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Trigger factors and mechanisms in migraine

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TRIGGER FACTORS AND MECHANISMS IN MIGRAINE

Geurt Gerhard Schoonman (roepnaam: Guus)

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CHAPTER 1

GENERAL INTRODUCTION

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Clinical features of migraine

Migraine is a severe paroxysmal neurovascular disorder and considered a major cause of disability by the World Health Organisation[1,2]. The duration of a migraine attack is between 4 to 72 hours[3] and a full blown attack consists of four phases: premonitory, aura, headache and recovery[4,5]. The premonitory phase can last up to 24 hours and consists of a wide range of symptoms, such as mood disturbances, autonomic symptoms and concentration problems. The prevalence of premonitory symptoms is unclear and ranges from 8%[6] to 80%[7] in a clinic based sample. The second phase is the aura phase. Approximately 33% of migraine patients report aura symptoms during an attack[8] which mostly consist of visual or sensory phenomena[9]. Headache is the third part of an attack and for many patients the most prominent phase. The typical headache during a migraine attack is moderate to severe, unilateral, pounding and aggravates during physical activity. The headache is accompanied by nausea, vomiting and phono/photophobia (Table 1). The final phase of a migraine attack is the recovery phase consisting of symptoms that are similar to the premonitory phase[7]. The clinical presentation of a migraine attack can differ within and between migraine patients[9].

Epidemiology and attack susceptibility

The one year prevalence of migraine in the Netherlands is 25% in women and 7.5% in men[8] and in the USA the one year prevalence is 17.2% in women and 6% in men[10]. Everybody can have a migraine attack, but it is the recurrence of attacks that is abnormal[11]. A patient is considered a migraine patient only after five MO attacks or two MA attacks according to the IHS criteria[3]. Attack frequency varies between and within patients and the occurrence of a migraine attack is the result of a misbalance between susceptibility and trigger factors[12]. Migraine susceptibility is strongly influenced by genetic factors[13] and prophylactic treatment[14]. Up to now three genes have been identified in familial hemiplegic migraine which is a subtype of migraine with aura[15-17]. Whether these genes are involved in the common types of migraine is unknown[18,19]. Besides genetic factors, prophylactic drugs have shown to alter susceptibility for migraine. Beta-blockers and anti-epileptic drugs are first choice, however, their efficacy is rather limited[14].

Table 1 IHS diagnostic criteria for migraine with and without aura

1.1 Migraine without aura	
A. At least 5 attacks fulfilling criteria B–D	
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)	
C. Headache has at least two of the following characteristics:	1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing voidance of routine physical activity (*eg*, walking or
D. During headache at least one of the following:	1. nausea and/or vomiting 2. photophobia and phonophobia
E. Not attributed to another disorder	
1.2 Migraine with aura	
A. At least 2 attacks fulfilling criteria B–D	
B. Aura consisting of at least one of the following, but no motor weakness:	1. fully reversible visual symptoms including positive features (*eg*, flickering lights, spots or lines) and/or negative features (*ie*, loss of vision) 2. fully reversible sensory symptoms including positive features (*ie*, pins and needles) and/or negative features (*ie*, numbness)
C. At least two of the following:	1. homonymous visual symptoms and/or unilateral sensory symptoms 2. at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
D. Headache fulfilling criteria B–D for 1.1 *Migraine without aura* begins during the aura or follows aura within 60 minutes	
E. Not attributed to another disorder	

Trigger factors for migraine

A trigger for migraine is any factor that on exposure or withdrawal leads to the development of a migraine attack.[20] An extensive list of factors has been proposed as possible trigger factors for migraine (Table 2). Observational questionnaire studies often suggest strong associations between possible trigger factors and migraine which rarely is confirmed by prospective studies and experimental trials. Using questionnaires

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it is easy to reach a large number of patients, however associations are mainly based on retrospective data and should be regarded as hypothesis generating[21]. On the other hand experimental studies mainly focus on one factor at the time. In the next section, possible trigger factors will be grouped into six categories: food products, stress, female hormones, atmospheric, pharmacological and other factors.

A) Food products

The occurrence of migraine is often linked to the intake of certain food products and migraine has been described as food allergy[22]. Despite many studies, the association between food products and migraine remains unclear. Based on retrospective questionnaires a long list possible migraine triggering products has been formulated (Table2). Among the most frequently mentioned products are alcohol (including wine), cheese, chocolate as well as withdrawal of caffeine and missing a meal.[23-30] Furthermore, several diet elimination studies suggest a positive association between food and migraine.[22,31-33] On the other hand, experimental provocation studies are less positive. Red wine provoked migraine in 9 out of 11 migraine patients who were pre-selected on being sensitive for red wine.[34] Chocolate triggered migraine in 5 out of 12 "chocolate sensitive" migraine patients[35], whereas in a second study the headache response after chocolate did not differ from placebo[36]. Tyramine 200mg has also been tested in a provocation study in 80 migraine patients and there was no difference in the occurrence of headache between tyramine and placebo.[37] Prospective studies in which the intake of food and the occurrence of migraine attacks are scored independently using electronic diaries to prevent retrospective data entries are missing.

B) Stress

Although no clear definition of stress exists[38], it has been linked to a whole range of diseases including multiple sclerosis[39], asthma[40] and risk factors for cardiovascular disease.[41] In migraine, both mental and physical stressors are frequently reported as trigger factor. In retrospective questionnaire studies between 30.5% and 81.8% of patients reported psychosocial stressors as trigger factor, whereas between 15.5% and 43.1% of patients identified physical stressors as possible trigger factor (Table 2). Also prospective studies using diaries suggest a positive association between mental stress and migraine.[42,43] However, this seemingly apparent association between stress and migraine is difficult to replicate in observational and experimental studies using biological stress parameters such as cortisol and cardiovascular parameters. In experimental studies no difference was found in cardiovascular response between the migraine attack and the inter-ictal state.[44,45]

Table 2 Potential trigger factors for migraine.

	Trigger factor	Response rate* Range (%)
Food products[24-30,119]	Various food items	10 – 36
	Missing a meal	0.9 – 55.8
	Chocolate	0 – 22.5
	Wine	1.4
	Alcohol	20
	Dairy products	18.5
	Caffeine (withdrawal)	6.4
Atmospheric[24-29,120]	Weather changes	6.9 – 52.3
	Sunlight exposure	4.2 – 38
	Altitude/ hypoxia	
	Chinook winds	
	Smoking	2 – 26
Stress[24-30,121]	Psychosocial	30.5 – 81.8
	Physical	15.5 – 43.1
	Vacation and travel	8 – 54.6
Female Hormones[24-30,122]	Menstruation	20.7 – 53.5
Pharmacological	Nitroglycerin[55,56,78,116,123-129]	20 -83%
	Sildenafil[58]	83
	Dipyridamole[130]	50
	Histamine[64]	50
	M-chlorophenylpiperazine[59]	53
	Calcitonin gene related peptide[61]	33.3
	Acetazolamide[65]	Not tested in RCT
	Prostaglandine E1[68]	Not tested in RCT
	Reserpine[69]	Not tested in RCT
	Calcineurin inhibitors[70]	Not tested in RCT
	Polidocanol foam[71]	Not tested in RCT
Other	Sleep (lack or excess) [72]	31 – 52.4
	Visual stimulation[73]	
	Cerebral angiography[72]	
	Sexual activity[74]	0 – 11
	Use of personal computer[24]	6.6

*Response rate are based on findings in questionnaire studies, prospective diary studies or experimental provocation studies.

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C) Female hormones

Based on clinical arguments there is a strong association between female hormones and the occurrence of migraine attacks. The life time prevalence of migraine is 3 times higher in females compared to males[8], between 20.7% and 53.5% of females reported an association between menstruation and migraine (Table 2) and there is a decrease in migraine frequency during pregnancy.[46] In a study of 40 female migraine patients, the incidence of migraine attacks was inversely associated with urinary oestrogen concentration across the menstrual cycle. There was no association between migraine and urinary concentrations of progestogens.[47]

D) Atmospheric

Weather changes have also been linked to a wide variety of medical diseases[48] including migraine.[49] Retrospective questionnaires showed that between 6,9% and 52,3% of migraine patients identify weather changes as possible trigger factor (Table 2). In contrast three prospective studies, combining objective weather data from meteo institutes with information from headache diaries or visits to the emergency room for migraine, showed no positive associations.[50-52] Only one study found a positive relation between weather changes and the occurrence of headache in 77 migraine patients.[53] Furthermore there is a large discrepancy between what patients think and what can be objectified. For instance a positive association between Chinook winds and migraine attacks was suggested by 88% of 34 migraine patients, whereas an objective correlation could only be found in 21% of patients.[54] Experimental studies including atmospheric parameters are limited in number.

E) Pharmacological

Nitroglycerin (NTG) is frequently used in migraine provocation studies (Table 2). The clinical response after NTG (0.5 micrograms/kg/20min) consists of an immediate type headache during infusion and a delayed headache attack after 5 to 6 hours which fulfils the criteria of migraine without aura in 20% to 83% of patients (Table 2). Migraine patients without aura might be more susceptible to nitroglycerin than patients with aura.[55,56] Sildenafil (Viagra) is a highly selective phosphodiesterase type 5 inhibitor used to treat patients with erectile dysfunction[57] and in migraine susceptible patients Viagra has shown to provoke delayed migraine attacks in 10 out of 12 patients.[58] A third drug shown to provoke migraine is m-chlorophenylpiperazine (mCPP). Migraine attacks were triggered in 10 out of 19 migraine patients (53%) in a randomized controlled trial.[59] Also in a study including patients with bulimia and anorexia nervosa, mCPP triggered severe headache 28 out of 52 patients (54%).[60] Calcitonin gene related

peptide (CGRP) is a vasoactive peptide that is increased during spontaneous migraine attacks[61]. In turn, infusion of CGRP triggers migraine in 3 out of 9 susceptible migraine patients.[62] The neurotransmitter histamine has also shown to trigger moderate to severe throbbing headache in migraine susceptible patients[63] fulfilling the criteria for migraine in 50% of the migraine patients.[64] Besides aforementioned drugs, several others drugs might be capable of triggering migraine, but they are up to now never been tested in a formal randomized controlled trial (RCT). Acetazolamide (Diamox), a carbonic anhydrase inhibitor, is both used to provoke and to treat migraine. Oral administration of acetazolamide (14.3 mg/kg) in 20 migraine patients caused migraine headache accompanied by photophobia, phonophobia and nausea after 1 to 8 hours.[65] The number of patients fulfilling the criteria for migraine was not specified in this study. In contrast, diamox (500 to 750 mg daily) has also been used as treatment in migraine and it might be effective in the acute treatment of migraine aura status.[66] Furthermore, diamox (500mg) has been tested as prophylaxis for migraine in 53 patients and was not effective.[67] And finally prostaglandine E1[68], reserpine[69], calcineurin inhibitors (eg, cyclosporine and tacrolimus) [70] and polidocanol foam[71] might be able to provoke migraine attacks in susceptible patients.

F) Other possible trigger factors

Sleep (lack or excess) and fatigue are frequently associated with migraine attacks (Table 2). Also in a prospective diary study the quality of sleep seemed to be negatively associated with the occurrence of migraine attacks.[72] Visual stimulation has been used to trigger migraine in a fMRI study.[73] Two (out of 10) migraine patients with aura experienced a typical migraine aura and 8 (out of 12) experienced migraine headache within 7.3 minutes after provocation. Whether these headache episodes fulfilled migraine criteria was not described. Cerebral angiography using contrast agent has shown to induce headache in 15 (out of 45) patients after 2 hours.[72] In four patients (8.8%) symptoms fulfilled criteria for migraine without aura. Sexual activity has also been associated with a wide range of positive as well as negative effects, including headache and migraine (Table 1). There is even a sub classification for "preorgasmic" and "orgasmic" headache.[3] In a group of 51 patients with "headache associated with sexual activity" co morbidity with migraine was 25%.[74] Whether it is just physical stress causing headache or something extra during sexual activity is not known. The use of personal computer (PC) is a rather new factor and identified as possible trigger factor in 6.6% of Japanese migraine patients.[24] This factor has not been included in other questionnaire studies or experimental trials.

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Pathophysiology of a spontaneous migraine attack

Activation of the trigeminovascular system is pivotal during the headache phase of a migraine attack[75]. The mechanism causing activation of the trigeminovascular system remains to be elucidated[12,76]. Several mechanisms might be involved in the initiation of a migraine attack. A) Cortical spreading depression (CSD) is a steady depolarization of neuroglial membranes and is the pathophysiological mechanism underlying migraine aura[12]. A long-lasting blood flow change in meningeal arteries have been observed after CSD depending on trigeminal and parasympathetic activation[77]. B) Vasodilatation of cerebral and meningeal arteries might activate trigeminal nerves. Vasoactive substances such as nitroglycerin can trigger migraine in susceptible patients[78] and triptans may exert their anti-migraine effect through vasoconstriction of cranial blood vessels[75]. C) Neurogenic inflammation caused by vasoactive peptides released from the trigeminal nerve or other sources such as blood have shown to activate and sensitize meningeal perivascular nerve ending causing activation of the trigeminovascular system[79] and possible disruption of the blood-brain barrier[80]. D) Nociceptive information from the trigeminal nerve is modulated in the brainstem[81]. Activation of brainstem area's, such as the peri-aquaductal grey, has been shown during spontaneous and provoked migraine attacks[82,83]. E) The occurrence of premonitory symptoms (such as fluid retention, sleep problems and food craving) prior to the onset of headache suggest involvement of the hypothalamus.[84,85] Hypothalamic activation has also been shown in other trigeminal neuralgias, such as cluster headache[86]. For further information on the pathophysiology of migraine please read some excellent reviews that have been published recently[12,75,79,87].

Mechanism of action of trigger factor in migraine: stress, hypoxia and nitroglycerin

As presented, there are many (potential) trigger factors for migraine all with a different mechanism of action. Since it is not feasible to study all we will focus on three trigger factors: mental stress, normobaric hypoxia and nitroglycerin. The study of trigger factor mechanisms may provide further insight into the first phases of a migraine attack

A) Stress and the autonomic nervous system during migraine

Mental stressors are commonly perceived as important trigger factors by both patients and physicians[88], although direct evidence for this claim is lacking. In retrospective questionnaire studies, up to 62% of migraine patients reported that psychosocial stress

was an important trigger-factor for their attacks[25,29,89], but patients have a tendency to overestimate stress on retrospective measures[90]. In cross-sectional studies, migraine patients were found to have elevated plasma levels of cortisol, an indicator for stress, both outside a migraine attack compared to healthy volunteers[91] and during attacks compared to the inter-ictal phase[92]. Stress-provocation studies, involving mental and physical stressors, have suggested sympathetic and parasympathetic changes in migraine patients outside attacks compared to healthy volunteers [93-96]. However, experimental prospective studies examining whether stress-related biological changes are actually temporally related to the onset of migraine attacks, are lacking. We therefore performed a prospective, longitudinal ambulatory study, assessing perceived stress and objective stress-related biological changes in the four days prior to an impending migraine attack (chapter 2).

B) Hypoxia and blood brain barrier dysfunction

Hypoxia might also be a trigger factor for migraine. Firstly, acute exposure to high altitude may induce acute mountain sickness (AMS), which is characterized by headache, insomnia, dizziness, lassitude, fatigue and gastrointestinal symptoms such as anorexia, nausea, or vomiting in an unacclimatized person who has recently reached an altitude above 2500 m [97]. Up to one third of subjects with acute AMS also fulfill the criteria for migraine [3,98,99]. Secondly, chronic exposure to high altitude is associated with an increased migraine prevalence [100,101] and thirdly, sumatriptan is an established drug for the acute treatment of migraine [75], and was also shown to be effective in some studies in AMS[102,103]. In chapter 3 we have tested whether normobaric hypoxia may trigger migraine attacks in migraine patients under experimental conditions. Hypoxia has many biological effects and one of the mechanisms involved in the pathophysiology of AMS is disruption of the BBB causing cerebral edema[97]. In severe cases of AMS there are clear signs of vasogenic edema as shown by MRI[104]. Also in migraine disruption of the BBB has been suggested[105]. Whether hypoxia causes cerebral edema in mild cases of AMS (resembling migraine) is unclear. This question was studied in chapter 4.

C) Nitroglycerin and changes in cerebral blood flow

Nitroglycerin is an exogenous donor of nitric oxide[106], which is involved in central pain mechanism[107] and regulation of cerebral blood flow[108]. Infusion of NTG has shown to increase the diameter of the middle cerebral artery[109] and meningeal media artery[110] as well as to decrease blood flow velocity in the internal carotid artery and middle cerebral artery[111-113]. The effects of NTG on cerebral blood flow are caused either through the release of CGRP from the trigeminal nerve[114,115] or via a direct effect on vascular smooth

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muscle cells in blood vessels[106]. Infusion of NTG results in immediate type headache in >80% of migraine patients and <20% in healthy volunteers[116]. A delayed migraine attack is observed several hours after infusion of NTG in approximately 60% to 80% of migraine patients and very rarely in healthy volunteers without a family history of migraine[55,78,116]. Whether there is a difference in cerebrovascular response to NTG between migraine patients and healthy controls is unclear. One study suggested an increased cerebrovascular response during NTG infusion in migraine patients[117], whereas in a second study no increased response was observed.[118] This will be studied in chapter 6. In the same provocation study (chapter 7) we have studied cerebrovascular changes (both blood vessel diameters and blood flow) during the provoked migraine attack.

Aims of this thesis

As discussed there are many potential trigger factors for migraine. We have chosen to study three (potential) trigger factors: mental stress, normobaric hypoxia and nitroglycerin. The following aims for this thesis were defined:

1. To assess the prevalence of premonitory symptoms in a clinic based sample of migraine patients and to study a potential overlap between premonitory symptoms and trigger factors (chapter 1).

2. To assess both subjective and objective stress related parameters during the development of a spontaneous migraine attack (chapter 2).

3. To test normobaric hypoxia as a trigger factor for migraine in migraine susceptible patients and to compare the response to nitroglycerin (chapter 3).

4. To test whether normobaric hypoxia caused cerebral edema in healthy volunteers (chapter 4).

5. To develop a method to measure vasodilatation in cranial blood vessels as small as the middle meningeal artery in healthy volunteers and migraine patients using magnetic resonance angiography (chapters 5 and 6).

6. To assess the initial vascular response to nitroglycerin in migraine as a predictor for the development of a provoked migraine attack (chapter 6).

7. To assess vasodilatation in cranial blood vessels during a provoked migraine attack (chapter 7).

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CHAPTER 1

THE PREVALENCE OF PREMONITORY SYMPTOMS IN MIGRAINE: A QUESTIONNAIRE STUDY IN 461 PATIENTS

Cephalalgia 2006;26:1209-13

Abstract

Migraine attacks are often preceded by premonitory symptoms. Prevalence rates of migraine patients reporting one or more premonitory symptoms show considerable variability and rates range between 12% and 79%. Sources of variability might be differences in study population or research design. Using a questionnaire we retrospectively studied the prevalence of 12 predefined premonitory symptoms in a clinic based population. Of 461 migraine patients, 374 responded (81%). At least one premonitory symptom was reported by 86.9%, and 71.1% reported two or more. The most frequently reported premonitory symptoms were fatigue (46.5%), phonophobia (36.4%) and yawning (35.8%). The mean number of premonitory symptoms per person was 3.2 (± 2.5). Women reported 3.3 premonitory symptoms compared to 2.5 symptoms in men (p=0.01). Age, education, migraine subtype (with or without aura), and mean attack frequency had no effect on the mean number of symptoms per individual. In conclusion, premonitory symptoms are frequently reported by migraine patients. Sensitivity and specificity of premonitory symptoms for migraine need to be assessed using prospective methods.

Introduction

Migraine is a severe paroxysmal neurovascular disorder and considered a major cause of disability by the World Health Organization[1]. The primary cause of a migraine attack is unknown but probably lies within the central nervous system[12]. Prior to the start of the headache phase several non-headache symptoms (often called premonitory symptoms) are reported by migraine patients, such as changes in mood, behavior and sensory perception[4]. In a selected population migraine patients were able to predict an upcoming migraine attack well before the start of the headache phase[131]. Prevalence rates of patients reporting one or more premonitory symptoms ranges between 12%[132] and 79%[133]. One soure of variability in prevalence rate might be differences in study population. In population based studies rates range from 12% in migraine patients without aura to 18% in migraine patients with aura[132], whereas in clinic based studies prevalence rates range from 33%[134,135] to 79%[133]. Other sources of variability might be differences in study design such as preselection of patients or unclear definitions of premonitory symptoms. In this study we assessed the prevalence of 12 frequently reported premonitory symptoms using a questionnaire in a large unselected clinic based population and only symptoms preceding 2/3 of attacks or more were considered a premonitory symptom.

Methods

Migraine patients (diagnosed according to the criteria of the IHS[3]) from the Neurology outpatient clinic of the Leiden University Medical Centre received a questionnaire by mail. A reminder was send out to the patients who had not responded after 8 weeks. The questionnaire addressed migraine characteristics, sociodemographic factors and possible premonitory symptoms. Migraine related variables were: migraine subtype (migraine with or without aura according to the criteria of IHS[3]) and mean attack frequency per month in the last half year. The following sociodemographic variables were included: age, sex and education in 3 categories: primary school or low vocational training, middle academic/vocational training, and higher academic/vocational training. Twelve possible premonitory symptoms were included based on reports in the literature[4,131,135]: Concentration problems, depression, food craving, physical hyperactivity, irritability, nausea, phonophobia, fatigue, sleep problems, stressed feeling, stiff neck and yawning. For every possible premonitory symptom patients answered the question: "How often is a migraine attack preceded by this symptom?" Answers were categorized as never, less

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than 1/3 of attacks, 1/3 to 2/3 of attacks or in more than 2/3 of attacks. Photophobia was not included in the questionnaire since co-occurrence of aura symptoms and visual hypersensitivity might introduce bias. The duration of the premonitory phase was not strictly defined. The local ethical committee had approved the study. Symptoms were considered a premonitory symptom when at least 2/3 of migraine attacks were preceded by this particular symptom.

Prevalence of every premonitory symptom was calculated and presented as percentage. The number of premonitory symptoms per individual was calculated and presented as mean (and SD). A difference in mean number of symptoms between subgroups was tested using the non-paired t-test (for sex and migraine subtype) or one-way ANOVA (for age, education and attack frequency). In case of non-normality the Mann-Whitney U test or Kruskal Wallis test were used. The Bonferroni correction was applied for multiple testing and a p value <0.01 was considered significant. The co-occurrence of PS within patients was tested using Spearman's rank correlation coefficient and presented as correlation matrix.

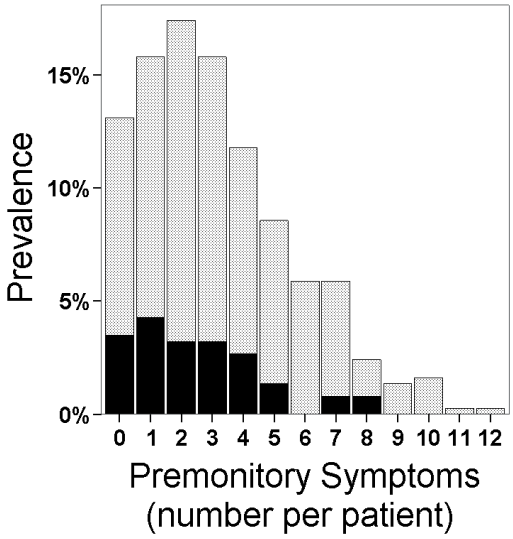

Figure 1 Number of premonitory symptoms per subject. Black bars represent males, gray bars females.

Results

The questionnaire was sent to 461 migraine patients; 374 (81%) responded. The characteristics of the study population are shown in Table 1. Forty-nine patients (13.1%)

reported no premonitory symptoms, 86.9% of patients reported at least one symptom and 71.1% reported two or more (Figure 1). The most frequently reported premonitory symptoms were fatigue (46.5%), phonophobia (36.4%) and yawning (35.8%) (Table 2). The mean number of premonitory symptoms reported per person was 3.2 (SD 2.5). Women reported a mean of 3.3 symptoms compared to a mean of 2.5 in men (p=0.01). The effects of age, education, migraine subtype, and mean attack frequency on the mean number of symptoms per individual were not statistically significant (Table 1). Of the migraine patients 52% had migraine with aura (Table 1). No significant difference in premonitory symptoms was found between migraine subtypes (with and without aura) (Table 2). The co-occurrence of symptoms is presented in Table 3. Depression and irritability showed the strongest correlation, followed by depression and concentration problems and depression and a stressed feeling.

Table 1 Migraine and sociodemographic properties of all interviewed patients.

	Subgroups	N (%)	Mean number of PS per individual (SD)	
Total population		**374**	**3.2 (2.5)**	
Sex				
	Male	74 (20%)	2.5 (2.1)	
	Female	300 (80%)	3.3 (2.5)	**p=0.01**
Age (years)				
	<30	29 (8%)	3.6 (2.5)	
	30-50	172 (46%)	3.0 (2.2)	
	50>	173 (46%)	3.2 (2.7)	p=0.59
Education				
	low	147 (39%)	3.5 (2.4)	
	middle	78 (21%)	2.9 (2.7)	
	high	148 (39%)	3.0 (2.5)	p=0.03
Migraine subtype				
	without aura	179 (48%)	2.9 (2.4)	
	with aura	195 (52%)	3.4 (2.6)	p=0.12
Attack frequency				
(per month)	<2	94 (25%)	2.9 (2.4)	
	2-4	139 (37%)	3.1 (2.4)	
	>4	140 (38%)	3.3 (2.6)	p=0.65

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Table 2 Prevalence of premonitory symptoms

Premonitory symptom	Prevalence (%)						
	All patients (N=374)	Male (N=74)	Female (N=300)	P value	MO	MA	P value
Fatigue	**46.5**	39.1	48.3	0.16	47.5	45.6	0.72
Phonophobia	**36.4**	24.3	39.3	0.02	30.7	41.5	0.03
Yawning	**35.8**	31.1	37.0	0.34	34.6	36.9	0.65
Stiff neck	35.0	32.4	35.7	0.60	40.8	29.7	0.03
Nausea	28.6	16.2	31.7	**0.008**	22.9	33.8	0.02
Concentration problems	28.1	29.7	27.8	0.74	20.7	35.1	0.002
Irritability	28.1	25.6	28.6	0.59	24.0	32.0	0.09
Depression	17.6	13.5	18.6	0.29	18.4	16.9	0.70
Craving	17.4	6.7	20.0	**0.007**	14.0	20.5	0.10
Stressed feeling	15.2	14.8	15.3	0.92	14.0	16.4	0.51
Physical hyperactivity	15.0	6.7	17.0	0.03	12.8	16.9	0.27
Sleep problems	13.9	10.8	14.6	0.39	14.0	13.9	0.98

*Prevalence is the percentage of patients of the total population (or subgroup) reporting a certain symptoms. MO denotes migraine without aura, MA migraine with aura.

