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Cerebral blood flow and vasomotor reactivity assessment by using transcranial Doppler among Iraqi migraineurs-case control study

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Abstract

The pathogenesis of migraine is still unknown, the hemodynamics and vascular hypothesis had been tested by many investigators using different methods including angiography, isotopes scan, PET and SPECT scans. In this study, we are assessing the use of TCD to determine cerebral blood flow and vasoreactivity response by using breath-holding test among Iraqi migraine patients. Study group included a total of 57 patients diagnosed with migraine; 42 female patients and 15 male patients, they ranged in age from 15 to 37 years. Migraine of twenty patients were accompanied with aura and thirty-seven patients had no aura. We found no significant difference in peak systolic velocity, diastolic velocity, resistive index, and pulsatility index between the study and the control groups and between the patients with and without aura. Using breath holding index, we found a significant difference between the study and the control group but no significant difference between patients with and without aura and no difference in gender. For the best of our knowledge, this is the first study that supports the role of neurovascular changes via assessment of cerebral blood flow and breath hold vasoreactivity using TCD testing.

Keywords: Transcranial doppler ultrasound; Cerebral blood flow; Breath-holding vasoreactivity

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Introduction

Migraine is a highly prevalent and largely familial disorder that affects approximately 12% of the world's population [1]. It is characterized by recurrent episodes of neurological, gastrointestinal, and autonomic symptoms, alone or in combination [2, 3]. It is commonly unilateral, often pulsatile headaches that begin in childhood, adolescence, or early adult life and recur with diminishing frequency during advancing years [1], it may occur with or without aura. Although the condition is very common in both genders, its post-pubescent prevalence is about two to three times greater among women than men [4]. It is bilateral in about 40% of adults and 60% of children [5]. The lifetime prevalence of migraine is 10-20%, depending on the case definition and on the age and sex distribution of the study population [1,6,7]. Migraine is usually hereditary, and the inheritance is polygenic, although studying the rare monogenic forms (autosomal dominant with high penetrance) may provide information about migraine in general [6,7]. After puberty, the incidence of migraine increases, and it does so more rapidly in women than in men [1,8-10]. Approximately 90% of all patients have their first attack before the age of 50 [6-8]. As a leading cause of disability [3,7], migraine has considerable impact on quality of life and it imposes a substantial burden on society. Pathogenesis of migraine is still unknown. Many hypotheses have been proposed so far; vascular, neuronal (cortical spreading depression), serotoninergic, neurogenic inflammation or trigeminovascular effects [11]. Wolff et al (1963) reported that during a migraine attack there is vasospasm followed by vascular relaxation and local vascular edema [11], Leao (1944) described that vascular elements probably associated with neuronal dysfunction in migraine patient [12]. Harold Wolff and his co-workers (1941) were the first to subject the phenomenon of vasodilation to rigorous scientific testing including intracranial vasospasm of the cerebral arteries causing the aura of migraine and extra cranial vasodilatation causing migraine pain [13, 14]. The hemodynamics and vascular hypothesis had been tested by many investigators using different methods including angiography, isotopes scan, PET and SPECT scans. Several studies used TCD (transcranial Doppler ultrasound) to evaluate the cerebral blood flow and vasoreactivity response by different tests (CO_2, hyperventilation, apnea, breath holding, cold pressure, handgrip, head-up tilt, cognitive/motor tasks, and intravenous injection

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of acetazolamide) during the headache-free interval, 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 equivocal. Some findings showed a moderate increase in blood flow [15-19] and others showed normal flow velocity patterns [20-22]. Most vasoconstrictor stimuli studies have demonstrated an increased response in the headache-free interval in migraineurs [23-27], while studies using vasodilator paradigms gave contradictory results [28, 29]. In this first-time study, we are assessing TCD cerebral blood flow and vasoreactivity response using breath-holding test among Iraqi migraine patient. The presence or absence of aura and the gender of the patient are evaluated also. Such data will help to guide interventions to reduce risks and mitigate disparities.

