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Transcranial Doppler Assessment of Cerebrovascular Reactivity in Migraine Patients

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ABSTRACT
Background: Migraine is considered as a neurovascular coupling disorder where the cerebral vascular reactivity is malfunctioning and measuring hemodynamic changes during migraine without causing more disturbances has always been a challenge. **Objective:** This study aimed to detect the role of transcranial Doppler ultrasound in assessing the vasomotor reactivity of cerebral blood vessels in migraine patients. **Patients and Methods**: This case control study included thirty-two migraine patients and thirty-two healthy individuals that were recruited from Neurology Department at Zagazig University Hospital and Neuropsychiatry Department at El-Sahel Teaching Hospital Outpatient Clinics during the period from April to December 2020. We performed Transcranial Doppler (TCD) on all participants and Breath Holding Index (BHI) was measured on both sides from the middle cerebral artery (MCA). **Results**: There was a significant decrease in breath holding index in patients of migraine. There was a statistical significance decrease in BHI and Maximum flow velocity in the left MCA (Max. FV Lt MCA) among severe patients compared to moderate patients. **Conclusion**: Migraineurs have significantly lower BHI compared to control group. The noninvasiveness of TCD and the possibility it provides for obtaining instantaneous information about cerebral blood flow changes indicates its usefulness in the study of vascular changes in different types of migraine.
Keywords: Cerebrovascular Reactivity, Migraine, Transcranial Doppler, Ultrasound.

INTRODUCTION

Migraine is a common, chronic, multifactorial neurovascular disorder typically characterized by recurrent attacks of disabling headache and autonomic nervous system dysfunction. Migraine is a painful and disabling disorder that imposes substantial burden on individual sufferers and society as a whole[1].

Multiple hypotheses have been suggested to explain the pathogenesis of migraine, yet it remains not well understood. Substantial data support the vascular hypothesis of migraine pathogenesis. The aura phase of the migraine is caused by vasoconstriction in the intracranial vessels, while vasodilatation is likely the cause of the headache phase[2]. Impulses originating from neural structures, such as the trigeminal nucleus, might lead to vascular phenomena by modifying the excitability potential of the vascular structures[3].

The evolution of the pulsed Doppler technique has resulted in TCD device which offers a non-invasive and relatively easy tool for the determination of blood flow velocities as a representation of flow in intracranial vessels[4]. Transcranial Doppler ultrasound is a sensitive real-time tool that is used for monitoring cerebral blood flow velocity. Immediate responses can be tracked using this tool, and, thus, hemodynamic changes are evaluated accordingly. Cerebrovascular reactivity can be evaluated using the breath holding test. Human brain has the ability to regulate blood flow by changing the size of its small arteries and capillaries to meet its regional oxygen and glucose needs. The amount of CO_2 accumulated as a response to cerebral blood flow changes is used to calculate the breath holding index, and the cerebrovascular response capacity is then estimated. Physiological changes in systemic perfusion pressure are compensated by cerebrovascular autoregulation. Vasomotor reactivity indicates the dilatation potential of a vessel, and it is closely related to autoregulation. In some conditions, vasomotor reactivity has the potential to keep cerebral blood flow stable, lower, or increase it[3].

This study was performed to the role of transcranial Doppler ultrasound in assessing the vasomotor reactivity of cerebral blood vessels in migraine patients.

PATIENTS AND METHODS

This case-control study was carried out in Neurology Department at Zagazig University Hospital and Neuropsychiatry Department at El-Sahel Teaching Hospital Outpatient Clinics during the period from April to December 2020. The patients studied were 32 migraine patients diagnosed according to International Classification of Headache Disorders diagnostic criteria for migraine; 9 males (28.1%) and 23 females (71.8%), with ages ranging from 18- 45 years and mean age of 29.4 years. Of those 26 patients were diagnosed with migraine without aura (81.25%) and 6 patients (18.75%) were diagnosed with migraine with aura. The control group contains 32 healthy individuals matched for age and gender; 12 males (37.5%) and 20 females (62.5%),

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with ages ranging from 18- 45 years and mean age of 30.13 years.