Table 3 Co-occurrence of premonitory symptoms: Spearman's rank correlation coefficient matrix. Field shading indicates correlation strength.

	SF	SN	PHH	IR	YA	DE	FA	CR	PH	CP	NA	SP
Stressed feeling (SF)												
Stiff neck (SN)	,234											
Physical hyperactivity	,197	,116										
Irritability (IR)	,198	,126	,171									
Yawning (YA)	-,038	,129	,171	,144								
Depression (DE)	,350	,160	,179	,397	,151							
Fatigue (FA)	,171	,203	,149	,290	,220	,313						
Craving (CR)	,120	,048	,262	,200	,113	,084	,053					
Phonophobia (PH)	,082	,144	,228	,306	,084	,190	,164	,211				
Concentration problems (CP)	,132	,101	,137	,324	,057	,350	,267	,137	,294			
Nausea (NA)	,044	,130	,049	,130	,206	,188	,181	,100	,186	,170		
Sleep problems (SP)	,109	,125	,004	,127	,024	,138	,153	,121	,194	,075	,104	

Discussion

The proportion of migraine patients reporting premonitory symptom was high: 86.9% of patients reported at least one symptom. This high prevalence rate is comparable to one previous clinic based study where the rate was 79%[133], but in contrast with two other studies where rates were about 33%[134,135]. Variability in rates might be explained by differences in study design such as preselection of patients[133] or differences in symptoms that are included in the questionnaire[135]. Furthermore, the study of Amery[133] was conducted before the introduction of the IHS migraine criteria. Another source of variability might be the studied population. For instance prevalence rates in population based studies have shown to be as low as 12%[132]. It may be that patients identified in a population based setting are not informed about premonitory symptoms in migraine and, therefore, are less aware of these symptoms. Fatigue was the most common premonitory symptom and the order of reported symptoms is comparable with a previous study in a selected population[131]. In our study the percentage of patients presenting with aura was high. Patients with aura are more likely to consult a neurologist than patients without aura and this differences might be increased due to the fact that all patients in the Netherlands see there General Practioner first in case of complaints. However, no significant difference in PS was seen between migraine subtypes.

Females reported more premonitory symptoms than males. An overlap between premonitory symptoms and premenstrual syndrome might explain this difference[136]. Furthermore more females reported craving and nausea as premonitory symptom compared to males. This is an interesting finding since chocolate and sweet cravings are more common in females than males[137]. Nausea is also more frequently reported in females than in males in acute myocardial infarction[138] and after anaesthesia[139]. The physiological basis for this gender difference is not clear. Besides gender differences co-occurrence of premonitory symptoms within one subject were studied. The strongest associations were found between depression and symptoms such as irritability, concentration problems and fatigue. Co-occurrence of these mood symptoms might not be a coincidence since they are all part of the DSM IV criteria for dysthymic disorder and major depression[140].

There might also be an overlap between premonitory symptoms and trigger factors in migraine. A migraine trigger is any factor that on exposure or withdrawal leads to the development of a migraine attack whereas PS are a consequence of an ongoing attack. For instance mental stress (either the acute episode or the relieve period after an acute episode) is often considered a trigger factor in retrospective questionnaires. However, it is unclear whether migraine attacks can be triggered in an experimental provocation

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study[141]. So, It could be that mental stress trigger a migraine attack or that patients perceive more mental stress because they are in the premonitory phase of a migraine attack. Future prospective diary studies or experimental studies are needed to address this question.

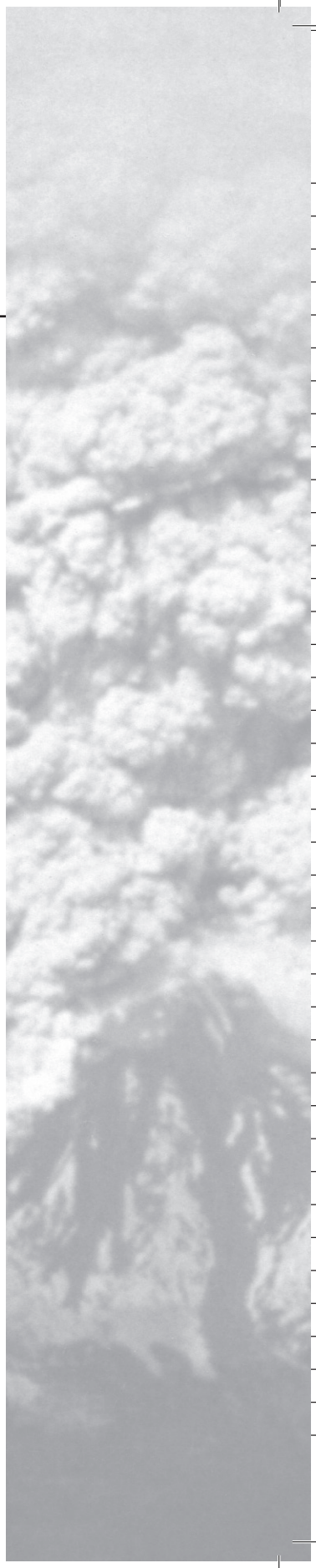
This study, as well as other retrospective studies assessing premonitory symptoms in migraine, has some limitations. First, the list of possible premonitory symptoms is based on previous studies[4,131,135] and may seem somewhat arbitrary. To be complete one should do a full exploration of all possible symptoms associated with a migraine attack. Second, non-responders might have introduced some bias. However, the response rate was 81% and there was no difference in age, sex or migraine subtype between responders and non-responders (data not shown). Third, when should a symptom be classified as a premonitory symptom? We excluded photophobia as a premonitory symptom but it could be argued that phonophobia and nausea are actually part of the headache phase and therefore no PS. Furthermore, in this study we considered symptoms as premonitory symptom if 2/3 of attacks were preceded by this particular symptom. In order to assess sensitivity and specificity of individual premonitory symptoms for migraine attacks, possible premonitory symptoms and migraine attacks need to be studied prospectively preferably[131,142]. Also the temporal relation between possible premonitory symptoms, aura and the occurrence of headache needs to be assessed in a prospective design.

In conclusion, premonitory symptoms are frequently reported by migraine patients. Sensitivity and specificity of premonitory symptoms for migraine need to be assessed using prospective methods.

CHAPTER 2

IS STRESS A TRIGGER FACTOR FOR MIGRAINE?

Psychoneuroendocrinology 2007;32:532-8



Abstract

Background

Although mental stress is commonly considered to be an important trigger factor for migraine, experimental evidence for this belief is lacking.

Objective: To study the temporal relationship between changes in stress related parameters (both subjective and objective) and the onset of a migraine attack.

Methods

This was a prospective, ambulatory study in 17 migraine patients. We assessed changes in perceived stress and objective biological measures for stress (saliva cortisol, heart rate average [HRA], and heart rate variability [low frequency power and high frequency power]) over four days prior to the onset of spontaneous migraine attacks. Analyses were repeated for subgroups of patients according to whether or not they felt their migraine to be triggered by stress.

Results

There were no significant temporal changes over time for the whole group in perceived stress (p=0.50), morning cortisol (p=0.73), evening cortisol (p=0.55), HRA (p=0.83), low frequency power (p=0.99) and high frequency power (p=0.97) prior to or during an attack. Post-hoc analysis of the subgroup of nine stress-sensitive patients who felt that >2/3 of their migraine attacks were triggered by psychosocial stress, revealed an increase for perceived stress (p=0.04) but no changes in objective stress response measures. At baseline this group also showed higher scores on the Penn State Worry Questionnaire (p=0.003) and the Cohen Perceived Stress Scale (p=0.001) compared to non stress-sensitive patients.

Conclusions

Although stress-sensitive patients, in contrast to non stress-sensitive patients, may perceive more stress in the days before an impending migraine attack, we failed to detect any objective evidence for a biological stress response before or during migraine attacks.

Introduction

Migraine is a multifactorial brain disorder characterised by recurrent, disabling attacks of headache, associated autonomic features and, in one third of patients, neurological aura symptoms[75]. Although the pathogenesis of the migraine features is reasonably well understood, it is not clear how migraine attacks are actually triggered. Mental stressors are psychological events that in potential threaten homeostasis of a living organism[143] and they are commonly perceived as important trigger factors by both patients and physicians[88], although direct evidence for this claim is lacking. In retrospective questionnaire studies, up to 62% of migraine patients reported that psychosocial stress was an important trigger-factor for their attacks[25,29,89], but patients have a tendency to overestimate stress on retrospective measures[90]. In cross-sectional studies, migraine patients were found to have elevated plasma levels of cortisol, an indicator for stress, both outside a migraine attack compared to healthy volunteers[91] and during attacks compared to the inter-ictal phase[92]. Stress-provocation studies, involving mental and physical stressors, have suggested sympathetic and parasympathetic changes in migraine patients outside attacks compared to healthy volunteers [93-96]. However, experimental prospective studies examining whether stress-related biological changes are actually temporally related to the onset of migraine attacks, are conspicuously lacking.

We therefore performed a prospective, longitudinal ambulatory study, assessing perceived stress and objective stress-related biological changes in the four days prior to an impending migraine attack. We included both patients who claimed that stress would trigger the majority of their attacks (stress-sensitive) and patients who denied such a relationship (non stress-sensitive).

Methods

Subjects

A total of 69 migraine patients were recruited from our headache outpatient clinic and 27 patients were included in the study. Inclusion criteria were (1) diagnosis of migraine with or without aura according to the criteria of the IHS (code 1.1. and 1.2.1; [3] and at least one migraine attack per month in the previous six months. Exclusion criteria were (1) pure menstrual migraine, (2) more than 15 days of headache per month, (3) use of beta-blockers and (4) inability to differentiate between migraine and other types of primary headache syndromes. We asked the patients whether they felt that their attacks were triggered by stress and if so, in what proportion. Patients who claimed that

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>2/3 of their attacks were triggered by stress were considered "stress sensitive" and those who reported that <2/3 of their attacks was triggered by stress were considered "stress non-sensitive". The study was approved by the local medical ethical committee and the subjects gave informed consent prior to the start of the study. The study was conducted in the period January to August 2004.

Procedure

Patients filled out two stress questionnaires at the start of the observation period. The first was the Cohen Perceived Stress Scale (Cohen PSS)[144] which is a measure for perceived stress in the past month. It is a 14 item questionnaire and the score ranges from 0 (no stress) to 56 (maximum stress). The second questionnaire was the Penn State Worry Questionnaire (PSWQ) [145], a 16 item questionnaire to assess the trait of worrying (ranging from 16 (minimal worries) to 80 (maximum). Both questionnaires are used to characterize the study population.

The observation period started at least three days after an attack and lasted up to the first day of the next attack. Migraine symptoms and stress events were scored daily around 22.00 hours using an electronic diary (described below). Saliva samples were taken 3 times per day (30 and 45 minutes after waking up and around 22.00 hours, before filling out the stress and migraine questionnaire); Heart rate was measured daily between 18.00 and 22.00 hours using an ambulatory monitoring system. The timings were chosen in such a way that the recordings would be influenced as little as possible by physical activity during the day.

Perceived daily stress and migraine symptoms

'Personal digital assistants' devices (Palm Tungsten E) were used as electronic diaries. Data were entered daily around 22.00 hours using a database application (Pendragon Forms 3.2, Pendragon Software Corporation, Libertyville, USA)[146]. Perceived daily stress was measured with the validated Daily Stress Inventory (DSI). In short, this is a 58 item inventory of events experienced in the last 24 hours[147]. The amount of stress felt in response to each event is rated on a Likert-type scale (0 = event did not happen, 1 = event occurred but was not stressful to 7 = event caused panic). The perceived daily stress is the sum total of all ratings (DSI-sum). Migraine symptoms were assessed using the criteria of the IHS. The diaries were easy to use and retrospective data entry or alterations were disallowed by the PDA program. An alarm sounded daily at 22.00 hours to remind patients to fill out the questionnaires.

Salivary cortisol

Saliva samples for cortisol assessment were obtained with 'Salivette' saliva collection tubes (Sarstedt, Germany). Each day patients collected three saliva samples. 30 minutes and 45 minutes after waking up and around 22.00 hours. Patients were instructed not to eat, exercise, smoke or brush their teeth 30 minutes prior to sampling. Patients stored the samples at 7 °C until the end of the observation period. At the end of the observation period patients were asked to report sampling problems. After centrifugation, samples were stored at -80 °C until analysis. Cortisol concentrations were determined using Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The functional sensitivity of this assay is 2 nmol/L[148].

Heart rate and heart rate variability

Heart rate was measured using the Vrije Universiteit Ambulatory Monitoring System (VU-AMS, version 4.6, Vrije Universiteit Amsterdam)[149] between 18.00 and 22.00 hours during periods of 10 minutes every half hour. R-R wave intervals were recorded on line from a 3-lead ECG. Fast Fourier transformation was used to calculate spectral power of the RR interval [150]; a trend was removed from the data to reduce the influence of very low frequencies. A cubic spline function corrected for missing values in the time series to result in regularly sampled time series. The data were multiplied by a Tukey window and transformed from the time domain to the frequency domain with the discrete Fourier transform. The spectra were smoothed by a triangular window (width ~0.01 cycles per RR interval). After integration of the area under the curve, the low frequency (0.05-0.15 Hz) power (LF), reflecting a mix of sympathetic and parasympathetic activity, and the high frequency (0.15-0.30Hz) power (HF), largely reflecting parasympathetic activity were calculated.

Statistical analysis

Temporal changes and differences between the two stress sensitive subgroups in perceived stress, cortisol (morning and evening), HRA, LF and HF power were analysed using a linear mixed model, with observation day and subgroup as fixed factors. A maximum of four premigraine days were included in the analysis since the premonitory phase may start up to 48 hours prior to the onset of the headache phase[4,134]. Cohen PSS and PWSQ differences between stress sensitive subgroups were tested using an unpaired t-test. The Bonferroni correction was applied for multiple testing and $P<0.025$ was considered significant.

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Results

Study population and observation periods

Of the 27 patients included in the study, 17 patients had a migraine attack during the observation period (Table 1). In 10 patients we did not measure an attack: six patients dropped out because the ambulatory cardiovascular measurements interfered too much with daily activities and four patients did not have a migraine attack within the observation period. The duration of the pre-ictal observation period in the 17 patients who had a migraine attack was four days in 12 patients, three days in two patients, two days in two and only 1 day in one patient. Some patients developed an attack within a few days after starting the observation period which is the reason for the variability in observation duration. In 12 patients the migraine attack began in the morning and in 5 patients in the afternoon.

Table 1 Demographic information of study participants.

	All patients (n=27)	Patients ***without*** an attack (n=10)	Patients ***with*** an attack (n=17)	Stress sensitive patients (n=9)	Stress insensitive patients (n=8)
Mean age (SD)	40.8 (9.9)	39.1 (10.1)	41.8 (9.9)	41.3 (8.5)	42.3 (11.9)
Ratio of men to women	7 : 20	3 : 7	4 : 13	1 : 8	3 : 8
Ratio MO to MA	20 : 7	7: 3	13: 4	8 : 1	5 : 3
Attack frequency per month (SD)	4.4 (2.7)	3.9 (2.1)	4.7 (3.0)	3.7 (2.1)	5.8 (3.6)
PWSQ				58.3 ± 12.5	39.0 ± 9.8*
Cohen PSS				29.4 ± 7.9	16.4 ± 4.2**

MO denotes migraine without aura, MA migraine with aura, PWSQ Penn State Worry Questionnaire and Cohen PSS Cohen Perceived Stress Scale. (*p=0.003 and ** p=0.001).

Baseline characteristics

The demographics of the total study population and the various subgroups are given in table 1. There were nine stress sensitive and eight stress non-sensitive patients. The baseline mean PSWQ and Cohen PSS scores were higher in the stress sensitive patients.

Temporal changes in stress related variables

The temporal profiles of the mean scores for perceived stress, morning cortisol, evening cortisol, heart rate, LF and HF power are shown in Figures 1a-e for the whole study population and in Figures 2a-e for the subgroup of nine stress-sensitive patients compared to eight non stress-sensitive patients. In the total study population, the mean score for perceived stress was 17.8 ± 16.2 on the migraine day, the mean morning cortisol 15.6 ± 9.7 nmol/l, the mean evening cortisol 5.3 ± 2.7 nmol/l and the mean heart rate 79.7 ± 12.1 bpm. Differences between observation days were not significant. The comparison between the stress sensitive with non-sensitive patients revealed in the nine stress sensitive patients an increase in perceived stress in the days prior to an attack (Figure 2a), but no other differences between the two groups.

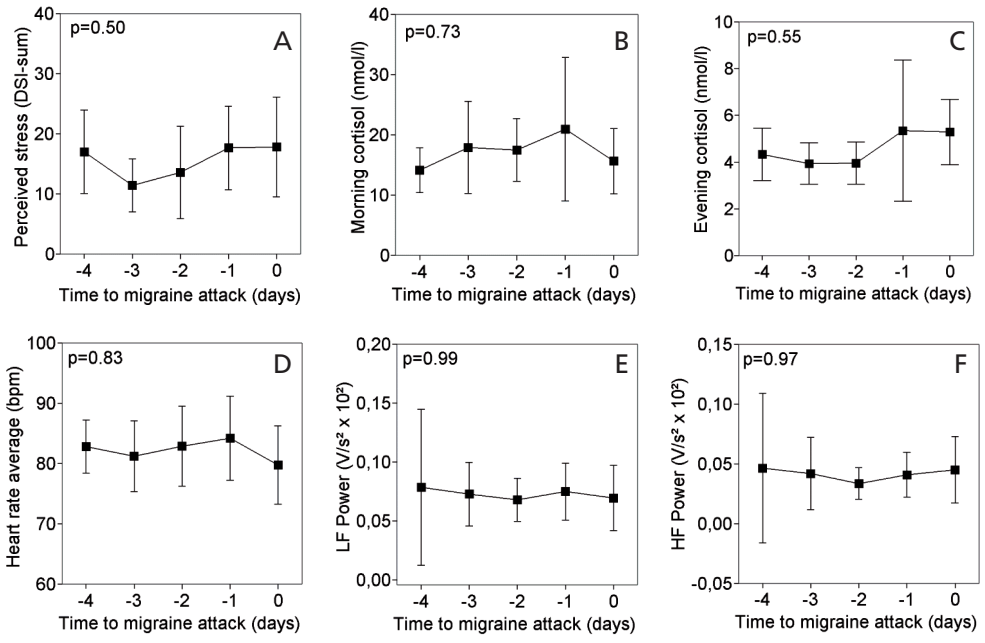

Figure 1A Perceived stress during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figures 1B** Morning corisol during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figure 1c** Evening cortisol during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figures 1D** Heart rate average during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figures 1E** LF power during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figures 1F** HF power during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals.

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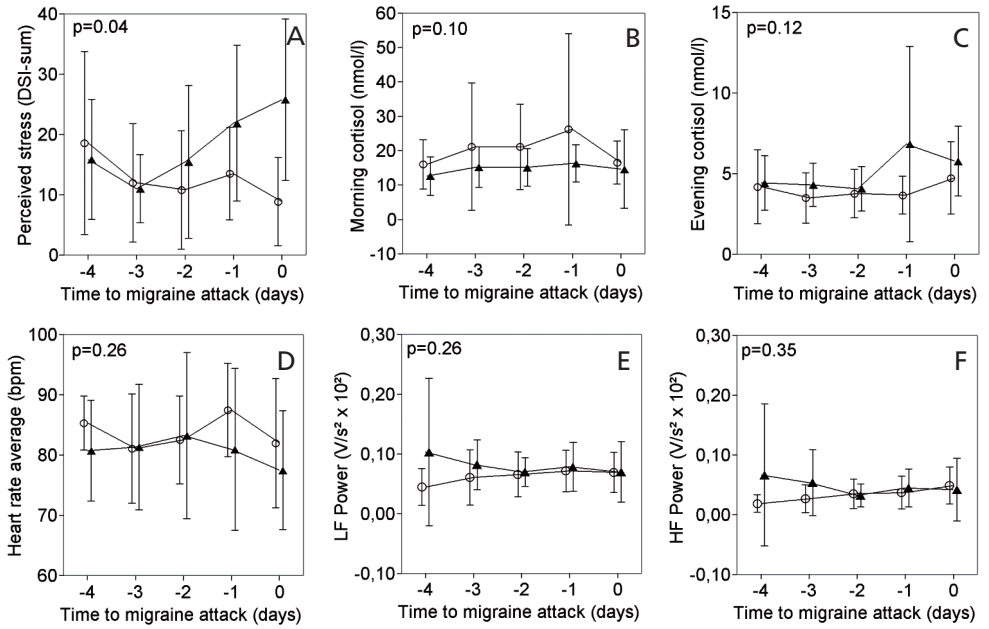

Figure 2A Perceived stress for the nine stress sensitive (filled triangles) and eight stress non-sensitive (open circles) patients, who were followed during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figure 2B** Morning cortisol for the nine stress sensitive (filled triangles) and eight stress non-sensitive (open circles) patients, who were followed during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figure C** Evening cortisol for the nine stress sensitive (filled triangles) and eight stress non-sensitive (open circles) patients, who were followed during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figures 2D** Heart rate average for the nine stress sensitive (filled triangles) and eight stress non-sensitive (open circles) patients, who were followed during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figures 2E** Mean LF power for the nine stress sensitive (filled triangles) and eight stress non-sensitive (open circles) patients, who were followed during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals. **Figures 2F** Mean HF power for the nine stress sensitive (filled triangles) and eight stress non-sensitive (open circles) patients, who were followed during an attack and for 1-4 days prior to the attack. Error bars represent 95% confidence intervals.

Discussion

In this prospective longitudinal study we failed to find any objective evidence for a temporal relationship between perceived stress, biological indicators for a stress-response, and the onset of migraine attacks. Although stress-sensitive patients indeed reported an increase in perceived stress in the days before an attack, this was not accompanied by objective signs indicating a biological stress response. The present results extend earlier negative findings on the putative relationship between stress and migraine. Autonomic function tests during migraine attacks failed to show changes in heart rate variability, blood pressure reaction[151] or transcranial Doppler response in the middle cerebral artery [44]. In contrast, in the inter-ictal phase changes in both sympathetic and parasympatic autonomic function have been described[95,96,152]. The increase in perceived stress in stress-sensitive patients is in accordance with previous prospective studies in which, however, no biological stress markers were included[42,43].

Stressors can be described as physical and psychological events that in potential threaten homeostasis of a living organism[143]. Both acute stressors and stressful daily events have shown to increase cortisol[153,154] and heart rate[155]. Although a profound effect of daily stressful events on migraine seems unlikely, we cannot fully exclude an association between mental stress and migraine. We could only measure 17 migraine patients because of the rather demanding design of the study (daily observations for, in some instances, several weeks because of the unpredictable timing of attacks). Due to the prospective nature of our study the pre-ictal interval varied between study subjects. Twelve out of 17 migraine patient were studied for the full length of 4 days, five patients for a shorter period of time because these five patients experienced their attack within a few days after starting the observation period. Because we did not observe differences for our parameters between day -4 and day -2 we believe that this shorter observation period will not influence our findings. Furthermore, the temporal resolution of our measurements was relatively low. Cortisol was measured only in the morning and evening, and heart rate only in the evening to reduce the effect of physical activity. Theoretically, a reduction in physical activity during evening hours because of the prodromal phase of a migraine attack[156] may have masked an association between changes in heart rate and migraine. Also theoretically, due to the low resolution of measurements this could have resulted in missing changes occurring immediately before the onset of an attack. We feel however that, based on the time course of premonitory symptoms, changes are to be expected to occur 12 to 24 hours prior to the onset of attacks[134].

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For our study we excluded pure menstrual migraine. Free salivary cortisol is decreased during the follicular phase of the menstruation period and in oral contraceptive users[157]. We did not correct for the temporal relation between menstrual cycle or oral contraceptive use and the occurrence of the migraine attack in the 13 women who were included in this study. Therefore, oral estrogens or the menstrual cycle might have influenced cortisol measurements.

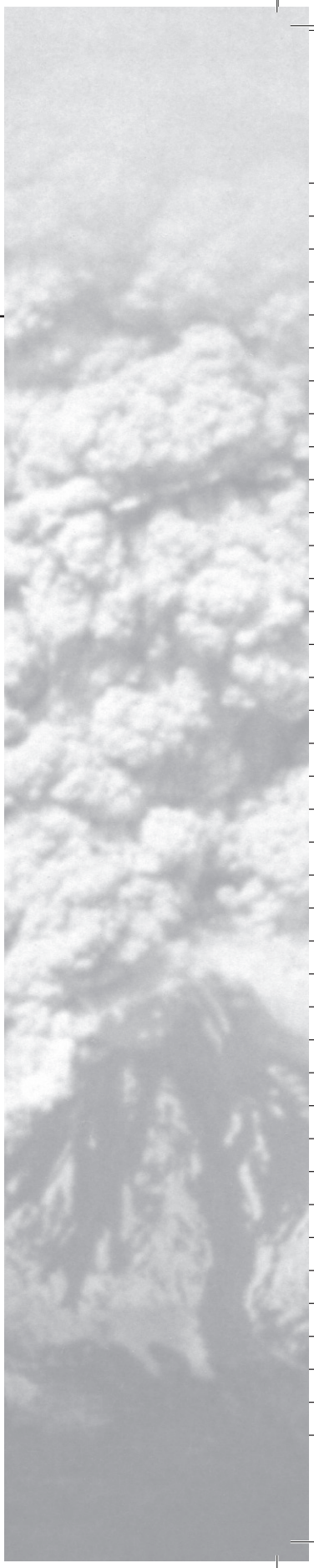
Future studies could include continuous measurements including the full 24 hours prior to the onset of attacks, although this will be logistically quite challenging. Although salivary morning cortisol is related to workstress[158], short lasting daily stressors are probably better assessed using high frequent daily measurements[153]. The cortisol response after acute stressors has shown to normalize after 1 to 2 hours[159]. Future longitudinal stress studies in migraine could also include epinephrine and norepinephrine as indicators for sympathetic-adrenal-medullary system related changes after mental and physical stressors[160]. Both catecholamines can be measured in urine enabling environmental measurements[161].

