

A Study of Cerebral Vasoreactivity: Middle Cerebral Artery (MCA) Versus Ophthalmic Artery (OPA)

Akeel AM Hassn Zwain " Ph.D U.K"

Correspondence to Dr. Akeel AMH.Zwain, Department of Clinical physiology, Kufa college of Medicine, university of Kufa. E-mail: drkeel49@yahoo.com

الخلاصة: حديثاً تم استخدام مسبار الدوبلر لفحص كفاءة شريين الدماغ لبيان مدى توسعها عند زيادة تركيز مادة ثاني اوكسيد الكربون في الدم أو تضيقها عند نقصان تركيزه لكن البحوث في هذا المضمار اظهرت نتائج متباينة. أجريت هذه الدراسة على ثلاثين شخص من الاصحاء ، وتم استخدام مسبار الدوبلر لفحص ومقارنة جريان الدم في الشريان المخي الوسطي والشريان البصري عند قطع النفس (لزيادة تركيز ثاني اوكسيد الكربون في الدم) وزيادة سرعة التنفس- اللهيث- بالشهيق والزفير القوي (لتردد ثاني اوكسيد الكربون). وجد انه عند قطع النفس حصول زيادة ملحوظة في جريان دم الشريان المخي الوسطي ونقصان ملحوظ في جريان دم الشريان البصري و عند زيادة سرعة التنفس بالشهيق والزفير القوي حصول نقصان ملحوظ في جريان دم الشريان المخي الوسطي و زيادة ملحوظة في جريان دم الشريان البصري. يستخلص من هذه الدراسة ان كل من الشريان المخي الوسطي والشريان البصري يتصرفان بصورة عكسية عند زيادة أو نقصان تركيز ثاني اوكسيد الكربون في الدم..

Abstract

Background: Recently, cerebral autoregulatory capacity in humans can be studied noninvasively by TCD. The degree of cerebral vasodilatation can be measured by the increased middle cerebral artery (MCA) blood flow in response to hypercapnea induced by either administration of 5% CO₂ or I.V acetazolamide; few studies available on breath hold induced cerebral vasodilatation. Cerebral vasoconstriction can be measured by the decreased MCA blood flow in response to hypocapnea induced by hyperventilation. However, conflicting reports exist on the modulatory effect of hypercapnea (induced by breath holding) or hypocapnea (Induced by hyperventilation) on the Ophthalmic artery (OPA) blood flow.

Objective: To demonstrate changes in MCA & OPA blood flow using physiological stimuli: Hypercapnea (induced by breath hold) and hypocapnea (induced by hyperventilation). Secondly, to investigate whether or not OPA would respond in a similar fashion to MCA, to the forementioned stimuli

Methods: 30 healthy individuals were enrolled, using a TCCD sonography; the MCA and OPA were insonated utilizing transtemporal and transorbital windows respectively. A mean of 10 cardiac cycles were used to estimate the base line control of Doppler derived spectral wave forms regarding mean flow velocities (MFV) and resistant indices (RI). The response of change of MCA flow or OPA flow to hypercapnea induced by breath hold (BH) was measured during the last 5 seconds and that to hypocapnea induced by hyperventilation (HV) was measured during 1.5min. Breath holding index (BHI) and full range of vasodilatation of both arteries were also calculated.

Results: In 30 Middle cerebral arteries examined, during breath hold, the MFV_(mca) was significantly increased from a mean of 41.15 ± 2.00 cm/s (range: 22- 54.33) to a mean of 55.22 ± 2.66 cm/s (range: 27.33-84.42) ($p < 0.001$). No significant increase of RI obtained ($P > 0.05$).. When performing hyperventilation, the MFV_(mca) significantly decreased from a mean of 41.15 ± 2.00 cm/s (range: 22- 54.33) to a mean of 26.72 ± 1.72 cm/s (range: 8.92- 53.33), ($p < 0.001$). There was significant increase in RI from a mean of 0.54 ± 0.011 (range 0.38-0.68) to a mean of 0.63 ± 0.015 (range 0.38-0.8), ($p < 0.001$). The calculated MCA full range of vasodilatation was of a mean of $60\% \pm 3.51$

(range 33%-103%). In 30 ophthalmic arteries examined, during breath hold, The $MFV_{(opa)}$ significantly decreased from a mean of 18.49 ± 1.12 cm/s (range: 7.33-32.33) to a mean of 14.55 ± 1.20 cm/s (range: 7.67- 37.00), ($p < 0.001$). No statistical significant decrease of RI during breath hold obtained. When performing hyperventilation, the $MFV_{(opa)}$ significantly increased from a mean of 18.49 ± 1.12 cm/s (range: 7.33-32.33) to a mean of 24.09 ± 1.27 cm/s (range: 8.67 -40.73), ($p < 0.001$). There was no statistical increase of RI, ($P: 0.05$). The calculated OPA full range of vasodilatation was of a mean of $57.03\% \pm 4.53$ (range: 22%-104%).

Conclusion: Ophthalmic artery flow behaves in a different and opposite manner to that of MCA in response to Hypercapnea and hypocapnea.

Key words: Middle cerebral artery, ophthalmic artery, cerebral vasoreactivity, breath hold, hyperventilation, Transcranial Doppler

Abbreviations: MCA, middle cerebral artery, OPA, ophthalmic artery, CBF, cerebral blood flow, MFV , mean flow velocity, PSV , peaked systolic velocity, DV , diastolic velocity, RI, resistant index, BH, breath hold, BHI, breath hold index, HV, hyperventilation, TCD, Transcranial Doppler, TCCD, Transcranial Colored Doppler.

