In The Name Of God

Kerman university of medical Sciences

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"COMPARISON OF BLOOD FLOW VELOCITY CHANGES IN POSTERIOR CEREBRAL ARTERY MEASURED WITH TRANSCRANIAL DOPPLER SONOGRAPHY IN MIGRAINEURS WITH VISUAL AURA AND NORMAL PERSONS AFTER PHOTOSTIMULATION"

"Thesis for neurology speciality in medicine "

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Dedicated to:

My dear parents

I would like to thank:

Behnaz Sedighi .MD and *Hosseinali Ebrahimi.MD* for their supervision

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ABSTRACT

INTRODICTION: An imbalance of the cerebrovascular response during functional activation of the brain has been postulated as a factor in the pathophysiology of migraine. The published results of transcranial Doppler (TCD) studies of main cerebral arteries, performed in the patients with idiopathic headaches, especially with migraine, are controversial.

MATERIAL AND METHODS: This study was carried out on 46 patients (23 cases and 23 controls). We used Doppler instrument via trans-temporal window and detected middle cerebral artery, anterior cerebral artery and posterior cerebral artery by4 MHz pro be. The flow velocity in the posterior cerebral artery before, mid- and immediately after stimulation were recorded. Stimulation was done using a flickering light in 100 seconds.

RESULTS: At the baseline the middle cerebral artery had more peak systolic velocity in migraineurs than the control group. Although peak systolic velocity changes in the Mid-photic period, this is not statistically significant. On the other hand, Post-photic peak systolic velocity increases significantly.

DISCUSSION: Using this stimulation we found altered cerebral vasomotor reactivity in the interictal phase in migraineurs with visual aura. There wasn't a significant change in normal persons. It seems to be an unavoidable hindrance for the wider implementation of functional TCD in diagnostic work up of migraine patients.

CONCLUSION: An increased cortical arousal interictally and reduced adaptation to environmental stimuli in migraineurs is suggested.

KEY WORDS: Transcranial Doppler sonography(TCD), Migraine with aura, Photostimulation

1. INTRODUCTION

1.1. MIGRAINE

1.1.1. Epidemiology

Migraine has afflicted humankind for centuries. Descriptions of acute migraine attacks appear as early as the second century AD in the writings of *Aretaeus* of *Cappadocia*. The term migraine is derived from the ancient Greek word *hemikranios* which means "half head," underscoring the unilateral distribution of head pain in many sufferers.

Migraine can begin at almost any age; most commonly, the initial attack occurs during adolescence, and by 40 years of age, 90% of those with the condition have had their first attack. After puberty, migraine is more common in females, whereas in children there is a small preponderance of males. Although there has been some inter-population variability, several large population based studies in Europe and United States have shown the prevalence of migraine in women to be approximately 20% and in men approximately 6%. Once migraine has developed, it tends to recur with varying frequency throughout much of a patient's life. Attacks have a tendency to get milder and occur less often in later years although this certainly is not a universal finding. Although migraine attacks have been separated into those that are and those that are not accompanied by transient focal neurological symptoms known as the aura, the two types are not mutually exclusive, and many patients have separate attacks of the two types[1].

For many years the first syndrome was referred to as classic or neurologic migraine and the second as common migraine. The ratio of classic to common migraine is 1:5. The genetic nature of classic migraine is apparent from its occurrence in several members of the family of the same and successive generations in 60 to 80 percent of cases; the familial frequency of common migraine is slightly lower[2].

1.1.2 Definition and Classification

Because reliable biological markers for migraine currently do not exist, diagnostic classification is based on clinical features of the acute episode. Migraine is now classified according to the scheme devised by the Second Headache

Classification Committee of the International Headache Society (Headache Classification Committee 2004), as shown in Table 75.5.[1]

Migraine without Aura

Migraine without aura occurs episodically and is not preceded or accompanied by any easily identifiable aura due to focal cerebral or brainstem disturbances. Many patients with migraine report that their headaches are preceded by a prodromal phase that may consist of alterations in mood or energy level (either euphoria or depression), excessive yawning, thirst, or food cravings. After these premonitory warnings, the headache may occur within hours or during the next day. The pain may be unilateral and is usually supraorbital,but it may be holocephalic. The quality of the pain of migraine is often described as throbbing (pulsatile) although in some patients the throbbing only occurs with more severe attacks. Photophobia and phonophobia are common and osmophobia (sensitivity to smells) may also occur. Gastrointestinal symptoms and blurred vision is common complain. The pain of an attack of migraine tends to build up to a peak over 30 minutes to several hours. The attack generally lasts several hours to a full day[1].