In conclusion, we were unable to show objective evidence for a biological stress response before and during migraine attacks. This could reflect a true negative finding or be the result of the discussed study limitations. The reported association between perceived stress and migraine in a sub-population of stress sensitive patients might suggest that these attacks were triggered by mental stress. It could be that in these patients migraine attacks are triggered by mental stress or that events are perceived as stressful due to functional brain changes occurring in the very early phase of a migraine attack.

CHAPTER 3

NORMOBARIC HYPOXIA AND NITROGLYCERIN AS TRIGGER FACTORS FOR MIGRAINE

Cephalalgia 2006;26:816-9



Abstract

Migraine prevalence is increased in high-altitude populations and symptoms of acute mountain sickness mimic migraine symptoms. Here we tested whether normobaric hypoxia may trigger migraine attacks. As positive control we used nitrolgycerine (NTG), which has been shown to induce migraine attacks in up to 80% of migraineurs. Sixteen patients (12 females, mean age 28.9 ± 7.2 years) suffering from migraine with (n=8) and without aura (n=8) underwent 3 different provocations (normobaric hypoxia, NTG and placebo) in a randomized, cross-over, double dummy design. Each provocation was performed on a separate day. The primary outcome measure was the proportion of patients developing a migraine attack according to the criteria of the International Headache Society within 8 hours after provocation onset. Fourteen patients completed all three provocations. Migraine was provoked in 6 (42%) patients by hypoxia, 3 (21%) by NTG and 2 (14%) by placebo. The differences among groups were not significant (p=0.197). The median time to attacks was 5 hours. In conclusion, the (remarkably) low response rate to NTG is surprising in view of previous data. Further studies are required to fully establish the potency of hypoxia in triggering migraine attacks.

Introduction

Migraine is a common neurovascular disorder that affects 15 to 20 % of the population[11]. Several substances are known to induce migraine attacks in susceptible patients. Nitroglycerin (NTG) is the most frequently studied trigger factor and has been shown to induce migraine attacks in 60 to 80% of migraineurs within 5 to 6 hours [55,56,78]. Hypoxia may also be a trigger factor for migraine. Firstly, acute exposure to high altitude may induce acute mountain sickness (AMS), which is characterized by headache, insomnia, dizziness, lassitude, fatigue and gastrointestinal symptoms such as anorexia, nausea, or vomiting in an unacclimatized person who has recently reached an altitude above 2500 m [97]. Up to one third of subjects with acute AMS also fulfill the criteria for migraine [3,98,99]. Secondly, chronic exposure to high altitude is associated with an increased migraine prevalence [100,101] and thirdly, sumatriptan is an established drug for the acute treatment of migraine [75], and was also shown to be effective in some studies in AMS [102,103]. In the present study we tested whether normobaric hypoxia may trigger migraine attacks in migraine patients under experimental conditions. We used NTG as a positive control.

Methods

Patients

Patients with a history of migraine with (MA) or without (MO) aura, aged 18-65 years, with a baseline attack frequency of 1 to 9 per 3 months in the last six months were recruited from the outpatient clinic, among hospital staff and university students. Exclusion criteria were headache on more than 10 days per month, pregnancy, lactation, psychiatric disorders including substance and drug abuse, neurological diseases other than migraine, and a medical disease that could, according to the judgment of the investigators, interfere with the study. Before each provocation it was made sure that no migraine attack had occurred within the previous 3 days, no pain or migraine medications were taken the previous 24 hours, and that the patient did not suffer from sinusitis or coryza. The study was approved by the local ethical committee.

Experimental Design

Patients were subjected to three different provocations (normobaric hypoxia, NTG and placebo) in a randomized, double-dummy controlled fashion using a cross-over design. The NTG and placebo part were double blind, and the hypoxia part was single blind, because arterial oxygen saturation (SaO_2) had to be monitored continuously.

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Each of the three provocations was performed on a different day. At the beginning of each provocation, the supine patient obtained a well fitting facial mask, which was connected with a tube for the administration of air with reduced or normal (placebo) oxygen content. Then an antecubital vein was cannulated for the infusion of NTG or saline (placebo). As soon as the patients stated that they became familiar with the facial mask and the attached tube, the provocation was started. An independent physician carried out randomization.

Exposure to normobaric hypoxia: An investigator progressively increased the concentration of nitrogen (N_2) in the inspired air to obtain SaO_2 values of 75 to 80% within 20 minutes. During exposure to normobaric hypoxia, intravenous (IV) saline was administered. The NTG provocation consisted of IV administration of 0.5 microgram / kg body weight NTG within 20 minutes using a free infusion set (Codan, the Netherlands), while the patient was breathing normal air. Placebo provocation: The participants breathed normal air during the whole provocation, whereas only IV saline was administered during the first 20 minutes of the provocation.

Headache Response to the Different Provocations

Migraine symptoms according to the criteria of the International Headache Society (IHS)[3] and headache severity on a visual analogue scale (VAS) ranging from 0 to 100 were assessed every 30 minutes. Each provocation was terminated after 5 hours, or earlier, if headache symptoms fulfilled the IHS criteria for migraine, or the experiment was not tolerated by the patient. The presence of headache symptoms was re-assessed 8 hours after the beginning of each provocation, because the time-course of migraine attacks induced by hypoxia might differ from those induced by NTG. After termination of every provocation the patient was asked which provocation they thought they were exposed to.

SaO_2 measurements

SaO_2 was measured using a fingertip pulse oximeter (Datex-Ohmeda, Helsinki, Finland).

Statistical analysis

The primary outcome measure was the migraine response, defined as the proportion of patients developing a migraine attack fulfilling the IHS criteria [3] for migraine within 8 hours after the start of the experiment. Differences in response between groups were tested using Friedman's test. Patients who did not complete all provocations were analyzed on a worst-case scenario basis (meaning an attack after placebo and no attack after provocation). Fourteen patients were required to detect a difference in migraine

response of 40% between hypoxia and placebo (alpha 0.05, beta 90%). The secondary outcome measure was the difference in headache response categorized as (1) absent, (2) mild, (3) moderate or severe headache not fulfilling the criteria for migraine or (4) migraine fulfilling the IHS criteria.

Results

A total of 16 patients (12 females, mean age 29 ± 7 years) were included in the study. The mean baseline attack frequency was 1.2 attacks per month (SD 0.76). Fourteen patients completed all three provocations, and two patients completed only two (Table 1).

Table 1 Patient characteristics (demographic and migraine)

Subject	Sex	Age	Migraine (IHS)	Migraine attacks per month	Attack positive provo-cations	Migraine characterics of provoked attacks								
						HS	UH	AH	PH	N	V	PT	PN	VAS
1	F	25	MO	0.33	Hypoxia	2	-	-	yes	yes	-	yes	-	59
2	M	26	MA	0.33										
3	M	36	MA	0.33	Placebo	2	-	yes	yes	yes	-	yes	yes	43
4	F	23	MO	3	Hypoxia	3	yes	yes	yes	yes	yes	yes	-	60
5	F	25	MO	1	Hypoxia	3	-	yes	yes	yes	-	yes	-	65
6	M	24	MO	2										
7	F	23	MO	1	Hypoxia	2	-	yes	yes	yes	-	-	-	49
					NTG	2	-	yes	yes	yes	-	-	-	31
8	F	28	MO	1	NTG	2	-	yes	yes	yes	-	-	-	61
9*	F	42	MO	1	NTG	2	yes	yes	yes	yes	-	yes	yes	38
10	F	33	MA	1	Hypoxia	2	yes	yes	yes	yes	-	-	-	70
11*	F	44	MA	2										
12	M	36	MA	2	Hypoxia	2	yes	yes	yes	yes	-	yes	yes	28
					NTG	3	yes	-	yes	yes	yes	yes	yes	29
13	M	23	MO	1										
14	F	29	MA	1										
15	F	22	MA	0.5										
16	F	22	MA	2	Hypoxia	2	yes	yes	yes	-	-	yes	yes	51
					Placebo	3	yes	yes	yes	-	-	yes	yes	61

F denotes female, M male, MA migraine with aura, MO migraine without aura, NTG nitroglycerine, HS headache severity (2=moderate, 3 =severe), UH unilateral headache, AH aggravation of headache during physical activity, PH pulsating headache, N nausea, V vomiting, PT photophobia and PN phonophobia

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Out of the 14 patients who underwent all three provocations, six patients (43%; 95% confidence interval (CI) 27% to 69%) developed a MO attack during exposure to normobaric hypoxia, three patients (21%; 95%CI 0% to 42%) after the administration of NTG, and two patients (14%; 95%CI –4% to 32%) after the administration of placebo. The frequency of migraine attacks did not differ among groups (p= 0.197). Both patients with incomplete provocations developed a MO attack, one after exposure to normobaric hypoxia and the other after administration of NTG. The inclusion of the two patients who underwent just two provocations did not change the study results (p=0.150). The median time to migraine attacks was five hours (4 hours for placebo, 4.5 hours for hypoxia and 6 hours for NTG). Headache responses (Figure 1) did not differ between groups (p=0.094). Both in the hypoxia and NTG group there were 4 patients who developed moderate to severe headache, but did not fulfull IHS criteria for migraine (no accompanying symptoms such as nausea, phonophobia or photophobia). The subjects' rating of whether they had been exposed to hypoxia, NTG or placebo was no better than by chance. Four patients guessed all three provocations correct, five guessed all three provocations and four were correct in one provocation (2 placebo and 2 hypoxia). Ratings were missing in one patient.

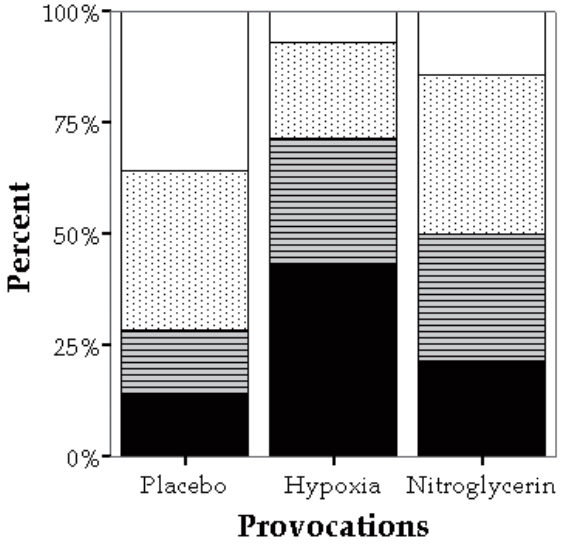

Figure 1 Headache and migraine response to placebo, normobaric hypoxia and nitroglycerin. Black bars represent migraine response, dark gray is moderate or severe headache not fulfilling migraine criteria, light gray is mild headache and white bars is no headache.

Discussion

The first remarkable finding in this study is the low migraine response of 21% after NTG. This is in line with a recent study in English subjects where the migraine response rate after NTG was only 20% [123]. However in most other studies NTG provoked migraine attacks in 60% to 80% of subjects [55,78,123,125]. The low response in our study could have been due to either differences in methodology or in study population. Although we administered the same NTG dose and used the same infusion systems (PVC free) as was done in previous studies [78], the experimental design of our study was entirely different [55,78]. Due to the double dummy design, the patients had to breathe through a facial mask during the whole duration of all experimental conditions, which was considered rather stressful, but tolerable by most participants. The stress could have prevented the occurrence of migraine attack [25,26]. Alternatively, our study population could have been less susceptible to NTG. We had 50% of MA patients in our study and such patients may have a lower migraine response to NTG than MO patients [55,56,162]. Why MA patients would be less susceptible to NTG is not known. A third explanation could be the clinical scoring system. In our study four patients in both the hypoxia and the NTG group had moderate to severe headache but did not fulfill the criteria for migraine.

Normobaric hypoxia provoked a migraine attack in 6 out of 14 patients as compare to only two after placebo and three after NTG. Although this difference between groups was not significant, the relatively high migraine response after hypoxia is remarkably and seems compatible with the results of a large study in mountaineers at high altitude. Of 1213 mountaineers 589 developed headache within 2 to 6 hours after arrival at 4559 m of altitude [99]. In 112 (19%) subjects the symptoms fulfilled the criteria for migraine whereas only 78 (13%) subjects had a history of migraine at sea level. We conclude that the migraine response to NTG was remarkably low in view of previous data , and normobaric hypoxia might be a trigger factor for migraine, but this requires further research.

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CHAPTER 4

EXPERIMENTAL HYPOXIA INDUCED ACUTE MOUNTAIN SICKNESS IS ASSOCIATED WITH INTRACELLULAR CEREBRAL OEDEMA. A 3 TESLA MAGNETIC RESONANCE IMAGING STUDY

Journal of Cerebral Blood Flow and Metabolism. 2008;28:198-206

Abstract

Acute mountain sickness is common amongst not acclimatized persons ascending to high-altitude; the underlying mechanism is unknown, but may be related to cerebral edema. Nine healthy male students were studied before and after 6-hours exposure to isobaric hypoxia. Subjects inhaled room air enriched with N_2 to obtain SaO_2 values of 75-80%. Acute mountain sickness was assessed with the environmental symptom questionnaire, and cerebral edema with 3 Tesla magnetic resonance imaging in 18 regions of interest in the cerebral white matter. The main outcome measures were development of intra- and extracellular cerebral white matter edema assessed by visual inspection and quantitative analysis of apparent diffusion coefficients, derived from diffusion-weighted imaging, and B0 signal intensities, derived from T2-weighted imaging. Seven of nine subjects developed acute mountain sickness. Mean apparent diffusion coefficient increased 2.12% (baseline, 0.80 ± 0.09; 6-hours hypoxia, 0.81 ± 0.09; p=0.034), and mean B0 signal intensity increased 4.56% (baseline, 432.1 ± 98.2; 6-hours hypoxia, 450.7 ± 102.5; p<0.001). Visual inspection of magnetic resonance images failed to reveal cerebral edema. Cerebral acute mountain sickness scores showed a negative correlation with relative changes of apparent diffusion coefficients (r=-0.83, p=0.006); there was no correlation with relative changes of B0 signal intensities. In conclusion, isobaric hypoxia is associated with mild extracellular (vasogenic) cerebral edema irrespective of the presence of acute mountain sickness in most subjects, and severe acute mountain sickness with additional mild intracellular (cytotoxic) cerebral edema.

Introduction

Unacclimatized subjects, who rapidly ascent to high-altitude, may develop acute mountain sickness (AMS) that is characterized by headache, anorexia, nausea, vomiting, insomnia and dizziness[97,163-165]. The underlying mechanism for AMS is unclear. Intracellular (cytotoxic) cerebral edema, extracellular (vasogenic) cerebral edema, and increased cerebral blood volume have all been implicated, but without convincing scientific evidence [97,164,166]. Some magnetic resonance imaging (MRI) studies, using 1.5 Tesla machines, found that exposure to moderate hypo- or isobaric hypoxia, corresponding to altitudes of 4500 m, increased brain volume by 0.5-2.8% [167,168] and decreased cerebrospinal fluid volume in the lateral and third ventricles by 10.3% [169]. Results with respect to the presence and type of cerebral edema were, however, conflicting [167-170]. This could have been related to the relatively low resolution of 1.5 Tesla MRI and because the MR images were only visually evaluated and not analyzed with more sensitive quantitative methods.
In the present study, we used 3 Tesla MRI to investigate whether experimental hypoxia-induced AMS is associated with intra- and/or extracellular cerebral edema. We compared diffusion-weighted (DWI) and T2-weighted (T2WI) MR images obtained before and after 6-hours exposure to isobaric hypoxia by visual inspection and quantitative analysis of apparent diffusion coefficients (ADCs) derived from DWI, and B0 signal intensities derived from T2WI.

Materials and methods

Subjects

Nine healthy male volunteers (mean age 26.4 ± 3.5 years) were recruited from students of the University of Zurich, Switzerland. Exclusion criteria were: altitude exposure (>1500 m) in the previous 3 months, a history of smoking, substance and drug abuse, or of lung, cardiac, neurological or psychiatric disease, and contraindication to undergo MRI (e.g., pacemaker).
The local medical ethical committee approved the study protocol, and written informed consent was obtained from all subjects.

Study design

The study subjects were in supine position and were fitted a facial mask which was connected with a tube of 3 m length. The total flow of fresh gas varied between 9 to 12 liters per minute, because 6 liters of compressed air per minute were mixed with

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3 to 6 liters of N_2 per minute. Thus, the stimulus was assumed to cause poikilocapnic hypoxia. Baseline examinations were done when the subjects were familiarized with the facial mask and the attached tube, and included assessment of the cerebral symptoms of AMS (AMS-C) by completion of the environmental symptom questionnaire (ESQ) [171], monitoring of arterial O_2 saturation (SaO_2), the measurement of the blood pressure, and baseline MRI. The supine subjects were then transported to a room adjacent to the MR suite, and the tube was connected with a gas container. Here, one investigator gradually increased the concentration of N_2 in the inspired air, over a period of 20 minutes, to obtain SaO_2 values of 75 to 80%. This corresponds to an altitude of about 4500 m. The SaO_2 values were measured using a fingertip pulse oximeter (Datex-Ohmeda, Helsinki, Finland). End-tidal pCO_2 was not determined for technical reasons. The SaO_2 was kept stable during the following 6 hours and the second MRI study by adjusting the mixture of inspired gas. After 6 hours of hypoxia, the subjects were transported in the supine position to the MR suite for the second MRI study. Symptoms of AMS and blood pressure were re-assessed every hour, and finally during the second MRI study.

MRI studies

MRI studies were performed using a 3 T Philips Intera whole body system (Philips Medical Systems, Best, The Netherlands). Identical protocols and volume positioning were used at baseline and during hypoxia. The DWI data were based on a spin-echo single excitation echo-planar imaging protocol. Whole brain scans with an in-plane resolution of 1.6 x 1.6 mm^2 (14 contiguous slices, slice thickness = 4 mm, matrix = 128^2, echo time = 79 ms, relaxation time = 3987 ms) were carried out along three orthogonal diffusion directions with a diffusion weighting of b = 1000 s/mm^2, of b=0 [172] and of B0 images (T2* weighted images from the same sequence, with no applied diffusion gradient). An isotropic diffusion-weighted image (Figure 3A) was calculated as the geometric mean of three orthogonal diffusion-weighted images. Additionally, for each slice a T2WI with minimal diffusion weighting (b < 20 s/mm^2) was acquired. The duration for the imaging procedure including the diffusion and the T2 protocol was 4 min and 6 s.

The MRI data were stored and independently analyzed after completion of the study by investigators who were not aware of the cerebral AMS (AMS-C) scores. Two physicists (TJ and UD) and neurologists (PSS and RWB), blinded to the AMS scores, looked for the presence of cerebral edema by comparing the second DWI and T2WI scans of each subject with the corresponding baseline scans (Figure 3). Another neurologist (ACN), also blinded to the AMS scores, measured the ADC values and B0 signal intensities in 22 regions of interest (ROI) as the average value of all pixels in the respective ROI.

The ROIs were circular and located on four consecutive slices (Figure 1). Slice A and B

were placed above, and the next two slices at the level of the cella media of the lateral ventricles. Eighteen of 22 ROIs were located in the cerebral white matter (nine in each hemisphere), and the other four in the cerebrospinal fluid (CSF) of both lateral ventricles. Cerebral white matter ROI were located in the anterior part in eight cases (beside the forceps minor; two measurements per slice), the middle part for two ROIs (beside the lateral ventricles; two measurements on the lowest slice), and the posterior part for eight ROIs (next to the forceps major, which corresponds to the lateral part of the corpus callosum fibers; two measurements per slice). Each white matter ROI consisted of 88 pixels, and each CSF ROI of 16 pixels. CSF ROIs contained fewer pixels than ROIs in the white matter, because not all ventricles were wide enough to accommodate larger circles. The use of smaller reference ROI in the CSF is appropriate, since the MRI signal is higher in the CSF than the white matter and thus provides a better signal-to-noise ratio. MRI signal intensities are arbitrary units with different absolute values at baseline and 6-hours sessions. Therefore, ROIs placed in the CSF were used to correct for intersession differences, because the CSF signal levels are assumed to remain unchanged during hypoxia. All ADC values and B0 signal intensities measured after 6-hours were thus corrected to achieve the same values in CSF as at baseline according to the proportion: $ROI_{6\text{-hours corrected}} = ROI_{6\text{-hours}} \times CSF_{baseline} / CSF_{6\text{-hours}}$, where CSF is the mean value of all CSF ROIs.

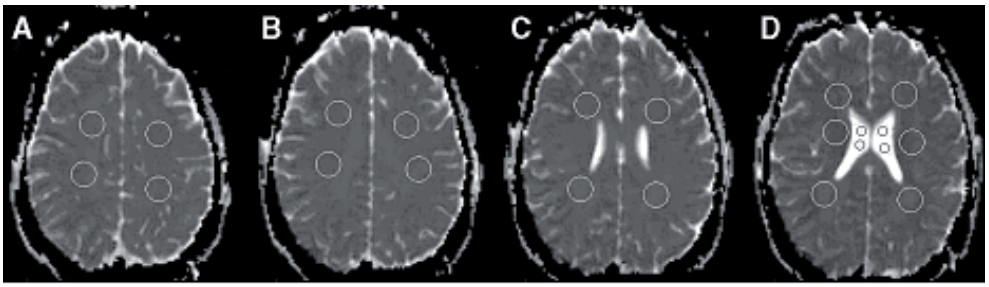

Figure 1 Axial T2-weighted MR images show the 22 regions of interest. Slice A placed above slice B, and slices C and D placed at the level of the cella media of the lateral ventricles.

Interpretation of ADC and B0 changes on MRI

Increase of both ADC and B0 values are indicative of extracellular (vasogenic) edema, whilst an increase of B0 values in combination with a decrease of ADC values is indicative for the development of intracellular (cytotoxic) edema [173-177].

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Assessment of AMS

The ESQ was translated to German and used as described previously [178]. Subjects were considered to suffer from AMS when the AMS-C score was ≥0.70[171] . The AMS-C score ranges from 0-5 and is based on eleven neurological symptoms.

Statistical analysis

Statistical analysis was performed using SPSS 12.0 (SPSS, Chicago, Illinois).

Mean ADC (primary outcome of the study) and B0 values obtained at baseline and after 6 hours were compared using a general linear model for repeated measurements including ROI location as covariate (total white matter ROI, n=162; anterior white matter ROI, n=72; middle white matter ROI, n=18; posterior white matter ROI, n=72). Associations between AMS-C scores and relative changes of ADCs and B0 signal intensities were assessed using the non-parametric Spearman correlation coefficients. P <0.05 was considered significant.

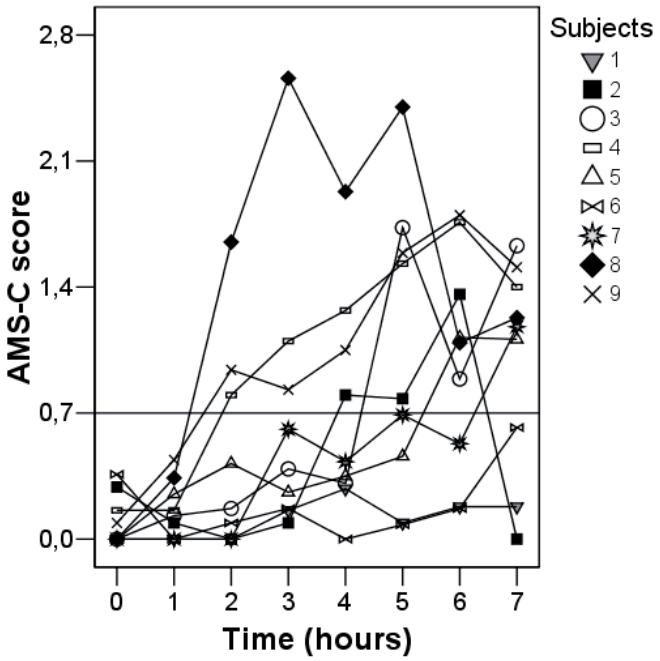

Figure 2 Cerebral acute mountain sickness (AMS-C) scores of all subjects at baseline and during hypoxia.

Results

All nine subjects completed the study. The data set was complete and was evaluated for all 9 subjects. Seven out of nine subjects (subjects 2-6, 8, 9) developed AMS during hypoxia. Six of the nine subjects had AMS during the second MRI scan (Figure 2). Baseline blood pressure did not differ between subjects with and without AMS. The mean AMS score of all subjects was higher at the time of MRI scanning than at baseline (Table 1). Systolic (baseline, 113 ± 9 mm Hg; during second MRI study, 115 ± 11 mm Hg; p=0.49) and diastolic (baseline, 72 ± 6 mm Hg; during second MRI study, 74 ± 4 mm Hg; p=0.71) blood pressure did not change during the study (values are means ± standard deviation).

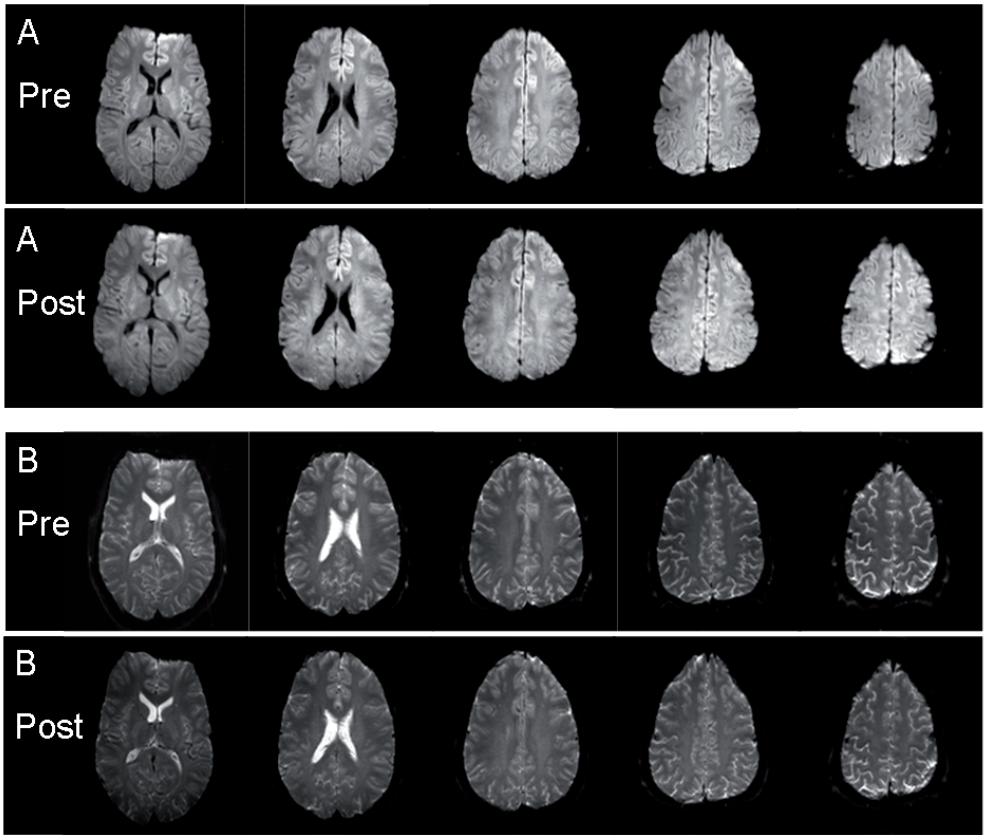

Figure 3 Axial diffusion-weighted (A) and T2-weighted (B) MR images obtained at baseline (upper rows) and after 6-hours exposure to hypoxia (lower rows) from subject 4 who suffered from severe acute mountain sickness. There is no evidence for the development of cerebral edema at visual inspection.