Introduction:

Cerebrovascular atherosclerotic disease may remain asymptomatic for decades, its first manifestation as stroke can be severe and even deadly. It has been shown that Pathologic processes affecting the brain vessels may damage cerebral vasodilatory capacity⁽¹⁷⁾; therefore early detection of cerebral dysfunction plays an important role in the prevention of Cerebrovascular diseases.

Cerebral vasoreactivity may be defined as the capability of cerebral arterioles to dilate and to constrict to enable a constant cerebral blood flow over a wide range of change in systemic arterial blood pressure⁽¹⁷⁾. In this sense it reflects the integrity of the cerebral auto regulatory mechanism in normal individuals or when possibly impaired in several pathomechanisms e.g. cerebral ischemia or trauma, cerebral microangiopathy, occlusive disease of the brain, malignant hypertension hyper perfusion syndrome and migraine^(11, 15).

When studying cerebral vasoreactivity, it seems feasible to shed light on certain anatomical and physiological considerations related to MCA and OPA, as these aspects bear vital interrelationship with the present investigation.

Middle Cerebral Artery (MCA): Anatomical background:

Is the largest branch of ICA; about 18-26 mm long with a diameter of approximately 3 mm, supplies most of the hemisphere including the bulk of the convexity⁽¹²⁾.

Angiographically, MCA is divided into 4 segments(fig.1): M1, describes the artery from its origin to the limen insulae, where the lenticulostriate arteries arise, M2 is the segment that runs along the insula, M3 follows the operculum superior to the insula, M4 describes branches of the MCA that perfuse nearly the entire convex surface of the cerebral hemisphere^(12, 19).

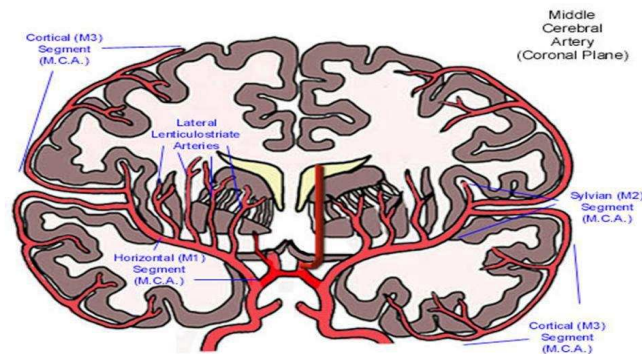


Figure1. Middle cerebral Artery segments

Autoregulation: CBF is maintained at a constant level in normal brain in the face of the usual fluctuations in blood pressure by the process of autoregulation. It is a poorly understood local vascular mechanism. Normally autoregulation maintains a constant blood flow between mean arterial pressures (MAP) 50 mmHg and 150 mmHg⁽²⁴⁾.

Literature review:

There are several physiological factors that affect or change cerebral blood flow (CBF), of these: Rises in CBF due to hypoxia, hypercapnea (raised blood CO₂). This phenomena has been frequently used to measure cerebral vasomotor reactivity⁽¹⁶⁾

It is to be pointed out that various studies exist, using different provocative measures for assessing cerebral vasomotor reactivity: Direct but expensive techniques e.g. using positron emission tomography (PET)⁽²⁰⁾ in which cerebral vasoreactivity is assessed as an interrelationship between cerebral blood volume (CBV) and cerebral blood flow (CBF). Other indirect technique which provides information about cerebral vasoreactivity is by simulating intracerebral arterioles to dilate: By inducing hypercapnea, by increasing arterial PCO₂ or by intravenous administration of 1g acetazolamide⁽¹²⁾. This technique is dose dependant and Diamox causes several unpleasant symptoms including disturbances of taste, headache, and nausea and vomiting.

Much easier method which provides comparable information about cerebral hemodynamic is by means of studying the interrelationship between cerebral blood flow and PCO₂ using TCD of the middle cerebral artery (MCA)^(15, 12). In these studies, hypercapnea is achieved by breathing a fixed mixture of 5% CO₂ or by intravenous injection of acetazolamide. However, a simple and non invasive method was utilized to assess cerebral haemodynamic using a TCD⁽¹⁶⁾ by monitoring the effect of breath holding with or without consecutive hyperventilation. This hypercapnea-hypocapnea semi quantitative technique has been shown to create S-shaped CO₂ – CBF curve; an increase in blood flow velocity of more than 15% is considered to be sufficient to rule out impaired cerebral vasoreactivity^(17, 26)

Recently, breath hold index (BHI) with TCD^(16, 27) was introduced as a parameter to assess vasomotor reactivity of the cerebral vessel, provided the patient is compliant and able to hold breath for at least 30 sec. This index is calculated using the mean flow velocities of the MCA obtained by TCD before breath holding (MFVbaseline) and at the end of 4 sec (MFV end) of breathing after 30 sec of breath holding test, applying

the following equation: $BHI = [(MFV_{end} - MFV_{baseline}) / MFV_{baseline}] \times [(100 / \text{seconds of breath hold})]$ ⁽²⁷⁾.

It was proposed that the normal values of BH index amounts to 1.2 ± 0.6 ; values of less than 0.69 is considered as a predictive of risk of stroke in patients with severe asymptomatic ICA stenosis and symptomatic occlusion ^(21, 25, and 27). This noninvasive maneuver can be used in outpatient clinic or at bed side to screen patients for vasomotor reactivity particularly those with ICA impaired flow ^(16, 21). However, an important limitation of this technique is that a relevant number of patients are unable to hold their breath for the longest time possible after normal inspiration, further, it is so difficult for some patients to perform this test particularly those with chronic obstructive pulmonary disease "COPD" or impaired left ventricular performance.

