

## Cerebral Blood Flow Velocity in Migraine and Tension Headache Patients

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### Abstract:

**Background:** Migraine is a genetically influenced complex disorder characterized by episodes of moderate-to-severe headache, most often unilateral and generally associated with nausea as well as light and sound sensitivity. Tension-type headache (TTH) is the most common primary headache disorder, with a worldwide lifetime prevalence of 46% to 78%. This study aimed to evaluate cerebral blood flow (CBF) velocities in migraine and TTH patients by using transcranial Doppler (TCD). **Methods:** This cross-sectional study was carried out on 50 patients with migraine headaches with or without aura and TTH in the age group (20-55 years old). All patients were subjected to evaluation according to the International Headache Society criteria. Clinical evaluation included full history taking, CT brain, and laboratory tests (CBC-ESR-CPR), general medical examination and neurological examination. **Results:** There is a highly significant difference between migraine, TTH, and control groups regarding middle and anterior cerebral artery Doppler parameters (PSV-EDV-PI-RI) ( $p < 0.001$ ). Posterior cerebral artery Doppler parameters were significantly different ( $p < 0.001$ ) between the three studied groups (PSV-EDV-PI) but regarding RI there was no statistically significant difference between the three groups ( $p > 0.05$ ). **Conclusion:** Cerebral blood flow velocity in migraine and TTTH patients is increased in the anterior, middle, and posterior cerebral arteries. **Keywords:** Cerebral Blood Flow; Velocity; Migraine; Tension Headache.

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## Introduction

Migraine is a genetically influenced complex disorder characterized by episodes of moderate-to-severe headache, most often unilateral and generally associated with nausea as well as light and sound sensitivity. Migraine affects approximately 2% of the world's population. Migraine affects three times as many women as men with this higher rate being most likely hormonally driven <sup>(1)</sup>. Migraine attacks can last for hours to days, and the pain can be so severe that it interferes with your daily activities <sup>(2)</sup>. Though migraine causes aren't fully understood, genetics and environmental factors appear to play a role <sup>(3)</sup>. Researchers are studying the role of serotonin in migraines. Other neurotransmitters play a role in the pain of migraine, including calcitonin gene-related peptide (CGRP) <sup>(4)</sup>.

Tension-type headache (TTH) is the most common primary headache disorder, with a worldwide lifetime prevalence of 46% to 78%. TTH causes greater disability and accounts for more missed workdays than migraine. The etiology of TTH is thought to be multifactorial, involving genetic and environmental factors. The three subtypes of TTH are infrequent episodic, frequent episodic, and chronic. Patients typically describe headache pain as pressing, dull, and with the sensation of a tight band around the head. Nonprescription analgesics are indicated for management of episodic TTH. Prophylaxis should be considered for patients with TTH <sup>(5)</sup>.

Transcranial Doppler (TCD) and transcranial color Doppler (TCCD) are types of Doppler ultrasonography that measure the velocity of blood flow through the brain's blood vessels by measuring the echoes of ultrasound waves moving transcranially (through the cranium). These modes of medical imaging conduct a spectral analysis of the acoustic signals they receive and can therefore be classified as methods of active acousto-cerebrography <sup>(6)</sup>. TCD is a

noninvasive technique that evaluates the velocity, direction, and other properties of blood flow in the cerebral arteries, as well as the cerebrovascular reserve, using a pulsed ultrasonic beam. The flow velocities measured with TCD are directly proportional to invasive flow measurements <sup>(7)</sup>.

However, TCD studies in migraine have contradictory results. Studies conducted during attack-free episodes have shown either increased or normal blood flow velocities in migraine patients <sup>(8)</sup>.

The present study seeks to use transcranial Doppler ultrasound to evaluate cerebral blood flow velocities in middle and posterior circulation arteries, during an attack-free episode in migraine patients, with and without aura, as well as in TTH patients who were not receiving prophylactic medication <sup>(8)</sup>.

