Cerebrovascular reactivity during the Valsalva maneuver in migraine, tension-type headache and medication overuse headache

Thomas-Martin Wallasch, MD[a]
Peter Beckmann, MD[b]
Peter Kropp, PhD[c]

[a] MEDAS Ostschweiz, Interdisciplinary Medicine, St. Gallen, Switzerland
[b] Private General Practice, Buxtehude, Germany
[c] Institute of Medical Psychology and Medical Sociology, Medical Faculty, University of Rostock, Germany

Corresponding author: Thomas-Martin Wallasch
MEDAS Ostschweiz, Kornhausstr. 3
9000 St. Gallen, Switzerland
E-mail: tomwallasch@aol.com

Summary

The aim of this study was to investigate, by means of transcranial Doppler ultrasound (TCD), cerebrovascular reactivity during the Valsalva maneuver (VM) during the headache-free interval in patients with migraine (M), migraine plus tension-type headache (M+TTH), and migraine plus medication overuse headache (M+MOH). A total of 114 patients (n=60 M, n=38 M+TTH, n=16 M+MOH) and n=60 controls were investigated; diagnoses were made according to the International Headache Society criteria. All subjects underwent TCD monitoring and, simultaneously, non-invasive assessment of arterial blood pressure and end-tidal CO_2. Two indices were determined: the cerebrovascular Valsalva ratio (CVR) was calculated as the maximum end-diastolic flow velocity acceleration during the late straining phase of the VM [cm/s^2] and the centroperipheral Valsalva ratio (CPVR) was defined as the quotient of CVR to the concomitant arterial blood pressure acceleration [cm/mmHg x s].

The dynamic cerebrovascular autoregulatory response to the VM, measured as CVR, was increased in patients with M and M+TTH compared to age-matched healthy subjects. By contrast, CPVR (i.e. the quotient of the cerebrovascular to the peripheral autonomic response), was increased in M patients compared to healthy subjects and all other headache conditions tested.

Cerebrovascular autoregulatory response during the VM was increased in M patients compared to age-matched normal healthy subjects, indicating a disturbed autonomic control of cerebral vasoreactivity. The CPVR seems to be a sensitive parameter for distinguishing between M patients and M+TTH or M+MOH patients.

KEY WORDS: cerebral autoregulation, cerebral vasoreactivity, migraine, transcranial Doppler, Valsalva maneuver

Introduction

Data on interictal cerebral vasoreactivity in migraine are contradictory. Several complementary tests using transcranial Doppler ultrasound (TCD) have been used to evaluate the cerebrovascular autoregulatory response in migraine during the headache-free interval, testing cerebrovascular reactivity under rest conditions and using vasoconstrictor or vasodilator stimuli. The findings of these TCD studies, which focused on recordings of blood flow velocity in basal cerebral arteries, were not unequivocal. Some findings showed a moderate increase in blood flow (1-5) and others normal flow velocity patterns (6-8). Studies analyzing cerebral vasoreactivity have used different methods and stimuli, i.e. CO_2, hyperventilation, apnea, breath holding, cold pressure, handgrip, head-up tilt, cognitive/motor tasks, and intravenous injection of acetazolamide. Most vasoconstrictor stimuli studies demonstrated an increased response in the headache-free interval in migraineurs (9-13). By contrast, studies using vasodilator paradigms gave contradictory results (14-16). Furthermore, a few studies have investigated the cerebrovascular autoregulatory (CA) response in other primary headaches, but none has evaluated patients with migraine plus tension-type headache (M+TTH) or migraine plus medication overuse headache (M+MOH).

There is evidence in the literature that migraine is a chronic sympathetic nervous system disorder (17). Migraine is characterized by an excessive response of intracranial resistance vessels to metabolic stimulus. However, analysis of dynamic CA response suggests that there is a lack of autonomic control of cerebral blood flow (CBF) in migraine (18). Thus, it makes sense to evaluate migraineurs using a paradigm known to stimulate the sympathetically-mediated (CA) response.

