Trigger factors and mechanisms in migraine

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Chapter 5

Magnetic Resonance Angiography of the Human Middle Meningeal Artery: Implications for Migraine

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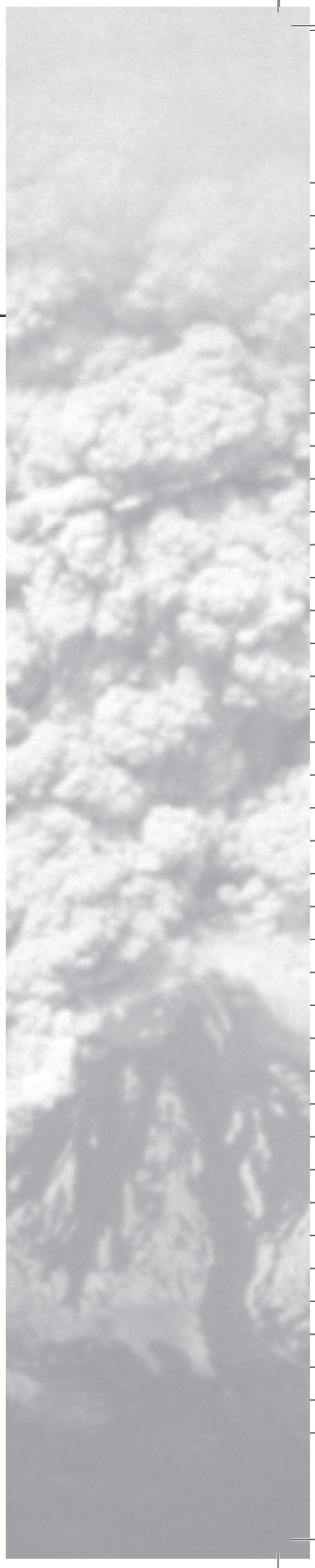

Abstract

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%).

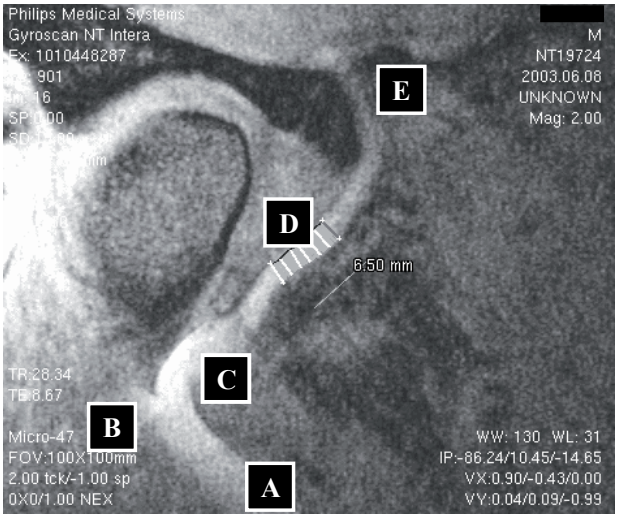

Figure 1 Anatomy of the MMA region and position of the measured segement. Explanation of letters: A= External Carotid Artery, B= Superficial Temporal Artery, C= Maxillary Artery, D= Middle Meningeal Artery, E= Foramen Spinosum

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

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].