This study aimed to evaluate CBF velocities in migraine and TTH patients by using TCD.

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## Patients and methods

This cross-sectional study was carried out on patients with migraine headaches with or without aura and tension headache in the age group (20-55 years old). The study was done from May 2021 to June 2022 in two outpatient clinics: Benha university hospital, headache clinic, and Kasr El - Ainy hospital, headache clinic. The study was performed after being approved by the institutional ethical committee (MS.36.6.2021) and informed consent was obtained from all participants.

**Inclusion criteria** were all patients that fulfilled the diagnostic criteria for migraine and tension-type headaches established in the International Headache Society's International Classification of Headache Disorders, second edition (**International Classification of Headache Disorders, 2013**) , Migraine headache with or without aura, TTH, patient's age ranged from 20-55 years old, Each patient had a normal neurological examination and patients were examined

during a headache-free episode and at least 72 hours after the last headache attack except 10 patients were examined during a headache attack.

**Exclusion criteria** were patients with psychiatric diseases, diabetes mellitus, cardiovascular disorders, cerebrovascular disease, epilepsy and patients with known systemic diseases such as anemia and hypertension, patients receiving prophylactic medication for headache, or any treatment known to affect CBF, or intake of analgesics. Moreover, smoking, and consumption of caffeine were forbidden on the day of testing.

**All patients were subjected to** evaluation according to the International Headache Society criteria (**International Classification of Headache Disorders, 2013**). Clinical evaluation included full history taking, general medical examination, and neurological examination. Clinical evaluation included imaging (CT brain) to exclude other causes of headache. Clinical evaluation included laboratory tests (CBC-ESR-CPR) to exclude any cause-effect CBF (DM-anemia- other systemic diseases). For the Doppler test, two 2-MHz probes were adjusted on an individually fitted headband to insonate the left posterior cerebral artery (PCA) and the right middle cerebral artery (MCA). The MCA was taken as a reference to monitor nonspecific changes. Beat-to-beat peak systolic flow velocities were recorded by a Doppler device (Multidop T2, DWL, Sipplingen, Germany). Since the systolic index is less influenced by Doppler artifacts, peak systolic data were recorded instead of end-diastolic or time-averaged mean flow velocity indices.

### **The transcranial Doppler method**

#### **Basic concepts**

Transcranial Doppler ultrasonography provides real-time measurements of blood flow velocity in cerebral vessels. The technique can be used to measure changes in velocity within the large diameter arteries <sup>(9)</sup>.

Sonographers usually aim for the MCA, which is easy to locate at depths of around 50-56 mm <sup>(10)</sup>.

The Doppler probe has two piezo transducers, one to transmit a pulsed ultrasound beam and a second to receive back the scattered echoes from the moving red blood cells. The difference in the frequency of the transmitted beam and the frequency received from the back-scattered beam (known as the Doppler shift) is dependent on the motion of the red blood cells traveling within the vessel <sup>(10)</sup>.

#### **Sample size:**

The sample size was calculated using EPI-Info (Epidemiological information package) software version 6.1, C.I (Confidence Interval) 95%, power 80%. Prevalence = 3.38% = 0.00338, (1-P) = (1-0.0338), =50.18, =50 patients, where Z = Z value (1.96 for 95% confidence level) p = percentage picking a choice, expressed as decimal (.5 used for sample size needed) C = confidence interval (0.05), the sample size was calculated with according to the prevalence of migraine and tension headache patients in a study <sup>(8)</sup> which was 3.38 %this yielded a sample size of 50 patients. Patients group: included 50 individuals and the control group included 50 healthy individuals.