More recently, it was suggested to combine both breath holding (hypercapnea) and subsequent hyperventilation (hypocapnea) with TCD of the MCA for assessing cerebral vasoreactivity ^(17, 12). The full range of vasodilatation was calculated as the rate of increase of MCA flow on breath holding and its decrease on hyperventilation ^(1,16), using the following equation:

$$100 \times [Vmca (\text{hypercapnea}) - Vmca (\text{hyperventilation})] / Vmca (\text{rest}).$$

Ophthalmic Artery (OPA): Anatomical Background:

The ophthalmic artery is the first major branch to arise from the internal carotid artery (ICA). It originates just after the ICA penetrates the dura to enter the cranial cavity ⁽¹⁴⁾, Fig.(2) ⁽⁹⁾. Occasionally it arises from the ICA within the cavernous sinus before dural penetration. After very short course in the cranial cavity (2-7mm in length), the ophthalmic artery again penetrates through the dura and enters the optic canal where the artery runs alongside the optic nerve ⁽¹⁴⁾ to supply the eye and other structures of the orbit. Just before the ophthalmic artery crosses the optic nerve the central artery of the retina branches out which is the most important branch, as it supplies the major blood flow to most important branch, as it supplies the major blood flow to the retina via branches which include the central retinal artery, the short and long posterior ciliary arteries, and the pial arteries. OPA also supplies a patch of skin on the medial aspect of the forehead to communicate with branches of the external carotid artery.

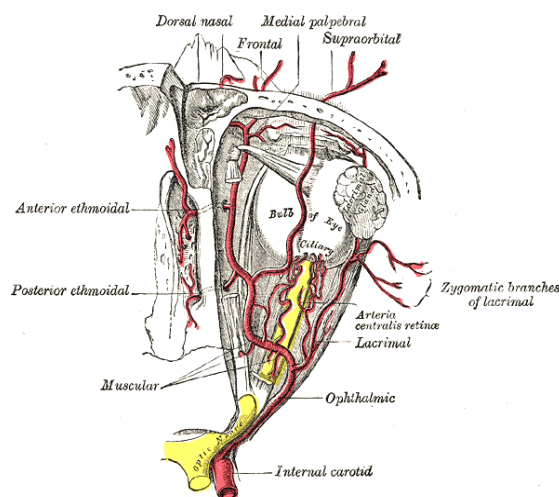


Figure 2. Ophthalmic artery

Literature review:

Concerning studies on OPA vasoreactivity, as stated earlier, the ophthalmic artery is the origin for the blood supply to the optic nerve, as well as the retina. Therefore, the

vasoreactivity of this vessel to CO₂ may have important clinical implications. The available studies on this subject are few and controversial: In a study performed in eight healthy awake subjects tested for Ophthalmic artery CO₂-reactivity using TCD, it was demonstrated that OPA blood flow velocity increased with hypocapnea, but is unaffected by hypercapnea⁽¹³⁾. In this study hypercapnea was achieved by inhalation 5% CO₂ in 40% oxygen for three minutes.

In another study⁽¹⁰⁾ performed in 30 adults, using color Doppler imaging, it was found that hypercapnea (mean end tidal CO₂ increased from 36.4 mmHg to 42.5 mmHg) increased OPA PSV by 13% and the mean end diastolic velocity EDV by 26%, with marked improvement in retrobulber haemodynamic. Similar results were obtained in a study performed in 8 healthy subjects, using TCD technique⁽²⁾, acetazolamide induced hypercapnea was reported to cause increased flow in both MCA and OPA. On the other hand in a study performed in 10 healthy subjects, using 2-vessel Transcranial Doppler sonography⁽⁸⁾, CO₂ inhalation was found to cause a decrease in OPA flow velocity and increase in ipsilateral MCA flow velocity.

The present study was devoted first, to demonstrate modulatory changes of MCA & OPA blood flow to hypercapnea and hypocapnea using physiological stimuli: Hypercapnea (induced by breath hold and hypocapnea (induced by hyperventilation). Secondly, to investigate whether or not OPA would respond in a similar fashion to MCA, to the fore mentioned stimuli; such stimuli may occur during daily activities.

Subjects and Methods:

The study was conducted on 30 adult healthy subjects of age ranging between 20-60y (Mean±SEM: 36±1.80), 20 were men and 10 were women. Changes in MCA and ipsilateral OPA blood flow were measured in the same individual using Siemens Versa Plus Sonoline equipment, (230V PAL version, Germany) with Color flow and TCD facilities. A phased array probe of 2-2.5MHz was used to insonate the MCA and a linear probe of 7.5- 10MHz to insonate the OPA. All subjects were allowed to rest quietly and examined in supine position. Before proceeding to the definitive recording, subjects were trained to perform the procedure of breath holding and hyperventilation correctly. To study the MCA blood flow velocities, the subject was asked to breathe normally, the MCA was first identified, usually M1 segment (Fig.1) by color flow utilizing a transtemporal window. To obtain MCA spectral wave form, PW Doppler sample volume was place in the middle of the artery, at an angle of 0° and the means of PSV, DV and RI of 10 cardiac cycles were measured. The mean flow velocity baseline control of MCA (MFVmca) was calculated as $[DV + 1/3(PSV - DV)]$ ⁽⁷⁾. To demonstrate the response of MCA flow to hypercapnea, the subject was asked to hold breath, for a longer time possible, after mild to moderate deep inspiration; the changes of blood flow of MCA is calculated as the means of the above cited parameters during the last 5 sec.(Fig.3). The mean flow velocity of MCA to breath hold (BHmca) was calculated in the similar manner as above. The breath hold index (BHI) is calculated as $BHI = [(MFV_{end} - MFV_{baseline}) / MFV_{baseline}] \times [(100 / \text{seconds of breath hold})]$. To demonstrate the effect of MCA to hypocapnea, the subject was asked to perform moderate hyperventilation for 1.5 min, the Doppler spectral parameters of changes in MCA blood flow and the mean flow velocity of MCA to hyperventilation (HVMca) were calculated in the same manner as above (Fig.3). The full range of vasodilatation is calculated as $100 \times [Vmca(\text{hypercapnea}) - Vmca(\text{hyperventilation})] / Vmca(\text{rest})$

