Pain Medicine, 21(11), 2020, 3012–3017
doi: 10.1093/pm/pnaa292
Advance Access Publication Date: 12 September 2020
Original Research Article

Transcranial Doppler Evaluation of the Cerebral Vasculature in Women Patients who Have Migraine with Aura

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Funding sources: The authors disclosed the receipt of the following financial support for the research, authorship, and/or publication of this article: IP received research grant support from the Ministry of Education, Science, and Technological Development, the Republic of Serbia (project No. III 41005), and JZT received research grant support from the Ministry of Education, Science and Technological Development, the Republic of Serbia (project No. 175022).

Conflicts of interest: No conflict.

Abstract

Background. Previous studies suggest that increased cerebrovascular reactivity might be a feature of patients who have migraine with aura (MwA). The correlation between the clinical presentation of migraine with aura and transcranial Doppler parameters remains unclear. **Objective**. The main aim of this study was to explore cerebral blood flow, vascular resistance, and cerebrovascular reactivity in women MwA. Also, the relationships between hemodynamic conditions and aura characteristics are examined. **Design**. Cross-sectional study. **Setting**. Headache Center, Neurology Clinic, Clinical Center of Serbia. **Subjects**. Fifty-four women MwA and 49 healthy controls (HCs). **Methods**. Transcranial Doppler sonography examination was used to determine blood flow mean velocity (MV) and pulsatility index (PI), as well as breath-holding index (BHI), in 15 arterial segments comprising the circle of Willis. **Results**. A total of 54 women MwA and 49 HCs were studied. The PIs of all segments of the left and right middle cerebral arteries and the left and right anterior cerebral arteries were significantly higher in MwA with regards to HCs. Also, both the left and right BHIs were significantly higher in MwA than HCs. In addition, MVs of the right vertebral artery and the first segment of the basilar artery were significantly lower in MwA than HCs. Longer duration of migraine aura showed a weak negative correlation with the PI of the left posterior cerebral artery. **Conclusions**. Our findings suggest increased vessel pulsatility, abnormal cerebrovascular reactivity, and decreased cerebral blood flow velocity in several arterial segments of the Willis circle in women MwA.

Key Words: Transcranial Doppler; Blood Flow Mean Velocity; Pulsatility Index; Cerebrovascular Reactivity; Sex Phenotype

Introduction

Migraine is considered a complex neurovascular disorder [1], combining the vascular and neural theories of migraine [2]. Brains of patients with migraine are prone to intermittent aberrant cortical activity, as they appear to be hyper-responsive [3], which could consequently lead to generation of cortical spreading depolarization followed by depression of neural activity. Recently, it was discussed that patients with migraine with aura (MwA) have a more hyper-responsive cerebral cortex compared with patients who have migraine without aura and that functional and structural differences between disease subtypes suggest at least partially different pathological mechanisms [4]. Thus, these two subtypes should be considered separate entities in future studies. Moreover, there is increasing evidence for an association between

migraine with aura and cerebrovascular disorders, including subclinical brain lesions and ischemic stroke [5]. Whether this connection is due to higher cerebrovascular reactivity in MwA or there is some other coexisting cause remains to be determined [6]. Last but not least, sex plays a critical role in the pathophysiology and clinical manifestations of migraine [7–9]. Recent studies suggest that the structural and functional networks in the brains of women and men may be affected differently in relation to migraine [10, 11]. Therefore, to understand the neurovascular pathophysiology of MwA, there is a need for a special focus on women in future studies of MwA, which will allow improvements in classification and treatment options.