Ethical approval:

A prior written consent was taken from patients, or their guardians, for ethical consideration. Approval for performing this study was obtained from Ethical Committee of Institutional Research Board (IRB), Faculty of Medicine, Zagazig University. This Work was performed according to the code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: Both genders were included. Patients aging 18-45 years was included. Patients presenting with migraine with aura and migraine without aura, diagnosed according to International Classification of Headache Disorders diagnostic criteria for migraine [5].

Exclusion criteria: Patients aging below 18 or above 45 years. Patients diagnosed with other causes of primary headache, such as; Tension type headache and mixed tension–migraine headache, drug induced headache (Medication Overuse Headache), trigeminal autonomic cephalgias: Cluster headache, paroxysmal hemicrania, hemicrania continua.

Patients diagnosed with secondary causes of headache, such as; thunderclap headache, cranial Neuralgia, giant cell arteritis, increased intracranial pressure, ENT causes, and dental causes of headache, ophthalmological causes, hepatic and cardiac patients, epileptic patients, pregnant women, subjects who suffered facial burn, facial trauma, or head trauma.

The migraine patients were subjected to full history taking, general and neurological examination including ophthalmological, ENT, and dental examination to exclude other causes of headache.

For assessing the severity of headache the MIGSEV questionnaire was used: A simple severity scale with seven items identified three dimensions; the first dimension covered four items relating to the intensity of attacks (intensity of pain, tolerability, disability in activity, and presence of nausea or vomiting), the second dimension related to resistance to treatment (resistance to treatment, duration of attack), and the third to frequency of attacks. It categorizes patients in three groups of intensity: mild, moderate, and severe. HIT-6 questionnaires for migraine impact on daily activities was also used[6].

Laboratory investigations included complete blood count (CBC), kidney and liver functions, erythrocyte sedimentation rate (ESR), C-reactive protein, antinuclear antibody (ANA) if ESR was suggestive of autoimmune disease, and thyroid-stimulating hormone (TSH).

Transcranial Doppler (TCD) was performed on all participants using a Nicolet Sonara/tek, manufactured by NATUS, USA. It was performed in a quiet room with the participant in supine position. Computerized Tomography Scan (CT) and/or magnetic resonance imagination scan (MRI), and electroencephalogram (EEG) were used to exclude epileptic forms of headache.

Middle cerebral artery was examined through the transtemporal approach using a 2 MHz probe. The middle cerebral artery (MCA) depth was approximately 45–55 mm from the surface, intracranial hemodynamic parameters such as the end-diastolic velocity (EDV), the peak systolic velocity (PSV), mean cerebral blood flow velocities (MFV), the resistivity index (RI), and the pulsatility index (PI) were recorded automatically [3].

Breath holding index was measured on both sides from the MCA, with temporal window insonation, in patients with migraine during a headache-free interval and in healthy controls, using the equation: [(Vbh-V) r/Vr] × 100 s1, where Vbh is the mean MCA blood velocity at the end of breath holding, Vr is the mean MCA blood velocity at rest, and s-1 indicates per seconds of breath holding [3].

Statistical analysis

Recorded data were analyzed using the Statistical Package for the Social Sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA) (IBM Corp. Released 2013). Quantitative data were expressed as mean± standard deviation (SD) and were compared by independent t-test. Qualitative data were expressed as frequency and percentage and were compared by Chi-square (X^2) test. P-value <0.05 was considered significant.

RESULTS

Table 1 shows that there was no statistical significance difference between cases and control groups in age or sex.

Table (1): Demographic data of the 2 studied groups

Variable		Patients (n=32)		Control (n=32)		t	P
Age:	Mean ± SD Range	28.75 ± 6.19 18 - 37		30.13 ± 8.58 5 - 44		0.74	0.47
Variable		**No**	**%**	**No**	**%**	**χ^2**	**P value**
Sex:	Female Male	22 10	68.8 31.3	20 12	62.5 37.5	0.28	0.60

SD: Standard deviation t: Independent t test χ^2: Chi square test

Figure 1 shows the severity of migraine in the studied patients.