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Table 1 Apparent Diffusion Coefficient Values at 3 Tesla MR Imaging in the Cerebral White Matter and Cerebrospinal Fluid, and Cerebral Acute Mountain Sickness Scores in Nine Healthy Subjects at Baseline and 6-Hours Exposure to Isobaric Hypoxia*

	ADC										
	Cerebral White Matter								CSF‡	AMS-C score	
	Anterior		Middle		Posterior		All			Score	
	Baseline	% Change at 6-h hypoxia†	Baseline	% Change at 6-h hypoxia†	Baseline	% Change at 6-h hypoxia†	Baseline	% Change at 6-h hypoxia†		Baseline	After 6-h hypoxia
Subject 1	0.70	7.72	0.66	-0.79	0.70	6.98	0.69	6.45	3.18	0.00	0.18
Subject 2	0.72	-5.11	0.71	-4.26	0.76	-3.40	0.74	-4.25	3.16	0.29	1.36
Subject 3	0.78	3.47	0.72	5.45	0.81	4.90	0.79	4.32	3.30	0.00	0.89
Subject 4	0.95	-7.27	0.92	-3.98	0.96	-6.53	0.95	-6.58	3.78	0.16	1.76
Subject 5	0.78	2.57	0.70	10.93	0.78	3.57	0.77	3.94	3.71	0.00	1.12
Subject 6	0.74	9.27	0.69	5.99	0.76	10.84	0.74	9.60	3.26	0.36	0.17
Subject 7	0.92	3.12	0.91	4.01	0.96	3.40	0.94	3.34	3.85	0.00	0.53
Subject 8	0.80	1.78	0.78	3.17	0.84	5.02	3.29	3.37	3.29	0.00	1.09
Subject 9	0.74	-0.20	0.70	0.06	0.75	-2.26	0.74	-1.09	2.78	0.09	1.80
Subjects 1-9 mean	0.79	1.71	0.75	2.29	0.81	2.50	0.80	2.12	3.37	0.10	0.99
SEM	0.03	0.90	0.03	1.20	0.03	0.88	0.09	0.57	0.35	0.05	0.20
Difference baseline vs 6 h at hypoxia							p=0.034			p=<0.01	

h denotes hours, and SEM standard error of the mean. * The concentration of N_2 in the inspired air was adjusted to obtain arterial SO_2 values of 75 to 80%. † The apparent diffusion coefficient values obtained before exposure to isobaric hypoxia were defined as 100% ‡ The values for the relative change of the apparent diffusion coefficient measured in the cerebrospinal fluid after 6-hours of isobaric hypoxia were zero, because they were corrected to achieve the same values as at baseline (for details see text).

MRI study

Visual inspection showed no evidence for cerebral edema (Figure 3).

Mean ADCs were increased by 2.12% (p=0.034, Table 1), and mean B0 values were increased by 4.56% (p<0.01, Table 2) after 6-hours exposure to hypoxia. The ADCs increased in 6 subjects (Figure 4), and B0 values in 8 subjects (Figure 5). ADCs (p=0.32) and B0 values (p=0.06) did not differ between the 3 white matter ROIs.

As shown in Figure 6, the AMS-C scores measured after 6-hours exposure to hypoxia showed a negative correlation with the relative change of ADC values (Spearman correlation coefficient -0.83, p = 0.006). There was no association between the AMS-C scores measured after 6-hours exposure to hypoxia and the relative change of B0 values (Spearman correlation coefficient -0.22, p = 0.576; Figure 7).

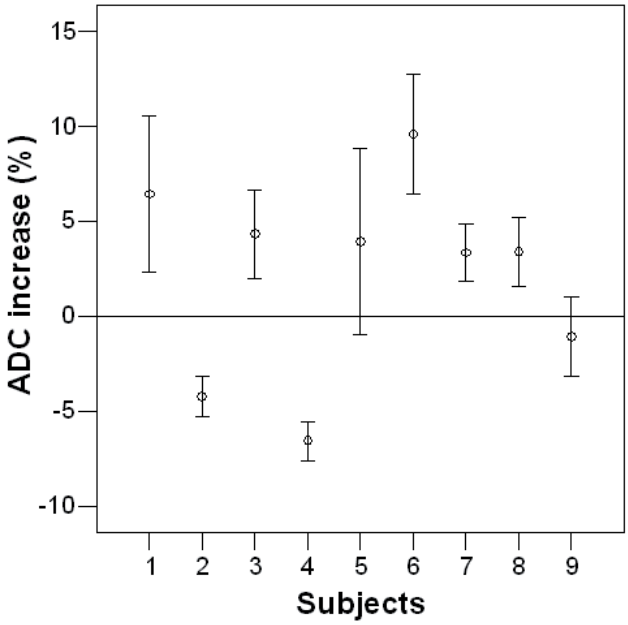

Figure 4 Relative changes of the apparent diffusion coefficient (ADC) after 6 hours of hypoxia compared to baseline in all nine subjects.

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Table 2 B0 Values at 3 Tesla MR Imaging in the Cerebral White Matter and Cerebrospinal Fluid, and Cerebral Acute Mountain Sickness Scores in Nine Healthy Subjects at Baseline and 6-Hours Exposure to Isobaric Hypoxia*

	B0 value									AMS-C score	
	Cerebral White Matter								CSF‡		
	Anterior		Middle		Posterior		All			Score	
	Baseline	% Change at 6-h hypoxia†	Baseline	% Change at 6-h hypoxia†	Baseline	% Change at 6-h hypoxia†	Baseline	% Change at 6-h hypoxia†		Baseline	After 6-h hypoxia
Subject 1	186.13	8.27	224.00	8.11	216.38	2.13	203.78	5.52	879.00	0.00	0.18
Subject 2	354.25	0.42	389.00	6.74	370.75	11.36	365.44	5.98	1353.75	0.29	1.36
Subject 3	452.38	10.86	489.50	12.37	441.75	11.10	451.78	11.13	1630.75	0.00	0.89
Subject 4	475.75	-4.97	488.00	1.16	490.50	0.93	483.67	-1.67	1544.00	0.16	1.76
Subject 5	489.63	5.23	569.00	6.54	563.88	4.08	531.44	4.87	2019.50	0.00	1.12
Subject 6	411.13	1.61	445.00	3.89	430.13	7.77	423.33	4.60	1477.75	0.36	0.17
Subject 7	469.25	1.92	502.50	3.50	508.63	0.80	490.44	1.60	1580.75	0.00	0.53
Subject 8	478.38	4.37	498.50	1.60	464.50	11.07	474.44	7.04	1724.00	0.00	1.09
Subject 9	439.50	6.03	504.00	7.09	479.13	-3.46	464.28	1.93	1373.75	0.09	1.80
Subjects 1-9 mean	417.38	3.75	456.61	5.67	440.63	5.09	432.07	4.56	1509.25	0.10	0.99
SEM	32.11	1.55	33.25	1.18	33.26	1.81	32.45	1.22	103.30	0.05	0.20
Difference baseline vs 6 h at hypoxia							p=<0.01			p=<0.01	

h denotes hours, and SEM standard error of the mean. * The concentration of N_2 in the inspired air was adjusted to obtain arterial SO_2 values of 75 to 80%. † The apparent diffusion coefficient values obtained before exposure to isobaric hypoxia were defined as 100% ‡ The values for the relative change of the apparent diffusion coefficient measured in the cerebrospinal fluid after 6-hours of isobaric hypoxia were zero, because they were corrected to achieve the same values as at baseline (for details see text).

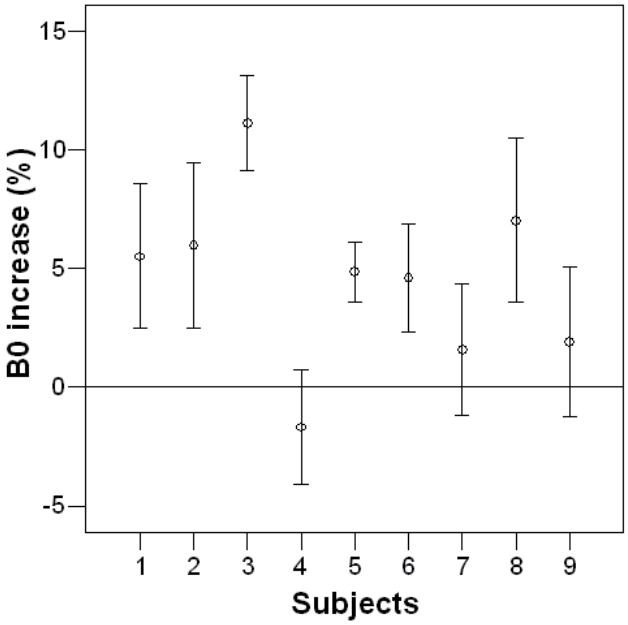

Figure 5 Relative changes of the B0 values after 6 hours of hypoxia compared to baseline in all nine subjects.

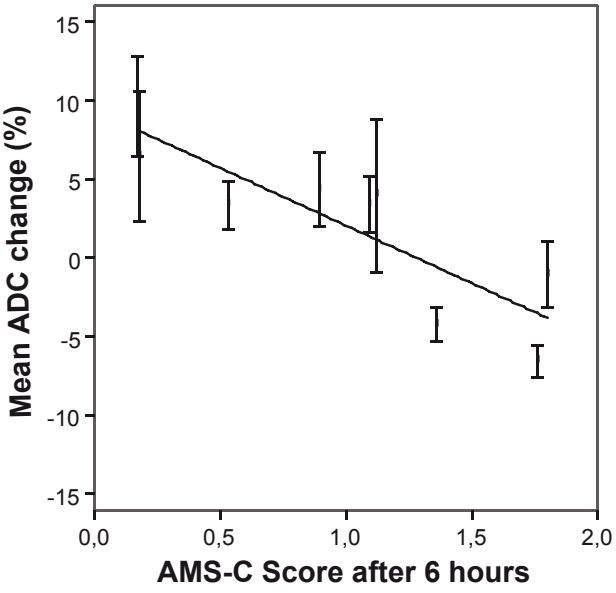

Figure 6 The mean value of two cerebral acute mountain sickness (AMS-C) scores measured immediately before and after MR imaging performed at hypoxia showed a weak but significant negative correlation with the relative change of the apparent diffusion coefficient (ADC).

diffusion coefficient measured in the cerebrospinal fluid after 6 hours of isobaric hypoxia were zero, because they were corrected to achieve the same values as at baseline (for details see text).

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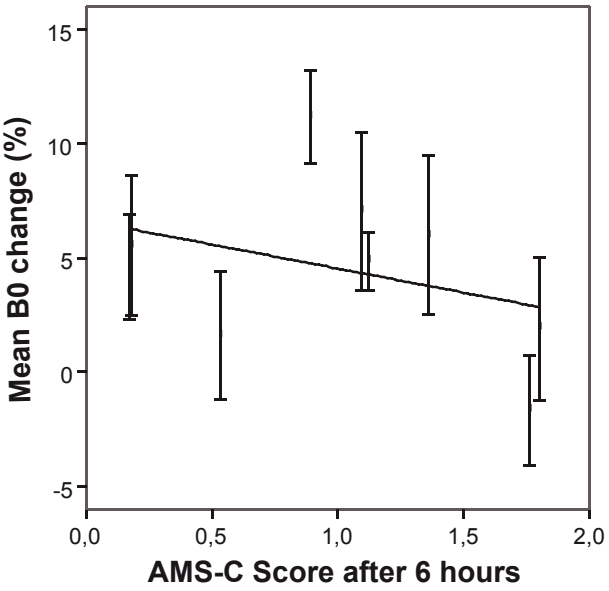

Figure 7 The mean value of two cerebral acute mountain sickness (AMS-C) scores measured immediately before and after MR imaging performed at hypoxia showed no correlation with the relative change of the B0 signal intensity values.

Discussion

In the present 3 Tesla MRI study, we found that experimental isobaric hypoxia for six hours: 1) caused AMS in seven (77%) of nine healthy volunteers; 2) produced a mild extracellular (vasogenic) cerebral edema, irrespective of the presence of AMS, which was identified by a small increase of both ADCs and B0 values, whereas visual inspection of the MRI data failed to detect any differences; and 3) that the AMS-C scores were negatively correlated with the ADC values. The prevalence of AMS in this series is in accordance with the results of two previous studies exposing 31 subjects to isobaric hypoxia corresponding to altitudes of 4500-4564 m during 9-16 hours [167,179]. In the study of [179], 6 (67%) of 9 subjects developed AMS, and in the study of [167] 11 (50%) of 22 subjects were affected by this altitude illness.

The fact that the mild extracellular (vasogenic) cerebral edema was just detected by quantitative but not visual analysis of the MRI data is in accordance with the results obtained in three 1.5 T MRI investigations [167-169]. These studies found no cerebral edema at visual inspection of T2WI and DWI in 41 subjects with mild to moderate AMS who were exposed to hypobaric or isobaric hypoxia corresponding to altitudes of 4500-

4572 m for 10 to 32 hours[167-169]. Furthermore, one of these 3 studies found a mild extracellular cerebral edema with increased B0 values and a trend for decreased ADCs [167] . The higher resolution and signal-to-noise ratio of 3 Tesla MRI used in the present study makes it more sensitive for detecting cerebral abnormalities[180] than 1.5 Tesla MRI employed in previous AMS investigations [167-169]. Despite this, visual inspection even of 3 Tesla MRI brain images was still not sensitive enough to detect the cerebral edema associated with AMS. This is in sharp contrast to high altitude cerebral edema (HACE). Here visual inspection of proton density- and T2-weighted MRI brain images revealed extracellular edema of the white cerebral matter at a mean of 58 hours (range, 16 to 132 hours) after the onset of HACE symptoms [104].

There was no association between AMS-C scores and BO signal intensities in this series, which confirms the results of a previous study [167]. In this respect it is important to note that, in reality, the degree of extracellular brain edema might have been higher. The B0 signal intensity increase due to cerebral edema may have been neutralized by the blood-oxygenation-level-dependent (BOLD) effect of hypoxia [181,182]. This effect is related to the intravascular concentration of deoxyhemoglobin, which lowers signal intensity of B0 images by increasing magnetic susceptibility [183-186]. As hypoxia will increase the intravascular concentration of deoxyhemoglobin, it will also lower the intensity of the B0 signal and thus the level of perceived cerebral edema. Therefore, the BOLD effect might have prevented the detection of an association between the B0 values and the AMS-C scores. Consequently, it cannot be completely excluded that the mild extracellular cerebral edema is in part responsible for AMS, e.g. by stimulating pain sensitive fibers in the meninges, the meningeal and pial vessels [187]. A potential role of vasogenic cerebral edema is underscored by two observations: Symptoms and signs of AMS as well as abnormal B0 values and ADCs occurring during exposure to isobaric hypoxia disappeared after the subjects were re-exposed to normoxia [167], and corticosteroids, which reduce extracellular cerebral edema, are an established therapy of AMS [188].

The third and most important result of the present study is based on the observation that subjects with the most severe AMS symptoms showed the lowest ADC values. Being in accordance with findings reported by [167], this would suggest that severe AMS is associated with intracellular (cytotoxic) edema of the cerebral white matter, on top of hypoxia-driven extracellular (vasogenic) edema. The cytotoxic edema may have been caused by a decreased activity and/or expression of the Na+, K+-ATPase in the cerebral white matter [189-191]. A reduction of ATPase activity is associated with reduced levels of tissue ATP and a shift from aerobic to anaerobic glycolysis, and lactate is built up causing acidosis[189,191,192]. Using declining intracellular pH (pHi) as an indicator of increased intracellular lactate production, ^{31}P MR spectroscopy (MRS) studies observed a pHi

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decline at arterial PO_2 (PaO_2) values of 30-45 mm Hg [189,191,193]. We observed PaO_2 values of 40-45 mm Hg in subjects exposed to an altitude of 4559 m [178,194] . Consequently, the subjects investigated in this series were exposed to levels of hypoxia, which might lead to PaO_2 values causing anaerobic glycolysis and reducing the cerebral metabolic rate of oxygen ($CMRO_2$), although no study has shown a decrease of $CMRO_2$ in humans exposed to high altitude [195,196] . However, the study of [196] was performed at a lower altitude of 3800 m, and the investigation of [195] in subjects who were chronically exposed to high altitude. More important is that a recent study comparing MRI with positron emission tomography (PET) findings in patients with acute ischemic stroke has shown that ADCs are not reliable predictors of reduced $CMRO_2$ at the levels of hypoxia applied in our subjects [197]. These PET findings question the assumption that more severe forms of AMS are associated with intracellular (cytotoxic) edema. Further studies assessing also the $CMRO_2$ in the cerebral white matter are needed to answer this question.

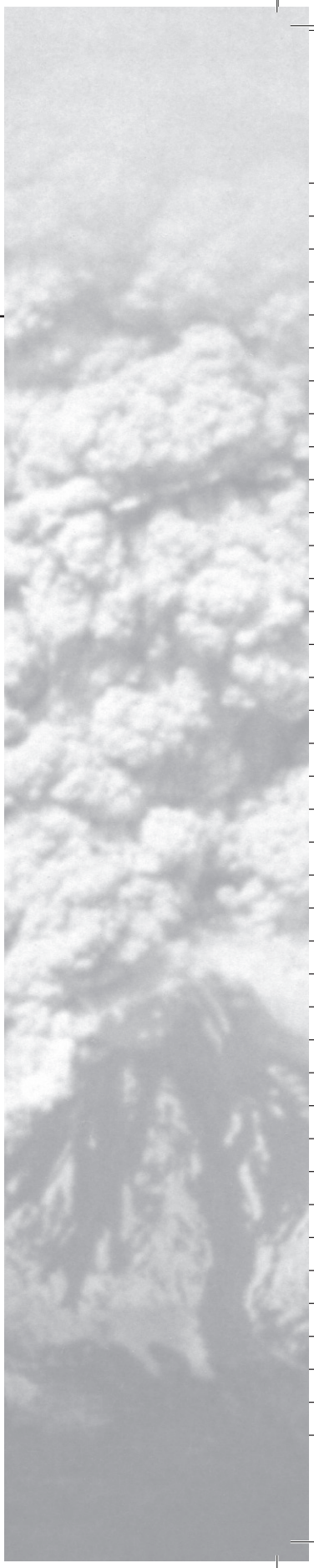
The study is limited by the low number of included subjects. Furthermore, the present findings may not be applicable to hypobaric hypoxia, because the severity of AMS has been shown to be increased during simulated altitude compared with isobaric hypoxia[179].

We conclude that experimental isobaric hypoxia is associated with mild extracellular (vasogenic) cerebral edema irrespective of the presence of AMS in the majority of subjects, and severe AMS with additional mild intracellular (cytotoxic) cerebral edema.

CHAPTER 5

MAGNETIC RESONANCE ANGIOGRAPHY OF THE HUMAN MIDDLE MENINGEAL ARTERY: IMPLICATIONS FOR MIGRAINE

Journal of Magnetic Resonance Imaging. 2006; 24: 918-21



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Abstract

Purpose

To describe a novel non-invasive method to study MMA diameter changes *in vivo* in humans. Dilatation of the middle meningeal artery (MMA) has been implicated in the pathophysiology of migraine headache but without direct evidence in humans.

Materials and methods

The diameter of the MMA (extracranial part) was measured in 19 healthy volunteers before and after administration of a vasodilator (nitroglycerin 1.2mg sublingual) known to provoke headache. We used magnetic resonance angiography (MRA) in combination with a 47mm microscopy coil and a semi-automatic contour detection program.

Results

The diameter of the MMA was 1.5 ± 0.26 mm (mean ± SD) before and 1.79 ± 0.30 mm after nitroglycerin administration. This increase was 20.1% (95% CI 12.9 to 27.3; $p<0.001$). The mean increase in subjects who developed headache (n=11) was 0.34 ± 0.19 mm as compared to 0.22 mm ± 0.20 mm in the 8 subjects who did not (95% CI for difference: -0.07 to 0.31; p=0.188).

Conclusion

MRA in combination with a 47mm microscopy coil is a novel, non-invasive method to measure diameter changes of human meningeal vessels with potential applications in migraine and other neurovascular research.

Introduction

Migraine is a common and disabling, multifactorial neurovascular headache syndrome[8,11]. The middle meningeal artery (MMA) has been implicated in the pathogenesis of migraine headache. The dura mater is a pain sensitive structure and mechanical stimulation of the MMA causes pounding migraine-like headache[198].

Sumatriptan is effective in the acute treatment of migraine[199] and may constrict the MMA as demonstrated by selective angiography[200]. Direct evidence, in humans, for the role of the MMA in migraine headache is, however, lacking. A major reason is that, due to its small diameter (less than 1.86 ± 0.60 mm)[201], there were no reliable non-invasive methods to measure the MMA *in vivo*. Here we present a Magnetic Resonance Angiography (MRA) based method to non-invasively monitor diameter changes of the MMA. To provoke dilatation of the MMA we used nitroglycerin which is a strong vasodilatator and is known to cause migraine headache in up to 60% of migraineurs. In spite of the advantages of contrast enhanced MRA (CE-MRA), we used a non CE-MRA acquisition technique because of medical ethical concerns: in a CE-MRA protocol gadolinium contrast should be delivered twice in relatively short time (less than 30 minutes) with administration of nitroglycerin in between.

Methods

Subjects

We recruited 22 healthy volunteers (age 18 - 65 years) by public announcement. Exclusion criteria were (A) a history of vascular disease, migraine or any other primary headache syndrome, (B) headache on more than 6 days per month, (C) current use of vasoactive medication, (D) use of more than 3 units of caffeine per day and (E) active smoking. The study was approved by the local ethical committee.

Experimental design

Subjects were asked to refrain from drinking alcohol 24 hours and caffeine containing beverages 12 hours prior to the experiments. MRI scans were performed before and shortly after sublingual administration of NTG 1.2 milligram[202]. Subjects remained in the MRI scanner and kept their position between scan 1 and 2 to ensure a constant localisation of the measurement. Blood pressure and heart rate were monitored during the experiment. Migraine symptoms were assessed before and after the experiments using the criteria of the IHS[3].

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Magnetic resonance angiography

MRA of the MMA was performed on a 1.5-T system (Philips Medical Systems, Best, the Netherlands). Subjects were positioned using flexible head restraints to minimise the influence of subject movement. Once the MMA was localised using the standard head coil, a small surface coil with a diameter of 47 mm was positioned over the MMA-region and high-resolution MRA images of the MMA were collected. In general the centre of the surface coil was positioned over the Temporo-Mandibular Joint. At this location the MMA is at a depth of around 3 to 4 cm from the skin. The MRA imaging protocol consisted of a sequential 2D acquisition time-of-flight T1-weighted Fast Field Echo MRA sequence with the following imaging parameters: repetition time/echo time, 28 ms/8.7 ms; flip angle, 20°; field of view, 100x100 mm; matrix size, 256 x 256; reconstruction matrix, 256x256; 0.39 x 0.39-mm pixel resolution (0.15-mm^2 pixel area); number of excitations: 2; slice thickness, 2.0 mm; slices overlapped 1.0 mm); number of slices, 40; total acquisition time 4 min 26 sec. In this scan protocol we applied relatively thick overlapping slices. This is because the image post processing tool makes use of a single 2D slice in which should contain the entire MMA length of interest. Since we expect a MMA diameter of about 1.4-1.5mm, the current scan protocol (2mm slice thickness-1mm overlap) avoids potential partial volume effects.

Image post processing and diameter calculations

All MRA images were transferred to a remote workstation for quantitative analysis using the MR Analytical System (MRI-MASS)[203]. The measurement procedure consisted of the manual identification of the borders of the vessel segment to be analyzed. The exact vessel boundaries were detected using an automated contour detection technique based on dynamic programming. The diameter of the vessel segment was automatically derived from the detected vessel contours. MMA-ex was measured in a segment of 7 mm (ranging between 6.5 and 7.5mm), approximately 10 mm from the origo of the Maxillary artery. The 18 diameter measurements that were obtained within the segment (one at every pixel position) were averaged to obtain a mean diameter for the segment. By obtaining multiple measurements the measurement precision could be improved to 0.39 / $\sqrt{18}$ = 0.09 mm. Reliability of the semi-automatic measurements was also assessed by a second independent observer and agreement between observers was measured by the intra class correlation.

Statistical analysis

The diameter of the MMA before and after nitroglycerin administration was compared with a paired t-test. Differences between subjects with and without headache were

compared with an unpaired t-test. A p value of <0.05 was considered statistically significant.

Sample size calculations

The minimally expected increase of the MMA during migraine headache is unknown. Friberg estimated a mean 20% increase of the diameter of the middle cerebral artery using trans-cranial Doppler[204] and administration of sublingual NTG resulted in a mean 30 ± 8% increase in the human coronary artery[205]. The mean diameter of the MMA in healthy volunteers was 1,4 mm with an SD of 0,18 (pilot study). We therefore calculated that we would require 20 subjects to detect a difference of at least 10% in means at the 5% level of significance (power 90%).