Cerebrovascular reactivity and blood flow velocity in MwA have been previously examined using different methodologies, and different results were presented [12–19]. In most of these studies, the number of investigated MwA was the main limitation, besides insufficient criteria for homogenization of MwA concerning their subtypes and matching them with healthy controls (HCs) to yield reliable conclusions. In the study of Totaro et al. [12], an examination was performed on 44 MwA during the headache-free period, and it did not find a significant increase in mean flow velocity in MwA compared with HCs. The same was concluded in our previous study [19], where 100 MwA were examined and compared with 30 HCs. However, in our study, the female-to-male ratio was not equal in the MwA group, where more than two-thirds were women, compared with the HC group, where less than half were women participants, which may have compromised the conclusions. Thus, knowledge about the cerebral blood flow difference between HCs and MwA examined during the interictal phase, as well as the correlation between the clinical presentation of migraine with aura and cerebral blood flow parameters, remains insufficient, and conclusions should be further validated.

The first objective of the current study was to evaluate cerebral blood flow and vascular resistance in women MwA by measuring blood flow mean velocity (MV) and pulsatility index (PI) in 15 arterial segments comprising the circle of Willis and its major arterial branches, as well as to evaluate cerebrovascular reactivity in women MwA using the breath-holding index (BHI). The second objective was to examine the relationship of measured hemodynamic parameters in women MwA and aura characteristics.

Methods

Participants were recruited from a registry of the Headache Center at the Neurology Clinic, Clinical Center of Serbia, and diagnosed as MwA using the third edition of the International Classification of Headache Disorders (ICHD-3) criteria [20]. The inclusion criteria were as follows: 1) female sex, 2) 21 to 55 years of age, 3) episodic migraine with aura, 4) absence of migraine-preventive therapy for one year before the present transcranial Doppler (TCD) examination, and 5) no structural pathology determined by magnetic resonance imaging. Inclusion and exclusion criteria, which included a presentation of other neurological or cardiovascular diseases and motor aura symptoms, were applied to a total of 153 MwA patients who were treated in the past five years in our Headache Center. Patients with motor aura were excluded because of a proven genetic basis and pathophysiological differences from migraine with typical aura [20]. The sample size was based on the available data. However, a sample size calculation ($N = z^2xp(1 - p)/d^2$) based on a confidence level of 95% ($z = 1.96$), a margin of error ($d = 5\%$), and an estimated female population proportion ($P = 3.31\%$) showed that 50 or more participants were needed to have a confidence level of 95% for the measured values in the women MwA population. The women population proportion was calculated according to the worldwide prevalence of migraine (14.7%) [21], which was adjusted for the female-to-male ratio (3:1) and the proportion of migraine patients who have migraine aura (30%) [22]. HCs were voluntarily recruited from clinical staff or their relatives and friends. HCs were balanced with MwA with regard to sex and age. They were without chronic pain, headache symptoms, and history of neurological or metabolic disorders, nor did they have family members who suffered from a migraine. HCs were excluded if they had more than three tension-type headaches per month for two years before the present TCD examination. All participants were screened and examined by neurologists (JZT or AR) to ensure that they met the inclusion/exclusion criteria. MwA were interviewed by physicians (IP or AP) to obtain information about MwA characteristics: average duration of the aura, the frequency of the auras per year, the occurrence of somatosensory and dysphasic auras, intensity of headache pain, quality of pain (pulsating or other), localization of pain (hemi-cranial or other), associated phenomena (photo-, phono-, and osmophobia), nausea, and disease duration in years. TCD examination was performed at the Ultrasound Laboratory in the Neurology Clinic, Clinical Center of Serbia. TCD examiners were blinded to patient/control status. The Doppler instrument, RIMED Digi-Lite, a dual-channel TCD system, was used for TCD sonography and breath-holding test performance. An insonation was performed interictally, throughout the temporal acoustic bone windows according to a standard approach using 2-MHz transducers to display flow through the middle cerebral artery (MCA). Bilateral monitoring of the MCA, from a depth of 45 mm to 65 mm, was performed with each probe held in place over the temporal bone by the head frame. Cerebrovascular reactivity has been examined by a breath-holding test, based on the vasodilatation effect of hypercapnia that resulted after 30 seconds of breath-holding [23]. Blood flow mean velocities and pulsatility