The Valsalva maneuver (VM), with its characteristic rapid changes in arterial blood flow (or arterial blood pressure, ABP), is an excellent paradigm for testing the dynamic CA response. Liang et al. (19) using a computational model of the cardiovascular and autonomic systems, observed that the VM-induced fall in cerebral perfusion pressure during phase II of a VM leads to compensatory vasodilatation of cerebral arterioles, which might be mediated by sympathetic nerve function.

The aim of the present study was to investigate, by means of TCD, cerebrovascular and centroperipheral autonomic response during the VM in migraine and in migraine combined with other headaches (M+TTH and M+MOH).

Materials and Methods

Population

A total of 114 patients [group A: 60 with M, mean age: 35±11 years (y); group B: 38 with M+TTH, mean age: 31±8 y; group C: 16 with M+MOH, mean age 47±10 y] and a group of 60 healthy volunteers (group N, mean age: 37±12 y) were studied after giving their informed consent. Headache diagnoses were made using the criteria set out in the International Headache Society's International Classification of Headache Disorders, second edition (20). Full general physical examination and case history were performed by a senior neurologist. To be included subjects had to be normotensive (ABP ≤140/90 mmHg) and free from cardiovascular, metabolic, pulmonary and psychiatric diseases. None had used prophylactic medication during the previous three months or any medication known to affect the autonomic nervous system or cardiovascular system. The subjects were asked to avoid alcohol-, nicotine-, or caffeine-containing products for at least 12 hours prior to all examinations. All subjects underwent extracranial continuous-wave Doppler ultrasound and a baseline TCD study to rule out the presence of extra- or intracranial stenoses. The local ethics committee approved the study protocol.

Methodology for measuring dynamic cerebral autoregulation during the Valsalva maneuver

In all the subjects dynamic cerebral autoregulation during the VM was measured using the TCD methodology. During the examination, the subjects sat comfortably in a quiet room. They performed a standardized VM as described by Ewing (21): in short, they blew into a mouthpiece connected to a modified sphygmomanometer and maintained a pressure of 40 mmHg for a duration of 15 seconds. The TCD was performed as described by Aaslid (22). Two commercially available dual TCD ultrasonographic devices were used, both specifically prepared for dual-channel recordings (TC 2-64, EME, Überlingen, Germany). The middle cerebral artery (MCA) was bilaterally insonated with fixed 2 MHz pulsed Doppler probes at a depth of 45-55 mm. Simultaneously, ABP was recorded continuously and noninvasively using the Finapres system (Amsterdam, The Netherlands) (23). Additionally, end-tidal CO_2 partial pressure (pCO_2) was measured (Capnolog, Dräger, Lübeck, Germany). All curves were monitored simultaneously using an analog-digital transducer and data were stored using a personal computer with specialized software (Datenlogger, Rhothron, Homburg/Saar, Germany). For each measurement, data were sent to an SPSS-readable file. TCD examinations were performed during the headache-free interval at least 24 hours after the last migraine attack. The cerebrovascular Valsalva ratio (CVR) was defined as the maximum end diastolic flow velocity acceleration during the straining phase of the VM (phase IIb) in cm/s^2. It was calculated as follows:

$$CVR\ (cm/s^2) = CBFV_{t2}\ (cm/s) - CBFV_{t1}\ (cm/s) / t_2\text{-}t_1\ (s)$$

CVR=cerebrovascular Valsalva ratio; CBFV=cerebral blood flow velocity; t_2-t_1=time interval between measurements; s=second

The centroperipheral Valsalva ratio (CPVR) was instead defined as the quotient of CVR to the concomitant arterial blood pressure acceleration in phase IIb (cm/mmHg x s). It was calculated as follows:

$$CPVR\ (cm/mmHg \times s) = \frac{CBFV\ t_2\ (cm/s) - CBFV\ t_1\ (cm/s) / t_2\text{-}t_1\ (s)}{ABP\ t_2\ (mmHg) - ABP\ t_1\ (mmHg) / t_2\text{-}t_1\ (s)}$$

CPVR=centroperipheral Valsalva ratio; CBFV=cerebral blood flow velocity; ABP=arterial blood pressure; t_2-t_1=time interval between measurements; s=second

Statistical analysis

Parameters were analyzed to identify significant differences between groups (groups A-C) and controls. The statistical evaluation was performed using Student's t test and Whitney-U test. For all tests, the level of significance was set at $p<0.05$.