Materials and methods

Patients: A study group of 57 patients with diagnosis of migraine according to IHS diagnostic criteria [2] consisting of 42 female and 15 male patients, their age ranged from 15 to 37 years. Twenty patients were with aura and thirty-seven patients were without aura. Patients were recruited at the neurology clinic of Middle Euphrates Neurology Center at Al-Najaf city, during the period of April 2015 to January 2016. Control group had 42 age and gender matched clinically healthy individuals and were recruited from the general population. The study was approved by the Medical Ethics Committee at Kufa University/college of medicine. To be included in the study group, migraine patients should be headache-free for at least three days and they should be free of any chronic illness with no smoking or alcohol consumption history, and not inflicted with diabetes or being polycythemic. Other inclusion criteria included not taking contraceptive pills or being on any other medication except NSAID when needed. Patients should have normal neurological and laboratory examination. subjects were not allowed to take coffee and tea for 12 hours before the start of study, and they were not allowed to take a triptan 24 hours or ergotamine 48 hours before the study. Transcranial Doppler examination. The examination was done at TCD department/Middle Euphrates Neuroscience center in Al-Najaf city by two expert doctors in this field, one is a board-certified neurologist with 15-year experience and

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the second expert was with 8 years' experience in this field. Transcranial Doppler used was M-mode WAKIe with continuous monitoring and physiological test software (Atys medical, France). This instrument was provided with headband as probe holder for pulse-wave 2 MHz phase array transducer that is used for examination of middle cerebral artery on both sides. All subjects were allowed to rest and examined in supine position in a quiet room. Before doing the definitive recording, subjects were willing to do the test and were trained to perform the procedure of breath hold. To study the MCA blood flow velocities, the subjects were asked to tilt his/her head to a side and to breath normally, the MCA was first identified, usually M1 segment by spectral waveform shape that is specific for MCA and after adjustment of the depth at 45-55 mm, utilizing a trans-temporal window. To obtain MCA spectral waveform, we directed the probe backward and upward and adjusted the pulse wave Doppler sample volume to maximum level in the device for identification and localization of middle cerebral artery spectral waveform. To recognize the waveform of middle cerebral artery, after localization of middle cerebral artery waveform and getting the optimal signal of middle cerebral artery, we fixed the TCD transducer to the head band (probe holder) by special screw provided with the device. We chose the diagnostic option in the device for examination of artery of interest and monitoring of the arterial wave. The means of peak systolic velocity, diastolic velocity, resistive index and pulsatility index (PI) of 10 cardiac cycles were automatically recorded by specific TCD devise software. The parameters that were measured for both study and control groups were the following: Hemodynamic parameters of MCA on both sides: PSV, DV, MFV, PI, and RI were recorded at rest state and MCA flow response to hypercapnia that was done by using breath hold test [30]; the subject was asked to hold breath, for 20 seconds, after normal breathing and take the changes in the means of the above-cited parameters during the last 5 seconds [31]. The mean flow velocity of MCA to breath hold (BH, MCA) was calculated similarly for all parameters.

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Statistics

Biostatistics was achieved by using Statistical Package for the Social Sciences (SPSS) version 20 software Chicago, IL, USA. For comparison between means of different groups, independent t-test was used for all groups (control and migraine groups) including migraine with and without aura.

Results

The clinical characteristics of study participants are shown in Table (1).

Table 1.

Age and gender distribution among study population

Demographic data	Study group Patient (57)	Control group (42)
Subjects no.	37 (without aura) 20 (with aura)	42
Age, year, Mean ± SD	28.85±5.6	28± 5.13
Number of Male	15	11
Number of Female	42	31
Female /male ratio	2.8/1	2.7/1

No significant difference was found between age and gender of both study and control groups. P value of ≤ 0.05 was considered significant. Mean ± SD, mean ± standard deviation. The measurement of peak systolic velocity indicated that there was no statistical difference between study and control groups and also between patients with and without aura as shown in Table 2 – 3, Figure 1- 2. The results of diastolic velocity study demonstrated a significant difference between study and control groups as shown in Table 2, Figure 1, while no significant difference was found between patients with and without aura as shown in Table 3, Figure 2. Resistive index and pulsatility index study showed no significant difference between study and control groups as shown in Table 2, Figure 3 and between patients with and without aura as demonstrated in Table 3, Figure 4. Our results of measuring the breath holding index indicated a highly significant difference between study and control groups as shown in Table 2, Figure 5 and no significant difference between patients with and without aura as shown in Table 3, Figure 6.

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Table 2.

TCD parameters among patients' group and control group.