Table 1. Demographic and aura features data of MwA

Demographic Data/Characteristics of the Aura	MwA (N = 54)
Years lived with migraine, mean ± SD, y	14.13 ± 11.00
Duration of the aura, mean ± SD, min	28.06 ± 21.07
Number of migraines with aura per year, mean ± SD	10.69 ± 12.19
Visual symptoms, No. (%)	54 (100)
Somatosensory symptoms, No. (%)	31 (57)
Dysphasic symptoms, No. (%)	19 (35)
Intensity of headache pain (scale 1–10), mean ± SD	8.09 ± 1.66
Pulsatile quality of pain during a headache, No. (%)	47 (87)
Occurrence of migraine without aura, No. (%)	20 (37)
Occurrence of photophobia during attack, No. (%)	41 (76)
Occurrence of phonophobia during attack, No. (%)	41 (76)
Occurrence of osmophobia during attack, No. (%)	19 (35)
Occurrence of nausea during attack, No. (%)	45 (83)
Positive family history of migraine with aura, No. (%)	25 (46)
Positive family history of cerebrovascular insult, No. (%)	7 (13)

MwA = patients who have migraine with aura.

indices were recorded before (MV1, PI1) and after (MV2, PI2) 30 seconds of breath-holding. The breath-holding index and the mean value of the BHI were calculated for each MCA using the formula BHI = (MV1 – MV2)/MV1 × 100/30, which has been explained elsewhere [19].

Also, MV and PI ([peak-systolic velocity – end-diastolic velocity]/mean flow velocity) were recorded for the first, second, and third segments of the right and left MCAs, right and left posterior and anterior cerebral arteries, right and left vertebral arteries, and first, second, and third segments of the basilar artery. Consequently, the MVs and PIs of 15 recorded points of the Willis circle were analyzed among the MwA and HC groups.

Subject demographics and migraine with aura characteristics were reported using descriptive statistics. The data were exported to the R statistics program (https://www.r-project.org/). A general linear model (GLM) analysis was used to investigate the differences in the MV, PI, and BHI between the MwA and HCs while controlling for the effect of age to avoid spurious results. The results for the GLM were corrected for multiple comparisons using the false discovery rate with Bonferroni-Holm correction ($P < 0.05$). A Spearman's *rho* correlation test was used to assess the correlations between the TCD parameters and the migraine with aura characteristics. The significance level for the Spearman's *rho* correlation test was set at 1% ($P < 0.01$).

This study was approved by the Medical Ethics Committee of the Neurology Clinic, Clinical Center of Serbia, and was conducted in accordance with the Declaration of Helsinki. Informed consent forms were completed by all the participants after receiving an explanation of the study.

Results

A total of 54 women MwA and 49 HCs were studied. They were balanced in age (36.72 ± 8.41 vs 36.88 ± 8.59, $P = 0.990$). The main demographic and clinical characteristics of MwA included in the study are shown in Table 1. The average aura duration (range) was 28.06 ± 21.07 (10–72) minutes. Of those, one patient had prolonged auras. Aura frequencies per year were highly diverse with an average value of 10.69 ± 12.19 (1–48 migraine with aura attack). All MwA patients had visual symptoms, such as flashes of bright light or zig-zag lines. Somatosensory and dysphasic symptoms during aura were reported by 57% and 35% of MwA, respectively. The occurrence of phobias during the migraine with aura attack was reported by 81% of MwA.

MVs and PIs for cerebrovascular arteries, as well as BHIs, in examined groups are presented in Table 2. Pillai's trace multivariate test, accounting for a confidence interval of 95%, showed significant differences between the groups (F (32,72) = 3.763, $P < 0.001$, partial eta^2 = 0.626) with regards to their TCD parameters but did not show a different influence of aging on TCD parameters between the groups (F (32,72) =1.144, $P = 0.313$, partial eta^2 = 0.337). After correction for multiple comparisons, the PIs of all segments of the left and right middle cerebral arteries and the left and right anterior cerebral arteries were significantly higher in MwA with regards to HCs, as it shown in the Table 2. Also, both the left and right BHIs were significantly higher in MwA with regards to HCs. In addition, MVs of the right vertebral artery and the first segment of the basilar artery were significantly lower in MwA with regards to HCs.