Migraine with Aura

In migraine with aura, periodic headaches are preceded or accompanied by an aura consisting of transient visual, sensory, motor, or language disturbance or other focal cerebral or brainstem symptoms. Aura occurs in about 15% of migraineurs and does not occur in every attack. Although each of the aura types may occur alone in a given attack, in some individuals they can occur sequentially. Classically, the visual disturbance is followed by sensory symptoms and then in turn by language or motor symptoms. When this occurs, the headache may overlap one or more of the later appearing aura symptoms. The head pain is identical to that of migraine without aura but is unilateral in a higher percentage of patients. Alterations in mood and other premonitory symptoms may precede the aura. The most common aura is the disturbance of vision known as a scintillating scotoma (teichopsia). This generally begins as a shimmering arc of white or colored lights in the homonymous part of the left or right visual field. The arc of light gradually enlarges. It may have a definite zigzag pattern. It may be a single band of light or may have a much more complex pattern. It has a shimmering or flickering quality, similar to that seen when a fluorescent light fixture is close to failure or a strobe light is just short of the flicker fusion frequency. Gradually, over the course of a few minutes, the scintillating pattern expands from the point just lateral to the of fixation to involve a quadrant or hemifield of vision in both eyes. Commonly, the positive scotoma is followed by a spreading zone of vision loss (negative scotoma). Even if there is no identifiable area of vision loss, the disturbance of vision produced by the scintillating scotoma makes it difficult to read or drive. The scotoma is believed to originate in the calcarine cortex of one cerebral hemisphere and should therefore be an essentially congruent homonymous field defect; however, it

is sometimes described as being seen in one eye only or as being worse on one side than the other. Patients often describe the visual disturbance in vague terms, such as "blurry vision," "double vision," or "jumpy vision." Close questioning or showing the patient an artist's representation of a scintillating scotoma generally clarifies the complaint. There are many variations of migrainous teichopsia (subjective visual images). The zigzag appearance may be so pronounced to justify the term *fortification spectrum* because of its fanciful resemblance to the ground plan of a fort. Occasionally, the scotoma is less complex and is simply described as a ball of light in the center of the visual fields. It may obscure vision to a significant degree. This type of teichopsia may represent a bilateral calcarine disturbance. The scintillating and positive (bright) scotoma can still be seen with the eyes closed or while in the dark. This is not a feature of the negative scotoma (areas of darkness), which disappear in the dark. The teichopsia of migraine may be more complex and formed than the usual lines and geometric patterns. Rarely, a complex scene is visible to the migraineurs; it may be recognizable as an image from the patient's past experience, or it may be an unknown scene. Disturbances of this complex type may be due to dysfunction in the posterior temporal lobe. Changes in the perception of the shape or form of viewed objects (metamorphopsia) can lead to frightening and bizarre visual hallucinations. The story of *Alice in Wonderland,* in which the heroine perceived herself shrinking, is believed to have been based on Lewis Carroll's own experience of migrainous metamorphopsia. Visual disturbances due to retinal dysfunction are relatively uncommon in migraine and may take the form of unilateral flashes of light (photopsia), scattered areas of vision loss, altitudinal defects, or even transient unilateral vision loss. When such monocular visual disturbances are followed by a headache, the term *retinal migraine* is appropriate. When the photopsia, teichopsia, and other disturbances are seen in both visual fields simultaneously, they probably originate from the calcarine cortex. A homonymous visual aura is generally followed by a headache on the contra lateral side of the head, but exceptions are not uncommon. In such patients, the headache is ipsilateral to the visual disturbance, or it is bilateral.
The second most common aura type is sensory aura and the next most common type is language aura.[1]