Parameter	Control Mean ± SEM	Migraine Mean ± SEM	P value
Peak Systolic Velocity	75.80 ± 1.97	83.14 ± 4.434	0.133
Diastolic Velocity	32.40 ± 0.51	39.71 ± 2.444	0.05
Resistive Index	± 0.56 0.1212	0.53 ± 0.14	0.139
Pulsatility Index	0.86 ± 0.034	0.76 ± 0.032	0.073
Breath Holding Index	0.25 ± 0.022	0.76 ± 0.097	<0.0001

Table 3.

TCD parameters among migraine patients with aura and migraine patients without aura

Parameter	Migraine Without Aura Mean ± SEM	Migraine with Aura Mean ± SEM	P value
Peak Systolic Velocity	79.63 ± 6.74	87.83 ± 5.17	0.381
Diastolic Velocity	36.88 ± 3.65	44.00 ± 1.75	0.141
Resistive Index	0.59 ± 0.015	0.49 ± 0.02	0.22
Pulsatility Index	0.81 ± 0.043	0.69 ± 0.034	0.59
Breath Holding Index	0.52 ± 0.15	0.55 ± 0.24	0.898

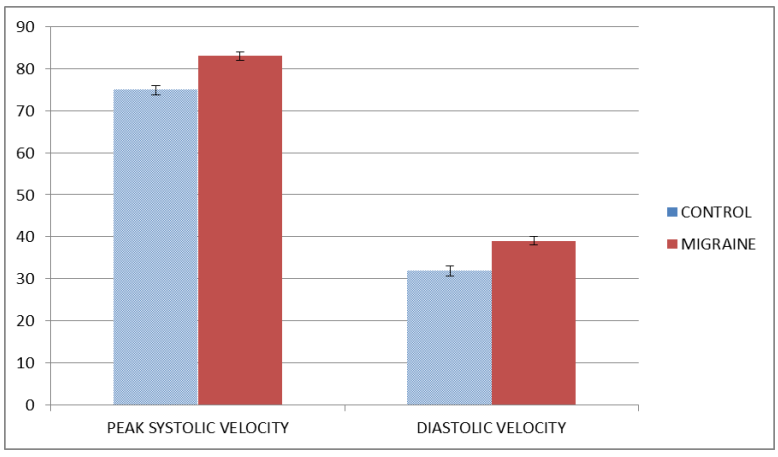

Figure 1.

Peak Systolic and Diastolic velocity in patients and control.

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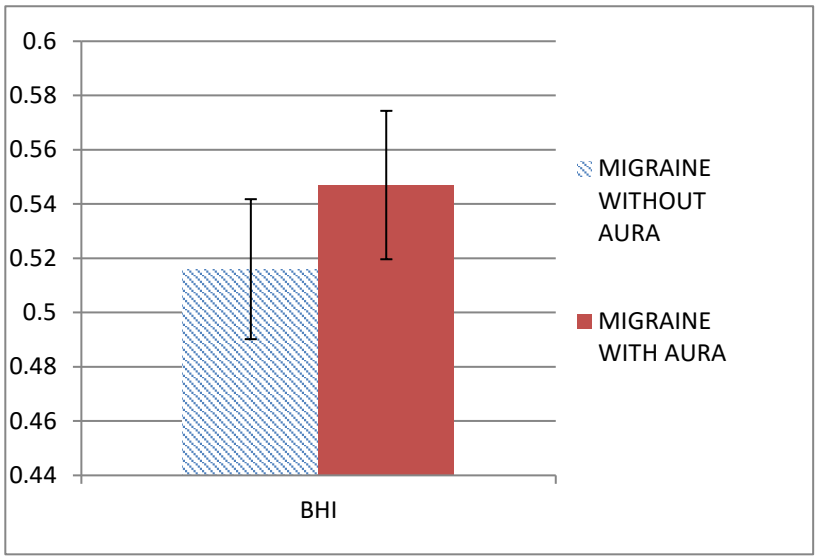

Figure 2.