Longer duration of migraine aura showed a weak negative correlation with the PI of the left posterior cerebral artery (Spearman's $rho = -0.363$, $P = 0.007$). Other characteristics of the migraine with aura did not affect the TCD parameters (Supplementary Data).

Discussion

This study analyzed the difference in TCD parameters between women MwA and women HCs balanced in age.

Table 2. Comparison of the blood flow mean velocity, pulsatility index, and the breath-holding index between MwA and HCs

MV, PI, and BHI Parameters	MwA (N = 54), Mean ± SD (95% CI)	HCs (N = 49), Mean ± SD (95% CI)	Statistics, *P*
MCAR1PI	0.72 ± 0.15 (0.68–0.75)	0.64 ± 0.11 (0.60–0.68)	0.003*
MCAL1PI	0.70 ± 0.15 (0.66–0.73)	0.64 ± 0.09 (0.60–0.67)	0.012*
MCAR2PI	0.72 ± 0.14 (0.69–0.76)	0.64 ± 0.10 (0.60–0.67)	<0.001*
MCAL2PI	0.70 ± 0.15 (0.66–0.73)	0.63 ± 0.09 (0.60–0.67)	0.008*
MCAR3PI	0.75 ± 0.14 (0.72–0.78)	0.65 ± 0.11 (0.61–0.68)	<0.001*
MCAL3PI	0.72 ± 0.15 (0.68–0.75)	0.64 ± 0.10 (0.60–0.67)	0.002*
ACPRPI	0.71 ± 0.16 (0.68–0.75)	0.68 ± 0.09 (0.65–0.72)	0.210
ACPLPI	0.70 ± 0.16 (0.68–0.75)	0.66 ± 0.09 (0.63–0.70)	0.165
ACARPI	0.72 ± 0.12 (0.69–0.75)	0.63 ± 0.11 (0.59–0.66)	<0.001*
ACALPI	0.72 ± 0.12 (0.69–0.75)	0.63 ± 0.10 (0.60–0.66)	<0.001*
VARPI	0.73 ± 0.16 (0.69–0.77)	0.69 ± 0.13 (0.65–0.73)	0.171
VALPI	0.73 ± 0.15 (0.70–0.77)	0.70 ± 0.12 (0.66–0.73)	0.159
BA1PI	0.75 ± 0.17 (0.71–0.79)	0.72 ± 0.10 (0.68–0.76)	0.228
BA2PI	0.75 ± 0.16 (0.71–0.79)	0.72 ± 0.11 (0.68–0.75)	0.238
BA3PI	0.74 ± 0.14 (0.71–0.78)	0.71 ± 0.12 (0.67–0.75)	0.246
MCAR1MV	59.94 ± 10.65 (57.36–62.46)	63.87 ± 9.17 (61.30–66.50)	0.032
MCAL1MV	61.17 ± 11.43 (58.55–63.71)	62.77 ± 8.71 (60.17–65.43)	0.370
MCAR2MV	55.20 ± 10.59 (52.70–57.65)	58.60 ± 8.42 (56.10–61.15)	0.056
MCAL2MV	56.56 ± 11.79 (53.87–59.18)	57.96 ± 8.36 (55.29–60.70)	0.446
MCAR3MV	49.00 ± 9.52 (46.68–51.28)	50.25 ± 7.69 (47.93–52.61)	0.439
MCAL3MV	49.39 ± 10.54 (46.87–51.87)	49.75 ± 8.36 (47.23–52.32)	0.821
ACPRMV	34.54 ± 4.45 (33.26–35.80)	35.88 ± 5.06 (34.60–37.19)	0.140
ACPLMV	34.93 ± 5.07 (33.81–36.02)	36.60 ± 3.17 (35.48–37.74)	0.037
ACARMV	44.20 ± 7.61 (42.41–45.96)	43.79 ± 6.04 (42.00–45.62)	0.770
ACALMV	43.28 ± 7.03 (41.59–44.92)	44.13 ± 5.90 (42.46–45.85)	0.455
VARMV	34.33 ± 5.89 (32.99–35.66)	36.96 ± 3.98 (35.61–38.33)	0.007*
VALMV	35.46 ± 6.30 (34.00–36.89)	37.56 ± 4.79 (36.10–39.05)	0.043
BA1MV	38.00 ± 7.35 (36.50–39.46)	40.69 ± 3.50 (39.20–42.22)	0.012*
BA2MV	38.13 ± 7.41 (36.56–39.67)	39.23 ± 3.76 (37.66–40.83)	0.316
BA3MV	38.78 ± 7.59 (36.89–40.64)	36.71 ± 6.47 (34.81–38.64)	0.135
BHIR	1.60 ± 0.48 (1.49–1.71)	1.26 ± 0.28 (1.15–1.36)	<0.001*
BHIL	1.52 ± 0.43 (1.43–1.62)	1.23 ± 0.29 (1.14–1.33)	<0.001*