1.1.3.Pathogenesis

Clinical and experimental evidence supports the concept that there is abnormal intracranial and extracranial vascular reactivity in migraine and other vascular headaches. Dilatation of the scalp arteries causes increased scalp blood flow and large-amplitude pulsations during attacks of migraine. Radioactive xenon cerebral blood flow studies show significantly reduced regional flow through the

cortex during the aura stage of migraine with aura. At first sight, these studies seem to support the long-held theory of cerebral vasoconstriction during the aura and increased external carotid flow during the headache phase. However, the vasoconstriction-vasodilatation model has several difficulties. First, there is solid evidence from functional MRI studies that the phase of oligemia during the migraine aura is preceded by a phase of focal hyperemia[3]. Second, headache may begin while cortical blood flow is still reduced, thereby rendering obsolete the theory that vasodilatation is the sole mechanism of the pain. The oligemia that spreads across the cerebral cortex at a rate of 2-3 mm per minute does not conform to discrete vascular territories, making unlikely the theory that vasospasm of individual cerebral arteries with subsequent cerebral ischemia is the source of the aura. The headache after an aura is often on the inappropriate side. In other words, a right-sided visual field or somatosensory aura can be followed by an ipsilateral headache, despite the fact that the cerebral blood flow changes occurred in the opposite hemisphere. Finally, migraine is also associated with a premonitory phase in up to 60% of patients, which would be incompatible with a vascular or ischemic hypothesis. This premonitory phase consists of mood changes, thirst, food cravings, excessive yawning, and drowsiness. The brain location from which a migraine attack is initiated is still unclear, but brainstem and hypothalamic generators have been proposed [4].

The observations on spreading oligemia led to a resurgence of the central or neuronal theories of migraine. Briefly, the phase of oligemia demonstrated during the aura of migraine by the topographic blood flow techniques begins in one occipital pole and spreads forward over the ipsilateral hemisphere at a rate of about 3-4 mm per minute. The area of reduced cerebral blood flow does not correspond to the distribution of any particular cerebral artery but crosses the areas perfused by the middle and posterior cerebral arteries while advancing with a distinct wave front until some major change in cortical cellular architecture is reached (e.g., at the central sulcus). Recently, the description of a patient with migraine without aura who had an attack during positron emission tomography (PET) proved beyond a doubt the phenomenon of spreading oligemia. This study suggested the possibility that blood flow changes may occur in migraine with and without aura because this patient had only transient and mild visual blurring, a ubiquitous symptom in migraineurs.

The spreading depression noted by *Leao's* and *Lashley's* observations led to the hypothesis that the aura of migraine is primarily a neuronal event that causes the cortical circulation to close down in response to decreased metabolic requirements. Although spreading depression has not been documented to occur in human cortex, functional MRI studies have been strongly supportive. There is also a body of evidence suggesting the presence of a disturbance in energy metabolism in both the brain and extraneural tissues of patients with migraine. In addition, there is increasing evidence to support the presence of both systemic and brain magnesium

deficiency in migraineurs, particularly in the occipital lobes. Spreading depression might therefore be more aptly described as spreading activation, followed by a wave of spreading depression. This would support the clinical observation of "positive" visual "scintillations" followed by a "negative" visual scotoma or by the march of positive sensory (paresthesia) symptoms. This theory may also explain why spreading oligemia may be preceded by focal hyperemia. These findings taken together suggest that the changes in blood vessel caliber and blood flow may be due to a primary neuronal event, triggered by enhanced neuronal excitability and susceptibility to spontaneous depolarization, resulting in prolonged hypometabolism because of an impairment in energy metabolism caused by mitochondrial dysfunction. This hypothesis has also been supported by the finding of increased interictallactate levels in the occipital cortex of migraineurs using proton MRS.

Although the platelet may not have a direct role in the biochemical changes that appear to underlie the basic pathogenesis of migraine, it has been extensively studied because of its similarities to serotonergic nerve terminals. Serotonin constricts large arteries and is a dilator of arterioles and capillaries, also, perhaps of more importance, it is a neurotransmitter. But the role of serotonin in migraine has yet to be fully defined[1].

