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Transcranial Doppler measurements in migraine and nitroglycerin headache

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Abstract The objective of this study was to examine the cerebral circulation during spontaneous migraine attacks and to compare changes to an experimental headache model induced by nitroglycerin (NTG) infusion. This prospective study was carried out in a tertiary care hospital on migraineurs with or without aura. Healthy volunteers served as controls. There were no interventions. Flow velocity (FV) and pulsatility index (PI) were measured in migraineurs between and during headache attacks. In controls, FV and PI of the middle cerebral arteries were performed at baseline and after each IV infusion of 0.125, 0.25 and 0.5 μg/kg/min of NTG. In migraineurs, a significant increase in the mean flow velocity (MFV) in the left vertebral artery (VA) and the PI of the right VA during spontaneous migraine headache was found. In controls, all FV significantly decreased after infusion of NTG. The NTG model produces expected and substantially different vascular effects than those seen with spontaneous migraine headache.

Keywords Transcranial Doppler • Flow velocity • Pulsatility index • Nitroglycerin • Migraine • Headache

Introduction

Transcranial Doppler (TCD) has often been used to investigate cerebral blood flow during migraine headache. The mechanism underlying the pathogenesis of migraine is not well understood and multiple hypotheses have been proposed. Substantial data support the vascular hypothesis of migraine pathogenesis [1]. In this model, the aura phase of the migraine attack is ascribed to vasoconstriction in the intracranial vasculature, with ensuing vasodilatation thought to be the cause of the headache phase.

Past TCD studies were undertaken to determine blood flow velocity (FV) as an indirect measurement of diameters of the large intracranial arteries. These studies were largely limited to velocity measurements from middle cerebral arteries (MCA). The findings of these studies varied, with reports of increased [2,3], decreased [2,4-10] or unchanged velocities [11-13]. These discordant findings have been attributed to technical limitations of TCD; as only discrete segments of the vessel are insonated, operator dependent measurements, variability of migraine presentation, under sensitivity of limited number of vessels insonated, and limitations of the vascular hypothesis.

Recently, attention has been directed to other calculated TCD parameters such as the pulsatility index (PI), which is an index of vascular resistance. PI is a calculated

value that has been found to reflect the distensibility of the insonated vessel, and to be indicative of peripheral vascular resistance [14-16]. There is a paucity of published data on the PI in migraine.

The relative unpredictability of the onset of migraine as well as the inconvenience of transportation to study sites has made study of spontaneous migraine difficult. To address this, various experimental models have been promoted including nitroglycerin (NTG), acetazolamide, iodinated contrast material, reserpine, red wine, cold pressor challenge and mcpp [17-20]. Some models have the advantage of providing a known time of insult onset and duration of pain. As with all models, it is important to determine how much it mimics the condition of interest.

Because of its vasodilatory properties, short half-life, widespread clinical use and the ability to produce a pulsatile headache, NTG has emerged as the most widely used experimental model of migraine. Studies have shown that NTG induces regional blood flow changes in the cerebral vasculature that are similar to those seen in spontaneous migraine [21]. Additionally, the emerging role of nitric oxide (NO^-) in pain mediation may indeed make NTG an ideal model for migraine research. Moreover, it is found that NTG has more responsiveness in migraine patients compared to controls [22].

The primary objective of this study was to measure PI and FV using TCD in multiple cerebral vessels in persons with spontaneous migraine headache. The secondary objective was to compare the results of MCA insonation after NTG infusion in healthy volunteers with those observed in persons with spontaneous migraine headache.

Materials and methods

All human studies have been reviewed by the appropriate ethics committee and performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. All subjects signed informed consent prior to their inclusion in the study, underwent physical examination and electrocardiogram, and were screened with routine haematochemical lab tests. The study was approved by the human use committee.

For inclusion, patients needed to be 18–65 years of age with a minimum of one migraine attack per month (with or without aura, diagnosed according to the International Headache Society criteria) presenting within 24 h of the onset of a spontaneous migraine headache.

Patients were excluded on the bases of clinically significant cardiovascular, central nervous system or psychiatric disease. Patients who received vasoconstrictors, opiates (within 72 h of study), prophylactic migraine medications within one month or simple analgesic medications within six hours of study were excluded as well.

Nonsmoking healthy volunteers 18–45 years of age were recruited as controls. Exclusions were decided on the basis of personal or family history of migraine headache, and clinically significant cardiovascular, central nervous or psychiatric disorders.