ACALMV=mean velocity of the left anterior cerebral artery; ACALPI=pulsatility index of the left anterior cerebral artery; ACARMV=mean velocity of the right anterior cerebral artery; ACARPI=pulsatility index of the right anterior cerebral artery; ACPLMV=mean velocity of the left posterior cerebral artery; ACPLPI=pulsatility index of the left posterior cerebral artery; ACPRIP=pulsatility index of the right posterior cerebral artery; ACPRMV=mean velocity of the right posterior cerebral artery; BA1MV=mean velocity of the first segment of the basilar artery; BA1PI=pulsatility index of the first segment of the basilar artery; BA2MV=mean velocity of the second segment of the basilar artery; BA2PI=pulsatility index of the second segment of the basilar artery; BA3MV=mean velocity of the third segment of the basilar artery; BA3PI=pulsatility index of the third segment of the basilar artery; BHI = breath-holding index; BHIL=breath holding index for the left cerebrovascular side; BHIR=breath holding index for the right cerebrovascular side; CI=confidence interval; HCs=healthy controls; MCAL1MV=mean velocity of the first segment of the left middle cerebral artery; MCAL1PI=pulsatility index of the first segment of the left middle cerebral artery; MCAR1MV=mean velocity of the first segment of the right middle cerebral artery; MCAR1PI=pulsatility index of the first segment of the right middle cerebral artery; MCAL2MV=mean velocity of the second segment of the left middle cerebral artery; MCAL2PI=pulsatility index of the second segment of the left middle cerebral artery; MCAR2MV=mean velocity of the second segment of the right middle cerebral artery; MCAR2PI=pulsatility index of the second segment of the right middle cerebral artery; MCAL3MV=mean velocity of the third segment of the left middle cerebral artery; MCAL3PI=pulsatility index of the third segment of the right middle cerebral artery; MCAR3MV=mean velocity of the third segment of the right middle cerebral artery; MCAR3PI=pulsatility index of the third segment of the right middle cerebral artery; MV = mean velocity; MwA=patients who have migraine with aura; PI = pulsatility index; VALMV=mean velocity of the left vertebral artery; VALPI = pulsatility index of the left vertebral artery; VARMV=mean velocity of the right vertebral artery; VARPI=pulsatility index of the right vertebral artery.

*Results that survived the Bonferroni-Holm correction.

The main strength of this study is a very detailed collection of the data about migraine with aura characteristics, which allowed a comprehensive analysis of the correlation between migraine with aura characteristics and the TCD parameters. In our TCD study, the findings revealed increased arterial stiffness as indicated by higher PI in the middle and anterior parts of the Willis circle in MwA relative to HCs. Also, abnormal cerebrovascular reactivity was noted in women MwA. MVs did not differ between MwA and HCs, except for some segments of the posterior part of the Willis circle. In addition, aura duration might be linked to the PI of the left posterior cerebral artery.