During attacks of migraine with aura, studies of regional cerebral blood flow show a modest cOl1ical hypoperfusion that begins in visual cortex and spreads forward at a rate of 2 to 3 mm/min. The decrease in blood flow averages 25% to 30% (too little to explain symptoms; oligemic rather than ischemic) and progresses anteriorly in a wavelike fashion that is independent of the topography of cerebral arteries. The wave of hypoperfusion persists for 4 to 6 hours, follows the convolutions of the cortex, and does not cross the central or lateral sulcus but progresses to the frontal lobe via the insula. Sub clinical perfusion is normal. Contralateral neurologic symptoms appear during the period of tempro-parietal hypoperfusion; at times, hypoperfusion persists in these regions after symptoms cease. More often, frontal spread continues as the headache phase begins. A few patients experiencing migraine with aura show no abnormalities of blood flow; rarely, focal ischemia is sufficient to cause symptoms. Focal ischemia, however; does not appear necessary for focal symptoms to occur. In attacks of common migraine, no abnormalities of blood now have been seen[5].

1.1.4. Laboratory and diagnosis

Neurologic migraine should occasion no difficulty in diagnosis if a good history is obtained. The difficulties come from a lack of awareness that (1) a progressively unfolding neurologic syndrome may be migrainous in origin, (2) the neurologic disorder may occur without headache, and (3) recurrent migraine headaches take many forms, some of which may prove difficult to distinguish

from the other common types of headache. Some of these problems merit elaboration because of their practical importance[2].

No special investigations are useful for the clinical diagnosis of migraine. EEG, MRI, and CT scan abnormalities may be found during or shortly after an attack, but they are not specific for migraine and simply detect cortical or parenchymal changes that accompany the headache. The EEG changes can range from an area of focal slowing over the hemisphere ipsilateral to the headache to focal spikes, sharp waves, or the more generalized spike-wave discharges seen in idiopathic seizure disorders. Similar findings may be seen in basilar migraine. Visual evoked potentials are slowed in some subjects with repeated attacks of migraine. This observation, although important for evaluation of the pathophysiology of the condition, is of little use clinically. CT and MRI scans can reveal large areas of decreased attenuation and signal changes over the hemisphere ipsilateral to the headache, especially if it is severe and prolonged. These changes, which are temporary and resolve in a few days, are believed to represent edema of the affected region[1].

Detection of anti phospholipid antibodies in a migraineur should lead to the administration of anticoagulants or antiplatelet agents. CT and MRI scans are useful in the investigation of migraine only to the extent that they allow exclusion of other causes of recurrent headache[1].

1.2. Transcranial Doppler sonography

1.2.1. CEREBRAL HEMODYNAMIC

Any single rule invoked to explain hemodynamics of the living brain is too simplistic or will often be proven wrong by clinical experience. Hemodynamics is a term used to describe the flow of blood through the vascular system. [6]

The measurement and augmentation of hemodynamics requires an understanding of complex physiologic mechanisms that foster systemic autoregulation, the body's ability to adjust blood flow despite marked changes in arterial blood pressure. Autoregulation is dependent upon complex mechanisms that enable rapid detection of flow alterations coupled with multisystem responses that aim to maintain optimal perfusion, especially to critical organ systems.

The brain is metabolically dependent on a continuous supply of oxygen and glucose which are delivered at a rate of approximately 750 mL/min or 15% of the total CO. Resting *cerebral blood flow* (CBF) is relatively stable despite changes in CO, body position and arterial blood pressure; it amounts to approximately 50 mL per 100 g of brain tissue per minute [1]. Focal changes in CBF correlate with metabolic demands, in that activity in specific brain regions is accompanied by a focal increase in blood flow secondary to autoregulation. When autoregulatory processes are functional, the brain is capable of producing varying levels of arterial perfusion pressures across a wide range of systemic arterial pressures. When autoregulation is dysfunctional, brain perfusion pressures become dependent on systemic homodynamic flow parameters.

Cerebral blood flow (CBF) rates change with vasodilatory or constricting stimuli that affect the diameter of brain resistance vessels. As a rule, the smaller the diameter of the arterial branches, the greater the capacity of these vessels to constrict or dilate. These changes also directly affect the velocity and waveforms in the proximal branches of the circle of Willis. The middle cerebral artery (MCA) velocity changes by 3-4% per mmHg change in end-tidal CO2.

The circle of Willis The circle of Willis is a unique network of vessels located at the basis of the brain that create anastomoses between both terminal carotid arteries and posterior circulation vessels. A complete circle of Willis delivers collateral flow through the anterior communicating or posterior communicating arteries. The first branches of the circle of Willis include anterior (ACA), middle (MCA) and posterior cerebral arteries (PCA). These arteries have first- and second degree branches (i.e. Ml and M2 segments of the MCA) that along with the intracranial vertebrobasilar system can be evaluated with cerebrovascular ultrasound through the intact skull.

