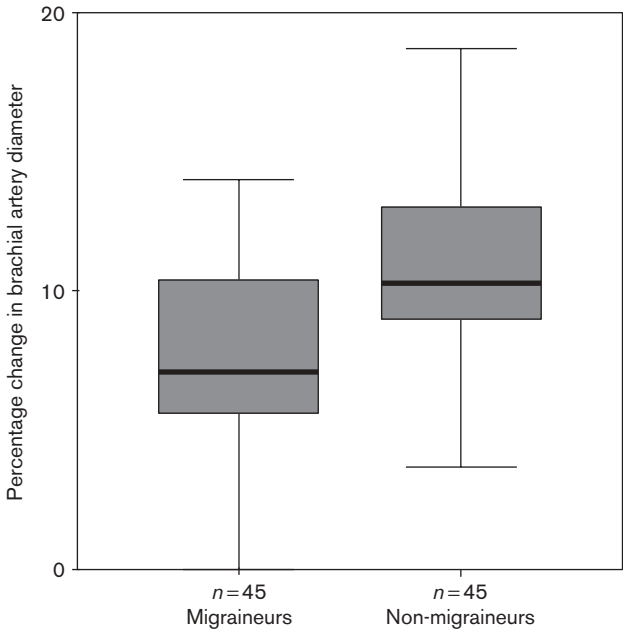
Results

Baseline characteristics of migraineurs are presented in Table 1. Mean ages of the patients were 33 ± 10 years in migraineurs (range: 18–52 years, 36 women, 9 men) and 33 ± 9 years in non-migraineurs (range: 17–50 years, 36 women and 9 men). Twenty-two patients (49%) had a family history of migraine. Three female migraineurs (8%) and four female non-migraineurs (11%) were in menopause. No statistically significant differences were found between migraineurs and controls with respect to systolic (113 ± 14 vs. 114 ± 13 mmHg) and diastolic (74 ± 6 vs. 74 ± 8 mmHg) blood pressure, heart rate (74 ± 5 vs. 76 ± 7 beats/min), body mass index (24.7 ± 2.9 vs. 24 ± 2.5), smoking status (10/45 vs. 14/45) and presence of hypercholesterolemia (11/45 vs. 15/45) ($P>0.05$ for all, Table 1). FMD of patients with migraine is significantly lower than that of controls (8.02 ± 4.095% vs. 10.72 ± 3.52%, respectively $P=0.001$) (see Fig. 2).

Table 1 **Baseline characteristics of migraineurs and non-migraineurs**

	Migraineurs	Non-migraineurs	*P* value
Age (years)	33 ± 10	33 ± 9	–
Sex (male/female)	9/36	9/36	–
Female in menopause	3/36	4/36	0.69
Heart rate (beats/min)	74 ± 5	76 ± 7	0.16
Systolic blood pressure (mmHg)	113 ± 14	114 ± 13	0.70
Diastolic blood pressure (mmHg)	74 ± 6	74 ± 8	0.83
Smoking	10/45 (25%)	14/45(31%)	0.16
Hypercholesterolemia (> 200 mg/dl)	11/45 (24%)	15/45(33%)	0.35
Body mass index	24.7 ± 2.9	24 ± 2.5	0.29
Baseline brachial artery diameter (mm)	3.27 ± 0.53	3.25 ± 0.5	0.85
Hyperemic brachial artery diameter (mm)	3.54 ± 0.6	3.60 ± 0.5	0.53
Flow-mediated dilatation (%)	8.02	10.72	0.001

Fig. 2



Flow-mediated dilatation in migraineurs and non-migraineurs. Each box represents mean ± SD of flow-mediated dilatation in migraineurs and non-migraineurs; $P<0.001$.

Discussion

It is well known that the meninges and large cerebral vessels are the predominant pain sensing structures in the cranium from the seminal work performed by Graham and Wolff [20] and Ray and Wolff [21] over half a century ago. Migraine headache may originate from dilatation of the large cranial vessels and dura mater, which are innervated by the trigeminal nerve as part of the trigeminovascular system [7–12].