#### **Statistical analysis:**

The data collected will be statistically presented and analyzed using the Statistical Package for Social Science (SPSS version 26.0. Armonk, New York, United States: IBM Corp). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi-square test ( $\chi^2$ ) and Fisher exact were used to calculate the difference between qualitative variables as indicated. Quantitative data were tested for normality by using the Kolmogorov-Smirnov test. Parametric data were expressed as mean  $\pm$  SD while non-parametric data were expressed as median

(Range). One-way analysis of the variance (One-way ANOVA) was used to compare three or more independent groups of normally distributed variables (parametric data) while the Kruskal-Wallis's test was used for non-normally distributed Data (non-parametric data). Pairwise intergroup significance was tested by the post-hoc Tukey test. Mann Whitney U test was used to compare two independent groups for non-normally distributed Data (non-parametric data). Correlation analysis was also performed. The accepted level of significance in this work was 0.05.

## Results

In the migraine group there were 7 (28%) males and 18 (72%) females, in TTH there were 8 (32%) males and 17 (68%) females while in control groups there were 27 (54%) males and 23 (46%) females with a statistically significant difference ( $p < 0.045$ ) in between the three groups but regarding age and BMI there was no statistically significant difference ( $p > 0.05$ ) between the three groups (**Table, 1**).

There is a highly statistically significant difference ( $p < 0.001$ ) between migraine, TTH, and control groups regarding middle and anterior cerebral artery Doppler parameters (PSV-EDV-PI-RI) (**Table, 2 and 3 respectively**).

**Table 4** shows that posterior cerebral artery Doppler parameters had a high statistically significant difference ( $p < 0.001$ ) between the three studied groups regarding (PSV-EDV-PI) but regarding RI there was no statistically significant difference ( $p > 0.05$ ) between the three groups.

Logistic regression analysis was conducted for the prediction of the headache underlying cause between the diseased groups (migraine + tension headache) and control group using age, gender, BMI, and doppler parameters. A higher risk of migraine and tension headache was related to BMI, MCA-PSV, MCA-EDV, MCA-PI, MCA-RI, ACA-EDV, ACA-RI, PCA-PSV and PCA-EDV in univariate analysis. Parameters were both significant in univariate and multivariate analysis MCA-EDV, MCA-RI, ACA-PSV, ACA-EDV, ACA-PI, and PCA-PI (**Table, 5**).

**Table 1:** Comparison of the demographic data in the three study groups

Variable	Migraine group (N=25)	Tension type headache group (N= 25)	Control group (N= 50)	Test of significance.
Age (Years)	34.72 ± 7.92	33.88 ± 7.30	33.82 ± 7.04	F = 0.136 $p = 0.873$
		Sex		
Males	7 (28%)	8 (32%)	27 (54%)	$\chi^2 = 5.993$
Females	18 (72%)	17 (68%)	23 (46%)	$p = 0.045^*$
Body mass index (Kg/m <sup>2</sup> )	31.28 ± 4.16	29.72 ± 4.29	29.64 ± 4.59	F = 1.265 $p = 0.287$

F= test for analysis of variance (ANOVA),  $\chi^2$ = Chi-square test,  $p$ = probability value

**Table 2:** Comparison of middle cerebral artery (MCA) doppler parameters in the three study groups

Variable	Migraine group (N=25)	Tension type headache group (N= 25)	Control group (N= 50)	Test of significance.
Peak Systolic Velocity (PSV)	161.24 ± 25.04	119 ± 8.84	98.14 ± 4.35	F=180.342 p<0.001* p1<0.001* p2<0.001* p3<0.001*
End diastolic velocity (EDV)	80.20 ± 9.34	59.92 ± 6.03	48.80 ± 2.84	F=237.466 p<0.001* p1<0.001* p2<0.001* p3<0.001*
Pulsatility index (PI)	1.35 ± 0.12	1.38 ± 0.06	1.26 ± 0.09	F = 14.745 p <0.001* p1=0.643 p2= 0.001* p3<0.001*
Resistivity index (RI)	0.72 ± 0.10	0.74 ± 0.10	0.60 ± 0.13	F= 17.694 p<0.001* p1=0.887 p2<0.001* p3<0.001*

F=test for analysis of variance (ANOVA), \*= significant, p1= difference between migraine and TTH groups, p2= difference between migraine and control groups, p3= difference between TTH and control groups, p>0.05=statistically insignificant, p<0.001=statistically significant.