The transcranial Doppler (TCD) waveform should be compared to the ICP values at a closed drainage position as well as to the morphology of the ICP waveform. Furthermore, TCD waveforms

and velocity data should be reviewed in relation to systemic and intracranial homodynamic parameters. TCD velocities are not the measurement of CBF, and therefore TCD can provide only indirect evidence as to whether any given therapy is successfully enhancing brain tissue perfusion. Although the velocity is *not* flow volume , Newell and Aaslid state that the flow velocity can reflect CBF and the velocity *change* can be proportionate to the changes in CBF if:

1 the angle of insonation remains constant;

2 the perfused territory remains the same; and

3 the effect of only one stimulus is observed

A change in perfusion pressure leads to a proportionate change in flow volume. The brain, however, developed an intrinsic mechanism that adjusts the vascular resistance to maintain CBF constant in the physiologic range of blood pressure (BP) (50-150 mmHg for normotensive individuals) [10]. Ciller *et al.* showed that a BP decrease of 30 mmHg caused compensatory dilatation of the Ml MCA segment by 4% and M2 MCA segment by 20% [4]. Autoregulation guards the brain with the continuous supply of water, glucose and oxygen necessary for its function. Both VMR and autoregulation coexist and override each other when invoked by various stimuli. As a result, complex dynamic changes in the waveform shape and velocity values can be observed in a short time with breathing cycles, changes of cardiac output, coughing, sneezing, etc.

Cerebral autoregulation can be accomplished through a fast-acting myogenic mechanism to immediately compensate for changing perfusion status [10]. The *Bayliss effect (myogenic mechanisms)* postulates that smooth muscles of the resistance vessels respond to changes in the transmural pressure to increase or restrict the incoming flow. A long-term regulation of CBF is likely corrected by various *metabolic mechanisms* and vasoactive substances providing feedback and regulatory action. Regardless of the priority of each mechanism or the existence of other mechanisms (i.e. neurogenic, etc.), cerebral autoregulation can be disturbed by head trauma or cerebral ischemia, and its non-invasive measurement with ultrasound is still being developed[6].

Table 1.2.1 shows some important factors in cerebral hemodynamics

Practical models			TCD	Condition
Blood viscosity ↑	BP =	Stenosis (none or –)	⇒ Velocity ↓, PI ↑	Dehydration, pulmonary shunt
Blood viscosity ↓	BP =	Stenosis (none or –)	⇒ Velocity ↑, PI ↓	Hydration, anemia
Acute BP ↑	Blood viscosity –	Stenosis (none)	⇒ Velocity ↑, PI ↑	Hypertension (effect of dopamine)
Acute BP ↓	Blood viscosity –	Stenosis (none)	⇒ Velocity ↓, PI ↓	Hypotension, collapse
Chronic BP ↑	Proximal stenosis (none)		⇒ Velocity ↑, PI ↑	Effect of chronic hypertension
Chronic BP ↓	Proximal stenosis (none)		⇒ Velocity ↓, PI = or ↓	Congestive heart failure
Cardiac output ↑	Blood viscosity –	Spasm (no)	⇒ Velocity ↑, PI ↑	Normal autoregulation (liver failure)
Cardiac output ↑	Blood viscosity =	Spasm (no)	⇒ Velocity ↑, PI↓	Altered autoregulation (head trauma)
Cardiac output ↑	Blood viscosity =	Spasm (yes)	⇒ Velocity ↑, PI ↑	HHH therapy (success)
Cardiac output ↑	Blood viscosity –	Spasm (yes)	⇒ Velocity ↑, PI ↓↓	HHH therapy (failure)
Degree of stenosis ↑	Length of stenosis =	BP =	⇒ Velocity ↑	Focal stenosis progression
Degree of stenosis ↓	Length of stenosis =	BP –	⇒ Velocity ↓	Focal stenosis regression
Length of spasm ↑	Degree of spasm =	BP =	⇒ Velocity = or ↓	Diffuse vasospasm
Length of spasm ↓	Degree of spasm –	BP –	⇒ Velocity – or ↑	Focal vasospasm

↑, Increase; –, unchanged; ↓, decrease; PI, the pulsatility index (Gosling); HHH, hypertension–hemodilution–hypervolemia.