Regarding OPA Doppler study: In the first place, history was taken to rule out previous eye disease, e.g. glaucoma, retinopathy or eye surgery concerning intraocular

lens implantation. To insonate OPA, a transorbital window used, by placing the probe directly on the eye ball, keeping the head and neck straight. Care was taken to minimize the power of the equipment at the lowest level consistent with satisfactory recordings; a stretcher used to support the handheld probe so that keeping the probe just touching the closed eye lid. A sufficient length of OPA segment was identified by color flow, and then Doppler sample volume was placed in the middle of the artery at 0° to obtain OPA wave form during normal respiratory activity. The means of PSV, DV and RI were taken as a baseline control (Fig.5). The effects of hypercapnea (breath holding) and hypocapnea (hyperventilation) on OPA blood flow and full range of dilatation were studied using the above described protocol applied to MCA. All data were videoed and stored in PC computer for further analysis

Statistical Evaluation: All values were given as mean \pm SEM. Paired T test was used and the differences were considered statistically significant at $P \leq 0.05$. Correlations between variables were analyzed using SPSS program version 12.

Results:

30 Middle cerebral arteries as well as 30 ipsilateral ophthalmic arteries were studied during breath holding and subsequent hyperventilation. Both MCA and OPA spectral wave form tracings were noted to exhibit pulsatile diphasic high diastolic flow with Spontaneous fluctuating pattern. Such oscillation of MCA flow was found to be more pronounced in young individuals and less apparent in the elderly (Personal observation).

MCA Vasoreactivity:

Figure 3, a and b, an example of Doppler derived spectral waveform which illustrates respective increase of MCA blood flow during breath holding and decrease of flow during hyperventilation in a normal individual.

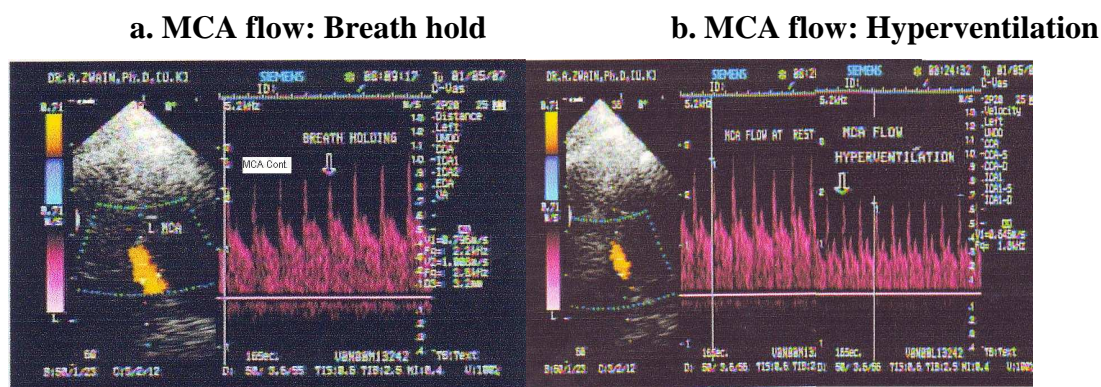


Figure 3. Doppler derived spectral wave form showing changing of MCA blood flow during breath hold (a) and subsequent hyperventilation (b) in a normal subject.

During breath hold, there was statistically significant increase of $PSV_{(mca)}$ from a mean of $64.53 \pm 3.31 \text{ cm/s}$ (range: 34- 110) to a mean of $83.03 \pm 3.75 \text{ cm/s}$ (range: 42- 125), $p > 0.0001$, and diastolic velocity $DV_{(mca)}$ increased from a mean of $29.47 \pm 1.48 \text{ cm/s}$ (range: 15-42) to a mean of $42.085 \pm 2.34 \text{ cm/s}$ (range: 18-69.75), $p < 0.0001$. The mean flow velocity (MFV_{mca}) was significantly increased from a mean of $41.15 \pm 2.00 \text{ cm/s}$ (range: 22- 54.33) to a mean of $55.22 \pm 2.66 \text{ cm/s}$ (range: 27.33-84.42) $p < 0.001$, figure 4,(a). No significant increase of RI obtained, the decrease of RI was from a mean of 0.54 ± 0.011 (range 0.38-0.68) to a mean of 0.51 ± 0.013 (range 0.38-0.71), Fig 4(b).

The % Change of MCA flow during breath holding was 30.75 % (range 12.8-59.8). The calculated breath hold index (BHI) of MCA was of a mean of 0.764 ± 0.051 (range: 0.394 - 1.27).