Theoretically, the main common point of migraine and endothelium-dependent vasodilatation is NO. Many blood vessels respond to an increase in flow, or more precisely shear stress, by dilating. Hyperemic stimulus provokes the endothelium to release NO with subsequent vasodilatation that can be imaged and quantitated as an index of vasomotor function. This phenomenon is designated FMD [4].

The main finding of our study is that FMD in patients with migraine is significantly lower than that of controls during the pain-free period. Additionally, the presence of hypercholesterolemia and smoking status affecting endothelial function in patients with migraine are not different from those of non-migraineurs. As there is no difference between migraineurs and non-migraineurs with respect to smoking, hyperlipidemia, age and sex, we can suggest that these risk factors are not responsible for the decreased endothelium-dependent response in migraineurs. Besides, there are some reports indicating associations with migraine and other vascular-related situations such as variant angina and Raynoud's phenomenon in which the vascular endothelium is mainly involved [16,17].

Prevalence of migraine has been found to be higher in patients with vasospastic angina than in controls in a Japanese population [16]. Miller *et al.* [17] reported that the prevalence of migraine was 26% in 62 patients with variant angina, which was higher than that in a coronary control group (6%) and a non-coronary control group (10%). The prevalence of Raynoud's phenomenon was 24% in patients with variant angina, which was higher than in a coronary control group (5%) and a non-coronary control group (3%). Smyth *et al.* [18] reported that in patients with primary Raynoud's 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 the primary Raynoud's phenomenon is part of a more widespread disorder of vascular tone [18].

The prodromal phase of migraine is caused by inappropriate vasoconstriction of cranial arteries [22–24] and enzymatic markers of cerebral ischemia can be detected in the cerebrospinal fluid after an attack. Decreased endothelium-dependent functions may play a role in the prodromal phase of migraine by facilitating the vasoconstriction.

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 [25–27]. It has been suggested that NO may play a pivotal role in the initiation and maintenance of migraine headache [28]. NO has also shown to play a role in the main mechanism for endothelium-dependent vasodilatation. As NO causes vasodilatation, decreased FMD in migraineurs seems to be an unexpected or controversial finding. It has been demonstrated, however, that migraine response appears 3–10 h after administration of NO [29]. This finding has suggested that an intermediate pathway has to be activated first. Infusion of the NO donor nitroglycerine has shown to cause greater dilatation of the middle cerebral artery in migraineurs than in non-migraineurs. A similar greater dilatation in the coronary artery has also been shown in patients with spasm arteries than in controls after NO infusion [30].

Study limitation

NO acts directly at the level of the arterial smooth muscle cells and produces an endothelium-independent dilatation response. Nitrate-mediated dilatation 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 [31]. Atherosclerosis has known to affect nitrate-mediated response. Recent evidence indicates that in addition to influencing endothelial function, atherosclerosis may also induce changes in arterial dilatation responses to exogenous NO [32,33]. Another reason for not giving nitrate is to avoid potentially precipitating a migraine headache in persons prone to them. Although it seems to be necessary to evaluate nitrate-mediated dilatation in the present study, exclusion of all patients with known coronary artery disease and absence of differences between the study groups with respect to major coronary risk factors may partially eliminate this limitation.

Conclusion

To our knowledge, this study is the first to show that endothelial function is abnormal in patients with migraine compared with controls. The use of young patients without other known risk factors of ischemic heart disease, who were not using drugs, indicates that migraine is associated with the abnormality of endothelial function. The clinical observation that attacks in different arterial beds usually occur at different times and usually have different triggering mechanisms suggests that local factors may also play a part in the pathogenesis of these disorders. Our results may suggest that the mechanism underlying migraine is a diffuse vascular vasomotion abnormality rather than a primary cerebral phenomenon, and migraine may be a local manifestation of a systemic vascular vasomotion abnormality. Further studies evaluating the mechanism underlying the decreased endothelium-dependent vasodilatation need to be carried out.

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