1.2.2.TCD INTRODUCTION

The advantages of ultrasound for vascular diagnosis are well known. It is a fast, portable, non-invasive, repeatable and inexpensive technique[6-8].

Diagnostic ultrasound provides an evaluation of cerebrovascular hemodynamic, structure, and anatomy. Hemodynamic information usually is obtained using Doppler ultrasonography, or its derivatives. Transcranial color flow imaging with ultrasound provides a fast way to visualize the spatial course and flow direction in the arteries of the circle of Willis in a two-dimensional plane image in real time.

The chief advantages of TCD are as follows: It can be performed at the bedside and repeated as needed or applied for continuous monitoring; it is frequently less expensive than other techniques; and dye contrast agents are not used. Its chief limitation is that it can demonstrate cerebral blood flow velocities only in certain segments of large intracranial vessels, although large-vessel intracranial arterial disease commonly occurs at these locations. which remain relatively constant in diameter during moderate pressure fluctuations or changes in microcirculatory function, can provide an index of relative flow changes in response to small blood pressure changes and physiologic stimuli to assess autoregulation and vasomotor reactivity (VMR) of the distal cerebral arteriolar bed. VMR testing techniques of static (i.e., at rest) or dynamic (i.e., after provocative stimuli) cerebral autoregulation include measuring changes in flow velocities following 1) hemodynamic stimuli (rapid leg cuff deflation, Valsalva maneuver, deep breathing, ergometric exercise, head-down tilting, orthostatic and lower body negative pressure, beat-to beat spontaneous transient pressor and depressor changes in mean arterial pressure), 2) CO2 inhalation (hypercapnia/hyperventilation hypocapnia), 3) the breath-holding index (BHI), 4) acetazolamide injection,and 5) the transient hyperemia response and its variants[6].

In recent years this technique has been refined to the point where it has become a principal methodology for clinical study of the fetal and neonatal brain and an important ancillary test for the cerebral vessels and the heart in adults. The instrument for this application consists of a transducer capable of converting electrical energy to ultrasound waves of a frequency ranging from 5 to 20 kHz. These are transmitted through the intact skull into the brain. The different tissues have a variable acoustic impedance and send echoes back to the transducer, which displays them as waves of variable height or as points of light of varying intensity[6-8].

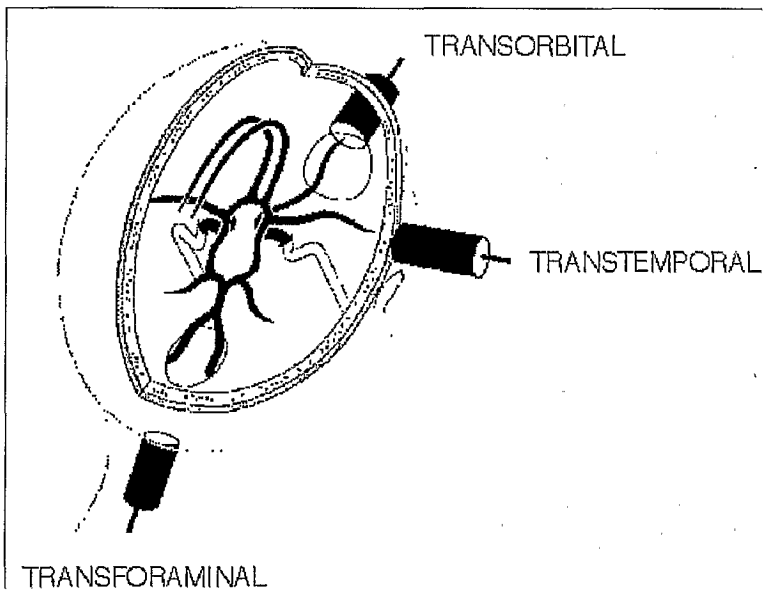
Similar instruments are used to insonate the basal vessels of the circle of Willis ("transcranial Doppler"), the cervical carotid and vertebral arteries, and the temporal arteries for the study of cerebrovascular disease. Their greatest use is in detecting and estimating the degree of stenosis of the origin of the internal carotid artery. In addition to providing a sound image of the vascular

structures, the Doppler frequency shift caused by flowing red blood cells creates a display of velocities at each site in a vessel. The transcranial Doppler utilizes a 2-MHz pulsed signal that is able to transgress the calvarial bone in adults and then receives a frequency-shifted signal from the blood flowing in the lumen of the basal vessels. This allows the detection of vascular stenosis and the greatly increased blood flow velocity caused by vasospasm from subarachnoid hemorrhage. This methodology has several advantages, notably that it is noninvasive, harmless (hence can be used repeatedly), convenient because of the portability of the instrument, and inexpensive.