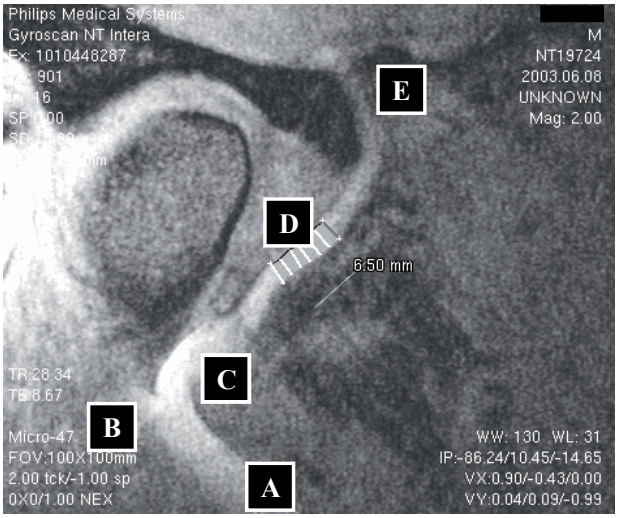

Figure 1 Anatomy of the MMA region and position of the measured segement. Explanation of letters: A= External Carotid Artery, B= Superficial Temporal Artery, C= Maxillary Artery, D= Middle Meningeal Artery, E= Foramen Spinosum

Results

Three patients were excluded during the experiment. The first volunteer had an unexpected MRI finding, the second had a double extra cranial MMA (possibly an accessory meningeal artery) and in the third volunteer the MMA could not be reliably measured. In the remaining 19 subjects (9 males; mean age 21.8 ±2.9 years) the MMA could be easily identified (Figure 1). The mean MMA diameter (extra cranial part) was

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1.5 ± 0.26 mm before and 1.79 mm ± 0.30mm after NTG administration (Table 1). The increase after NTG was 20.1% (CI: 12.9% to 27.3%; p<0.001) from baseline.

Table 1 MMA diameter at baseline and increase after sublingual nitroglycerin (NTG).

Subjects	N	Baseline (mm)	Post NTG (mm)	Difference post NTG vs baseline (mm)	
		Mean (SD)	Mean (SD)	Mean (SD)	% from baseline
All	19	1.50 (0.26)	1.79 (0.3)	0.29 (0.20)*	20.1%
Headache post NTG	11	1.52 (0.31)	1.87 (0.32)	0.34 (0.19)	23.9%
No headache post NTG	8	1.48 (0.18)	1.7 (0.27)	0.22 (0.20)	14.8%

(* = p<0.001)

Within five minutes after nitroglycerin administration, eleven volunteers experienced mild, bilateral, pulsating headache of short duration (<30 minutes) and without associated phonophobia, photophobia or nausea. None of the headaches fulfilled the IHS criteria for migraine. No adverse events or significant effects on blood pressure occurred. The mean diastolic blood pressure at baseline was 74.1 (SD 5.7) and the mean systolic blood pressure was 122.6 (SD 8.6). The mean MMA diameter in the 11 subjects who developed headache was 1.52 ± 0.31 mm before and 1.87 ± 0.32 mm after nitroglycerin administration as compared to 1.48 ± 0.18 mm before and 1.7 ± 0.27 mm after nitroglycerin administration in the 8 subjects who did not develop headache (CI for difference: -0.07 to 0.31; p=0.188; Table 1). The post-hoc power to detect a difference in MMA diameter increase of 9.1% between subjects with and without headache was only 27% (alfa 0.05, SD 0.18). Agreement between observers (intra class correlation) was 0.74 (0.7 or more is considered acceptable).

Discussion

MRA in combination with a 47 mm microscopy coil is a novel, promising non-invasive method to study the MMA *in vivo*. The whole scan procedure takes 15 minutes making it very suitable for repeated clinical studies. Localization and measurement of the MMA was possible in 20 out of 22 subjects. The measurement precision of the used technique is 0.09 mm, which is sufficient for valid measurements of both the baseline MMA diameter as well as diameter changes after nitroglycerin administration[206].

A relatively recent development in MRA is contrast-enhanced MRA (CE-MRA). For CE

MRA fast scan times and adequate timing based on a test bolus are required to avoid venous over projection of the jugular veins. After the injection of a test bolus, current available CE MRA methods acquire high contrast arterial signal in the first 10 seconds, within the time-window of arterial enhancement. Thereafter, the acquisition is continued to increase the resolution of the depicted arteries. With the injection of an intravenous contrast bolus of gadolinium the T1 of the blood is shortened and larger flip angles can be used to generate a stronger signal with improved background suppression and less signal saturation. CE MRA provides morphological information over a long track starting at the neck arteries via to the circle of Willis up to the distal intracranial smaller vessel segments. Extra-cranially, CE-MRA may also provide better resolution of the MMA. However, currently no studies have been performed in this matter. In spite of the advantages of CE-MRA, we used an non CE-MRA acquisition technique because of medical ethical concerns: in a CE-MRA protocol gadolinium contrast should be delivered twice in relatively short time (less than 30 minutes) with administration of nitroglycerin in between.

A potential limitation of this method may be that the observed diameter increase is overestimated due to increase of the blood flow velocity when using MRA (time of flight) diameter measurements. However, we do not think this is the case for two reasons. Firstly, Bednarczyk et al. measured an increase in global cerebral blood flow (positron emission tomography) after nitroglycerin administration without an increase in flow velocity in the middle cerebral artery (trans-cranial Doppler)[207], and secondly, the contour of the blood vessel is automatically detected using MRI-MASS. An increase in flow velocity will increase the intravascular signal intensity, but this will probably not affect the automatic contour detection. A potential effect of flow velocity changes can however not be ruled out.

This new research method may have important implications for the study of migraine (notably for measuring the MMA during spontaneous and experimental migraine attacks and after treatment with antimigraine agents)[208]. The current study was not designed to prove or disprove a causal relationship between vasodilatation of the MMA and the occurrence of migraine headache. We found a mean 23.9% dilatation of the MMA in subjects with non-migrainenous headache after nitroglycerin administration and 14.8% dilatation in those without headache. This difference was non-significant which may have been due to the small number of study subjects. The post hoc power to detect a statistically significant difference in vasodilatation between subjects with and without headache was only 27%. Further studies are needed to address this issue. Besides migraine, this method might be of interest for other neurovascular research areas, such as meningeal vasospasms in subarachnoid hemorrhage[209].

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CHAPTER 6

CEREBRAL BLOOD FLOW RESPONSE TO NITROGLYCERIN PREDICTS THE OCCURRENCE OF A PROVOKED MIGRAINE ATTACK

Submitted

Abstract

Background

Nitroglycerin (NTG) triggers migraine attacks in susceptible migraine patients. The mechanism of action is unclear. The cerebrovascular response to NTG may be impaired in migraine patients, however, previous studies are inconclusive. In this study we assessed the cerebrovascular response to NTG in healthy volunteers and in migraine patients with and without a provoked attack.

Methods

In a double blind desing migraine patients (n=32) received NTG (n=27) IV 0.5 µg/kg/min for 20 min or placebo (n=5). Healthy volunteers (n=12) all received NTG. Using 3T MRA, we measured blood flow and diameter in the internal carotid arteries (ICA) and basilar artery (BA) as well as diameters of the middle meningeal (MMA), external carotid (ECA), middle cerebral (MCA) and posterior cerebral (PCA) arteries at baseline and during infusion of NTG.

Results

During infusion of nitroglycerin, ICA blood flow decreased 118.9 ml/min in healthy volunteers and 19.5 ml/min in migraine patients (p=0.05). A sub-analysis of migraine patients showed an ICA blood flow decrease of 100.4 ml/min in patients who did not develop a provoked migraine attack after NTG (n=7) compared to an increase of 10.2 ml/min in patients who developed a provoked migraine attack (n=20; p=0.01). Blood flow in the BA did not change. Diameters of all selected blood vessels increased significantly (p<0.01) during infusion of NTG without differences between groups.

Conclusions

The cerebral blood flow response to nitroglycerin is impaired in migraine patients mainly due to an impaired response in patient who develop a migraine attack after approximately 4 hours.

Introduction

Migraine is a severe paroxysmal neurovascular disorder[75]. Attacks can be reliably[55,78] and reproducibly[56] triggered in migraine susceptible subjects using the vasoactive drug nitroglycerin. In healthy volunteers without a family history of migraine it is very seldom that migraine attacks are triggered after infusion of NTG[116]. The mechanism of nitroglycerin in migraine is unclear[210]. Nitroglycerin is an exogenous donor of nitric oxide[106], which is involved in central pain mechanism[107] and regulation of cerebral blood flow[108]. Infusion of NTG has shown to increase the diameter of the middle cerebral artery[109] and meningeal media artery[110] as well as to decrease blood flow velocity in the internal carotid artery and middle cerebral artery[111-113]. The effects of NTG on cerebral blood flow are caused either through the release of calcitonin gene related peptide (CGRP) from the trigeminal nerve[114,115] or via a direct effect on vascular smooth muscle cells in blood vessels[106]. Whether there is a difference in cerebrovascular response to NTG between migraine patients and healthy controls is unclear. One study suggested an increased cerebrovascular response during NTG infusion in migraine patients[117], whereas in a second study no increased response was observed.[118]

Infusion of NTG triggers a migraine attack in approximately 60 to 80% of migraine patients[55,56,78,116,124,125]. Why some patients are susceptible to NTG an others not is unknown. Migraine patients without aura are more susceptible to NTG as compared to patients with aura[55]. Furthermore, in a NTG provocation study an association between increase in plasma CGRP and the provocation of a migraine attack has been found[124]. Whether the cerebrovascular response to NTG is different in patients who develop a provoked attack as compared to patients without an attack is unclear.

The primary aim of this study was to assess the cerebrovascular response (blood flow and blood vessel diameters) to infusion of NTG in healthy volunteers and migraine patients. The hypothesis is that the cerebrovascular response to nitroglycerin is impaired in migraine patients compared to healthy volunteers. The secondary aim is to assess the relation between cerebrovascular response to NTG and the development of a provoked migraine attack.

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Methods

Subjects

In total 32 migraine patients (without aura n=27 and with aura n=5) and 12 healthy volunteers were included. Patients were recruited from the neurology outpatient clinic of Leiden University Medical Centre. Inclusion criteria for migraine patients were (1) age between 18 and 55 years, (2) diagnosis of migraine according to the criteria of the IHS[3], (3) baseline attack frequency between 1 attack per 2 months to 4 attacks per month in the six months prior to the study, (4) moderate or severe headache during spontaneous migraine attacks. Exclusion criteria were (1) more than 10 days of headache per month, (2) inability to differentiate between migraine and other forms of headache, (3) contra-indications for use of triptans, (4) current use of vasoactive drugs and (5) MRI specific contra-indications (such as claustrophobia). Healthy volunteers were recruited among hospital staff, medical students and relatives of migraine patients. Inclusion criteria for healthy volunteers were (1) age between 18 and 55 years. Exclusion criteria were (1) personal or first degree relative history of migraine, (2) headache on more than 2 days per month, (3) MRI specific contra-indications and (4) current use of vasoactive drugs. The study was approved by the local medical ethical committee and the subjects gave informed consent prior to the start of the study.

Experimental procedure

All subjects arrived at the hospital without headache between 8 and 10 a.m. on the day of the study. No medication, coffee, tea or alcohol was allowed 12 hours prior to the start of the experiment. In migraine patients the last spontaneous migraine attack was at minimum three days prior to the experiment. Healthy volunteers were scanned at baseline and during infusion of NTG 0.5 µg/kg/min during 20 min (open label). Migraine patients were scanned at baseline, during infusion of NTG/ placebo (double blind) and during a provoked migraine attack (or 6 hours after infusion of NTG/placebo). Duration of scan sessions was approximately 25 minutes. Between the baseline session and the NTG/placebo session patients remained in the scanner and the NTG/placebo session started 10 minutes after the start of the infusion. Heart rate and blood pressure were monitored before and after the MR session. Two days after the experiment subjects were contacted by telephone to make sure no migraine attack had occurred within 12 hours after the experiment.

Magnetic resonance angiography

The MR investigations were performed on a 3.0-Tesla whole-body system (Philips

Medical Systems, The Netherlands). The MRA protocol consisted of two parts. Part A) Diameter protocol: a thick two-dimensional phase contrast (2D PC) sagittal localiser survey through the circle of Willis, followed by a three-dimensional time-of-flight (3D TOF) MRA sequence to visualise the BA and ECA, ICA, and MCA on both sides This scan had the following imaging parameters: repetition time / echo time (TR/TE): 22 ms / 3.5 ms; flip angle 15°; field of view: 220 x 220 mm; number of excitations: 1; slice orientation: transverse; slice thickness: 0.65 mm; number of slices: 200; scan percentage 100%, matrix reconstruction size: 512 x 512 resulting in a nominal voxel size (x,y,z) of 0.43 x 0.43 x 0.65 mm; total acquisition time: 4min 30sec. Based on the reconstruction of this 3D-TOF a second 3D-TOF with a higher spatial resolution was performed to visualise the extra- and intracranial parts of the MMA on both sides. This scan had the following imaging parameters: TR/TE: 15 ms / 2.1 ms; flip angle 15o; field of view: 200 x 200 mm; number of excitations: 1; slice orientation: transverse; slice thickness: 0.25 mm; number of slices: 130; scan percentage 100%, matrix reconstruction size: 512 x 512 resulting in a nominal voxel size (x,y,z) of 0.39 x 0.39 x 0.25 mm; total acquisition time: 8min 31sec.

Part B) Blood flow protocol (in BA and ICA): On the basis of two thick slab localizer MRA scans in the coronal and sagittal plane, a 2-dimensional phase-contrast (2D-PC) section was positioned perpendicular on the ICAs and the BA at the level of the skull base to measure the volume flow. The MRA volume flow measurements in the present study are derived from previously developed and optimized protocols[211-214]. Acquisition parameters: repetition time / echo time (TR/TE): 16 ms / 8.5 ms; flip angle 10°; field of view: 150 x 150 mm; number of excitations: 20; slice orientation: transverse; slice thickness: 5.0 mm; number of slices: 1; scan percentage 100%; PC velocity encoding: 140 cm/s; matrix reconstruction size: 256 x 256 resulting in a nominal voxel size (x,y,z) of 0.59 x 0.59 x 50 mm; total acquisition time: 56sec. Figure 1 illustrates the positioning of the 2D PC section through the internal carotid arteries (ICAs) and the basilar artery (BA).On an independent workstation, quantitative flow values were calculated in each vessel by integrating across manually drawn regions of interest that enclosed the vessel lumen closely.

Image post processing: diameter calculations

All MRA images were transferred to a independent workstation for quantitative analysis using the QMRA software package developed at our institution. A full description of the contour detection methods used and the validation have been described previously [215]. The software provides automated contour detection and quantification of the luminal

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boundaries in selected vessel segments in 3D MRA datasets. The only user interaction required is the definition of the vessel segment of interest by placing a proximal and distal point in the 3D dataset. Subsequently, the software detects a 3D path line following the centre of the vessel lumen and cross-sectional MPR's are generated perpendicular to the centreline at 0.5 mm intervals. In each of these MPR's a contour around the vessel lumen is detected automatically. From these contours, based on the assumption of circular vessel cross-sections, the average diameter of the selected vessel segment is derived. Blood vessel segments were selected as following: A) The MMA was measured in an extra cranial segment (start at the origo in the maxillary artery and stop 5 to 6 mm distal). B) The ECA start at the origo of the superficial temporal artery and stop 10 mm proximal. C) The ICA, start just proximal of the Syphon and stop 15 mm proximal. D) The MCA, start after A1 segment and stop 8 mm distal. E) The BA, start origo posterior cerebral artery stop 12 mm proximal. F) The PCA, start at the origo in the basilar artery and stop 8 mm distal). Location of measured vessel segments were kept constant within subjects.

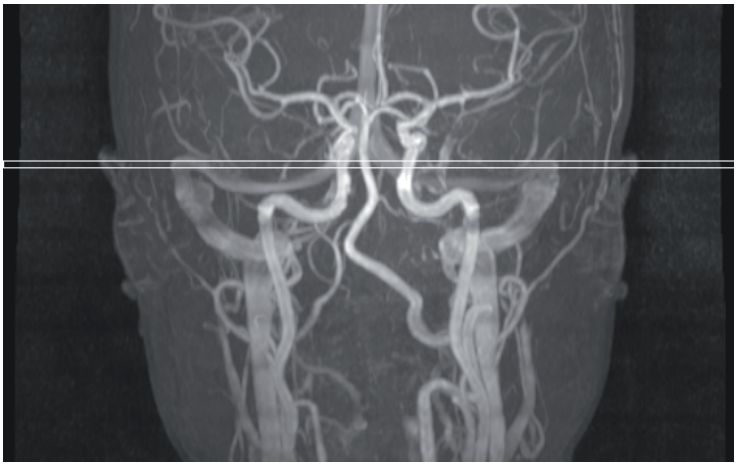

Figure 1 Magnetic resonance angiography, coronal maximum intensity projection. Horizontal line indicates the positioning of the 2-dimensional phase-contrast section through the ICA and the BA.

Statistical analysis

Data were analysed using SPSS 12.0.1 (SPSS Inc, Chicago, USA). Left-to-right differences in diameters for bilateral blood vessels (MMA, ICA, ECA, MCA and PCA) were tested using the paired t-test. Since differences were not significant (as shown in the results section) means of the right and left vessel were used throughout this paper. Difference in blood vessel diameter and blood flow at baseline between migraine patients and

healthy volunteers was tested using the Mann Whitney U test. Linear mixed models were used to analyse the effect of nitroglycerin, subjects (healthy volunteers/ migraine) and provoked migraine attack (yes/ no) on vessel diameters and blood flow. Data from patients receiving placebo was not used for statistical testing. P<0.05 was considered significant.

Results

In total 32 migraine patients (27 NTG and 5 Placebo) and 12 healthy volunteers were included in the study (Table 1). A provoked migraine attack was observed in 20 migraine patients (74%) and no attack after placebo or in healthy volunteers. The median time to attack was 3.75 hours (range 1.5 – 5.5 hours).

Table 1 Demographic characteristics of study participants

	HV (n=12)	Migraine (n=32)		
Intervention	NTG	NTG (27)		Placebo (n=5)
Attack	No	Yes (n=20)	No (n=7)	No
Age in years (SD)	40.6 (11.1)	45.5 (8.5)	34 (8.9)	44.8 (13.3)
Ratio female to males	10 : 2	15 : 5	7 : 0	3 : 2
Ratio MO to MA		17 : 3	6 : 1	4 : 1
Attack frequency; mean (SD)		2.6 (1.0)	2.1 (0.38)	2.4 (1.1)

HV denotes healthy volunteer, MO migraine without aura, MA migraine with aura.

Baseline measurements

There were no differences in blood vessel diameters or blood flow at baseline between migraine patients and healthy volunteers (Table 2 and 4).

Side to side differences of blood vessel diameter

There were no (p>0.05) right to left differences for the diameters of the five bilateral blood vessels (MMA, ICA, ECA, MCA, PCA) in any of the conditions. Therefore, mean right-left diameters are presented throughout.

Blood flow changes in BA and ICA during NTG

Blood flow in the ICA decreased 118.9 ml/min in healthy controls and decreased 19.5 ml/min in migraine patients (p=0.05; Table 2). In migraine patients who later developed a migraine attack blood flow in the ICA increased 7.2 ml/min during NTG and decreased

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112.5 ml/min in patients without an attack (p=0.01; Table 3). Blood flow changes in the BA during NTG was not different between migraine patients and healthy volunteers nor in migraine patients with and without an attack.

Table 2 Blood flow in BA, ICA and total cerebral blood flow in migraine patients and healthy volunteers at baseline and during infusion of nitroglycerin or placebo.

Blood vessel	Subjects	Inter-vention	N	A) Baseline	B) During NTG or placebo	Change (B vs A)
				ml/min (SD)	ml/min (SD)	ml/min (%)
BA	HV	NTG	12	145.8 (55.5)	149.0 (50.9)	3.3 (2.3)
	Migraine	NTG	27	174.6 (68.7)	169.3 (57.9)	-5.4 (-3.1)
		Placebo	5	170.5 (39.4)	128.6 (49.9)	-41.9 (-24.6)
ICA	HV	NTG	12	700.5 (200.4)	581.7 (154.8)	-118.9 (-17.0)*
	Migraine	NTG	27	577.1 (121.6)	557.5 (139.4)	-19.5 (-3.4)
		Placebo	5	542.0 (211.1)	523.2 (161.9)	-18.8 (-3.5)
TCBF	HV	NTG	12	850.9 (199.8)	735.1 (139.9)	-115.9 (-13.6)
	Migraine	NTG	27	751.7 (117.3)	726.8 (149.5)	-24.9 (-3.3)
		Placebo	5	712.6 (202.4)	651.8 (198.8)	-60.7 (-8.5)

HV denotes healthy volunteers, NTG nitroglycerin, ICA internal carotid artery, BA basilar artery, tCBF total cerebral blood flow. *ICA blood flow is significantly different between healthy volunteers and migraine (p=0.05)

Table 3 Blood flow in BA, ICA and total cerebral blood flow in migraine patients with and without a provoked migraine attack at baseline and during infusion of nitroglycerin.

Blood vessel	Subjects	Inter-vention	Migraine attack	N	A) Baseline	B) During NTG or placebo	Change (B vs A)
					ml/min (SD)	ml/min (SD)	ml/min (%)
BA	Migraine	NTG	Yes	20	173.7 (69.4)	170.8 (64.7)	-2.8 (-1.6)
		NTG	No	7	177.2 (71.9)	165.0 (36.8)	-12.2 (-6.9)
ICA	Migraine	NTG	Yes	20	589.6 (128.5)	599.9 (128.1)	10.2 (1.7)*
		NTG	No	7	542.9 (101.2)	442.5 (103.3)	-100.4 (-18.5)
TCBF	Migraine	NTG	Yes	20	763.3 (124.1)	770.7 (140.7)	7.4 (1.0)
		NTG	No	7	720.1 (97.7)	607.5 (105.4)	-112.5 (-15.6)

HV denotes healthy volunteers, NTG nitroglycerin, ICA internal carotid artery, BA basilar artery, tCBF total cerebral blood flow. *ICA blood flow is significantly different between healthy volunteers and migraine (p=0.05)

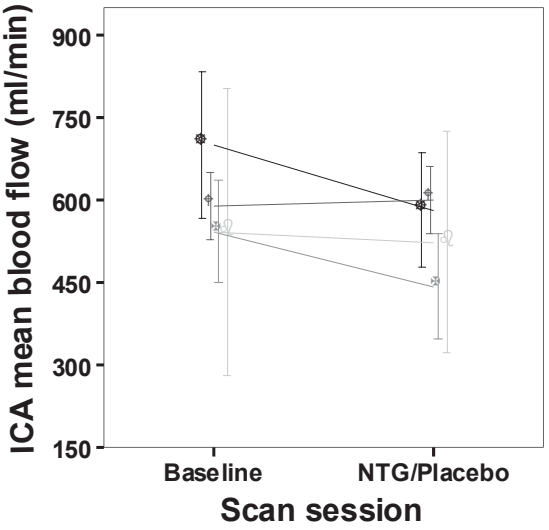

Figure 2A Blood flow in internal carotid artery at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, **X** Migraine patients (placebo) without an attack)

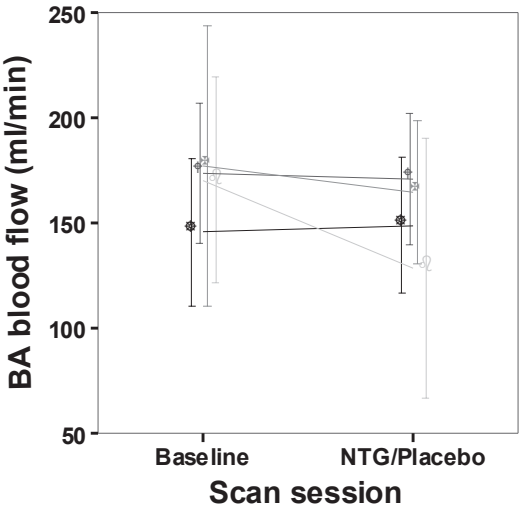

Figure 2B Blood flow in basilary artery at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, **X** Migraine patients (placebo) without an attack)

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Table 4 Blood vessel diameters of six selected cranial blood vessel in healthy volunteers and migraine patients at baseline and during infusion of nitroglycerin or placebo.

Blood vessel	Subjects	Inter-vention	N	A) Baseline	B) During NTG or placebo	Change (B vs A)
				mm (SD)	mm (SD)	mm (% from A)
MMA	HV	NTG	12	1.61 (0.11)	1.93 (0.21)	0.32 (19.9)*
	Migraine	NTG	27	1.65 (0.18)	1.93 (0.24)	0.27 (16.4)*
	Migraine	Placebo	5	1.67 (0.73)	1.64 (0.12)	-0.02 (-1.2)
ECA	HV	NTG	12	3.63 (0.46)	4.61(0.39)	0.98 (27.0)*
	Migraine	NTG	27	3.46 (0.38)	4.50 (0.38)	1.05 (30.3)*
	Migraine	Placebo	5	3.51 (0.27)	3.56 (0.39)	0.05 (1.4)
ICA	HV	NTG	12	4,87 (0.16)	5,38 (0.30)	0.51 (10.5)*
	Migraine	NTG	27	4.81 (0.49)	5.32 (0.42)	0.51 (10.6)*
	Migraine	Placebo	5	4,86 (0.41)	5,02 (0.44)	0.15 (3.1)
MCA	HV	NTG	12	3,14 (0.15)	3,46 (0.24)	0.33 (10.5)*
	Migraine	NTG	27	3.16 (0.29)	3.52 (0.24)	0.37 (11.7)*
	Migraine	Placebo	5	3,10 (0.20)	3,10 (0.22)	-0.01 (-0.3)
BA	HV	NTG	12	3,00 (0.42)	3,41 (0.50)	0.41 (13.7)*
	Migraine	NTG	27	2.95 (0.53)	3.57 (0.57)	0.61 (20.7)*
	Migraine	Placebo	5	2,86 (0.42)	2,80 (0.38)	-0.06 (-2.1)
PCA	HV	NTG	12	2.53 (0.16)	2.68 (0.11)	0.14 (5.5)*
	Migraine	NTG	27	2.55 (0.15)	2.72 (0.19)	0.17 (6.7)*
	Migraine	Placebo	5	2.67 (0.15)	2.62 (0.28)	-0.04 (-1.5)

HV denotes healthy volunteers, NTG nitroglycerin, MMA middle meningeal artery, ECA external carotid artery, ICA internal carotid artery, MCA middle cerebral artery, BA basilar artery and PCA posterior cerebral artery. *Significant increase in diameters in all blood vessels during infusion of NTG as compared to baseline ($p<0.01$).

