

# Normobaric hypoxia and nitroglycerin as trigger factors for migraine

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## Cephalalgia

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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 nitroglycerin (NTG), which has been shown to induce migraine attacks in up to 80% of migraineurs. Sixteen patients (12 females, mean age  $28.9 \pm 7.2$  years) suffering from migraine with ( $n = 8$ ) and without aura ( $n = 8$ ) underwent three 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 h after provocation onset. Fourteen patients completed all three provocations. Migraine was provoked in six (42%) patients by hypoxia, in three (21%) by NTG and in two (14%) by placebo. The differences among groups were not significant ( $P = 0.197$ ). The median time to attacks was 5 h. In conclusion, the (remarkably) low response rate to NTG is surprising in view of previous data. Further studies are required to establish fully the potency of hypoxia in triggering migraine attacks. □ *Acute mountain sickness, migraine, nitroglycerin, normobaric hypoxia, trigger factor*

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## Introduction

Migraine is a common neurovascular disorder that affects 15–20% of the population (1). 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 60–80% of migraineurs within 5–6 h (2–4). Hypoxia may also be a trigger factor for migraine. First, 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 (5). Up to one-third of subjects with acute AMS also fulfil the criteria for migraine (6–8). Second, chronic exposure to high altitude is associated with an increased migraine prevalence (9, 10). Third, sumatriptan is an established drug for the acute treatment of migraine (11), and was also shown to be effective in some studies in AMS (12, 13).

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 (MoA) aura, aged 18–65 years, with a baseline attack frequency of one to nine per 3 months in the last 6 months were recruited from the out-patient 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 judgement 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 had been taken during the previous 24 h, and that the patient did not suffer from sinusitis or coryza. The study was approved by the local ethics 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<sub>2</sub>) had to be monitored continuously. 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 were 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<sub>2</sub>) in the inspired air to obtain SaO<sub>2</sub> values of 75–80% within 20 min. During exposure to normobaric hypoxia, intravenous (i.v.) saline was administered. NTG provocation consisted of i.v. administration of 0.5 µg/kg body weight NTG within 20 min using a PVC free infusion set (Codan, the Netherlands), while the patient was breathing normal air. In placebo provocation, the participants breathed normal air during the whole provocation,

whereas only i.v. saline was administered during the first 20 min of the provocation.

### Headache response to the different provocations

Migraine symptoms according to the criteria of the International Headache Society (IHS) (7) and headache severity on a visual analogue scale (VAS) ranging from 0 to 100 were assessed every 30 min. Each provocation was terminated after 5 h, 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 reassessed 8 h 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<sub>2</sub> measurements

SaO<sub>2</sub> 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 (7) for migraine within 8 h 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 analysed 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).

Out of the 14 patients who underwent all three provocations, six patients [43%; 95% confidence

**Table 1** Patient characteristics (demographic and migraine)

Subject	Sex	Age, years	Migraine (IHS)	Migraine attacks per month	Attack positive provocations	Migraine characteristics of provoked attacks								
						HS	UH	AH	PH	N	V	PT	PN	VAS
1	F	25	MoA	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	MoA	3	Hypoxia	3	Yes	Yes	Yes	Yes	Yes	Yes	-	60
5	F	25	MoA	1	Hypoxia	3	-	Yes	Yes	Yes	-	Yes	-	65
6	M	24	MoA	2										
7	F	23	MoA	1	Hypoxia	2	-	Yes	Yes	Yes	-	-	-	49
					NTG	2	-	Yes	Yes	Yes	-	-	-	31
8	F	28	MoA	1	NTG	2	-	Yes	Yes	Yes	-	-	-	61
9*	F	42	MoA	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	MoA	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

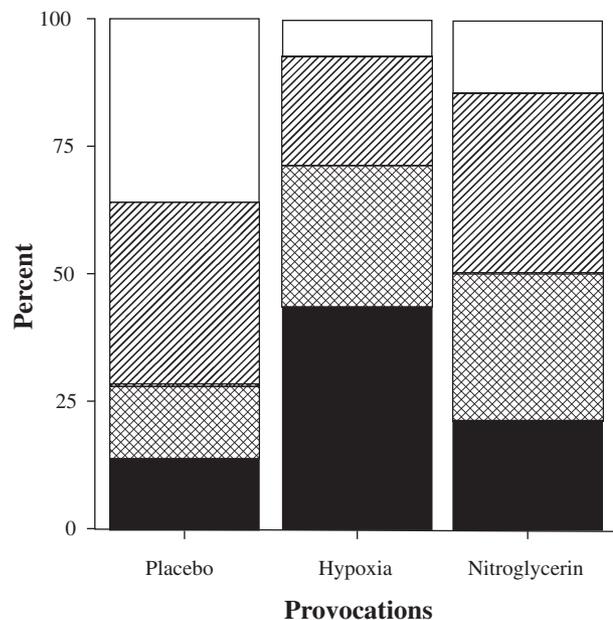
F, Female; M, male; MA, migraine with aura; MoA, migraine without aura; NTG, nitroglycerine; HS, headache severity (2 = moderate, 3 = severe); UH, unilateral headache; AH, aggravation of headache during physical activity; PH, pulsating headache; N, nausea; V, vomiting; PT, photophobia; PN, phonophobia.