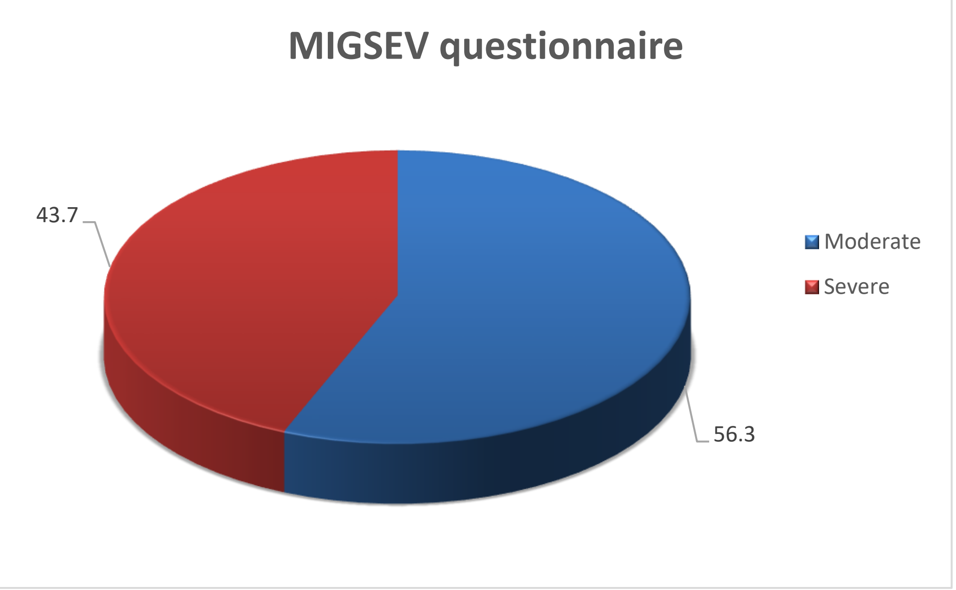

Figure (1): Severity of migraine among the patients group.

Table 2 shows the results of HIT-6 score and MIGSEV score. Regarding time 40.6% had migraine in nonspecific time.

Table (2): Clinical data of migraine among the patients group

HIT-6 questionnaire	Mean ± SD	52.59 ± 5.07	
MIGSEV questionnaire	Mean ± SD	2.44 ± 0.5	
	Variable	**No**	**%**
MIGSEV questionnaire	Moderate (grade 2)	18	56.3
	High (grade 3)	14	43.7

Table 3 shows the mean of systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and temperature.

Table (3): Examination among the patients group

Variable			**Patients (n=32)**
General	SBP (mmHg):	Mean ± SD	117.5 ± 5.68
	DBP (mmHg):	Mean ± SD	76.41 ± 4.62
	HR (beat/min):	Mean ± SD	71.88 ± 3.97
	RR (breath/min):	Mean ± SD	17.59 ± 0.76
	Temperature: (^{0})	Mean ± SD	36.98 ± 0.13

SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, HR= Heart Rate, RR= Respiratory Rate

Figure 2 shows that there was a statistical significance decrease in mean of Max. FV Lt MCA and BHI among patients compared to control group.