Diameter changes during infusion of NTG

Compared to baseline NTG caused a significant vasodilatation of all six selected blood vessels (Table 4 and Figures 3A to F; $p<0.01$ for all blood vessels). The immediate NTG-induced diameter increase was larger in the extra-cerebral blood vessels (MMA and ECA), with an increase ranging from 16.4% to 30.3% as compared to the diameter increase seen in the intra-cranial blood vessels (ICA, MCA, BA and PCA), with an

increase ranging form 5.5% to 20.7%. The diameter increase during NTG was not significantly different (p>0.05) between migraine patients and healthy volunteers (Table 4) nor between migraine patients with a provoked attack compared to patients without an attack (Table 5) in all measured blood vessels.

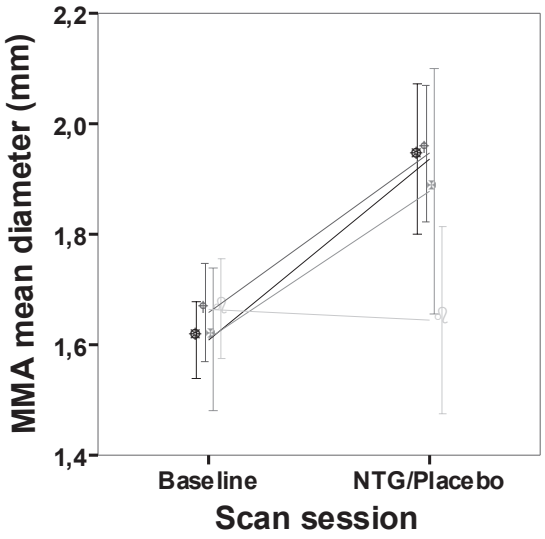

Figure 3A Blood vessel diameter of the MMA at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, X Migraine patients (placebo) without an attack)

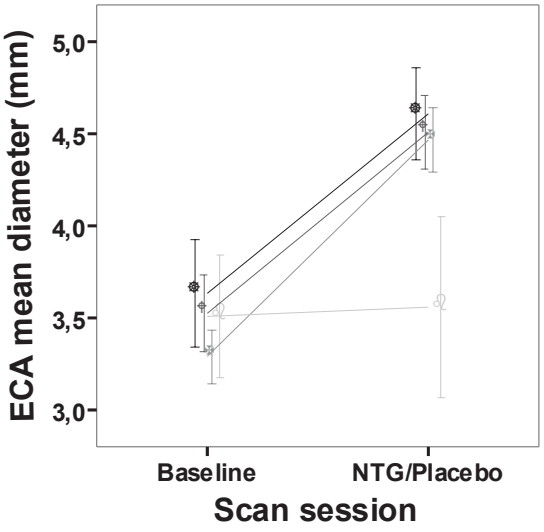

Figure 3B Blood vessel diameter of the ECA at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, X Migraine patients (placebo) without an attack)

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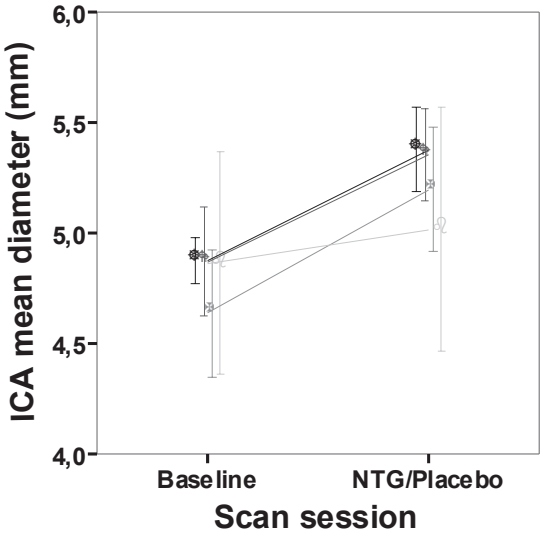

Figure 3C Blood vessel diameter of ICA at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, **X** Migraine patients (placebo) without an attack)

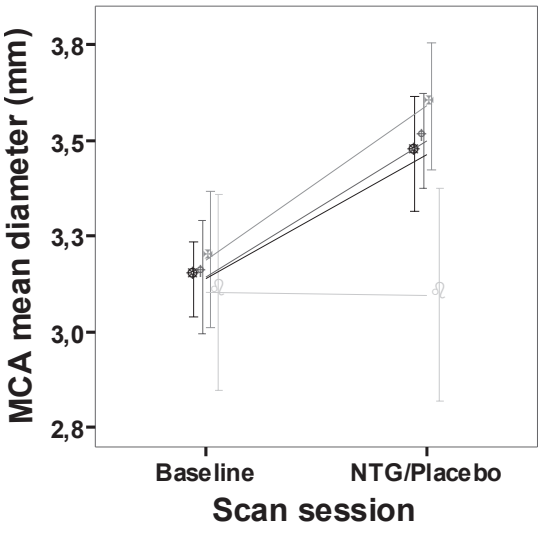

Figure 3D Blood vessel diameter of MCA at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, **X** Migraine patients (placebo) without an attack)

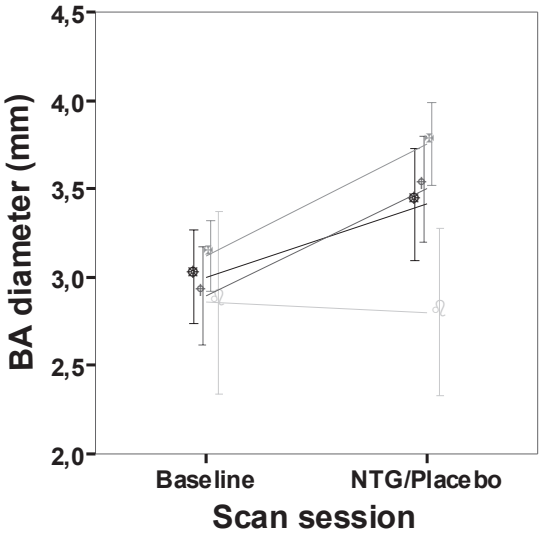

Figure 3E Blood vessel diameter of BA at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, X Migraine patients (placebo) without an attack)

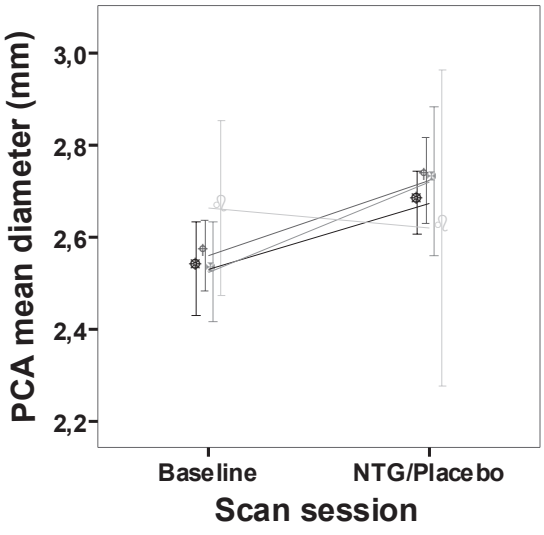

Figure 3F Blood vessel diameters in selected blood vessels at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, X Migraine patients (placebo) without an attack)

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Table 5 Blood vessel diameters of six selected cranial blood vessel in migraine patients with and without a provoked migraine attack at baseline and during infusion of nitroglycerin.

Blood vessel	Subjects	Inter-vention	Migraine attack	N	A) Baseline	B) During NTG or placebo	Change (B vs A)
					mm (SD)	mm (SD)	mm (% from A)
MMA	Migraine	NTG	Yes	20	1.66 (0.19)	1.95 (0.24)	0.28 (16.9)
	Migraine	NTG	No	7	1.61 (0.12)	1.88 (0.20)	0.27 (16.8)
ECA	Migraine	NTG	Yes	20	3.53 (0.42)	4.51 (0.43)	1.00 (28.3)
	Migraine	NTG	No	7	3.29 (0.16)	4.47 (0.19)	1.18 (35.9)
ICA	Migraine	NTG	Yes	20	4,87 (0.53)	5,36 (0.45)	0.49 (10.1)
	Migraine	NTG	No	7	4,64 (0.31)	5,20 (0.31)	0.56 (12.1)
MCA	Migraine	NTG	Yes	20	3,14 (0.32)	3,50 (0.26)	0.36 (11.5)
	Migraine	NTG	No	7	3,19 (0.19)	3,59 (0.18)	0.4 (12.5)
BA	Migraine	NTG	Yes	20	2,89 (0.60)	3,50 (0.64)	0.6 (20.8)
	Migraine	NTG	No	7	3,12 (0.21)	3,75 (0.25)	0.63 (20.2)
PCA	Migraine	NTG	Yes	20	2.56 (0.16)	2.73 (0.20)	0.17 (6.6)
	Migraine	NTG	No	7	2.53 (0.12)	2.72 (0.17)	0.20 (7.9)

HV denotes healthy volunteers, NTG nitroglycerin, MMA middle meningeal artery, ECA external carotid artery, ICA internal carotid artery, MCA middle cerebral artery, BA basilar artery and PCA posterior cerebral artery.

Discussion

In the present study we found that the decrease in ICA blood flow during NTG infusion was more pronounced in healthy volunteers as compared to migraine patients. Changes in BA blood flow and blood vessel diameter were not different between groups. Previous NTG studies in migraine showed either no difference in blood velocity decrease in the middle cerebral artery between migraine and controls[118], or a more pronounced decrease in migraine patients[117]. An explanation for the difference in results could be that these studies did not take into account the occurrence of a provoked attack. In this study the difference between migraine and healthy volunteers is mainly explained by a difference between migraine patients with and without a provoked attack. Patient without an attack showed a decrease in ICA blood flow similar to healthy volunteers whereas in patients with an attack ICA blood flow did not decrease.

Blood flow in the ICA is affected by several parameters; i) ICA blood vessel diameter, ii) cardiac output and iii) vasomotor tone in small resistance vessels. The ICA diameter increased during NTG infusion, but there was no difference between groups. Nitroglycerin has shown to decrease cardiac output[216]. In this study we did not measured cardiac output but we did not observe a difference in blood pressure response during NTG infusion between groups (data not shown), suggesting that there was no difference in decrease of cardiac output between groups. So a difference in vasomotor tone of small resistance vessels might be the main explanation for the observed difference between patients with and without an attack.

Many factors are involved in the regulation of cerebral blood flow; for review see Hamel[217]. Nitroglycerin has shown to affect cerebral blood flow via release of CGRP from trigeminal perivascular nerves[114,115] and through a direct effect on vascular smooth muscle cells[106]. An increased release of CGRP during NTG infusion in patients with an attack would fit previous findings in provoked attacks: the occurrence of a provoked attack was associated with an increase in CGRP during NTG provocation[124]. Whether there could be a different effect of NTG on vascular smooth muscle cells between migraine patients with an attack as compared to patients without an attack is unclear.

Another interesting finding was that nitroglycerin decreased cerebral blood flow healthy volunteers, whereas other vasodilators have shown to increase tCBF in studies using phase contrast MRA. Acetazolamide infusion showed a tCBF increase of 41% in healthy volunteers[218] and CO2 increased tCBF by 64%[219]. An explanation could be that cardiac output is increased in acetazolamide[220] and decreased during nitroglycerin infusion[216]. Future studies on the effect of nitroglycerin on cerebral blood flow should include measures for cardiac output.

In conclusion, the ICA blood flow response to nitroglycerin is impaired in migraine patients compared to healthy volunteers, mainly due to an impaired response in patients who developed a provoked migraine attack after several hours. These findings suggest that provocation of an attack after NTG is associated with an impaired response in small resistance blood vessels.

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CHAPTER 7

MIGRAINE HEADACHE IS NOT ASSOCIATED WITH CEREBRAL OR MENINGEAL VASODILATATION - A 3T MAGNETIC RESONANCE ANGIOGRAPHY STUDY

Brain. 2008 May 23 (epub ahead of print)

Abstract

Background

Migraine headache is widely believed to be associated with cerebral or meningeal vasodilatation. Human evidence for this hypothesis is lacking. 3 Tesla Magnetic resonance angiography (3T MRA) allows for repetitive, non-invasive, sensitive assessment of intracranial vasodilatation and blood flow. Nitroglycerine (NTG) can faithfully induce migraine attacks facilitating pathophysiological studies in migraine.

Methods

Migraineurs (n=32) randomly received NTG (IV 0.5 µg/kg/min for 20 min; n=27) or placebo (n=5; for blinding reasons). Using 3T MRA, we measured: a) blood flow in the basilar (BA) and internal carotid (ICA) arteries and b) diameters of the middle meningeal (MMA), external carotid (ECA), ICA, middle cerebral (MCA), BA and posterior cerebral (PCA) arteries at three timepoints: i) at baseline, outside an attack; ii) during infusion of NTG or placebo; and iii) during a provoked attack or, if no attack had occurred, at 6 hours after infusion.

Findings

Migraine headache was provoked in 20/27 (74%) migraineurs who received NTG, but in none of the five patients who received placebo. The headache occurred between 1.5 – 5.5 hrs after infusion and was unilateral in 18/20 (90%) responders. During NTG (but not placebo) infusion, there was a transient 6.7% – 30.3% vasodilatation ($p<0.01$) of all blood vessels. During migraine, blood vessel diameters were no different from baseline, nor between headache and non-headache sides. There were no changes in BA and ICA blood flow during either NTG infusion or migraine.

Interpretation

In contrast to widespread belief, migraine attacks are not associated with vasodilatation of cerebral or meningeal blood vessels. Future antimigraine drugs may not require vasoconstrictor action.

Introduction

Migraine is a neurovascular disorder typically characterised by attacks of severe, throbbing, unilateral headache, associated autonomic symptoms, and, in one third of patients, focal neurological aura symptoms [75]. Since the seminal work by Wolff and colleagues [198], showing that stimulation of cerebral and meningeal arteries caused headache, there is a widespread belief that vasodilatation of intracranial blood vessels is the underlying mechanism for migraine headache [221]. This hypothesis was further fed by a number of other observations. Balloon dilatation of the middle cerebral artery (MCA) may cause migraine-like headache [222]. Vasoactive substances such as the nitric oxide (NO) donor nitroglycerin (NTG) [78] and calcitonin gene related peptide (CGRP) [62] can trigger migraine in susceptible subjects. In fact, the recent development of novel CGRP antagonists for treating migraine attacks was at least partly based on the hypothesis that prevention or reversal of vasodilation would block migraine headache [223,224]. Animal and *in situ* pharmacological experiments [75,225] and human *in vivo* studies using transcranial Doppler (TCD) [204,226,227] have shown that acute antimigraine agents (ergots and triptans) constrict cerebral and meningeal blood vessels [228]. In fact, the triptan class was specifically designed to selectively constrict intracranial blood vessels [221].

The role of vasodilatation in migraine has been vividly debated in the past (for review see: [229]) and more recently [75,87]. Some researchers view vasodilation of meningeal or cerebral blood vessels as a primary trigger for migraine headaches, and consider vasoconstriction necessary for acute antimigraine efficacy [230]. Others feel that vasodilation is a secundary phenomenon, due to activation of the trigeminovascular system and release of vasoactive neuropeptides. Vasodilation would primarily be involved in sustaining and worsening of the headache during migraine attacks [79]. A third line of thinking holds that vasodilation is irrelevant or, at best, "an innocent bystander" in the pathogenesis of migraine headache. Consequently, vasoconstriction may not be needed to treat migraine headaches [231] [232,233]. This would be an enormous advantage as the currently available most effective antimigraine agents, triptans and ergots, all possess (sometimes strong and sustained) vasoconstrictor activity [234]. They may cause myocardial and cerebral ischaemia in patients with (risk factors for) vascular disease [235]. Novel antimigraine agents, which are devoid of vasoconstrictor activity, would be safer and could thus also be used by the many migraineurs with vascular disease.

Remarkably, the three opposing views on the role of vasodilation in migraine are all primarily based on extrapolations of observations in experimental animal models, with

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very little evidence from human studies. This is primarily due to lack, until recently, of sensitive non-invasive imaging techniques to directly and reliably assess intracranial blood flow and blood vessel diameters in humans. Previous studies have used invasive methods such carotid angiography [236], or could only indirectly estimate diameter changes of cerebral blood vessels using TCD [204,237] Meningeal blood vessels proved too small to be investigated quantitatively. With the advent of 3 Tesla Magnetic Resonance Imaging (3T MRA) a sensitive and non-invasive imaging technique has become available to reliably measure intracranial blood flow and diameter changes of cerebral and meningeal blood vessels [238] as small as the middle meningeal artery (MMA) [110].

Infusion of NTG can reliably and faithfully provoke migraine headaches in migraineurs [55,83,210]. The response to NTG infusion is typically biphasic: an initial, brief and mild bilateral headache during the infusion in nearly all migraine and non-migraine study subjects [83], followed by a typical migraine, 4 to 5 hours later, in 60% to 80% of migraine. but not in non-migraine study subjects. [55,78] The symptomatology of provoked attacks is no different from that of spontaneous attacks of migraine without aura [78], including premonitory symptoms [56], response to anti-migraine drugs [239], and increase of CGRP, a marker for activation of the trigeminovascular system [124]. This provocation model has greatly facilitated the logistics of studying pathophysiological changes during migraine attacks.

In the present study we used 3T MRA to intra-individually compare: a) blood flow in the basilar (BA) and internal carotid (ICA) arteries; and b) the diameters of the external carotid (ECA), internal carotid (ICA), middle cerebral (MCA), BA, posterior cerebral (PCA) and middle meningeal arteries (MMA) between three conditions: i) at baseline, outside an attack; ii) during infusion of NTG or placebo (to assess the immediate vascular effects of NTG); and iii) during NTG-provoked migraine attacks or, if no attack had occurred, at 6 hours post infusion (to assess whether migraine attacks are associated with vasodilatation). We will demonstrate that there is no detectable vasodilation of cerebral or meningeal blood vessels during NTG-provoked migraine attacks, suggesting that vasoconstriction may not be required to treat migraine headaches.

Methods

Subjects

In total 32 migraine patients (n = 5 with aura; n = 27 without aura) were recruited from the neurology outpatient clinic of Leiden University Medical Centre. Inclusion criteria were: i) age between 18 and 55 years; ii) diagnosis of migraine according to the diagnostic criteria of the International Headache Society [3]; iii) an average attack frequency between 1 - 8 attacks per 2 months in the six months prior to the study; and iv) moderate or severe headache during spontaneous migraine attacks. Exclusion criteria included: i) more than 10 days of headache per month; ii) inability to differentiate between migraine and other forms of headache; iii) contra-indications for the use of triptans; iv) current use of vasoactive drugs; and v) MRI-specific contra-indications (such as claustrophobia). The study was approved by the local medical ethics committee and the subjects gave informed consent prior to the start of the study.

Experimental procedure and NTG provocation

All subjects arrived at the hospital between 8 and 10 a.m. on the day of the study. No medication, coffee, tea or alcohol was allowed in the 12 hours prior to the start of the experiment. From one hour before the experiments until the very end of the experiments, study subjects were not allowed to smoke. Patients had to be free of migraine for at least the three days prior to the study day and they could not have any form of headache at the beginning of the experiment.

Migraine patients (n=32) were scanned: i) at baseline (outside an attack; ii) during randomly allocated and double-blind infusion of NTG (0.5 µg/kg/min over 20 min; n=27) or placebo (n=5); and iii) during an ensuing migraine attack or, if no migraine had occurred, at 6 hours after infusion. The duration of the scan sessions was approximately 25 minutes. The study subjects remained in the scanner between the baseline and the NTG or placebo infusion scanning sessions which began 10 minutes after onset of the infusion. Heart rate and blood pressure were monitored during the experiments. Two days after the experiment, subjects were contacted by telephone to check whether a migraine attack had occurred beyond the 6-hour time window [221].

Placebo administration was included in the protocol to minimise patient and observer's bias for diagnosing whether or not NTG infusion had provoked a migraine headache (as this diagnosis is based on subjective assessment of symptoms [3]). We choose for an unequal and incomplete allocation to receiving NTG or placebo mainly for two

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reasons. First, NTG administration was only used as a well established tool to provoke migraine attacks. Our study objective was primarily to assess intra-individual changes from baseline, rather than comparing the effect of NTG with that of placebo. Secondly, we wanted to minimise the number of patients who would contribute only very little to the study results (placebo was only given for masking reasons) to reduce unnecessary burden to patients, investigators, and MRI scanning time (the study protocol was very time consuming).

Magnetic resonance angiography

The MR investigations were performed on a 3.0-Tesla whole-body system (Philips Medical Systems, The Netherlands). The MRA protocol consisted of two parts, one to assess blood vessel diameter changes and one to assess blood flow changes.

The "blood vessel diameter protocol" consisted of a thick two-dimensional phase contrast (2D PC) sagittal localiser survey through the circle of Willis, followed by a three-dimensional time-of-flight (3D TOF) MRA sequence to visualise the BA and ECA, ICA, PCA and MCA on both sides. This scan had the following imaging parameters: repetition time / echo time (TR/TE): 22 ms / 3.5 ms; flip angle 15^{o}; field of view: 220 x 220 mm; number of excitations: 1; slice orientation: transverse; slice thickness: 0.65 mm; number of slices: 200; scan percentage 100%, matrix reconstruction size: 512 x 512 resulting in a nominal voxel size (x,y,z) of 0.43 x 0.43 x 0.65 mm; total acquisition time: 4min 30sec. Based on the reconstruction of this 3D-TOF a second 3D-TOF with a higher spatial resolution was performed to visualise the extra- and intracranial parts of the MMA on both sides. This scan had the following imaging parameters: TR/TE: 15 ms / 2.1 ms; flip angle 15o; field of view: 200 x 200 mm; number of excitations: 1; slice orientation: transverse; slice thickness: 0.25 mm; number of slices: 130; scan percentage 100%, matrix reconstruction size: 512 x 512 resulting in a nominal voxel size (x,y,z) of 0.39 x 0.39 x 0.25 mm; total acquisition time: 8min 31sec.

For the "blood flow protocol", a 2-dimensional phase-contrast (2D-PC) section was positioned on the basis of two thick slab localiser MRA scans in the coronal and sagittal plane at the level of the skull base, perpendicular on the ICA and BA, to measure the flow volume. The MRA flow volume measurements in the present study are derived from previously developed and optimized protocols [211-214]. Acquisition parameters: repetition time / echo time (TR/TE): 16 ms / 8.5 ms; flip angle 10^{o}; field of view: 150 x 150 mm; number of excitations: 20; slice orientation: transverse; slice thickness: 5.0 mm; number of slices: 1; scan percentage 100%; PC velocity encoding: 140 cm/s; matrix

reconstruction size: 256 x 256 resulting in a nominal voxel size (x,y,z) of 0.59 x 0.59 x 50 mm; total acquisition time: 56sec. Figure 1 illustrates the positioning of the 2D PC section through the ICA and BA. On an independent workstation, quantitative flow values were calculated in each vessel by integrating across manually drawn regions of interest that enclosed the vessel lumen closely.

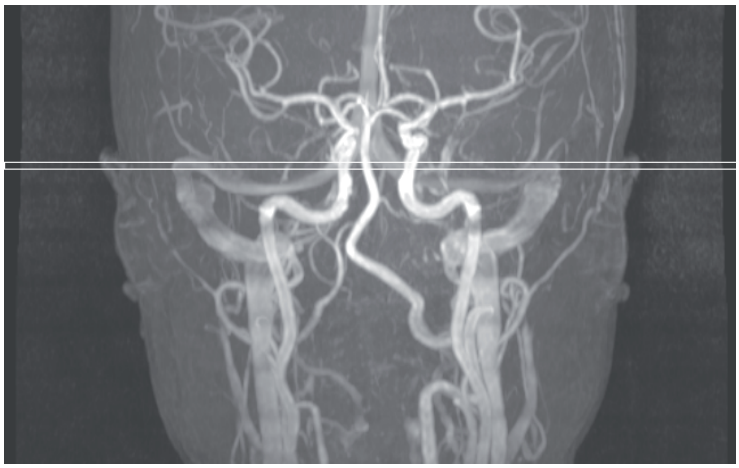

Figure 1 Magnetic resonance angiography, coronal maximum intensity projection. Horizontal line indicates the positioning of the 2-dimensional phase-contrast section through the ICA and the BA.

Image post processing: diameter calculations

All MRA images were transferred to a remote workstation for quantitative analysis using the Quantitative-MRA (QMRA) software package developed at our institution. A full description of the contour detection methods used and the validation have been described previously [215]. The software provides automated contour detection and quantification of the luminal boundaries in selected vessel segments in 3D MRA datasets. The only user interaction required is the definition of the vessel segment of interest by placing a proximal and distal point in the 3D dataset. Subsequently, the software detects a 3D path line following the centre of the vessel lumen and cross-sectional multiplanar recontructions (MPR's) are generated perpendicular to the centreline at 0.5 mm intervals. In each of these MPR's a contour around the vessel lumen is detected automatically. From these contours, based on the assumption of circular vessel cross-sections, the average diameter of the selected vessel segment is derived. Blood vessel segments were selected as follows: A) the MMA was measured in an extra-cranial segment (from the origin at the maxillary artery to the end, 5 to 6 mm distally; Figure2); B) the ECA from

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the origin at the superficial temporal artery to the end, 10 mm proximally; C) the ICA from just proximally of the syphon to the end, 15 mm distally; D) the MCA, onset after A1 segment and end 8 mm distally; E) the BA, from the origin at the PCA to the end 12 mm proximally; F) the PCA, beginning at the origin at BA and end 8 mm distally). Location of measured vessel segments were kept constant within subjects.

Figure 2 Magnetic resonance angiography of the MMA region and position of the measured segment: (A) maxillary artery, (B) middle meningeal artery (MMA).

Statistical analysis

We first tested the left-to-right differences in diameters for bilateral blood vessels (MMA, ICA, ECA, MCA and PCA) using paired t-tests. Since the differences were not statistically significant, we only present the mean diameters for the right and left blood vessels throughout the manuscript. The effect of NTG and migraine attack on blood vessel diameters and blood flow were tested using a linear mixed model. Patients with a migraine attack (n=20) were compared to patients without an attack after NTG (n=7). Data from patients receiving placebo were not used for statistical testing. $P<0.05$ was considered statistically significant.

Results

Clinical effects of infusion of NTG or placebo

In total 32 migraine patients were randomly infused with either NTG (N=27) or placebo (N=5). Demographic characteristics of the study population are summarised in Table 1. No attack occurred after placebo (0/5). In contrast, infusion of NTG provoked a migraine attack (all without aura) in 20/27 (74%) migraine patients after a median time of 3.75 hours (range: 1.5 - 5.5 hours). In 18/20 attacks the headache was unilateral (left: n=9; right n=9). The clinical characteristics of the patients who developed a migraine attack in response to NTG and the clinical features of the provoked attacks are summarised in Supplemental Table s1.