**Table 3:** Comparison of anterior cerebral artery (ACA) doppler parameters in the three study groups

Variable	Migraine group (N=25)	Tension type headache group (N= 25)	Control group (N= 50)	Test of sig.
Peak Systolic Velocity (PSV)	125.52 ± 3.53	110.64 ± 4.07	92.50 ± 4.73	F= 517.498 p<0.001* p1<0.001* p2<0.001* p3<0.001*
End diastolic velocity (EDV)	64.52 ± 2.62	53.20 ± 2.99	50.42 ± 4.01	F=140.650 p<0.001* p1<0.001* p2<0.001* p3=0.004*
Pulsatility index (PI)	2.09 ± 0.12	1.61 ± 0.08	0.91 ± 0.08	F=150.071 p<0.001* p1<0.001* p2<0.001* p3<0.001*
Resistivity index (RI)	0.87 ± 0.06	0.74 ± 0.05	0.61 ± 0.09	F= 106.747 p<0.001* p1<0.001* p2<0.001* p3<0.001*

F= test for analysis of variance (ANOVA), \*= significant, p1= difference between migraine and TTH groups, p2= difference between migraine and control groups, p3= difference between TTH and control groups, p>0.05=statistically insignificant, p<0.001=statistically significant

**Table 4:** Comparison of posterior cerebral artery (PCA) doppler parameters in the three study groups

Variable	Migraine group (N=25)	Tension type headache group (N= 25)	Control group (N= 50)	Test of sig.
Peak Systolic Velocity (PSV)	100.28 ± 14.08	88 ± 6.53	82.42 ± 2.92	F= 41.640 p<0.001* p1<0.001* p2<0.001* p3=0.015*
End diastolic velocity (EDV)	48.80 ± 2.93	44.92 ± 2.45	38.50 ± 3.44	F=101.114 P <0.001* p1<0.001* p2 < 0.001* p3 < 0.001*
Pulsatility index (PI)	1.97 ± 0.16	1.75 ± 0.15	0.93 ± 0.08	F = 37.273 p < 0.001* p1 < 0.001* p2 < 0.001* p3 < 0.001*
Resistivity index (RI)	0.79 ± 0.10	0.74 ± 0.09	0.77 ± 0.09	F= 2.013 p = 0.139 p1= 0.116 p2= 0.502 p3= 0.460

F= test for analysis of variance (ANOVA), \*= significant, p1= difference between migraine and TTH groups, p2= difference between migraine and control groups, p3= difference between TTH and control groups, p>0.05=statistically insignificant, p<0.001=statistically significant.

**Table 5:** Logistic regression analysis for diseased groups among the studied patients.

	Univariable			Multivariable		
	p	OR	95% C.I	P	OR	95% C. I
Age	1.000	1.000	0.951-1.052	0.844	1.000	0.997-1.003
Gender (Male)	0.663	0.826	0.351-1.947	0.514	0.983	0.932-1.036
BMI	<b>0.044*</b>	0.906	0.823-0.997	0.857	1.000	0.995-1.006
MCA-PSV	<b>&lt;0.001*</b>	0.690	0.574-0.83	0.208	1.001	0.999-1.003
MCA-EDV	<b>&lt;0.001*</b>	0.647	0.533-0.784	<b>0.020*</b>	1.004	1.001-1.008
MCA-PI	<b>&lt;0.001*</b>	0.000	0.002-0.023	0.726	1.055	0.78-1.428
MCA-RI	<b>&lt;0.001*</b>	0.000	0.004-0.036	<b>0.008*</b>	0.756	0.614-0.931
ACA-PSV	0.917	0.000	0.003-5.629	<b>0.030*</b>	0.995	0.99-0.999
ACA-EDV	<b>&lt;0.001*</b>	0.722	0.628-0.83	<b>0.034*</b>	1.007	1.001-1.014
ACA-PI	0.996	0.000	-	<b>0.011*</b>	0.770	0.629-0.943
ACA-RI	<b>&lt;0.001*</b>	0.000	0.001-0.045	0.776	0.955	0.697-1.309
PCA-PSV	<b>&lt;0.001*</b>	0.778	0.696-0.87	0.697	0.999	0.997-1.002
PCA-EDV	<b>&lt;0.001*</b>	0.405	0.273-0.602	0.072	0.994	0.987-1.001
PCA-PI	0.997	0.000	-	<b>&lt;0.001*</b>	0.485	0.409-0.575
PCA-RI	0.194	39.398	0.154-10090.431	0.276	1.200	0.864-1.666