Results

The clinical characteristics of the patients are given in Table 1. There were no significant differences in age between the groups (A/N, p=0.717, n.s.; B/A, p=0.358, n.s.; C/A, p=0.230, n.s.). The results of the patients in group A (M) differed significantly from those recorded in the age-matched healthy subjects (CVR r/l = 0.001/0.001 and CPVR r/l = 0.001/0.001) and in the group B (M+TTH) patients (CVR r/l = 0.011/0.009 and

Table 1 - Demographics and clinical characteristics of patients

	M (Group A)	M+TTH (Group B)	M+MOH (Group C)
Age (years ± SD)	34 ± 11	31 ± 8	47 ± 10
Gender female (%)	83.3	84.2	87.5
male (%)	16.7	15.8	12.5
BMI (kg/m^2)	22.2	22.6	23.5
Family history of headache (%)	73.3	60.5	87.5
Migraine attacks / month ± SD	3.0 ± 2.1	2.2 ± 1.3	4.6 ± 2.8
Intake of analgesics / month ± SD	3.0 ± 3.9	8.7 ± 9.8	49.0 ± 41.0
Intake of triptans / month ± SD	2.2 ± 4.9	1.3 ± 2.9	6.4 ± 8.5

Abbreviations: M=migraine; M+TTH=migraine and tension-type headache; M+MOH=migraine and medication overuse headache.

CPVR r/l = 0.001/0.001). The results of group A (M) compared to those of group C (M+MOH) showed no significant difference in CVR, but significant differences in CPVR (r/l = 0.001/0.001) (Table 2). No correlations emerged between changes in end-tidal pCO_2 and measurements of CBFV and ABP.

Discussion

Testing cerebral vasomotor reactivity using TCD and continuous ABP recordings during the VM, which is characterized by rapid and distinct changes in ABP, seems to be an adequate method of provoking and assessing the CA response, which might be based on compensatory sympathetically-mediated vasodilatation of the small cerebral vessels (19,24-27). Additionally, vasoreactivity during the VM is not affected by end-tidal pCO_2 changes (28).

Altered cerebral vasoreactivity has been implicated in migraine. In the present study, vasomotor reactivity in patients with M was found to show characteristic flow velocity abnormalities. Therefore, we determined two indices to quantify cerebrovascular (CVR) and centroperipheral (CPVR) dynamic CA responses. CVR reflects the vasomotor reactivity of the MCA vascular territories during the late straining phase of the VM (phase IIb), while CPVR represents the quotient of the central to the peripheral autoregulatory response concomitant to the dynamic vascular changes occurring during phase IIb. Both CVR and CPVR were found to be increased in M in comparison with age-matched healthy controls. These results are in accordance with most TCD studies, which showed exaggerated interictal cerebrovascular reactivity in M (1-3,10,14,28). Our observation supports the hypothesis that M is associated with an abnormality in the mechanism of the CA response (17). Support for our theory of sympathetically-mediated hyper-responsiveness in M is provided by the observations of Micieli et al. (12), who recorded different functional noradrenergic reactivity in M compared with healthy controls using cold pressure testing. Additionally, Müller and Marziniak (18) found impaired cerebrovascular autoregulation in M using frequency analysis of the dynamic CA response.

To the best of our knowledge, this is the first study to use TCD ultrasound to investigate the dynamic CA response not only in M alone, but also in M plus other headaches. Patients suffering from M+TTH showed increased CVR and CPVR indices, although the values were significantly lower than those recorded in M. These findings suggest that patients with M+TTH might show a lack of autonomic control of CBF, as has already been suggested in patients with M (18). However, the combination of the two headache disorders might have reduced the sympathetic hyper-responsiveness. In other TCD studies, there was no evidence of altered CA response in TTH (29,30).