When performing hyperventilation, there was statistically significant decrease of $PSV_{(mca)}$ from a mean of 64.53 ± 3.31 cm/s (range: 34- 110) to a mean of 45.86 ± 2.84 cm/s (range 16.75-88), and the $DV_{(mca)}$ significantly decreased from a mean of 29.47 ± 1.48 cm/s (range:15-42) to a mean of 17.14 ± 1.28 cm/s (range:5-36) $p < 0.001$. The $MFV_{(mca)}$ significantly decreased from a mean of 41.15 ± 2.0 cm/s (range: 22- 54.33) to a mean of 26.72 ± 1.72 cm/s (range 8.92- 53.33), $p < 0.001$, figure 4,(a). There was significant increase in RI from a mean of 0.54 ± 0.011 (range 0.38-0.68) to a mean of 0.63 ± 0.015 (range 0.38-0.8), $p < 0.001$, figure 4 (b).

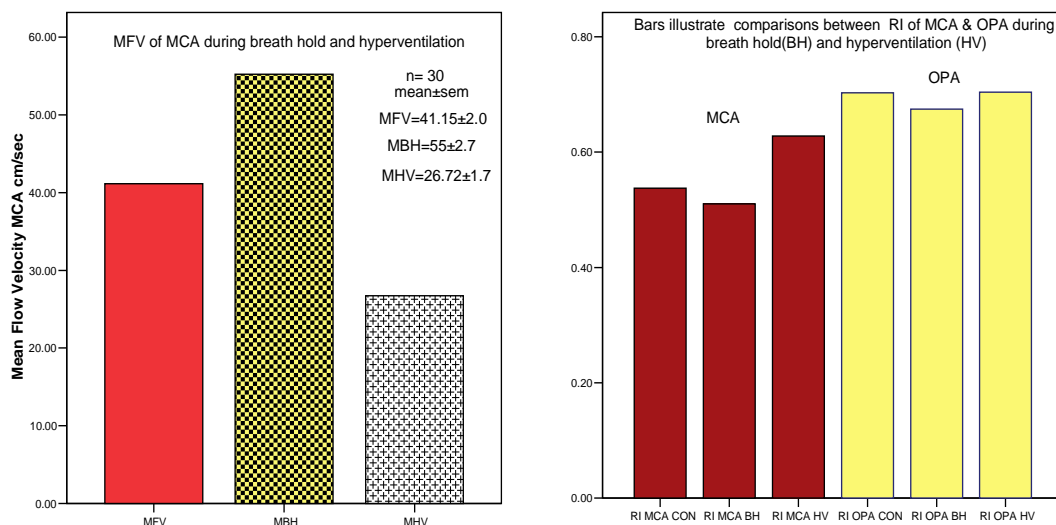


Figure 4. (a) shows the response of MCA flow to breath hold and hyperventilation in 30 MCAs. MFV: mean flow velocity of MCA as a baseline control, MBH: mean flow velocity of MCA during breath hold, MHV: mean flow velocity during hyperventilation. **(b).** Bars illustrate comparisons between resistant indices “RI” of MCA & OPA, during breath hold “BH” and hyperventilation “HV”. RIMCA CON: RI base line control of MCA flow. RIOPACON: RI baseline control of OPA flow

The calculated MCA full range of vasodilatation was of a mean of $60\% \pm 3.51$ (range 33%-103%), figure (7).

OPA Vasoreactivity: Figure 5(a) and (b) an example of Doppler derived spectral wave form showing respective decrease of OPA flow during breath holding and an increase of flow during hyperventilation in a normal individual.

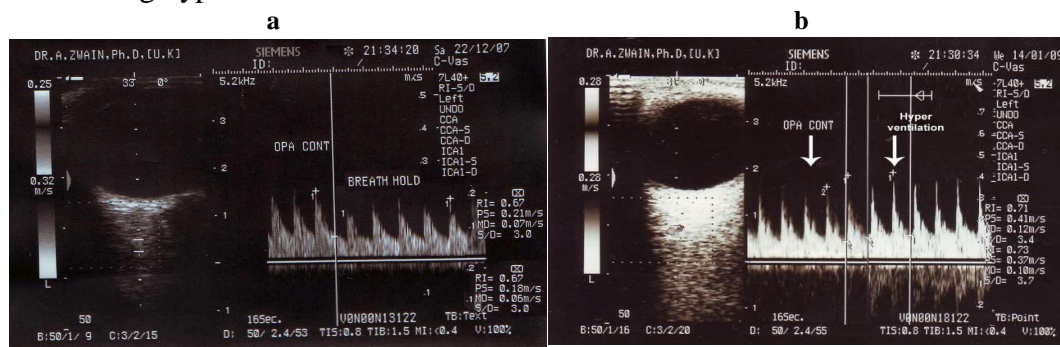


Figure 5. Doppler derived spectral wave form showing changing of OPA blood flow during breath hold (a) and subsequent hyperventilation (b) in a normal subject.

During breath holding, there was statistically significant decrease of $PSV_{(opa)}$ from a mean of 34.56 ± 1.72 cm/s (range :12-55) to a mean of 26.68 ± 1.75 cm/s (range :10-51), $p < 0.001$, and the $DV_{(opa)}$ significantly decreased from a mean of 10.48 ± 0.91 cm/s (range:4-21) to a mean of 8.39 ± 1.02 cm/s (range: 3-30) , $p < 0.001$. The $MFV_{(opa)}$ significantly decreased from a mean of 18.49 ± 1.12 cm/s (range: 7.33-32.33) to a mean of 14.55 ± 1.20 cm/s (range:7.67- 37.00) , $p < 0.001$. No statistical significant decrease of RI during breath hold obtained; the decrease was from a mean of 0.703 ± 0.017 (range: 0.53-0.86) to a mean of 0.67 ± 0.019 (range: 0.41-0.85), figure (6).