PSV and DV among migraine without aura and migraine with aura

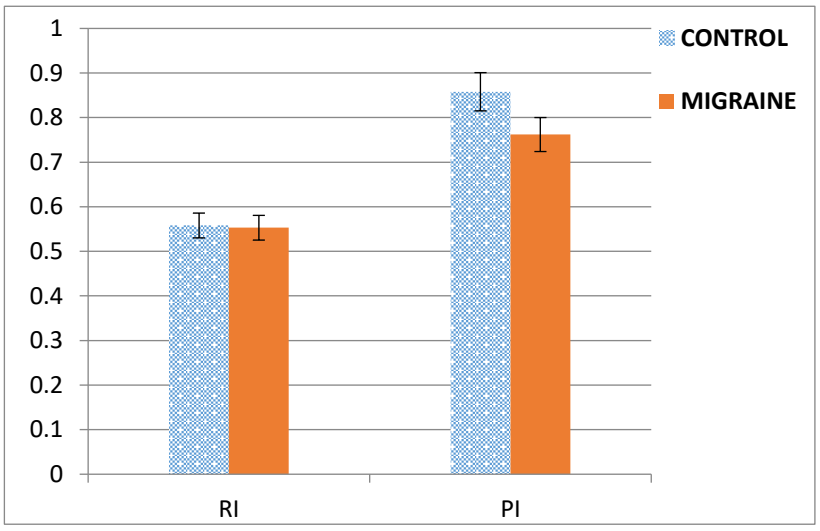

Figure 3.

RI and PI in patients and control

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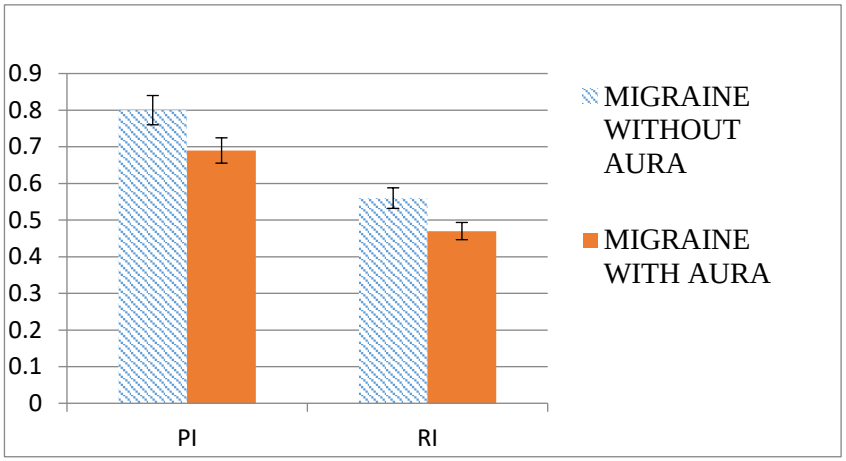

Figure 4.

PI and RI in migraineurs with and without aura.

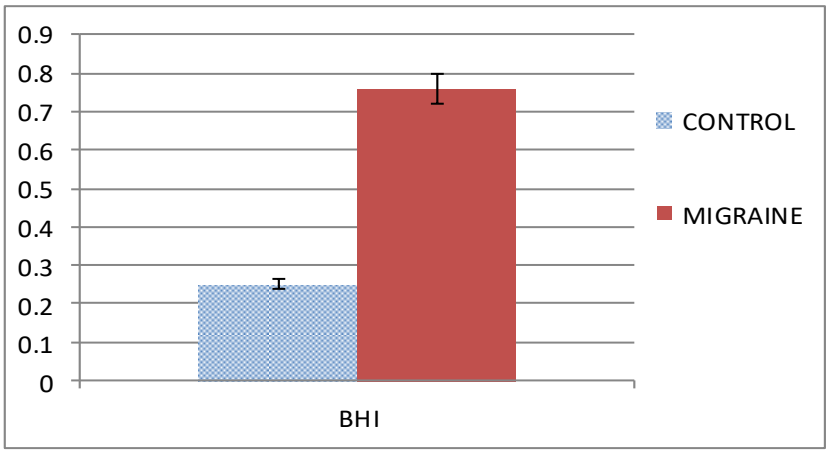

Figure 5.

