Trigger factors and mechanisms in migraine

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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.

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

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.

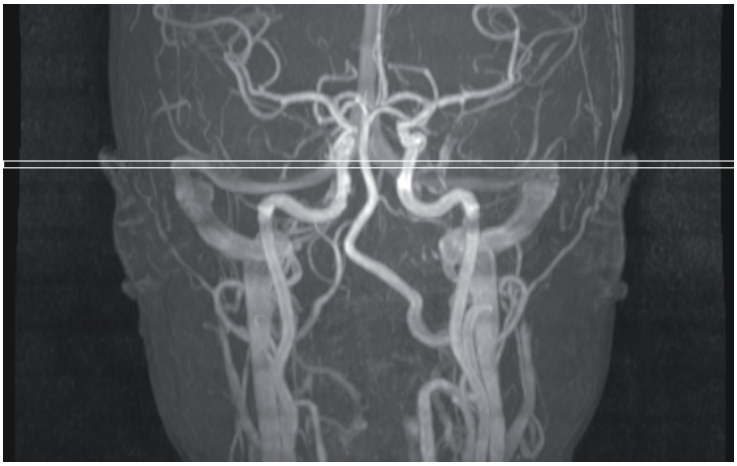

Figure 1 Magnetic resonance angiography, coronal maximum intensity projection. Horizontal line indicates the positioning of the 2-dimensional phase-contrast section through the ICA and the BA.

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

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)

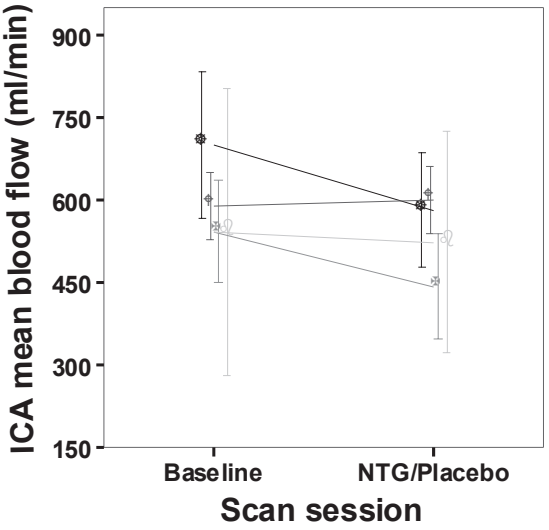

Figure 2A Blood flow in internal carotid artery at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, **X** Migraine patients (placebo) without an attack)

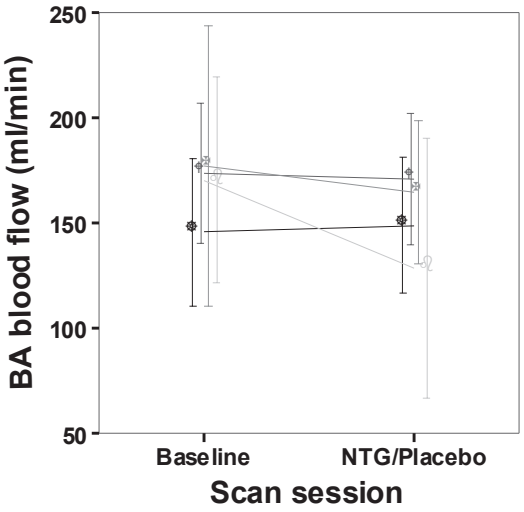

Figure 2B Blood flow in basilary artery at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, **X** Migraine patients (placebo) without an attack)

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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.

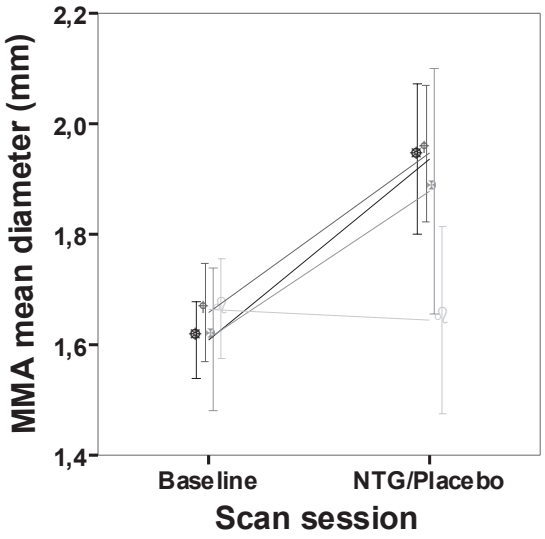

Figure 3A Blood vessel diameter of the MMA at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, X Migraine patients (placebo) without an attack)

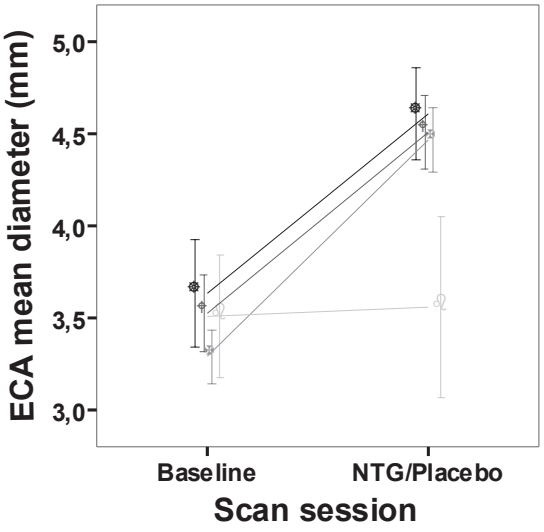

Figure 3B Blood vessel diameter of the ECA at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, X Migraine patients (placebo) without an attack)