Table 1 Demographic characteristics of study participants

	Migraine (n=32)		
Intervention	NTG (27)		Placebo (n=5)
Attack	Yes (n=20)	No (n=7)	No
Age in years (SD)	45.5 (8.5)	34 (8.9)	44.8 (13.3)
Ratio female to males	15 : 5	7 : 0	3 : 2
Ratio MO to MA	17 : 3	6 : 1	4 : 1
Attack frequency; mean (SD)	2.6 (1.0)	2.1 (0.38)	2.4 (1.1)

MO denotes migraine without aura, MA migraine with aura.

Side to side differences for blood vessel diameters

There were no ($p>0.05$) right-to-left differences for the diameters of the four bilateral blood vessels (MMA, ICA, ECA, MCA, PCA) in any of the three conditions (data not shown), except for the MCA during session three ($p=0.024$). This difference was considered not significant after correction for multiple testing. Similarly, in the 18 patients with a unilateral headache, there were no significant ($p>0.05$) differences between the diameters on the headache and the non-headache side (Supplemental Table s4). Therefore, the mean diameters of the right and left blood vessels are presented throughout the paper.

Diameter and blood flow changes during infusion of NTG or placebo

During NTG infusion there was a significant vasodilatation of all blood vessels compared to baseline (Figures 3A to F and Supplemental Table s2; $p<0.01$ for all blood vessels). The diameter increase was greatest in the extra-cerebral blood vessels (MMA and ECA), ranging from 16.4% to 30.3%, as compared to 6.7% - 20.7% diameter increase in the

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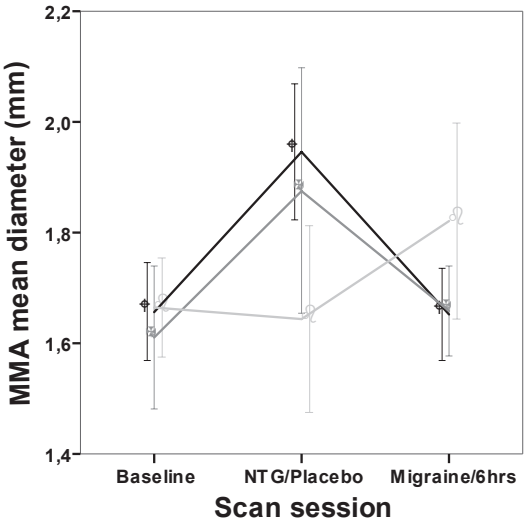
intra-cranial blood vessels (ICA, MCA, BA and PCA). During infusion of placebo, there were no changes in diameter for any of the blood vessels. There were no changes in ICA or BA blood flow during infusion of NTG or placebo (Figure 4A – B and Supplemental Table s3).

Figure 3A -F Mean blood vessel diameter changes (mean of left and right in bilateral vessels) in six selected intracranial blood vessels at baseline, during infusion of nitroglycerin (NTG) or placebo, and during an NTG-provoked migraine or, if no attack had occurred, at 6 hours after infusion. (● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, **X** Migraine patients (placebo) without an attack).



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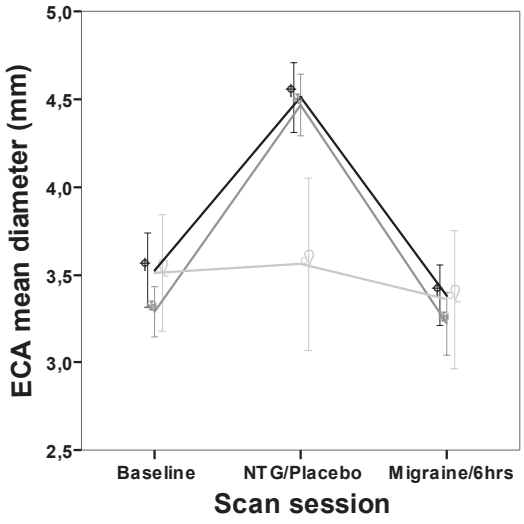

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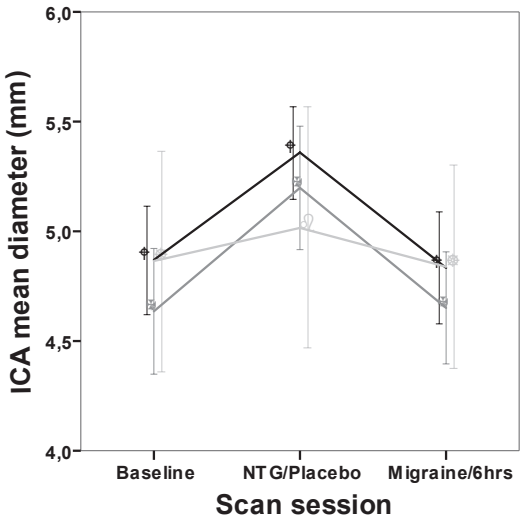

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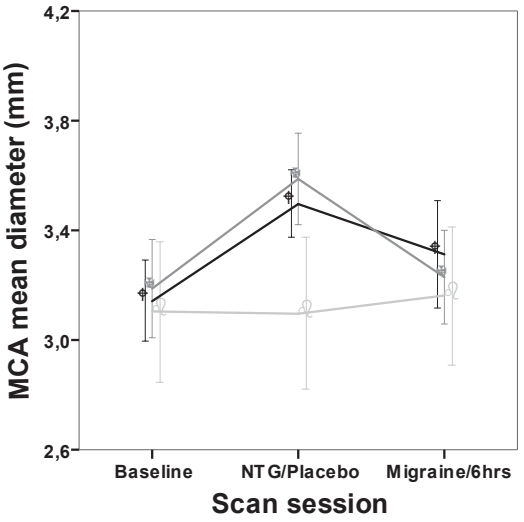

Figure 3D

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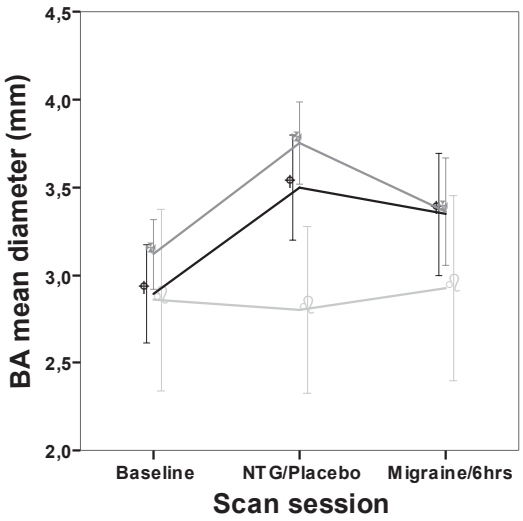

Figure 3E

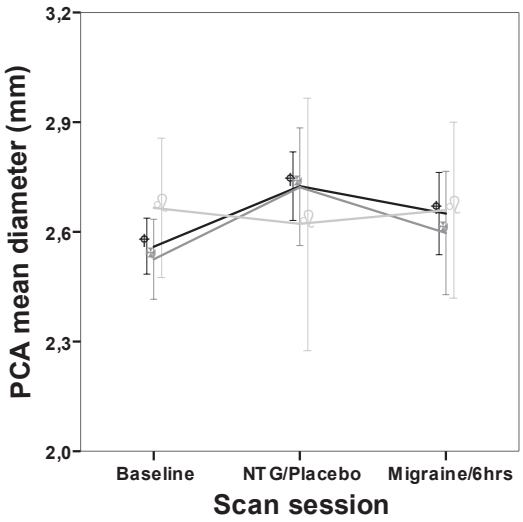

Figure 3F

Table 2 Mean blood vessel diameters (mean of right and left for bilateral blood vessels) of six selected intracranial blood vessel at baseline and during an NTG-provoked migraine attack or, if no attack had occurred, at 6 hours after infusion in 32 migraine patients.

Blood vessel	Inter-vention	Migraine attack	N	A) Baseline	B) During migraine or at 6 hours	Change (B vs A)
				mm (SD)	mm (SD)	mm (% from A)
MMA	NTG	Yes	20	1.66 (0.19)	1.65 (0.17)	-0.01 (-0.6)
	NTG	No	7	1.61 (0.12)	1.66 (0.08)	0.05 (3.1)
	Placebo	No	5	1.67 (0.73)	1.82 (0.14)	0.16 (9.6)
ECA	NTG	Yes	20	3.53 (0.42)	3.38 (0.36)	-0.12 (-3.4)
	NTG	No	7	3.29 (0.16)	3.22 (0.19)	-0.07 (-2.1)
	Placebo	No	5	3.51 (0.27)	3.36 (0.32)	-0.15 (-4.3)
ICA	NTG	Yes	20	4,87 (0.53)	4,83(0.53)	-0.04 (-0.8)
	NTG	No	7	4,64 (0.31)	4,65(0.28)	0.01 (0.2)
	Placebo	No	5	4,86 (0.41)	4,84(0.37)	-0.02 (-0.4)
MCA	NTG	Yes	20	3,14 (0.32)	3,31 (0.41)	0.17 (5.4)
	NTG	No	7	3,19 (0.19)	3,23 (0.19)	0.04 (1.3)
	Placebo	No	5	3,10 (0.20)	3,16 (0.20)	0.06 (1.9)
BA	NTG	Yes	20	2,89 (0.60)	3,35 (0.72)	0.48 (16.6)
	NTG	No	7	3,12 (0.21)	3,36 (0.33)	0.24 (7.7)
	Placebo	No	5	2,86 (0.42)	2,93 (0.42)	0.07 (2.5)
PCA	NTG	Yes	20	2.56 (0.16)	2.65 (0.23)	0.09 (3.5)
	NTG	No	7	2.52 (0.12)	2.60 (0.18)	0.07 (2.8)
	Placebo	No	5	2.67 (0.15)	2.66 (0.19)	0.01 (0.4)

NTG denotes nitroglycerin, MMA middle meningeal artery, ECA external carotid artery, ICA internal carotid artery, MCA middle cerebral artery, BA basilar artery and PCA posterior cerebral artery. There were no significant changes in diameter during the migraine attack.

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Tabel 3 Blood flow in the basilary (BA) and internal carotid artery (ICA) (mean of left and right) in migraine patients at baseline and during a migraine attack or, if no attack had occurred, at 6 hours after infusion of NTG or placebo.

Blood vessel	Inter-vention	Migraine Attack	N	A) Blood flow Baseline	B) Blood flow During Migraine or at 6 hours	Difference (B vs A)
				ml/min (SD)	ml/min (SD)	ml/min
BA	NTG	Yes	20	173.7 (69.4)	128.5 (40.1)	-46.2
	NTG	No	7	177.2 (71.9)	189.7 (26.3)	12.5
	Placebo	No	5	170.5 (39.4)	176.9 (63.6)	6.4
ICA	NTG	Yes	20	589.6 (128.5)	542.0 (166.8)	-57.7
	NTG	No	7	542.9 (101.2)	468.6 (151.2)	-74.3
	Placebo	No	5	542.0 (211.1)	522.8 (276.7)	-19.2
Total cerebral blood flow	NTG	Yes	20	763.3 (124.1)	670.5 (166.6)	-92.8
	NTG	No	7	720.1 (97.7)	658.3 (153.4)	-61.8
	Placebo	No	5	712.6 (202.4)	699.7 (253.9)	-12.8

NTG denotes nitroglycerin, BA basilary artery and ICA internal carotid artery. Difference between patients with an attack compared to patients without an attack after NTG were not significant.

Diameter and blood flow changes during migraine attacks

Compared to baseline, there were no significant (p>0.05) diameter changes during attacks for any of the blood vessels (Table 2 and Figures 3A to F). This was also true when controlling for the headache side in the 18 patients with an unilateral headache; the changes on the headache side were no different compared to those on the non-headache side (Supplemental Table s4). Similarly, there were no significant (p>0.05) differences when comparing the mean diameter changes (baseline vs. attack) in the 20 patients who developed a migraine attack after NTG with the changes (baseline vs. 6 hours post infusion) in the 7 patients who did not develop an attack and were measured 6 hours after infusion. The attack vs. no-attack change-differences were for the MMA = 0.06 mm (95% CI: -0.8; 0.21), for the ECA = 0.05 mm (95% CI: -0.14; 0.24), for the ICA = 0.06 mm (95% CI: -0.19; 0.31), for the MCA = -0.13 (95% CI: -0.41; 0.14), for the BA = -0.24 (95% CI: -0.59; 0.11), and for the PCA = -0.02 (95% CI: -0.22; 0.18). There were also no significant (p>0.05) changes in total-, BA-, or ICA-blood flow during a migraine

attack when compared to baseline, nor were there significant (p>0.05) differences in the changes observed during attacks when compared to the changes in the patients who did not develop an attack and were measured 6 hours after infusion (Supplemental Table 4).

Figure 4A -B Mean blood flow in ICA (mean of left and right) and BA at baseline, during infusion of nitroglycerin (NTG) or placebo, and during an NTG-provoked migraine or, if no attack had occurred, at 6 hours after infusion. (● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, **X** Migraine patients (placebo) without an attack)

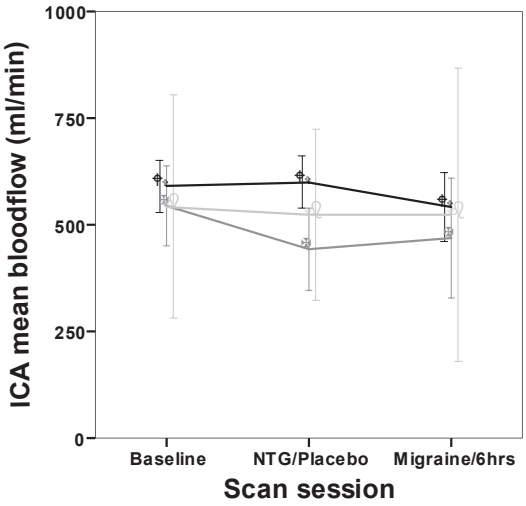

Figure 4A

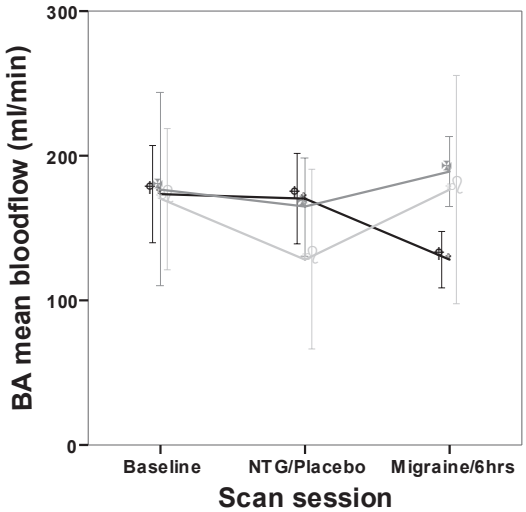

Figure 4B

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Discussion

We used a well established NTG provocation model to induce faithfully migraine attacks and a highly sensitive, non-invasive 3T MRA technique to visualise and measure even small intra-individual diameter changes of cerebral and meningeal blood vessels. Contrary to longstanding and widespread belief, we failed to detect any evidence for a clinically relevant vasodilatation of major cerebral or meningeal blood vessels during migraine attacks. This finding has important implications for the understanding of the pathophysiology of the migraine headache and the development of future antimigraine agents. Novel antimigraine treatments may not require vasoconstrictior activity as predicted earlier [61].

In our provocation experiments, we infused NTG over a 20 min period and observed a vessel-dependent 7 – 30% vasodilatation at 10 minutes after beginning of the infusion. The vasodilatatory effect is believed to be due to a direct local effect of NO on vascular smooth muscle cells [240] or through the release of vasoactive peptides such as CGRP [114,241]. Our findings on the early vascular effect of NTG are in accordance with those of [109]. Using 1.5T MRA they found a peak vasodilatation at 10 - 15 minutes after beginning of the NTG infusion and a normalisation of the vascular diameters back to baseline at 45 minutes after stopping of the infusion. For logistic reasons, we did not scan at 45 min after the infusion to confirm normalisation of the blood vessel diameter. However, in view of the well known short duration of action of NTG [242] and the observed time course of the early vascular responses by [109], we feel confident that blood vessel diameters had returned to baseline by one hour after the second (infusion) scan. It therefore seems justified to compare measurements during attacks with those obtained at baseline, before infusion.

The most important finding of the present study is that migraine headache was not associated with a clinically relevant vasodilatation of major cerebral or meningeal blood vessels, not even when controlled for headache side. We feel confident that this was not due to too low a sensitivity of the detection method. The very fact that we were able to detect an early transient vasodilatation in response to NTG of as low as 7% shows that the method we used is sufficiently sensitive to measure even small diameter changes. The clinical relevance of smaller changes is doubtful as during NTG infusion we observed an up to 30% increase in blood vessel diameter without associated migraine headache. Our results are also in agreement with at least some older TCD studies failing to show blood velocity changes indicative for vasodilatation during migraine attacks. [243-246]

Finally, BA and ICA blood flow did also not change during migraine attacks. Cerebral blood flow is dependent on cardiac output, arterial caliber, and vasomotor tone in small resistance vessels.[247] As blood pressure (as a measure for cardiac output; data not shown) and the BA and ICA diameters had not changed, It seems likely that there were also no changes in the intracranial resistance microvasculature during migraine attacks. In conclusion, our data seem to refute an important role of cerebral or meningeal vasodilatation in causing migraine headache. This would certainly be in accordance with observations that non-vascular mechanisms, such as exposure to sildenafil, [58] are capable of inducing migraine attacks.

Potential limitations of our study include that we didn't measure just before or at the onset of the migraine headache. We could thus have missed a brief transient vasodilatation at the very beginning of the migraine headache. Although unlikely, we cannot exclude this possibility. Another important question is whether and to what extent NTG-provoked migraine attacks are similar to spontaneous attacks. There are strong clinical and pathophsyiological arguments in favour of this notion. The clinical symptoms and features, including the occurrence of premonitory symptoms several hours before the headache[56] and the response to anti-migraine drugs[239], are strikingly similar between spontaneous and NTG-induced attacks. Likewise, in both there is an increase of CGRP in jugular venous blood [61,124] and activation of the dorsal rostral brainstem on positron emission tomography.[82,202] The fact that NTG provokes migraine aura's only rarely, even in patients with migraine with aura [162] [248], seems to point at a trigger site of action beyond the aura triggering mechanism. We thus feel confident that our findings in NTG-provoked attacks can be extrapolated to spontaneous migraine headaches.

In this study, we did not observe significant changes in blood vessel diameter or blood flow during the headache phase of provoked migraine attacks. However, there were some (non-significant) changes in the posterior circulation that need to be discussed. First, the diameter of the BA did not return to baseline levels, unlike the other blood vessels. This was, however, true for both patients who had developed a delayed migraine headache and for those who had not. Secondly, the blood flow in the BA was decreased (although not significantly) from 174 ml/min at baseline to 129 ml/min in patients who had developed a migraine headache after GTN, whilst there was no such change in patients who had not developed a migraine headache. Whether these findings are clinically relevant, needs to be explored. A tentative correlation, for instance, could be made with previous findings of In previous studies our group has shown our group demonstrating increased prevalence of pontine hyperintensities and cerebellar infarcts in migraineurs from the general population [249] [250].

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We conclude that, contrary to a longstanding and widespread belief, cerebral and meningeal diameter changes in migraine attacks, if at all happening, appear not to be of primary importance to the pathophysiology of the migraine headache.

Supplemental Tables

Table s1 (only for publication on the web)
Characteristics of the NTG provoked migraine attack per subject

Subject	Sex	Age	Attack freq (per month	Characteristics of provoked attack								Time to attack (hours)
				HS	UH	PH	AH	N	V	PT	PN	
1	M	40	2	2			+			+	+	4.5
2	M	35	3	2	+	+		+	+			2.5
3	F	42	2	2	+	+	+	+				4.5
4	M	54	4	2	+	+	+	+				4
5	F	49	4	2		+	+	+		+	+	4.5
6	F	55	2	2	+		+	+		+	+	3
7	F	48	1	2	+	+	+			+	+	3
8	F	37	2	2	+	+		+	+	+	+	2.5
9	F	33	2	2	+		+	+	+	+	+	4
10	F	32	2	2	+	+	+	+			+	5
11	F	51	3	2	+	+	+	+		+	+	3
12	F	28	3	2	+		+			+	+	3
13	F	55	4	2	+	+	+	+		+		5.5
14	F	55	4	2	+	+	+			+	+	2
15	F	53	2	2	+		+			+	+	5
16	M	46	3	2	+		+	+	+	+		2
17	M	51	4	2	+		+	+	+	+		4
18	F	49	0.5	2	+		+			+	+	4
19	F	50	4	2	+		+	+	+	+	+	3.5
20	F	31	1	2	+	+	+	+	+	+	+	1.5

F denotes female, M male, HS headache severity (2=moderate), UH unilateral headache (+ indicates yes, empty box no), PH pulsating headache, AH aggravation of headache during physical activity, N nausea, V vomiting, PT photophobia, PN phonophobia

Table s2 (only for publication on the web)
Mean blood vessel diameters (mean of right and left for bilateral blood vessels) of six selected intracranial blood vessel at baseline and during infusion of nitroglycerin or placebo in 32 migraine patients.

Blood vessel	Inter-vention	N	A) Baseline	B) During NTG or placebo	Change (B vs A)
			mm (SD)	mm (SD)	mm (% from A)
MMA	NTG	27	1.65 (0.18)	1.93 (0.24)	0.27 (16.4)*
	Placebo	5	1.67 (0.07)	1.64 (0.12)	-0.02 (-1.2)
ECA	NTG	27	3.46 (0.38)	4.50 (0.38)	1.05 (30.3)*
	Placebo	5	3.51 (0.27)	3.56 (0.39)	0.05 (1.4)
ICA	NTG	27	4.81 (0.49)	5.32 (0.42)	0.51 (10.6)*
	Placebo	5	4,86 (0.41)	5,02 (0.44)	0.15 (3.1)
MCA	NTG	27	3.16 (0.29)	3.52 (0.24)	0.37 (11.7)*
	Placebo	5	3,10 (0.20)	3,10 (0.22)	-0.01 (-0.3)
BA	NTG	27	2.95 (0.53)	3.56 (0.57)	0.61 (20.7)*
	Placebo	5	2,86 (0.42)	2,80 (0.38)	-0.06 (-2.1)
PCA	NTG	27	2.55 (0.15)	2.72 (0.19)	0.17 (6.7)*
	Placebo	5	2.67 (0.15)	2.62 (0.28)	-0.04 (-1.5)

NTG denotes nitroglycerin, MMA middle meningeal artery, ECA external carotid artery, ICA internal carotid artery, MCA middle cerebral artery, BA basilar artery, PCA posterior cerebral artery. * NTG effect on diameter was significant in all six blood vessels ($p<0.01$).

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Table s3 (only for publication on the web)
Blood flow in BA, ICA and total cerebral blood flow in migraine patients at baseline and during infusion of nitroglycerin or placebo.

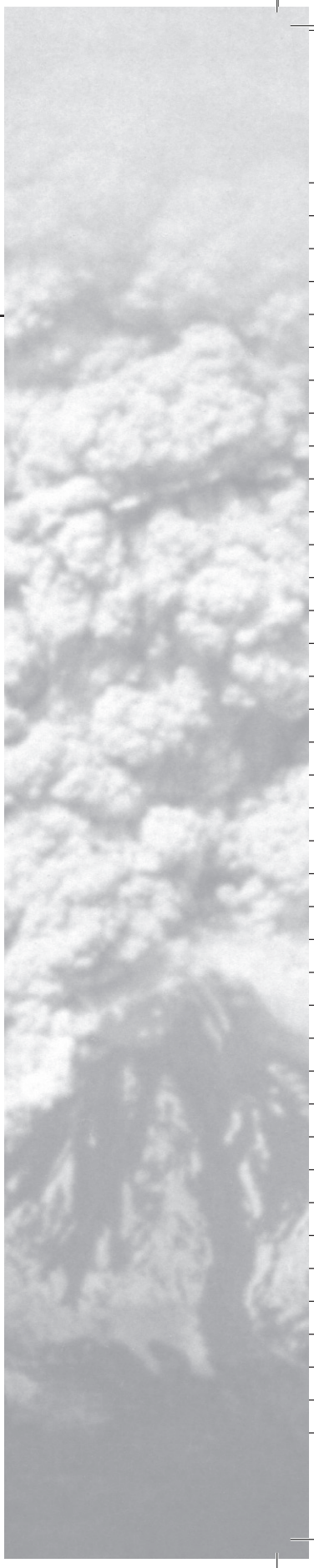
Blood vessel	Inter-vention	N	A) Baseline	B) During NTG or placebo	Change (B vs A)
			ml/min (SD)	ml/min (SD)	ml/min (%)
BA	NTG	27	174.6 (68.7)	169.3 (57.9)	-5.4 (-3.1)
	Placebo	5	170.5 (39.4)	128.6 (49.9)	-41.9 (-24.6)
ICA	NTG	27	577.1 (121.6)	557.5 (139.4)	-19.5 (-3.4)
	Placebo	5	542.0 (211.1)	523.2 (161.9)	-18.8 (-3.5)
TCBF	NTG	27	751.7 (117.3)	726.8 (149.5)	-24.9 (-3.3)
	Placebo	5	712.6 (202.4)	651.8 (198.8)	-60.7 (-8.5)

NTG nitroglycerin, ICA internal carotid artery, BA basilar artery, tCBF total cerebral blood flow.

Table s4 (only for publication on the web)
Blood vessel diameter of five bilateral intracranial blood vessels at baseline and during an NTG-provoked migraine attack in 18 migraine patients with unilateral headache.

Blood vessel	Side	A) Baseline	B) During migraine	Change (B vs A)
		mm (SD)	mm (SD)	mm (% from A)
MMA	Headache	1.69 (0.22)	1.67 (0.21)	-0.03 (-1.78)
	Non-headache	1.60 (0.18)	1.58 (0.17)	-0.03 (-1.88)
ECA	Headache	3.51 (0.39)	3.34 (0.38)	-0.18 (-5.13)
	Non-headache	3.43 (0.46)	3.33 (0.39)	-0.04 (-1.17)
ICA	Headache	4.87 (0.59)	4.79 (0.64)	-0.09 (-1.85)
	Non-headache	4.89 (0.55)	4.87 (0.55)	-0.02 (-0.41)
MCA	Headache	3.19 (0.34)	3.32 (0.44)	0.13 (4.08)
	Non-headache	3.15 (0.34)	3.36 (0.45)	0.24 (7.62)
PCA	Headache	2.58 (0.19)	2.72 (0.30)	0.13 (5.0)
	Non-headache	2.58 (0.21)	2.66 (0.23)	0.08 (3.1)

MMA denotes middle meningeal artery, ECA external carotid artery, ICA internal carotid artery, MCA middle cerebral artery and PCA posterior cerebral artery. There were no significant differences in diameter change between headache side and non-headache side.