When performing hyperventilation, there was statistically significant increase of $PSV_{(opa)}$ from a mean of 34.56 ± 1.72 cm/s (range: 12-55) to a mean of 45.25 ± 1.93 cm/s (range:18-62) $P < 0.0001$, and significant increase of $DV_{(opa)}$ from a mean of 10.48 ± 0.91 cm/s (range:4.0-21) to a mean of 13.51 ± 1.07 cm/s (range:4-31), ($p < 0.001$). The $MFV_{(opa)}$ significantly increased from a mean of 18.49 ± 1.12 cm/s (range: 7.33-32.33) to a mean of 24.09 ± 1.27 cm/s (range: 8.67 -40.73) , $p < 0.001$, figure (6). There was no statistical increase of RI, $P :> 0.05$, the increase of RI was from a mean of 0.703 ± 0.017 (range:0.53-0.86) to a mean of 0.704 ± 0.016 (range:0.41-0.83), figure 4(b).

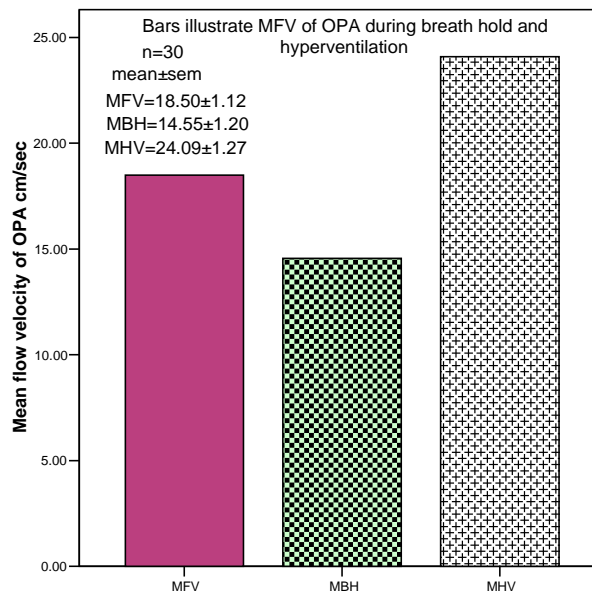


Figure 6. Shows the response of OPA flow to breath holding and hyperventilation in 30 OPAs. MFV: mean flow velocity of OPA as a baseline control, MBH: mean flow velocity of OPA during breath hold, MHV: mean flow velocity during hyperventilation.

The calculated OPA full range of vasodilatation was of a mean of $57.03\% \pm 4.53$ (range: 22%-104%), (fig.7)

As compared with MCA, there was no statistical significant between the two arteries (fig.7)

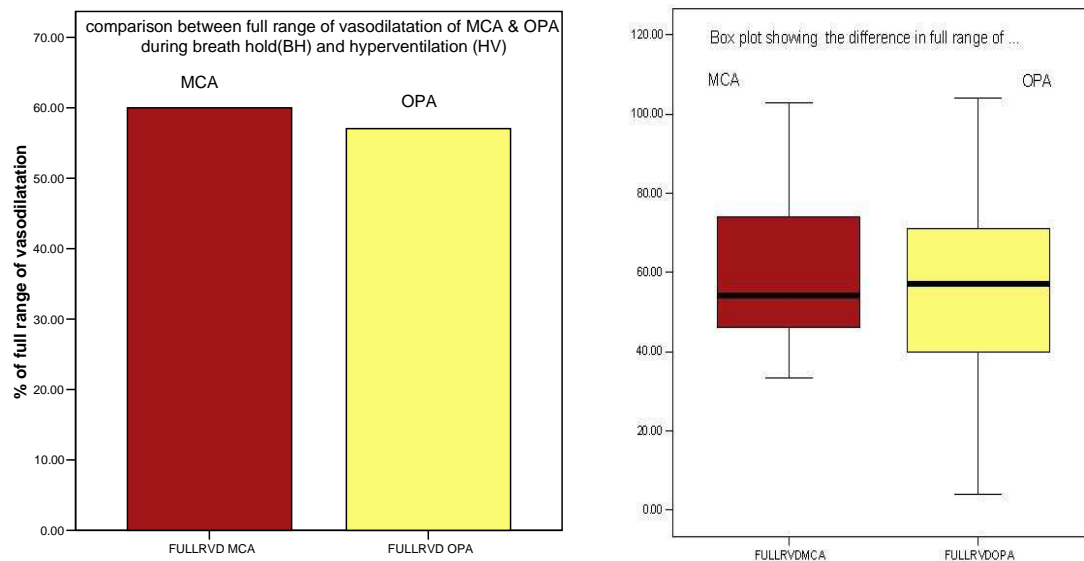


Figure 7. Demonstrates Comparisons between the full ranges of vasodilatation of MCA and OPA.

Discussion:

Cerebral vasoreactivity describes the ability of the cerebral circulation to respond to vasomotor stimuli; the changes in cerebral blood flow in response to such stimuli can be studied by TCD. This technique is rather cheap, simple and can be done at bed side or at outpatient clinic.