TCD was performed using the same device in both cases and controls; however control subjects for the NTG study underwent bilateral insonation of the MCA only. Baseline measurements were obtained, and then followed by IV NTG infusions at 0.125, 0.25 and 0.5 μg/kg/min for approximately 15 min at each level. Measurements were made at the end of each dosing interval.

TCD (Neuroguard, Fremont, CA) studies were performed by the same experienced technician at the Veterans Administration Medical Center, Buffalo, NY. Blood FV was measured during a migraine headache in the right and left MCAs, right and left vertebral arteries (VAs), and the basilar artery (BA). Participants returned for the same measurements following a spontaneous headache-free interval of at least 48 h.

Gosling's PI [23] was calculated automatically by the Doppler machine using the formula: (PSV–EDV)/MV (peak systolic velocity–end diastolic velocity)/mean velocity

Statistics

Student's *t*-test was applied. The level of significance was set as α=0.05. Systat® was used for all comparisons.

Results

Ten migraineurs (four males and six females) and 12 volunteers (six males and six females) were enrolled in the respective studies. Characteristics of these populations are given in Table 1.

TCD measurements from migraineurs during the headache and the headache-free periods are listed in Table 2.

Amongst migraineurs, velocity changes were variable.

Table 1 Characteristics of migraineurs and healthy volunteers

	Migraineurs	Healthy volunteers
Number	10	12
Migraine type (with aura/without aura/both)	4/5/1	NA
Headache side R/L/bilateral	7/2/1	NA
Headache started (hours before test)*	9.5 (7.6)	NA
Age (years)*	38.9 (12.3)	27.75 (9.06)
Gender M/F	4/6	6/6
Smokers	1	0

*Mean (SD)

When compared to the headache-free measurements, a statistically significant increase in the mean flow velocities (MFV) was observed in the left VA (p=0.043). The mean velocity (MV) in the right VA increased as well, but it failed to reach statistical significance (p=0.067). Headache PI measurements changed significantly in only the right VA (p=0.019) (Tables 1 and 2).

The velocity measurements in healthy volunteers participating in the NTG study are given in Table 3. Consistent and significant decreases in velocities were observed following each dose of NTG infusion. PI measurements were unchanged significantly (Table 3).

Discussion

Consistent with many TCD studies [2-13], this study detected no significant change in FV in the MCAs in patients with migraine during the headache phase. The lack of significant FV changes during the headache phase of migraine as explored by TCD has been explained by several theories including the various technical limitations of TCD [16]. TCD is a blind procedure and due to that, the angle of insonation is not always optimal, it is operator-dependent and it measures only a short span of cardiac cycles. Also it insonates only a small segment of the vessel at any given time. Our study has a small sample size, and migraine with and without aura were mixed in the same group. A homogeneous and a much larger sample size may be needed to fully answer this question. Also, the size and calibre of the VAs in each subject in our study were not checked, a factor that could have influenced the asymmetry in TCD findings.

The two significant findings in this study were the increase in the mean blood FV in the left VA and the decrease in the PI of the right VA during the headache phase of migraine.

The decreased PI is usually an indirect indication of a decreased upstream vascular resistance, which in turn would cause an increase in mean blood FV inside the insonated segment (this was actually observed in both VAs in our study although it was not statistically significant on the right). As the above measurements took place during the headache phase of migraine, the finding may very well support the presence of a posterior cerebral circulation small vessel dilatation as a primary or secondary phenomenon during the headache phase of migraine.

The mild asymmetry in flow and the PI measurements observed over the right and left VAs in our study could very well be due to the higher frequency of right-sided headache in our migraineur group (8/2). If this is the reason, then we spec-

Table 2 TCD measurements in migraineur

	Headache free	Headache	Change
Mean velocity[a]			
RMCA	62.90 (17.86)	55.45 (14.39)	–7.45
LMCA	64.63 (15.44)	61.90 (17.73)	–2.73
RVERT	33.27 (9.98)	33.81 (6.06)	+0.54
LVERT**	35.54 (4.43)	37.81 (4.75)	+2.27
BA	40.36 (9.44)	39.09 (10.56)	–1.27
Peak velocity[a]			
RMCA	90.16 (19.0)	87.22 (20.9)	–2.94
LMCA	96.10 (17.7)	92.91 (26.5)	–3.19
RVERT	47.69 (9.8)	50.90 (10.6)	+3.21
LVERT	48.28 (5.6)	54.98 (9.5)	+6.70
BA	58.88 (12.57)	57.98 (14.5)	–0.9
PI			
RMCA	0.79 (0.1)	0.73 (0.2)	–0.06
LMCA	0.76 (0.1)	0.70 (0.1)	–0.06
RVERT*	0.74 (0.2)	0.66 (0.1)	–0.08
LVERT	0.68 (0.1)	0.67 (0.1)	–0.01
BA	0.70 (0.1)	0.69 (0.1)	–0.01