We failed to detect significant differences in CVR (i.e. CA response) between M and combined M+MOH. Conversely, there did emerge a significant difference in CPVR between these groups, which seems to indicate that the quotient of cerebrovascular to peripheral autoregulatory response during phase IIb of the VM is the more sensitive parameter of autonomic dysregulation. The M+MOH group patients had a higher mean age than the other study subgroups, and this difference, in particular, might explain our findings. Patients with MOH regularly present a long disease duration and it is possi-

Table 2 - Cerebrovascular Valsalva ratio (cm/s^2) and centroperipheral Valsalva ratio (cm/mmHg x s) for right(r)and left(l) side MCA measurements

	GROUP A (M) n=60		GROUP B (M+TTH) n=38		GROUP C (M+MOH) n=16		N (controls) n=60			
CVR	(r)	(l)	(r)	(l)	(r)	(l)	(r)	(l)		
	8.08 (3.22)	8.03 (3.31)	6.64 (2.78)	6.47 (2.68)	4.78 (2.80)	4.55 (2.58)	4.74 (1.64)	4.66 (1.70)	right:	A vs N: $p < .001$
										A vs B: $p < .01$
										A vs C: $p > .01$
									left:	A vs N: $p < .001$
										A vs B: $p > .05$
										A vs C: $p > .05$
CPVR	(r)	(l)	(r)	(l)	(r)	(l)	(r)	(l)		
	1.60 (0.60)	1.53 (0.46)	1.19 (0.45)	1.15 (0.83)	0.89 (0.39)	0.82 (0.30)	0.97 (0.21)	0.95 (0.22)	right:	A vs N: $p < .001$
										A vs B: $p < .001$
										A vs C: $p < .001$
									left:	A vs N: $p < .001$
										A vs B: $p < .001$
										A vs C: $p < .001$

Abbreviations: CVR=cerebrovascular Valsalva ratio; CPVR=centroperipheral Valsalva ratio; M=patients with migraine only; M+TTH=patients with migraine + tension-type headache; M+MOH=patients with migraine + medication overuse headache; N=age-matched group of normal healthy controls. Statistical tests refer to comparisons between headache groups (Student´s t-test).

ble that chronic sympathetic hyper-responsiveness might decrease over time. There are sparse data on CBFV and none on cerebrovascular reactivity evaluated with TCD in MOH patients. Savrun et al. (31) reported elevated CBFVs in the middle cerebral and basilar arteries in MOH induced by ergotamine abuse, but not in MOH caused by analgesic overuse. By contrast, Diener et al. (32) did not observe CBFV changes induced by ergotamine or sumatriptan treatment. Atasoy et al. (33) reported changes in sympathetic skin response latencies in migraine and MOH patients, which were significantly longer than those recorded in controls, but also mainly affected by comorbid psychiatric diseases, which often occur in MOH. Further studies should pay particular attention to these problematic points.

Our study has some limitations. In particular, the time from the last attack, or to the next one, might be crucial, as shown in other studies concerning headache disorders (34). In our study, recordings were made in the headache-free interval and a minimum of 24 hours had to have elapsed since the last migraine attack. Therefore we can confirm that the interval since the last attack was always more than one day. However, there was no standardization of timing of measurements during the interictal period and this circumstance might have influenced our results. In accordance with the study protocol TCD recordings during a migraine attack were excluded, as was any intake of medication.

In conclusion, the results of our study support the hypothesis of a sympathetically-mediated hyper-responsiveness in M during the headache-free interval. Several investigators using different stimuli have demonstrated, through TCD ultrasound, an elevated interictal CA response in M. Our findings are in accordance with these observations. The CPVR seems to be a suitable index for testing dynamic autoregulatory response in migrainous headaches and for distinguishing between migraineurs with and without additional headaches such as TTH and MOH. Further work is needed to clarify the autonomic and hemodynamic alterations in MOH and other headaches.

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