The Doppler derived spectral wave forms of both MCA and OPA obtained in this study, showed a fluctuation of flow. This pattern of flow has been demonstrated by several workers who also regarded MCA flow as a good representative of CBF, as MCA carries approximately 80% of the flow volume received by the cerebral hemisphere⁽²²⁾. In another study, Newell et al⁽¹⁸⁾, Droste et al⁽⁶⁾ attributed such fluctuations in CBF to intrinsic mechanism of the regulating arteries, resulting in phasic dilation and contraction of the arterial smooth-muscle cells of the regulating arteries. Further, Terry et al⁽²³⁾ explored the mechanism underlying MCA oscillating flow and hence CBF fluctuations was due to involvement of both fluctuations of arterial blood pressure (ABP) induced by respiration and cerebral autoregulation. These facts would justify our protocol of taking a mean of 10 cardiac cycles flow measurements during baseline control of MCA or OPA flow and when performing the procedure. The more pronounced fluctuation in younger age groups than in the elderly, observed in the present study, would indicate compliant vessels and may be regarded as healthy sign.

In the available literature reports, little information provided on the estimation of MFV; the calculated mean velocity values were from velocity samples using the mean of systolic velocities in at least 10 to 15 heart cycles⁽⁵⁾. In the present study, since cerebral blood flow is pulsatile, the estimation of MFV adopted was according to the formula $[DV + 1/3(PSV - DV)]$. Such estimate would provide a reliable indicator of the effective flow or changes in cerebral blood flow to the stimuli performed.

Further, we are of the concept of using physiological stimuli to induce vasomotor reactivity comprising breath holding followed by subsequent hyperventilation. In previous studies, using CO₂ administration to induce hypercapnea, it was reported that certain adverse effects may develop including intolerance or episodes of angina like symptoms⁽¹⁶⁾. It is to be pointed out that it is difficult for some subjects to hold breath for 30 sec to induce the response of change in MCA or OPA flow, therefore, it seems

feasible to perform breath holding after mild to moderate deep inspiration as suggested by some investigators⁽¹⁷⁾. Further, in other studies the period used for performing hyperventilation was 2min.; in our study, the period adopted for performing this procedure was 1.5 min. This period was chosen to prevent dizziness and the response of change in MCA or OPA flow was noted to reach a steady state during this period; no appreciable change in the response occurred in the remaining half min.

The results of mean base line control of MCA and OPA are rather consistent with the previous studies; however, the results of MFV base line control are slightly lower than that previously reported^(16,13). This slight discrepancy may be attributed to technical cause, as the angle of insonation of MCA was not announced in these studies. Further, data on diastolic velocities or resistant indices in these studies are lacking.

The finding of consistent and significance increase in MCA flow to breath holding is in accordance with previous studies, using breath hold maneuver after normal inspiratory breath or using CO₂ induced hypercapnea⁽¹⁶⁾. The lack of significant change in RI may be attributed to the increase of both systolic and diastolic elements during breath holding. The consistent and significant decrease of MCA flow in response to hyperventilation is similar to those previously demonstrated^(5, 13, 16, 26).

Markus & Harisson in their popular contribution reported in 17 healthy individuals, the BHI was of a range of 0.47- 2.56 and the full range of vasodilatation of MCA after 5% CO₂ administration was 50% -140%. Our results were slightly lower, the BHI was of a range of 0.394 - 1.27 and that of the full range of vasodilatation was 33% -103% . This controversy may be due to the fact that longer time of breath holding tolerated when using the maneuver of breath holding after mild to moderate deep inspiration.

Concerning changes of OPA flow: In contrast to MCA, breath holding (Hypercapnea) resulted in significant decrease in the mean OPA flow of both systolic and diastolic elements. This finding is in agreement with that reported by Harer and Thomas⁽⁸⁾ who showed significant relative decrease of OPA velocity in response to increase in end-tidal CO₂ pressure by 5 mm Hg. Conversely, this result is conflicting with that obtained by other investigators who demonstrated that hypercapnea induced by CO₂ resulted in either no change in OPA flow⁽¹³⁾ or increase of OPA flow⁽¹⁰⁾. Whereas acetazolamide induced hypercapnea resulted in increase of OPA flow⁽²⁾. In all above cited studies OPA was insonated at a depth of 50mm. It is pertinent to point out that insonating OPA is not an easy task; the best way to obtain reasonable flow is by color flow mapping.

On the other hand hyperventilation (Hypocapnea) resulted in highly significant increase of OPA flow. This result is in accordance with that reported by lorri et al.⁽¹³⁾.

The results of the present investigation demonstrate that ophthalmic artery behaves in a different and opposite manner to that of MCA in response to hypercapnea or hypocapnea induced by physiological stimuli. A feasible explanation for these modulatory effects is perhaps due to the occurrence of "steal effect" during hypercapnea induced by breath holding which is known to have a significant dilatory effect on the large cerebral blood vessels resulting in reduction of flow velocity in the OPA. Conversely, during hypocapnea induced by hyperventilation an "inverse steal" may occur, as hyperventilation has a profound constrictor effect on cerebral blood vessels with the result of increased flow in the OPA. Furthermore, the finding of increased flow of the OPA on hyperventilation may be explained on the bases of the following argument: It is known that hyperventilation results in an increase of cardiac output through increase of heart rate and stimulation of pulmonary stretch receptors. As a result, "retrograde" flow in ophthalmic artery occurs through many anatomic connections with branches of the external carotid artery^(9, 14).

Our Data may provide a “gold standard” for further study. This work was extended to investigate the effect of sildenafil on cerebral vasoreactivity (MCA&OPA blood flow) in normal individuals and Type2 diabetic patients. Some avenues for further research may be suggested, e.g., studying the effect of sildenafil on central retinal artery vaso reactivity.