[a]cm/s, mean (SD); *p=0.017, **p=0.046

Table 3 Healthy volunteers TCD with NTG infusion

PI	Baseline	0.125 μg/kg/min	0.25 μg/kg/min	0.5 μg/kg/min
RMCA	0.71 (0.12)	0.68 (0.13)	0.67 (0.15)	0.64 (0.13)
LMCA	0.69 (0.08)	0.66 (0.06)*	0.65 (0.13)	0.64 (0.11)
Peak				
RMCA	98.83 (15.96)	82.67 (6.99)*	78.33 (12.56)*	78.58 (14.29)*
LMCA	94.58 (16.41)	80.17 (10.89)*	79.58 (8.53)*	74.92 (10.87)*
Mean				
RMCA	69.00 (12.76)	58.50 (9.77)*	54.83 (7.93)*	55.08 (8.64)*
LMCA	66.83 (12.03)	57.83 (8.31)*	56.08 (6.01)*	53 (7.25)*

*p<0.05

ulate that the medulla and/or lower pons may be involved in the genesis of migraine as both VAs usually join rostral to lower pons to form the BA and factors that affect flow after that point should result in flow changes in both VAs. Statistical analysis on patients with only right-sided headaches showed higher statistical significance of the MFV of the left VA (p=0.029). However, PI change remains insignificant. This may also be due the small number of subjects in our study.

In our previous positron emission tomography study of cerebral blood flow in migraineurs [21], we observed significant decreases in blood flow in the posterior brain region during the headache phase. This cannot be explained by the peripheral vasodilatation and increased blood FV noted in this region in this study. One possible intriguing interpretation that we can offer here is the existence of micro-arteriovenous malformations that shunt blood away from their target. The presence of arteriovenous shunts in that region in migraineurs has been documented and their role in migraine headache has been postulated [24].

Taking the significant increase in FV in the left VA alone, one can interpret this finding as vasoconstriction of the left VA that increases the blood FV without affecting PI. It is possible that vasoconstriction of the posterior circulation is the reason for some of the symptoms of the migraine aura, attack or the postdromal phase. For example, frequent migraine history has been reported in cases of VA dissections [25]; even strokes and white matter lesions in the posterior circulation distribution were found to be more common in people with migraine [26].

The triggers that caused our findings, and whether our findings are the cause or a result remain unclear. Perhaps more emphasis should be put on the posterior circulation in migraine research, especially as the posterior circulation differs in its autonomic innervation, which renders it more vulnerable to subtle changes in flow [27, 28].

All TCD findings of FVs in the experimental NTG study were in accordance with the expected vasodilatation induced by NTG. The increase in FV is an indirect indication of the generalised vasodilatation effect of NTG. These changes, however, are remarkably different to those observed in the same vessels in spontaneous migraine headache. This questions the validity of healthy volunteers receiving NTG as a migraine headache model in migraine research.

A limitation of our study may be the low sample size and that we did not differentiate between migraine with and without aura, which may have different mechanisms of action or haemodynamic effects. A larger sample size and/or a more homogeneous sample comparing only migraine with aura or migraine without aura may have led to more precise findings. Also, we did not retrospectively ask when the last migraine attack of our migraineurs occurred, a factor that may be of significance if haemodynamic effects of the migraine extended for longer than the inclusion/exclusion criteria time-after-attack required.

Conclusions

In spontaneous migraine headache, TCD measurements of FVs and PIs do not change in a manner consistent with a simple, generalised, intracranial vasodilatation. Rather, TCD measurements indicate the presence of significant asymmetrical changes in the VAs during a spontaneous migraine headache attack. The exact role of this finding needs to be further investigated.

NTG infusion induces predicted changes in TCD parameters in healthy volunteers. The changes in the cerebral blood flow following NTG infusion do not resemble those seen during the migraine headache attack.

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