## Discussion

TTH is very common, with a lifetime prevalence in the general population ranging in different studies between 30% and 78%. Neck pain is highly prevalent in the general population and even more prevalent in individuals with primary headaches <sup>(11)</sup>.

The value of TCD sonography has been illustrated in migraine patients. However, few studies have been performed on patients either with TTH or have directly compared TTH and migraine and few have emphasized the importance of vascular factors in TTH.

In the current study, there was no statistically significant difference between the three study groups regarding the mean age or the mean BMI. However, there was a high female predominance of female gender in the migraine and TTH groups compared to the control group.

This came in accordance with a study that included a total of 50 subjects (32 females, 18 males). 10 subjects served as a control group while the remaining 40 were equally divided into two groups (20 patients with migraine and the other 20 with TTH). The study showed that there was a higher prevalence of females in the migraine and TTH groups compared to the control (75%, 65%, 50% respectively) <sup>(14)</sup>.

It has been hypothesized that repeated episodes of migraine may alter cerebrovascular function through repeated exposure to neurogenic inflammation, plasma protein extravasation and the release of vasoactive neuropeptides during migraine episodes. If so, abnormalities of cerebrovascular function may be expected to be more evident in migraine patients without aura than in controls <sup>(12, 13)</sup>. The differences between the studies could be explained due to differences in disease severity and disease control as the sample size is not the same.

In the current study, there is a highly significant difference between the migraine, TTH, and control group

regarding middle cerebral artery Doppler parameters (PSV-EDV-PI-RI). The PSV and EDV were statistically significantly higher in the migraine group compared to the TTH group and control group. Also, the same parameters were significantly higher in the TTH compared to the control group. On the other hand, both PI and RI were significantly higher in the migraine and TTH groups compared to the control group with no statistically significant difference between them. This agreed with a trial that showed that MCA show a significant difference in PSV between the migraine group and the TTH group and also between the migraine group and control group but no significant difference was reported between the groups regarding EDV <sup>(14)</sup>. This also came in agreement with a study that observed that mean blood flow velocity in the MCA of patients with migraine is higher (8 cm/sec) than in patients with episodic tension headache <sup>(15)</sup>.

Our results were also in partial agreement with a study that reported increased cerebral blood flow velocities (CBF) in the MCA as well as decreased PI in patients with episodic TTH compared to controls, but there was no difference between controls and patients with TTH <sup>(16)</sup>. Studies conducted during attack-free episodes have shown either increased <sup>(17, 18)</sup> or normal blood flow velocities in migraine patients <sup>(19, 20)</sup>.

On the other hand, the current results disagreed with a study that showed that there was no statistically significant difference in the MCA Doppler parameters between cases with TTH and migraine as compared to each other and to the healthy controls <sup>(8)</sup>.

Also, the current results disagreed with a study that showed that on comparing with the control group there was a significantly lower PSV and MFV of the MCA of the TTH group <sup>(7)</sup>.

According to another study, the results were consistent with the theory of

cerebrovascular alteration in TTH with the predominant involvement of the MCA <sup>(7)</sup>. Also, a previous study reported that exercise-induced changes in the amplitude of temporal artery pulsation were smaller in patients with TTH than in a healthy control group. The authors suggested that this was due to extracranial vasoconstriction <sup>(21)</sup>.