\*Completed only two provocations.

interval (CI) 27, 69] developed a MoA attack during exposure to normobaric hypoxia, three patients (21%; 95% CI 0, 42) after the administration of NTG, and two patients (14%; 95% CI -4, 32) after the administration of placebo. The frequency of migraine attacks did not differ among the groups ( $P = 0.197$ ). Both patients with incomplete provocations developed a MoA 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 5 h (4 h for placebo, 4.5 h for hypoxia and 6 h for NTG).

Headache responses (Fig. 1) did not differ between groups ( $P = 0.094$ ). Both in the hypoxia and NTG groups there were four patients who developed moderate to severe headache, but did not fulfill 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 correctly, five guessed all three provocations wrong and four were correct in one



**Figure 1** Headache and migraine response to placebo, normobaric hypoxia and nitroglycerin. ■, Migraine response; cross-hatched, moderate or severe headache not fulfilling migraine criteria; hatched, mild headache; □, no headache.

provocation (two placebo and two hypoxia). Ratings were missing in one patient.

## 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% (14). However, in most other studies NTG provoked migraine attacks in 60–80% of subjects (2, 4, 14, 15). The low response in our study could have been due to differences either 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 (4), the experimental design of our study was entirely different (2, 4). 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 a migraine attack (16, 17). 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 MoA patients (2, 3, 18). 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 groups had moderate to severe headache but did not fulfil the criteria for migraine.

Normobaric hypoxia provoked a migraine attack in six out of 14 patients compared with only two after placebo and three after NTG. Although this difference between groups was not significant, the relatively high migraine response after hypoxia is remarkable and seems compatible with the results of a large study in mountaineers at high altitude. Of 1213 mountaineers, 589 developed headache within 2–6 h after arrival at 4559 m of altitude (8). 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. However, this requires further research.

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## References

- 1 Ferrari MD. Migraine. *Lancet* 1998; 351:1043–51.
- 2 Sances G, Tassorelli C, Pucci E, Ghiotto N, Sandrini G, Nappi G. Reliability of the nitroglycerin provocative test in the diagnosis of neurovascular headaches. *Cephalalgia* 2004; 24:110–9.
- 3 Afridi SK, Kaube H, Goadsby PJ. Glyceryl trinitrate triggers premonitory symptoms in migraineurs. *Pain* 2004; 110:675–80.
- 4 Thomsen LL, Kruuse C, Iversen HK, Olesen J. A nitric oxide donor (nitroglycerin) triggers genuine migraine attacks. *Eur J Neurol* 1994; 1:73–80.
- 5 Hackett PH, Roach RC. High-altitude illness. *N Engl J Med* 2001; 345:107–14.
- 6 Appenzeller O. Altitude headache. *Headache* 1972; 12:126–9.
- 7 Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 2nd edition. *Cephalalgia* 2004; 24:1–160.
- 8 Schneider M, Bernasch D, Weymann J, Bartsch P. Characteristics of high altitude headache. *High Alt Med Biol* 2002; Abstract Vth World Congress on Mountain Medicine Barcelona: 100.
- 9 Arregui A, Leon-Velarde F, Cabrera J, Paredes S, Vizcarra D, Umeres H. Migraine, polycythemia and chronic mountain sickness. *Cephalalgia* 1994; 14:339–41.
- 10 Jaillard AS, Mazetti P, Kala E. Prevalence of migraine and headache in a high-altitude town of Peru: a population-based study. *Headache* 1997; 37:95–101.
- 11 Goadsby PJ, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. *N Engl J Med* 2002; 346:257–70.
- 12 Bartsch P, Maggi S, Kleger GR, Ballmer PE, Baumgartner RW. Sumatriptan for high-altitude headache. *Lancet* 1994; 344:1445.
- 13 Burtscher M, Likar R, Nachbauer W, Schaffert W, Philadelphia M. Ibuprofen versus sumatriptan for high-altitude headache. *Lancet* 1995; 346:254–5.
- 14 Tvedskov J, Iversen H, Olesen J. A double-blind study of SB-220453 (Tonerbasat) in the glyceryltrinitrate (GTN) model of migraine. *Cephalalgia* 2004; 24:875–82.
- 15 Bellantonio P, Micieli G, Buzzi MG, Marcheselli S, Castellano AE, Rossi F, Nappi G. Haemodynamic correlates of early and delayed responses to sublingual administration of isosorbide dinitrate in migraine patients: a transcranial Doppler study. *Cephalalgia* 1997; 17:183–7.
- 16 Rasmussen BK. Migraine and tension-type headache in a general population precipitating factors, femal hormones, sleep pattern and relation to lifestyle. *Pain* 1993; 53:65–76.
- 17 Robbins L. Precipitating factors in migraine: a retrospective review of 494 patients. *Headache* 1994; 34:214–6.
- 18 Christiansen I, Thomsen LL, Daugaard D, Ulrich V, Olesen J. Glyceryl trinitrate induces attacks of migraine without aura in sufferers of migraine with aura. *Cephalalgia* 1999; 19:660–7.