BHI in control and migraine groups

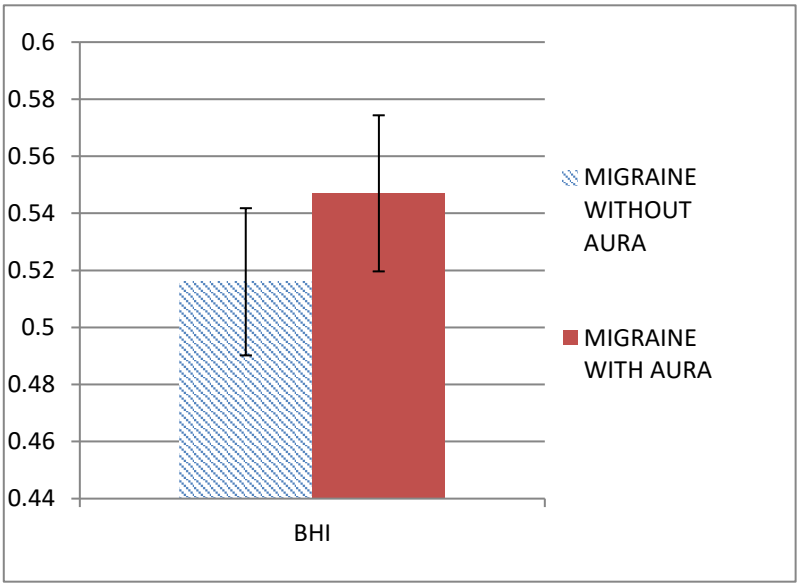

Figure 6.

BHI in migraineurs with aura and migraineurs without aura

Discussion

It is well known that unbalanced cerebrovascular response plays an important role in migraine pathophysiology. It was assumed that habituation of cerebrovascular response among migraineurs contributed to disturbance in brain homeostasis that lead to migraneous attacks [1, 17], this is consistent with the results of our study. The study was conducted on Iraqi migraineurs patients with and without aura, testing cerebrovascular hemodynamic changes by using TCD as a less invasive, less costly and available in comparison to other studies using SPECT and PET scan for assessing cerebral blood flow parameter and vasoreactivity response. The TCD testing was done within 1 month after the attacks as it is difficult to include them in ictal period. We used hemodynamic parameters of MCA (PSV, DV, PI and RI) in both sides and the response of MCA flow to hypercapnia by breath hold test [31, 32]. Several reported TCD studies of the main cerebral arteries, performed among patient groups with idiopathic headaches, especially with migraine, were controversial. Some findings showed a moderate increase in blood flow [15-19] and others showed normal flow velocity patterns [20-22]. All TCD parameters including PSV, DV, RI, and PI in both study and healthy control groups showed no statistical difference, this might indicate that there

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were either no change in cerebral blood flow at rest in patients with migraine versus control patients or the study group reading was not done in ictal period which was consistent with previously reported studies by Agnieszka et al and G. De Benedettis *et al* [32, 33]. Furthermore, there was no statistical difference among migraine patients with aura versus without aura in relation to PSV, DV, RI, and PI, while similar blood flow velocity at rest in migraine patients with and without aura which was similar to previously reported studies by De Benedettis *et al* and Reinhard et al [33, 34]. The relationship between cerebrovascular reactivity to hypercapnia that was induced by breath-holding, a strong significant increase was found in MCA blood flow in response to vasodilator test (hypercapnia) in study versus control groups (P value <0.0001), this may be due to changes at the level of the cerebral arterioles that affected the cerebral blood flow, and in turn led to changes in blood flow velocity as a response to hypercapnia (vasoreactivity) in migraineurs. This is similar to previously reported studies by Thie *et al* 1990 [18], Andreas *et al* 1998 [35], Thomas *et al* 2011[36], Suk-tak *et al* 2009 [37], and Harer et al 1991 [38]. Meanwhile, no significant change was observed between patients with and without aura in MCA blood flow in response to vasodilator test which is an indication of a similarity in blood flow velocity in response to hypercapnia in these patients. This is similar to the studies reported by G. De Benedittis *et al* [33] and Reinhard *et al* 2007 [34].

In conclusion, for the best of our knowledge, this was the first study that supports the role of neurovascular changes via assessment of cerebral blood flow and breath holding vasoreactivity by using TCD testing. No significant difference among patients with aura versus without aura or among gender. We recommend including a larger sample size of patients in Ictal state and to study the different cerebral vasculature at both anterior and posterior circulation of the brain

Consent for publication

Not applicable.

Competing interests

The author declare that he has no competing interests.

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