Given that migraine with aura is three times more common in women than in men [24] and that migraine is ranked as the second leading cause of the global burden of disability [25], studies that are focused on women MwA are deeply needed. Moreover, adequate design of such studies should be reflected in clear methodology and systematic data collection about migraine with aura

characteristics. In our study, the women MwA from the studied group had been suffering from migraine for an average of 14 years and had migraine auras that usually lasted for 30 minutes and occurred 10 times per year. In every migraine with aura attack, MwA had visual symptoms. Somatosensory and dysphasic symptoms were also noted in every second and third attack, respectively. In addition, the number of included patients in this study was sufficient according to the sample size calculation and GLM analysis; therefore, the conclusions of this study can be applied to the general women MwA population.

The finding that BHI is higher in MwA relative to HCs supports the literature data that increased cerebrovascular reactivity is a feature of migraine with aura [6, 18]. Moreover, the results of our previous study [19], which investigated MwA patients who are not included in this study, identified BHI as a distinguishing feature for migraine with aura relative to other types of primary headache disorders. The isolated finding of altered cerebrovascular reactivity in the absence of concomitant data on neural activity hampers a valid conclusion, but studies that have evaluated changes in cerebral blood flow together with changes in cortical activity in migraine patients suggest altered neurovascular coupling [26, 27]. Future multimodal studies that include functional magnetic resonance imaging, evoked potentials, and TCD examination performed on a clinically homogenized group of MwA may allow definitive conclusions.

The PI is used for evaluation of the peripheral resistance of blood vessels [28]. Increased PI can indicate an increased resistance in the distal area of the blood vessel, which shows that there is hypoperfusion in the given area [29]. Our results show increased PI in the middle and anterior cerebral arteries in the women MwA group, which may alter perfusion in the frontal, parietal, and temporal lobes in the interictal stage. This study also demonstrated that women MwA have decreased MVs of blood flow in the posterior cerebrovasculature when compared with HCs. This finding is contradictory to previous studies [13, 30, 31] and thus questions the increased flow velocity as a hallmark of migraine [32]. Further, our study investigated changes of MV in a well-homogenized group of women MwA relative to other studies that have investigated female and male MwA as one group, which can hamper the results [33, 34]. In addition, the inclusion of both patients who have migraine with aura and those without aura in previous studies may explain the different findings from our study [31]. Also, we did not investigate cerebrovascular reactivity in the posterior vasculature of the Willis circle; however, the decreased MVs of the basilar and right vertebral arteries in women MwA require further study of posterior cerebrovascular reactivity and its role in migraine with aura pathophysiology.

Another interesting finding in our study is that decreased PIs of the left posterior cerebral artery were linked to a longer duration of migraine aura. It is worth mentioning that alteration in the posterior cerebral artery distribution could also be associated with posterior cerebral artery territory infarcts in the women MwA [5, 16, 32, 35]. In our study, there were no MwA patients with cerebrovascular insult history or T2-hyperintense lesions shown by magnetic resonance examination. In the literature, there is no information about the influence of the PI on aura duration in MwA; therefore, the association of the change in posterior cerebral circulation and pathophysiology of migraine with aura focused on mechanisms that influence the duration of the aura will have to be determined in future studies.

The limitations of this study include the cross-sectional design, which limits conclusive inferences on changes with age. However, the strength of the study is the relatively large number of examined patients who formed a homogeneous MwA group. Also, this study is limited by the lack of comparison between male MwA and male HCs; thus our results could not be interpreted as specific to women MwA. Investigation of the male MwA would resolve this dilemma. Further, our TCD parameters are measured only interictally; therefore, a correlation between clinical features of migraine with aura and TCD parameters could not be objectivized.

Conclusions

In conclusion, we report increased PI, abnormal cerebrovascular reactivity, and decreased cerebral blood flow velocities in a few arterial segments of the Willis circle in women MwA. There may also be a link between the duration of the aura and the PI of the left posterior cerebral artery. These findings of different cerebrovascular hemodynamics in women MwA may have important implications for further understanding of the neurovascular pathophysiology of migraine with aura and its consequences.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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