GENERAL DISCUSSION AND CONCLUSIONS

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This thesis deals with the association between potential trigger factors and the occurrence of a migraine attack as well as the action mechanism of trigger factors in migraine. We have focused our research on three trigger factors; mental stress, normobaric hypoxia and nitroglycerin. The most remarkable findings will be summarized and discussed.

Premonitory symptoms are frequently reported by migraine patients in a clinic based sample (chapter 1)

In a clinic based sample of 374 migraine patients we found that 86.9% of patients reported at least one symptom and 71.1% reported two or more. Forty-nine patients (13.1%) reported no premonitory symptoms. Other clinic based studies found prevalence rates for premonitory symptoms of 79%[133] and 84%[7], although rates of around 33% also have been found[134,135]. The most frequently reported premonitory symptoms were fatigue (46.5%), phonophobia (36.4%) and yawning (35.8%). This is in accordance with other studies assessing premonitory symptoms. In a prospective study in 100 migraine patients the most frequent symptoms were anxiety, phonophobia, irritability, unhappiness and yawing[7]. Several important questions regarding premonitory symptoms in migraine remain to be answered. For instance how specific are premonitory symptoms for migraine? Many possible premonitory symptoms are rather a-specific and are also associated with other conditions such as premenstrual syndrome[136] and depression[140]. Future studies could try to assess the occurrence of possible premonitory symptoms in combination with other migraine symptoms in a prospective design using electronic diaries in an unselected migraine population[131].

The association between mental stress and the occurrence of a migraine attack is less clear than previously assumed (chapter 2)

In chapter 2 we described findings of a prospective longitudinal study. We failed to find any objective evidence for a temporal relationship between changes in perceived stress, biological indicators for a stress-response, and the onset of a migraine attack. Although stress-sensitive patients indeed reported an increase in perceived stress in the days before an attack, this was not accompanied by objective signs indicating a biological stress response. These findings are in accordance with previous stress studies. Retrospective and prospective questionnaire studies suggest an increase in the perception of potential stressors around the migraine attack[27,42]. On the other hand stress provocation studies including biological stress response measures during and outside a migraine attack are either negative or not conclusive[141]. Furthermore, there is also no association between migraine and major life stressors[251]. Possibly mental stress is not a trigger factor for migraine but do migraine patients perceive daily hassles as

stressful due to the development of a migraine attack. The lack of a biological stress response (eg cortisol) in patients who perceived more stress could be the result of the temporal resolution of our measurements as discussed in chapter 2. Future studies will have to answer the question whether mental stress is a trigger factor for migraine or not. An option could be to design an experimental provocation study using a mental stressor sufficient enough to trigger migraine attacks.

Normobaric hypoxia is a possible trigger factor for migraine (chapter 3)

A high altitude environment causes acute mountain sickness in healthy volunteers [97] and might be able to trigger migraine in susceptible patients[126], mainly through hypoxia, although an additional effect of hypobaria can not be excluded[179]. Several symptoms in acute mountain sickness are comparable to migraine including headache, nausea, fluid retention and disturbance of sleep[97] and as we have shown in chapter 3 normobaric hypoxia triggered a migraine attack in 6 out of 14 migraine patients. The results for hypoxia were not significant but in the light of a very low response after the positive control nitroglycerin it could be that the studied population was not very susceptible for migraine. Combined with previous studies in mountaineers[99] it was concluded that hypoxia is a possible trigger factor for migraine. For the dutch migraine population there are no direct consequenses of this finding, since the highest mountain in the Netherlands is only 321 meters. Airflights might cause a problem; current regulations require that cabin air pressure must be no lower than the air pressure that naturally occurs at 2400 meter. In our experiments subjects were exposed to hypoxia corresponding to 4500m. Whether 2400m would be enough to trigger migraine is unclear.

The migraine response after NTG infusion is variable ranging between 20% and 83% (chapter 3 and 6)

The migraine response after infusion of a nitric oxide donor ranges from 20% to 83% between studies. The reason for the observed variability is unclear. A low baseline attack frequency could be a likely explanation. A study comparing the migraine response in patients with <4 attacks per year with patients 12 attack per year showed a trend towards more migraine attacks in frequent sufferers.[252] The second explanation could be the occurence of aura's. Two studies found a lower migraine response in patients with aura; 67% MA vs 83% MO[56] and 31.8% MA vs 78% MO[55]. A third factor could be age. In the three studies with the lowest migraine response the mean age is rather low ranging from 29.1[126] to 34.3 years.[123,129] Also in our second NTG study in migraine patients the mean age in non-responders was 34 year whereas the mean age in responders was 45.5 year (chapter 6). Whether there are other factors involved in migraine susceptibility for NTG is unclear.

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Normobaric hypoxia causes cerebral edema in healthy volunteers (chapter 4)

Research in acute mountain sickness has mainly focused on the development of cerebral edema. Severe AMS is associated with high altitude cerebral edema[104]; whether edema also occurs in mild cases of AMS was unclear. In chapter 4 we have shown that hypoxia caused vasogenic edema in healthy volunteers irrespective of AMS symptoms and that cytotoxic edema might be associated with severe AMS. Our findings are in accordance with other studies which have been published while our study was drafted[167]. These findings in AMS might have implications for migraine. Approximately 30% of healthy climbers develop AMS at 3000m altitude[97]. Whether migraine patients are more susceptible for AMS is unclear. One of the mechanisms involved in the development of vasogenic and/or cytotoxic edema is Na(+)-K(+)-ATPase[190]. A mutation in the Na(+)-K(+)-ATPase gene was found in familial hemiplegic migraine[253], possibly causing blood brain barrier disruption and cerebral edema[254]. Future studies in migraine using hypoxia as a trigger will have to show whether cerebral edema is involved in the pathophysiology of the common types of migraine.

Nitroglycerin induced vasodilatation in both healthy volunteers and migraine patients (chapter 5 and 7) can be measured reliably with MRA

Nitroglycerin is an exogenous donor of nitric oxide[255] and causes vasodilatation either through relaxation of vascular smooth muscles or through the release of CGRP[114]. A common technique to measure the diameter of cerebral blood vessels in vivo in humans is using trans-cranial Doppler. The advantages of TCD are that it is a continuous, cheap and non-invasive measurement, however, the outcome is operator dependent and TCD is an indirect measurement of the blood vessel diameter since it measures blood flow velocity[237]. To study blood flow diameters in migraine patients the aim was to have a direct and non-invasive method which would enable us to study blood vessel as small as the middle meningeal artery. Using magnetic resonance we have been able to reliably measure blood vessel diameters as shown in chapter 5 and 6. MRA images were measured by two independent observers and the agreement between observers was 0.74 (an intra class correlation of 0.7 or more is considered acceptable).The MMA diameter increase during NTG in healthy volunteers in chapter 5 was 20.1%, whereas the diameter increase in an other sample of healthy volunteers in chapter 6 was 19.9%.

The blood flow response but not vasodilatory response to nitroglycerin in migraine is related to the development of a delayed migraine attack (chapter 6)

Nitroglycerin caused a decrease in ICA blood flow without affecting BA blood flow. The ICA blood flow decreased significantly more in healthy volunteers as compared to migraine patients. Previous NTG studies in migraine showed either no difference in blood velocity decrease in the middle cerebral artery between migraine and controls[118], or a more pronounced decrease in migraine patients[117]. An explanation for the difference in results could be that these studies did not take into account the occurrence of a provoked attack. As shown in this study the patients without an attack (several hours after NTG infusion) showed a decrease in ICA blood flow similar to healthy volunteers whereas in patients with an attack ICA blood flow did not decrease. Blood flow in the ICA is affected by several parameters; i) ICA blood vessel diameter, ii) cardiac output and iii) vasomotor tone in small resistance vessels. The ICA diameter increased during NTG infusion, but there was no difference between groups. Nitroglycerin has shown to decrease cardiac output[216]. In this study we did not measured cardiac output but we did not observe a difference in blood pressure response during NTG infusion between groups (data not shown), suggesting that there was no difference in decrease of cardiac output between groups. So a difference in vasomotor tone of small resistance vessels might be the main explanation for the observed difference between patients with and without an attack.

There is no vasodilatation during the headache phase of a nitroglycerin provoked migraine attack (chapter 7)

This is the most important conclusion in this thesis. For many years there has been debate concerning vasodilatation in meningeal and cerebral arteries during the headache phase of a migraine attack. Studies by Wolff et al. showed that stimulation of cerebral and meningeal arteries caused headache and it was suggested that vasodilatation of cranial blood vessels was the cause for headache during a migraine attack[198]. Vasoactive substances such as nitroglycerin can trigger migraine in susceptible patients[78] and triptans might exert their anti-migraine effect through vasocontriction of cranial blood vessels[75]. However, in vivo measurements in humans using transcranial Doppler (TCD) are not conclusive[204,226,227,243-246]. In chapter 7 we have shown that there is no vasodilatation or change in cerebral blood flow during the headache phase of a provoked migraine attack as a model for spontaneous attacks. This finding does imply that future anti-migraine drugs do not have to constrict cerebral or meningeal blood vessels to treat the headache during a migraine attack.

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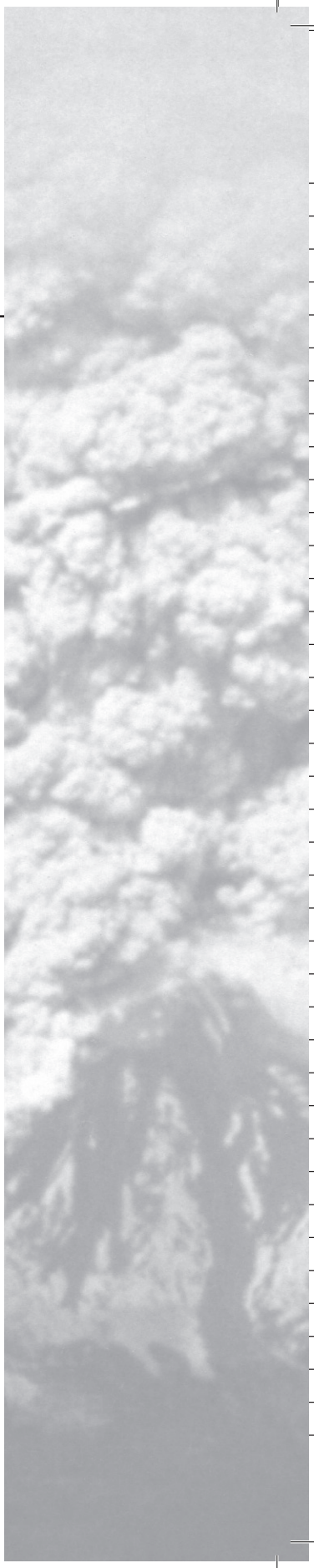
Conclusions and future perspectives

Based on the studies presented in this thesis several conclusions can be drawn. The most important conclusion is that there is no vasodilatation of cranial arteries during the headache phase of a migraine attack. Future drug development research should focus on non-vascular structures to treat migraine headache. The second conclusion is that there is no clear association between mental stress and the occurrence of a migraine attack in spite of previous reports. Based on this study it does not make sense to advise migraine patients to avoid potential mental stressors as part of there therapeutic plan. The discrepancy between objective and subjective stress measures needs further study. The third conclusion is that hypoxia might trigger migraine in susceptible patients through a process which may involve development of cerebral edema. This conclusion is rather speculative and needs more study in migraine patients using hypoxia as an experimental trigger factor.

SAMENVATTING EN CONCLUSIES



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In dit proefschrift wordt de relatie tussen mogelijke uitlokkende factoren en een migraine aanval beschreven als mede het werkingsmechanisme van uitlokkende factoren. Er is met name gekeken naar drie factoren: mentale stress, normobare hypoxie en nitroglycerine. De belangrijkste bevindingen zullen hierna samengevat en bediscussieerd worden.

Migraine (introductie)

In het eerste deel van dit proefschrift worden de klinische verschijnselen van migraine besproken evenals het mechanisme onderliggend aan een migraine aanval. Migraine is een neurologische aandoening waarbij hoofdpijn in aanvallen optreedt. Deze aanvallen duren 4 uur tot 3 dagen. De hoofdpijn is vaak eenzijdig, bonzend en neemt toe bij bewegen. Tevens treedt er misselijkheid, overgeven en overgevoeligheid voor licht, geluid en geuren op. Voorafgaand aan de hoofdpijnfase noemen veel patiënten het optreden van zogenaamde prodromale verschijnselen, zoals concentratie problemen, vocht vasthouden en stemmingsproblemen.

De aanvalsfrequentie kan uiteenlopen van 1 migraineaanval per jaar tot meerdere aanvallen per maand. Ondanks vele jaren van onderzoek weet men niet waardoor migraine aanvallen ontstaan. In de literatuur worden veel mogelijke uitlokkende factoren genoemd, zoals verschillende voedingsproducten, veranderingen in het weer, stress verhogende situaties en vrouwelijke hormonen. Of er inderdaad een causaal verband is tussen de mogelijke uitlokkende factoren en het optreden van een migraine aanval is onduidelijk. Tevens is het mechanisme leidend tot een migraine aanval voor een groot deel onbekend. Tijdens de hoofdpijnfase van een migraineaanval raakt de vijfde hersenzenuw geactiveerd, maar wat hieraan voorafgaat, is niet duidelijk. Mogelijk speelt vaatverwijding van hersenbloedvaten een rol. Een ander mogelijk mechanisme is een tijdelijk defect in de bloed-hersen barrière waardoor uitlopers van de vijfde hersenzenuw geprikkeld worden.

Prodromale verschijnselen worden frequent gemeld door migraine patiënten (hoofdstuk 1)

In een populatie van 389 migraine patiënten is gekeken naar het voorkomen van prodromale verschijnselen. Dit zijn verschijnselen die optreden voorafgaand aan de hoofdpijnfase van een migraine aanval. De meest genoemde verschijnselen waren vermoeidheid (46.5%), lichtschuwheid (36.4%) en gapen (35.8%). Het bleek dat 86.9% van de patiënten tenminste 1 prodromaal verschijnsel noemden en 71.1% noemde er twee of meer. De bevindingen komen overeen met resultaten uit eerdere studies. Enkele belangrijke vragen blijven echter onopgelost. Het is bijvoorbeeld onduidelijk hoe specifiek prodromale verschijnselen zijn voor het optreden van een migraine aanval. Er

bestaat bijvoorbeeld een aanzienlijke overlap tussen prodromale verschijnselen en het premenstrueel syndroom en depressiviteit. Goede prospectieve studies zijn nodig om de sensitiviteit en specificiteit van prodromale verschijnselen voor een migraine aanval te bepalen.

De relatie tussen mentale stress en het optreden van een migraine aanval is minder duidelijk dan voorheen aangenomen (hoofdstuk 2)

In hoofdstuk 2 worden de bevindingen van een prospectieve longitudinale studie naar de relatie tussen mentale stress en migraine beschreven. Ondanks aanwijzingen in de literatuur dat er een duidelijke relatie bestaat tussen stress en migraine liet deze studie geen duidelijk verband zien tussen veranderingen in subjectieve en objectieve stress parameters en het optreden van een migraine aanval. In een subgroep van subjectief stress gevoelige patiënten was er wel een relatie tussen waargenomen stress en het optreden van een migraine aanval, maar dit ging niet gepaard met veranderingen in objectieve stress maten, zoals cortisol. Wellicht is het zo dat er wel een relatie is tussen waargenomen stress en migraine, maar dat stress de aanval niet uitlokt. Het zou kunnen zijn dat migraine patiënten vlak voor een aanval gevoelig zijn voor stress omdat ze in de aanloop van een aanval zitten.

Normobare hypoxie is een mogelijke uitlokkende factor voor migraine (hoofdstuk 3)

Verblijf op grote hoogte in de bergen kan leiden tot hoogteziekte in gezonde vrijwilligers en kan eventueel een migraine aanval uitlokken in migraine gevoelige patiënten. Het meest belangrijke mechanisme is de hypoxie (te weinig zuurstof). Verschillende hoogteziekte symptomen kunnen ook tijdens een migraineaanval optreden zoals hoofdpijn, misselijkheid en slaapproblemen. In hoofdstuk 3 is beschreven hoe blootstelling aan hypoxie (vergelijkbaar met een hoogte van 4500m) gedurende 5 uur een migraine aanval provoceerde in 6 van de 14 migraine patiënten. Hoewel het resultaat niet significant is, lijkt het erop dat hypoxie een mogelijke uitlokkende factor is voor migraine. In Nederland is hypoxie geen belangrijke factor omdat we geen bergen van betekenis hebben, maar hypoxie tijdens een vliegreis zou een migraine aanval kunnen uitlokken. Officiële regels stellen dat de luchtdruk aan boord van een vliegtuig minimaal vergelijkbaar moet zijn met 2400 meter.

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Normobare hypoxie veroorzaakt cerebraal oedeem in gezonde vrijwilligers (hoofdstuk 4)

Onderzoek naar de pathofysiologie van hoogteziekte laat zien dat er tijdens ernstige hoogteziekte cerebraal oedeem ontstaat. Of er tijdens milde hoogteziekte ook oedeem ontstaat niet duidelijk. Om meer over de effecten van hypoxie op de hersenen te weten te komen is een groep studenten bloot gesteld aan een experimenteel model voor hoogteziekte waarbij ze gedurende 6 uur hypoxisch gemaakt werden. De hypoxie tijdens het experiment was vergelijkbaar met een hoogte van 4500m. Zoals beschreven in hoofdstuk vier blijkt er zogenaamd vasogeen oedeem (vocht rondom de cellen) op te treden na hypoxie; onafhankelijk van het optreden van hoogteziekte symptomen. Voorts treedt er cytotoxisch oedeem (vocht in de cellen) op in de groep met de meeste klachten. De bevindingen in de gezonde vrijwilligers hebben mogelijk implicaties voor migraine. Een van de mechanismen betrokken bij de ontwikkeling van cerebraal oedeem is het Na-K-ATP ase dat weer een rol speelt in familiare hemiplegische migraine (type 2).

De kans op het krijgen van een migraine aanval na toediening van nitroglycerine ligt tussen 20% en 83% (hoofdstuk 3 en 6)

Nitroglycerine is een bekende uitlokkende factor voor migraine. In twee verschillende studies is gebruik gemaakt van nitroglycerine (NTG) voor het uitlokken van migraine aanvallen (hoofdstuk 3 en 6). In de eerste studie was het percentage patiënten dat een aanval kreeg na NTG 20% en in de tweede studie was dit 74%. In de literatuur zijn er zelfs percentages tot 83% beschreven. De oorzaak voor deze variatie in het effect van nitroglycerine is niet goed te geven. Een eerste mogelijke verklaring zou een lage basale aanvalsfrequentie kunnen zijn. In een Deense studie is het effect van NTG vergeleken tussen patiënten met een lage aanvalsfrequentie (minder dan 4 aanvallen per jaar) en een hoge aanvalsfrequentie (meer dan 12 aanvallen per jaar). Deze studie liet een trend zien in de richting van meer aanvallen in de groep met veel aanvallen. Een tweede verklaring zou het wel of niet optreden van visuele aura's kunnen zijn. Er zijn verschillende studies waarin de kans op een migraine aanval na NTG kleiner is in patiënten die last van hebben van aura's. Een derde factor zou leeftijd kunnen zijn. In de tweede studie is de leeftijd in de groep die geen aanval krijgt gemiddeld 34 jaar, terwijl de leeftijd in de groep waarin wel een aanval optreedt gemiddeld 45.5 jaar is.

Nitroglycerine geïnduceerde vaatverwijding kan betrouwbaar gemeten worden met behulp van magnetic resonance angiografie (MRA) in zowel gezonde vrijwilligers als migraine patiënten (hoofdstuk 5 en 7)

Nitroglycerine veroorzaakt vaatverwijding in zowel veneuze als arteriële bloedvaten. Een veelgebruikte techniek om vaatverwijding in het hoofd te meten is zogenaamde transcraniele Doppler (TCD) waarbij er met geluidsgolven informatie over de bloedstroom in een bloedvat verkregen wordt. TCD is een goedkope en niet invasieve methode, echter de uitkomst van de meting is afhankelijk van de persoon die de meting doet. In verband met deze beperkingen hebben we gekozen om bloedvatdiameters te meten door middel van MRA. Alvorens het onderzoek in migraine patiënten uit te voeren is bij gezonde vrijwilligers naar de betrouwbaarheid van de MRA meting gekeken. Zoals besproken in hoofdstuk 5 is er een hoge correlatie (0.74) tussen twee onafhankelijke waarnemers, zodat de conclusie getrokken kan worden dat MRA een betrouwbare methode is.

De verandering in bloedstroom, in tegenstelling tot de verandering in bloedvat diameter, tijdens toediening van nitroglycerine is geassocieerd met het optreden van een migraine aanval (hoofdstuk 6)

In hoofdstuk zes is gekeken naar het effect van nitroglycerine op cerebrale bloedvaten (zowel diameter als bloedstroom) in gezonde vrijwilligers en in migraine patiënten. Het bleek dat nitroglycerine een forse vaatverwijding in alle gemeten bloedvaten gaf. Er was geen verschil in vaatverwijdend effect tussen migraine patiënten en vrijwilligers. Daarnaast daalde de bloedstroom in de arteria carotis interna (ICA) en bleef de bloedstroom in de arteria basilaris (BA) gelijk. In gezonde vrijwilligers daalde de bloedstroom veel sterker dan in migraine patiënten. Deze bevinding is in contrast met eerdere studies waarin de bloedstroom niet veranderde of juist meer veranderde in migraine patiënten. Een oorzaak voor het verschil zou kunnen zijn dat in eerdere studies geen onderscheid is gemaakt tussen patiënten met of zonder migraine aanval volgend op de NTG provocatie. Het bleek namelijk dat de ICA in patiënten zonder een migraine aanval sterk daalde (vergelijkbaar met gezonde vrijwilligers), terwijl de ICA bloedstroom in patiënten met een aanval zelf mild toenam. Bloedstroom in de ICA wordt bepaald door de ICA diameter, cardiac output en vasomotor tone in kleine weerstandsvaten. De diameter van de ICA nam toe, maar er was geen verschil tussen patiënten met of zonder aanval. Van nitroglycerine is bekend dat het hartminuut volume daalt kort na toediening, maar in deze studie is geen verschil gevonden in verandering in bloeddruk tussen patiënten met en zonder een migraine aanval. Dan blijft een mogelijk verschil in vasomotor tone in kleine weerstandsvaten over als verklaring voor het verschil.

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Er treedt geen vaatverwijding op in cerebrale bloedvaten tijdens de hoofdpijnfase van een door nitroglycerine geïnduceerde migraine aanval (hoofdstuk 7)

Er wordt reeds vele jaren gediscussieerd over de relatie tussen vaatverwijding in hersenvaten en migraine. Wolff et al. liet zien dat stimulatie van bloedvaten in de hersenen en hersenvliezen erg pijngevoelig zijn. Voorts kunnen migraine aanvallen uitgelokt worden door vasoactieve middelen zoals nitroglycerine. Echter, studies met transcraniele Doppler, om vaatverwijding tijdens de hoofdpijn fase aan te tonen zijn niet eenduidig. De conclusie van hoofdstuk zeven is dat tijdens de hoofdpijnfase van een door nitroglycerine uitgelokte migraineaanval geen vaatverwijding optreedt. Een implicatie van deze bevinding zou kunnen zijn dat antimigraine middelen in de toekomst geen vaatvernauwend effect hoeven te hebben.

Conclusies en toekomstperspectieven

Gebaseerd op de bevindingen gepresenteerd in dit proefschrift kunnen er verschillende conclusies getrokken worden. De meest belangrijke is dat er geen vaatverwijding van hersenbloedvaten optreedt tijdens de hoofdpijnfase van een migraineaanval. Bij de ontwikkeling van nieuwe antimigraine middelen dient men zich te focussen op non vasculaire mechanismen. De tweede conclusie is dat er geen duidelijke relatie is tussen het optreden van mentale stress en het ontstaan van een migraine aanval. Het advies aan patiënten om stressvolle situaties te vermijden lijkt dan ook geen zinvol advies. De derde conclusie is dat hypoxie, zoals dit voorkomt in het hooggebergte, mogelijk een uitlokkende factor is voor migraine mogelijk via de ontwikkeling van cerebraal oedeem. Deze conclusie is echter behoorlijk speculatief en dient verder bestudeerd te worden.

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Curriculum vitae

Geurt Gerhard Schoonman (roepnaam: Guus) werd geboren op 14 oktober 1974 in Deventer. Hij behaalde in 1993 zijn VWO diploma aan het Baudartius College te Zuthpen. Het doctoraalexamen Geneeskunde behaalde hij in 1998 aan de Universiteit Leiden. De wetenschappelijke stage (titel: "Decompression sickness and pyramidal tract demyelinisation in rats") werd gelopen aan de Universiteit van Kopenhagen (supervisor: dr. M. Ballegaard). Daarnaast heeft hij tussen 1994 en 1998 psychologie gestudeerd aan de Universiteit Leiden. De co-schappen in het Academisch Ziekenhuis Leiden (AZL, nu Leids Universitair Medisch Centrum, LUMC) sloot hij af met het artsexamen in 2000. Gedurende 6 jaar was hij arts-onderzoeker in het LUMC onder begeleiding van Prof. Dr. M.D. Ferrari. In 2002 was hij 6 maanden in Zwitserland voor wetenschappelijk onderzoek naar de relatie tussen hypoxie en migraine aan de Universiteit van Zurich (supervisor: Prof. Dr. R.W. Baumgartner). Naast wetenschappelijk onderzoeker was hij voorzitter van de Trainees and Residents subcommittee van de International Headache Society en bestuurslid van de vereniging voor arts-onderzoekers in het LUMC. In 2007 startte hij als arts-assistent neurologie in het Diaconnessenhuis te Leiden. Momenteel is hij wederom werkzaam in het LUMC als arts-assistent in opleiding tot neuroloog (opleider: Prof. Dr. R.A.C. Roos).