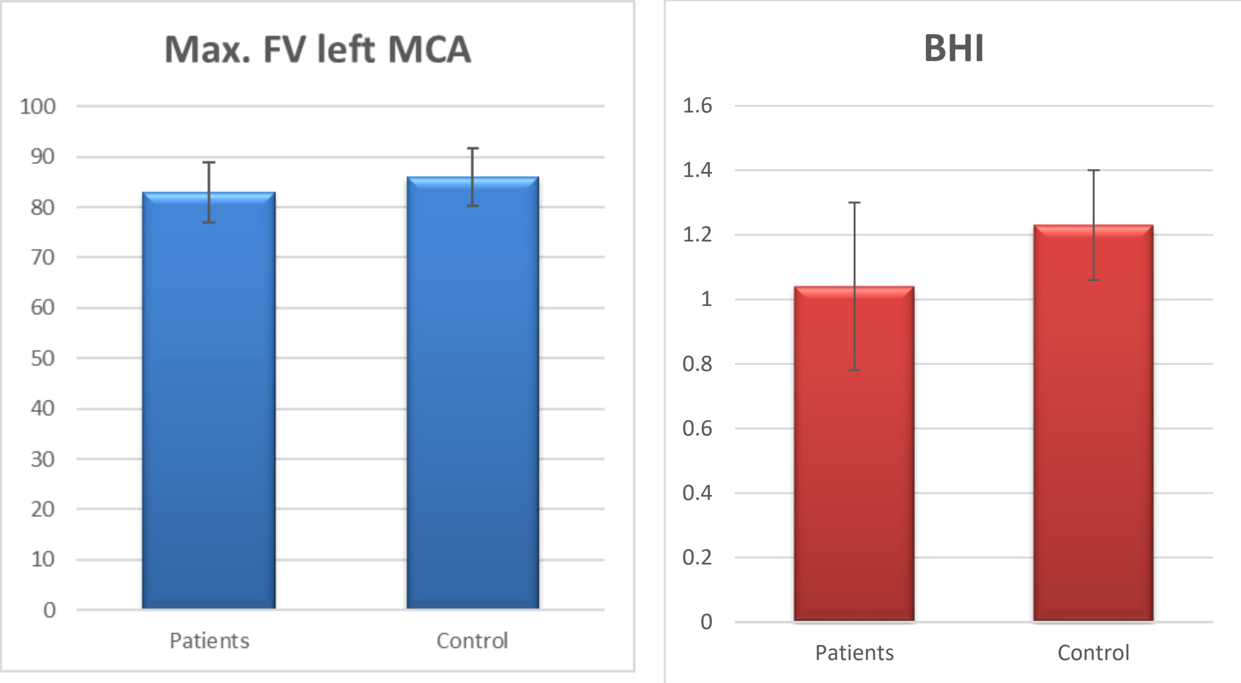

Figure (2): Transcranial Doppler, breath holding index (BHI) among the two studied groups

Figure 3 shows that there was a statistical significance positive correlation between BHI and both mean and max FV MCA in both right (Rt) and left (Lt) side and also there was a statistical significant +ve correlation between mean and max FV in both Rt and Lt side.

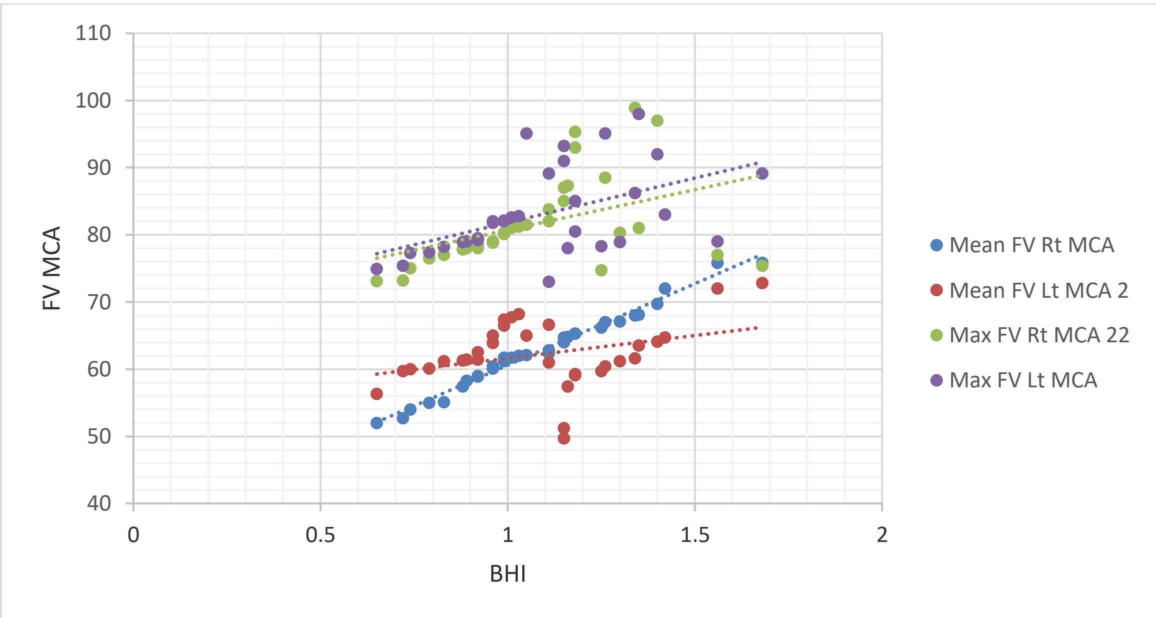

Figure (3): Correlation between TCD and BHI among cases group

Figure 4 shows that there was a statistical significance decrease in BHI and Max. FV Lt MCA among severe patients compared to moderate patients. No relation was found between TCD or BHI and other clinical data of migraine among patients group.