Another study reported that CBF velocities in MCA on the headache side during a migraine attack were reduced <sup>(22)</sup>. While another study reported no velocity changes at the headache and non-headache side MCAs during an acute attack of migraine <sup>(23)</sup>.

In the current study, there is a highly statistically significant difference between the migraine, TTH, and control group regarding posterior cerebral artery Doppler parameters (PSV-EDV-PI). The PSV, EDV, and PI were significantly higher in the migraine group compared to the TTH group and control group. Also, the same parameters were significantly higher in the TTH compared to the control group. On the other hand, there was no statistically significant difference between the three groups regarding RI.

The results were in partial agreement with a study that reported increased cerebral blood flow velocities (CBF) velocities in the PCA but decreased PI in patients with episodic TTH compared to controls, also there was no difference between controls and patients with TTH <sup>(16)</sup>.

This disagreed with a study that showed that TCD parameters of posterior circulation revealed no significant difference in all parameters in all studied groups. However, they agreed with our study in the point where they reported a statistically significant increase in the PI in the migraine group compared to the control group <sup>(14)</sup>.

Also, the current results disagreed with a study that showed that there was no statistically significant difference in the PCA Doppler parameters between the

cases with TTH and migraine as compared to each other and to the healthy controls <sup>(8)</sup>. These changes (the increase in PSV, EDV, and PI) could be explained by the vasodilator activity of neurotransmitters such as nitric oxide and calcitonin gene-related peptides, contributing to central sensitization. Others suggested downstream vasodilatation (arteriolar vasodilatation theory) <sup>(19, 24, 25)</sup>.

In a similar study, increased basilar artery CBF velocities in patients with tension-type headache (TTH) was also reported, and no difference was present in other examined arteries <sup>(26)</sup>.

Also, the current results disagreed with a study that showed no difference in the posterior circulation between patients with migraine without aura and controls <sup>(27)</sup>.

In the current study, there is a highly statistically significant difference between the migraine, TTH, and control group regarding anterior cerebral artery Doppler parameters (PSV-EDV-PI-RI). The PSV, EDV, PI, and RI were significantly higher in the migraine group compared to the TTH group and control group. Also, the same parameters were significantly higher in the TTH compared to the control group. This was in accordance with a study that showed that PSV, EDV, and PI of the ACA were significantly higher in the migraine group compared to the control group. Also, the PSV and EDV were significantly higher in the migraine group compared to the TTH group <sup>(14)</sup>.

A recent meta-analysis found that migraineurs have a higher resting mean blood flow velocity (MFV) in both anterior and posterior circulations than controls and it was argued that this could be a hallmark of migraine. An increase in CBF velocity could be due to a decrease in the cross-sectional area of a vessel at or near the point of insonation or to regional flow changes at the level of arterioles <sup>(28)</sup>.

In contrast to our results, no difference in cerebrovascular reactivity in the anterior circulation among patients with migraine with or without aura and controls <sup>(27)</sup>.



Many studies used TCD ultrasound to compare PI in the anterior circulation of migraineurs and controls <sup>(15, 29-32)</sup>. Most of them found no significant difference in PI between migraineurs and controls <sup>(29-31)</sup>.

Only two studies found significantly higher PI in the anterior circulation of migraineurs than controls <sup>(33, 34)</sup>, whereas one study found that migraine patients had lower PI than controls <sup>(35)</sup>.

A study reported increased cerebral blood flow velocities (CBF) velocities in the ACA but decreased PI in patients with episodic TTH compared to controls, also there was no difference between controls and patients with TTH <sup>(16)</sup>.

## Conclusion

Cerebral blood flow velocity in migraine and TTH patients is increased in anterior, middle, and posterior cerebral arteries. We recommend further research on doppler in other cerebral arteries among migraine and TTH patients.

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## Author contribution

The authors contributed equally in the study.

## Conflicts of interest

No conflicts of interest

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