However, the field of ultrasonic diagnosis also has it detractors and limitations. For many applications, ultrasound has not been thoroughly tested for its utility, accuracy and validity in multicenter studies.

Careful outcomes research investigating the accuracy and cost benefit of ultrasound is needed to establish the utility of this technique for any clinical situation where we surmise that it should be routine. Many such studies have been carried out and have established the value of ultrasound. Based on American academy of neurology guideline, There are insufficient data to support the routine clinical use of TCD/TCCS for other indications including migraine, cerebral venous thrombosis, monitoring during cerebral angiography, evaluation of arteriovenous malformations, and evaluation of cerebral autoregulation in other settings (Type U recommendation)[6].

Picture 1.2.1.Transcranial Doppler windows.



1.2.3.TCD SPECTRAL DISPLAY AND ANALYSIS[7]

Because RBC flowing in vessels move at a variety of speeds and directions,there is a spectrum of different blood flow velocities with any given sample volume at any time.

With the hemodynamic changes that occur throughout the cardiac cycle,the spectrum of velocities also change over time.This diversity of flow velocities within the vessel is displayed visually by use of the Fast Fourier Transform (FFT) display.

Many hemodynamic parameters are derived from analysis of FFT display of the Doppler velocity data.Analysis includes specific objective parameters such as flow direction, peak systolic flow velocity and end_diastolic flow velocity, as well as several indirect or derived parameters such as width or spread of the spectral band of velocities, flow acceleration time(systolic acceleration slope),pulsatility, or resistivity index.

Flow direction, peak systolic flow velocity,and end_diastolic flow velocity can be detected from spectra.

Pulsatility index: (PSV_EDV)/MFVResistivity index: (PSV_EDV)/PSV

1.2.4. TCD AND MIGRAINE[9-15]

Migraine is hypothesized to be a neurovascular coupling disorder, where the cerebral vascular reactivity is malfunctioning. Measuring homodynamic changes during migraine without causing more disturbance has always been a challenge.

During common migraine attacks CBF appears to decrease focally in the posterior part of the brain to a level around 20 ml/100 g/min which is consistent with a mild degree of ischemia. In most cases true CBF may change 50% or more in the low flow areas without giving rise to significantly measurable changes of CBF.

Transcranial Doppler ultrasound (TCD) has been used extensively to study the vascular feature of migraine. This method provides information about flow velocity changes in individual cerebral arteries as representation of cerebral blood flow.

Iversen and associates, by means of ultrasound measurements, documented a dilatation of the superior temporal artery on the side of the migraine during the headache period. The same dilatation in the middle cerebral arteries has been inferred from observations with transcranial Doppler imaging. The well established complication of cerebral infarction is also in keeping with a vascular hypothesis, but it involves only a tiny proportion of migraineurs. This vascular hypothesis must be regarded as uncertain, but clearly there is frequently a reduction in blood flow during auras. The

original opinion expressed by Wolf that a vascular element is responsible for the cranial pain of migraine is also unconfirmed, but this view is still favored by many headache experts.

Studies investigating the diagnostic value of ultrasonic features in migraine have not provided encouraging results because of their low sensitivity. However, preliminary results suggest that the study of cerebrovascular reactivity may enhance the diagnostic yield of TCD and provide information on the pathophysiology of migraine. Recent studies with TCD have suggested an alteration of vascular response to visual and motor stimulation as well as to CO_2 both outside and during attacks.