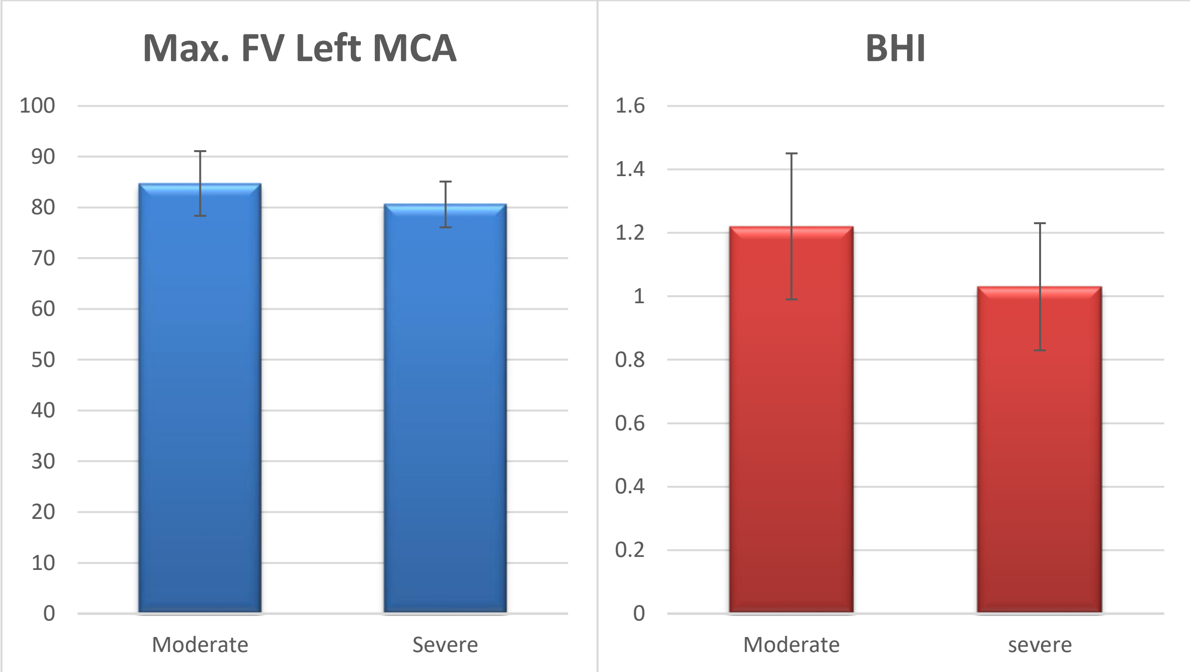

Figure (4): Relation between transcranial Doppler, breath holding index and severity among the patients group

DISCUSSION

Analysis of our findings revealed that the mean ± SD of age in case group was 28.75±6.19 years, and was 30.13 ± 8.58 years in control group, majority of participants in both groups were female, and there was no statistical significance difference between cases and control groups in age or sex distribution.

This study confirmed the female predominance in migraine; where female represent more than 50% in each group. This high female-to-male ratio was reported in several studies[7,8]**.**

In this study, the mean onset of migraine among the studied group was 22.36 years and mean duration was 10.53 years. The mean frequency was 3 times per week and regarding time 40.6% had migraine in non-specific time. While in the study of **Hsu *et al.*** [9]**,** positive family history was significantly more frequently observed in male patients, particularly in male patients without aura (50.3% vs 21.9%; P = 0.003); it was less frequently observed (58.7% vs 73.7%; P = 0.048) in female patients with aura. Family history was correlated with an earlier age at onset (20.7 years vs 22.8 years; P = 0.002), particularly in patients without aura (21 years vs 23.7 years; P = 0.002), who were women (20.9 years vs 23.9 years; P = 0.002).