References:

1. Alberto Marcos, José A. Egido, Marisa Barquero, Cristina Fernandez, Eduardo Varela de Seijas. *Cerebrovasc Dis* 1997; **7**:14-18.
2. Barbara Kiss, Susanne Dallinger, Oliver Findl, Georg Rainer, Hans-Georg Eichler, and Leopold Schmetterer. Acetazolamide-induced cerebral and ocular vasodilation in humans is independent of nitric oxide. *Am J Physiol Regul Integr Comp Physiol* 1999; **276**: R1661-R1667.
3. Dahl, A., Lindegaard, K.F. Russell, D.A. comparison of Transcranial Doppler and Cerebral Blood Flow Studies to Assess Cerebral Vasoreactivity. *Stroke* 1992; **23**: 15-19
4. Dahl A., Russell D., Kjell R., Nyberg-Hansen, R., & EE., Kerty, Cerebral Vasoreactivity Assessed With Transcranial Doppler and Regional Cerebral Blood Flow Measurements. *Stroke* 1995; **26**:2302- 2306.
5. Dahl, A., Russel, D., Nyberg - Hansen, R., Rootwelt, K.&bake, S.J.Cerebral Vasoreactivity in unilateral carotid artery disease. A comparison of blood flow velocity and regional cerebral blood flow measurement. *Stroke* 1994; **25**:621-6
6. Droste DW, Krauss JK, Berger W, Schuler E & Brown MM. Rhythmic oscillations with a wavelength of 0.5–2 min in transcranial Doppler recordings. *Acta Neurol Scand* 1994 ; **90**: 99–104.
7. Eicke B.M, Buss E., Bahr R.R, Haijak G., paulus W. Influence of Acetazolamide and CO₂ on Extracranial Flow Volume and Intracranial blood flow velocity. *Stroke* 1999; **30**: 76-80.
8. Harer C., Thomas Ch. Opposite Responses of Ophthalmic and Middle Cerebral Arteries to Carbon Dioxide Inhalation: A Transcranial Doppler Study. *Cerebrovasc Dis* 1996; **6**:114-117
9. http://en.wikipedia.org/wiki/Ophthalmic_artery
10. Klaudia K. Huber, Herbert Adams, Andreas Remky I and Kay O. Arend. Retrobulbar haemodynamics and contrast sensitivity improvements after CO₂ breathing. *Acta Ophthalmologica Scandinavica* 2007; **84** Issue 4: 481 - 487.
11. Klingerhofer, J.& Sander, D. Doppleer CO₂ test as an indicator of cerebral and prognosis in sever intracranial haemorrhage. *Stroke* 1992; **23**: 962-6.
12. Krayenbühl, Hugo; Yaşargil, Mahmut Gazi; Huber,., ; Bosse, George. *Cerebral Angiography Thieme* 1982; IS : 105-123
13. Lorri A. Lee, Monica S. Vavilala, Arthur M. Lam, Colleen Douville, BA, Anne Moore, Elizabeth Visco, and David W. Newell. Ophthalmic artery blood flow velocity increases during hypocapnia . *Canadian Journal of Anesthesia* 2004; **51**:388-392.
14. Louis R. Caplan, Warren J. Manning. *Anatomy of the arteries that supply the eyes. Brain embolism - Medical* 2006; 348 pages
15. Magae T.R, Davies A.H., Baird R.V., and Horrocks, M. Blood flow in the internal carotid artery and velocity in the middle cerebral artery during carotid endarterectomy. *Cardiovascular surgery* 1994; **2**: 37-40
16. Markus, H., S.,& Harrison, M.J.G. Estmation of cerebral using transcranial Doppler, including the use of breath holding ads the vasodilatory stimulus. *Stroke* 1992; **23**:668-73

- 17.** Michael G., H. and Stephen P. M. Cerebrovascular Ultrasound 2001; pp 152–153; 324-334; 328-329
- 18.** Newell DW, Aslid R, Stooss R & Reulen HJ. The relationship of blood flow velocity fluctuations to intracranial pressure B waves. J Neurosurg 1999; **76**: 415–421
- 19.** Osborn, Anne G.; Jacobs, John M. Diagnostic Cerebral Angiography, Lippincott Williams & Wilkins 1999; 143-144
- 20.** Powers, W.J & Raichle, M., E. Positron emission tomography and its application to the study of cerebrovascular disease in man. Stroke 1985; **16**: 361-75.
- 21.** Silvestrini M., Vernieri F., Pasqualetti P., et al: Impaired Cerebral Vasoreactivity and Risk of Stroke in Patients With Asymptomatic Carotid Artery Stenosis. JAMA 2000; **383**: 2122-2127
- 22.** Toole JF. Cerebrovascular Disorders 1984 (ed 3) New York, Raven Press; (pp) 1–18
- 23.** Terry Bo-Jau Kuo, Chang-Ming Chern, Wen-Yung Sheng, Wen-Jang Wong and Hwa Hu. frequency Domain Analysis of Cerebral Blood Flow Velocity and its Correlation With Arterial Blood Pressure. Journal of Cerebral Blood Flow & Metabolism 1998); 18: 311–318.
- 24.** Update in anesthesia, urticle 4 from issue 8(1998): page 3 of 4
- 25.** Vernieri F, Pasqualetti P, Matheis M et al : Effect of collateral flow and cerebral vasomotor reactivity on the outcome of carotid artery occlusion. Stroke 2001; **32**: 1552-1558
- 26.** Widder, B. The use of breath holding for evaluation of cerebrovascular reserve capacity. Stroke 1992; **23**, 1680.
- 27.** William J. Zweibel and John S. Pellerito. Introduction to vascular Ultrasound 2005; **5**: 117.