During the headache-free period, migraineurs with and without aura had significantly elevated mean velocities in all intracranial arteries except the right internal carotid artery at the level of the siphon. Velocities in migraineurs with aura did not differ significantly from velocities in those without aura. Markedly increased velocities were noted in a subset of interictal migraineurs. Two explanations are possible: 1) Blood flow velocities may increase in response to a decrease in the cross sectional area of a vessel at or near the point of insonation. 2) Alterations at the level of the cerebral arteriole may affect regional cerebral blood flow, thereby changing blood flow velocities at the point of insonation. Transcranial Doppler sonography alone cannot sort out which process is responsible for the vascular response.

1.3.Review articles

❋ In a study that has been published in "cephalalgia" journal in 2004, cerebrovascular response to repetitive visual stimulation in interictal migraine with aura was evaluated. TCD was used to access cerebral blood flow velocity (CBFV) changes in MCA and PCA in relation to repetitive checkerboard visual stimulation. Stimulation consisted of 10 consecutive cycle, each comprising 10s stimulation and 10s rest. TCD recording were analyzed using stimulated averaging algorithm. Data of 19 interictal migraineurs with aura were compared to those 19 headache free volunteers. The CBFV increases in PCA and MCA during visual stimulation was significantly larger and steeper in migraineurs than in controls (P= 0.017 and P= 0.005). The response in PCA remained stable over the 10 stimulation cycle both in migraineurs and in controls. The response in MCA was stable only in migraineurs. In controls it decreased over the last 5 stimulation cycle compared with the first cycles (P= 0.004).

Migraine with aura exhibit a larger cerebrovascular response to repetitive visual stimulation compared to headache free subjects. A reduction adaptation to environmental stimuli in migraine was suggested, since there was no habituation in migraineurs in contrast to healthy controls.

Differences between our study and the study in Swiss:

1. we selected only patients with classic migraine who have typical visual aura.
2. we considered the side of headache and visual aura. If there was a prominent side for headache and aura, both side were evaluated.
3. we evaluated MCA, ACA and PCA in both groups and photo-stimulation was done only for PCA.
4. This was the first study about migraineurs and TCD in Iran. So probable ethic difference can be removed[11].

❋ In study that was done in November 2003, blood flow velocity fluctuation in MCA of migraineurs was checked. The aim of study was to establish whether fluctuation in MCA blood flow velocity are fractal in physiologic conditions and if so, whether this feature has been lost in migraine. As the role of vasomotor disturbance has been already evidenced in pathophysiology of this disease, TCD was done via two channels through the transtemporal windows. The examination were performed in supine rest in two hour period in two groups of 7 patients with clinically confirmed migraine with aura during headache free interval and in control group of 4 young healthy volunteers. The finding justify a supposition that the breakdown of multifractal properties of MCA blood flow time series in migraine may results from the vasomotor disturbance present even during headache free intervals[16].

❋ In research institute of neuroscience in china, a study about EEG and TCD analysis in children with migraine was done. The EEG and TCD recording were carried out in 25 children with migraine during ictal and interictal period. The results were that the abnormal rate of EEG and TCD was 85% and 72%. The positive rate EEG provoked test was 60%. They concluded that EEG combined TCD examination in migraine can increase the correct rate of diagnosis and help to differ epilepsy from migraine[17].

❋ A study was done in 2004 in Italy to evaluate basilar and middle cerebral arteries reactivity in patient with migraine. The basilar artery of 1 control subjects and 30 patients with migraine (15 with aura and 15 without aura) during an attack free period, by means of TCD.

They measured changes in flow velocity during apnea in both MCA and The findings show that in patient with migraine with aura, there is impairment in adaptive cerebral hemodynamic mechanisms in the posterior circulation[13].

❋ In 2004, a pilot study was done on 10 migraineurs before and after acupuncture that was to evaluate the effect of repetitive somatosensory stimulation (acupuncture) on cerebrovascular response in migraineurs by functional TCD. Changes of cerebral blood flow velocity in the right PCA and left MCA were measuring by functional TCD during visual stimulation (flicker light over 57 seconds) in 10 migraineurs before and after 10 acupuncture session. The same stimulation paradigm was performed in 10 control subjects. Data indicated that repetitive somatosensory stimulation (acupuncture) might positively influence the abnormal cerebrovascular response in migraineurs. In a subgroup of migraineurs, the dysfunction of the cerebrovascular system deteriorated under the treatment. It is very interesting that in the study, cerebrovascular response to visual stimulation was used as a treatment scale[18].