In this study the mean HIT-6 score was 52.59 ± 5.07 and there was no significant correlation between BHI and HIT-6 score. This comes in accordance with the results found by **Cho *et al.*** [10]**.** Where the mean HIT-6 score was 53.4±8.7. However, these results differ from the results obtained in the study conducted by **Silvestrini *et al.*** [11] where the mean HIT-6 score was 64.6 ± 11.57. This difference could be attributed to the larger group of patients studied and the inclusion of other types of primary headache.

In this study as regards clinical examination, the mean SBP among the studied patient's group was 117.5 mmHg while mean DBP was 76.41 mmHg. Also mean HR was 71.88 beats/min, mean RR was 17.59 breath/min and mean temperature was 36.98 degree. In the control group, the mean SBP was 115.7 mmHg while mean DBP was 78.3 mmHg. Also mean HR was 68.52 beats/min, mean RR was 18.1 breath/min and mean temperature was 37.12 degree. Finally, all neurological and radiological examination was normal. This is in line with what **Silvestrini *et al.*** [11] reported, that there were no significant differences in mean blood pressure and heart rate in the baseline condition between control subjects and patients either outside or during attack. Moreover, no significant modification of the two variables occurred during the breath-holding.

The breath holding test is a non-invasive method used to evaluate cerebrovascular reactivity. The amount of CO_2 accumulated as a response to cerebral blood flow changes is used to calculate the BHI, and the cerebrovascular response capacity is then estimated[3]. Studies investigating vascular structures in migraine, cerebral blood flow, flow velocity, and flow rate showed a variety of responses to stimuli (vasoreactivity) during an attack, and in off-attack periods. Vasoreactivity is closely related to auto-regulation because the potential for veins to dilate demonstrates the tissue's potential to hold constant, increase, or decrease cerebral blood flow where necessary[13]**.**

In the present study, the mean blood flow velocities of MCA were 62.12 ± 5.17 cm/s in the migraine group and 63.34 ± 5.03 cm/s in the control group. Results revealed that there was a statistical significance decrease in mean BHI for MCA among cases (1.04 ± 0.26) compared to control group (1.23 ± 0.17) this comes in accordance with several previous studies. Furthermore, the present study revealed that there was a statistical significance positive correlation between BHI and both mean and max flow velocities MCA in both Rt and Lt side also there was a statistically significant +ve correlation between mean and max flow velocities in both Rt and Lt side. This is in line with the study of **Akgün *et al.* [3],** where the mean blood flow velocities of MCA were 58.17 ± 14.14 cm/s in the migraine group and 61.05 ± 11.74 cm/s in the control group (P = 0.229). The BHI for MCA was significantly lower in the migraine group (1.22 ± 0.47) compared to that of the control group (1.45 ± 0.57, P 0.001).

Harer and von Kummer[13] induced hypercapnia with CO_2 inhalation and showed a decrease of vasomotor reactivity in patients with migraine during the attack. **Rieke *et al.* [14]** have performed a functional TCD study on patients with migraine during the attack period (n = 30) and in the control group (n = 20). The MCA mean blood flow velocity measured at rest was higher on the side of the headache, and the vasomotor response to CO_2 was found to be lower, on the same side, in the migraine group compared to the controls. Also, **Totaro *et al.* [15]** measured the cerebrovascular reactivity by means of transcranial Doppler in 60 migraine patients with (*n* =30) or without aura (*n* =30) during the headache-free interval and in 30 healthy controls. The vasomotor response was evaluated during hypercapnia induced by inhalation of a mixture of CO_2 5% and O_2 95% and during hypocapnia obtained after voluntary hyperventilation. The data suggested a reduced vasodilatory response to hypercapnia of cerebral arterioles in patients suffering from migraine without aura with respect to controls that might be related to baseline arteriolar vasodilation.

CONCLUSION

Migraineurs have significantly lower BHI compared to control group. The noninvasiveness of TCD and the possibility it provides for obtaining instantaneous information about cerebral blood flow changes indicates its usefulness in the study of vascular changes in different types of migraine.

We recommend to conduct this study on larger sample size to fully address the multiple aspects of migraine and its impact on cerebral circulation. More studies are needed to investigate the effect of old prophylactic treatments and newer agents and their impact on vasomotor reactivity in migraine patients.

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