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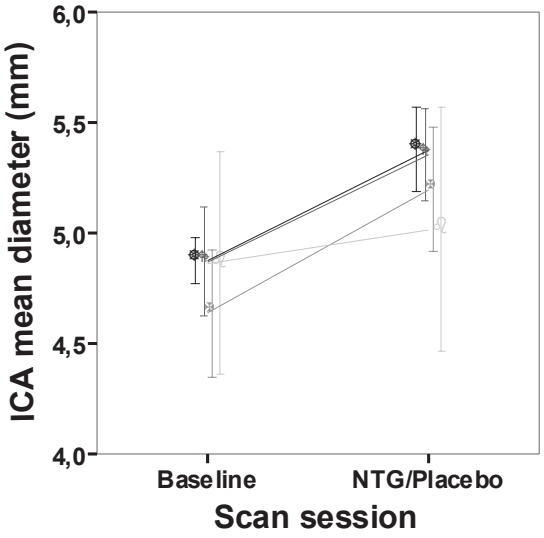

Figure 3C Blood vessel diameter of ICA at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, **X** Migraine patients (placebo) without an attack)

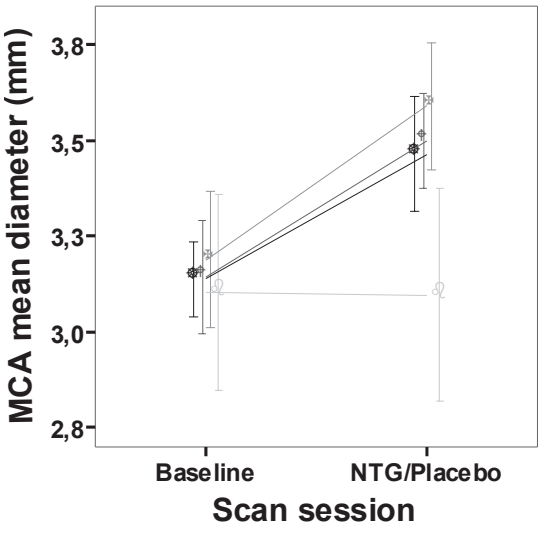

Figure 3D Blood vessel diameter of MCA at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, **X** Migraine patients (placebo) without an attack)

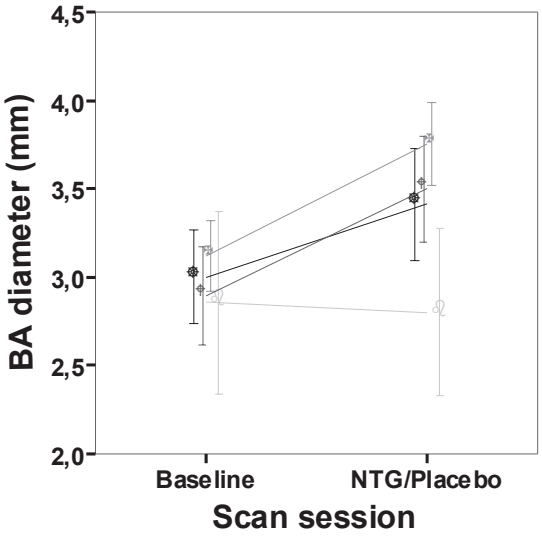

Figure 3E Blood vessel diameter of BA at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, X Migraine patients (placebo) without an attack)

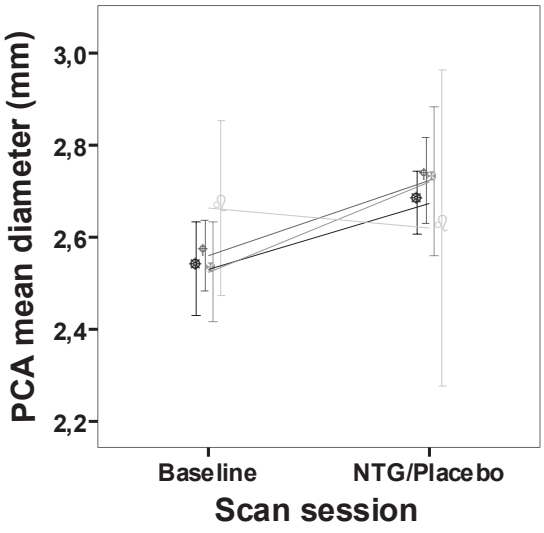

Figure 3F Blood vessel diameters in selected blood vessels at baseline and during infusion of nitroglycerin or placebo. (■ Healthy volunteers (NTG), ● Migraine patients (NTG) with a provoked attack, ▲Migraine patients (NTG) without an attack, X Migraine patients (placebo) without an attack)

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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.