Ultrasonographic assessment of the optic nerve sheath diameter during variations in $PetCO_2$ and controlled internal jugular venous occlusion: A volunteer study

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Background

Elevated intracranial pressure (ICP) is a common and potentially life threatening condition arising from a variety of pathological conditions including traumatic brain injury (TBI), intracranial hemorrhage, subarachnoid hemorrhage and brain tumors. Monitoring the ICP is the most important aspect of the management of these patients and use of ventricular catheter is the gold standard method of measuring ICP. The potential risks of misplacement, infection, hemorrhage and obstruction have led to development and implementation of alternative intracranial devices and techniques for monitoring ICP. However, the use of intracranial ICP monitoring devices is restricted to the patients in neurosurgical intensive care units and they often require neurosurgical team for the placement. Imaging modalities such as computerized tomography (CT) and magnetic resonance imaging (MRI) are used for the diagnosis for raised intracranial pressure but risk of radiation and accessibility are the main disadvantages. Recently, transorbital ultrasonography has gained popularity as a noninvasive bedside exam that has been shown to be useful in the diagnosis of raised ICP by evaluating the change in the optic nerve sheath diameter (ONSD). The optic nerve is surrounded by cerebrospinal fluid, which is connected to the intracranial subarachnoidal space. Hence any variations in the CSF pressure will have a direct effect on the ONSD[2]. Previous histological studies have revealed that the region approximately 3 mm behind the papilla segment of the optic nerve is where maximal diameter fluctuations are seen and this is the ideal region for ONSD measurement.[3] This has been validated by numerous studies showing significant correlation between ONSD and elevated ICP with good intra and inter-observer

reliability [4] [5]. Therefore, transorbital ultrasonographic measurement of ONSD appears to be a noninvasive, relatively inexpensive bedside examination for the diagnosis of raised ICP.

However the most of the literature on the use of changes in the ONSD for monitoring the changes in ICP came from the patients in the intensive care units with elevated intracranial pressure.[2,7] Currently there are no data on how ONSD changes with acute increase or decrease in ICP. In addition, we don't know how soon the ONSD changes with acute changes in intracranial pressure.

Intracranial pressure is determined by the intracranial volume which in turn determined by the intracranial content namely, brain tissue, intracranial vessels (artery and veins) and the cerebrospinal fluid. There are limited non-surgical options that can be used to alter the ICP. Increase in the volume of intracranial vessels by either arterial dilation and/or occlusion of venous drainage can lead to increase in intracranial pressure. Carbon dioxide (CO2) is a potent cerebral vasodilator, hypercapnia induced cerebral vasodilatation can lead to increase in ICP secondary to increase in intracranial volume. Similarly, obstruction to the cerebral venous drainage can also increase the intracranial pressure. Controlling the Co2 and improving the venous drainage are the two fundamental principles in the anesthesia management of patients with increased ICP. [6] [8]

In order to use transorbital ultrasonographic measurement of ONSD as a method of monitoring changes in ICP, we need to determine how reliable the change in ONSD with controlled acute changes in intracranial pressure is. Controlled changes in ICP can be produced by either manipulation PCO2 and/or cerebral venous

drainage. Among the methods available for CO2 manipulation, we have shown that Model-based Prospective End-Tidal Targeting (MPET) system (RespirAct™-Thornhill research Inc) is the most reliable method for accurate and precise targeting of Co2. [9-10] Briefly, the RespirAct™ is a custom designed breathing circuit that uses computer controlled gas blending to quickly and precisely control end-tidal carbon dioxide levels[9]. The RespirAct™ has two main features for this study. First, it is capable of rapidly and precisely targeting a series of $PetCO_2$ independent of the subject's breathing pattern[10]. These changes can be induced within three breaths, are accurate to within ± 1 mmHg, and can be sustained at constant levels. Second, it has been shown in humans and animals that a unique characteristic of this system is that the end tidal CO2 ($PetCO_2$) is precisely equal to arterial CO2 ($PaCO_2$).[9] With regards to venous outflow obstruction, both Valsalva maneuver (forced inspiration with closed glottis) and /or compression of internal jugular veins (IJV) are the two commonly used physiological methods that can cause an increase in ICP. However, compared to Valsalva maneuver which is dependent on the individual's effort and a variable effect, jugular venous compression is more reliable and reproducible method to increase ICP. Bilateral jugular occlusion is sometimes used during neurosurgical procedures during craniotomy opening especially in patients who are at risk of air embolism.[11] Jugular venous occlusion can be done using a custom made neck collar and previous investigations have used a similar device in a rat model to demonstrate the protective effects on slosh-mediated brain injury by increasing intracranial blood volume [12,13]. While the collars have not yet been studied on people for their effectiveness at preventing

concussions, many studies have looked at the effect of neck collars on both jugular compression and ICP.[14,15]

Aim of our study to determine the changes in ONSD with acute controlled changes in ICP in healthy volunteers. Transorbital ultrasound will be used for measuring the changes in ONSD. The controlled changes in ICP will be produced by manipulating the PCO2 with the use of Respiract and jugular venous compression with the use of custom made neck collar.

References

References

1. Lundberg N. Continuous recording and control of ventricular fluid pressure in neurosurgical practice. *Acta Psychiatr Scand Suppl* 1960;36(149):1-193.

2. Rajajee V, Thyagarajan P, Rajagopalan RE. Optic nerve ultrasonography for detection of raised intracranial pressure when invasive monitoring is unavailable. *Neurol India* 2010;58(5):812-3.

3. Helmke K, Hansen HC. Fundamentals of transorbital sonographic evaluation of optic nerve sheath expansion under intracranial hypertension II. Patient study. *Pediatr Radiol* 1996;26(10):706-10.

4. Bauerle J, Lochner P, Kaps M, Nedelmann M. Intra- and interobsever reliability of sonographic assessment of the optic nerve sheath diameter in healthy adults. *J Neuroimaging* 2012;22(1):42-5.

5. Dubourg J, Javouhey E, Geeraerts T, Messerer M, Kassai B. Ultrasonography of optic nerve sheath diameter for detection of raised intracranial pressure: a systematic review and meta-analysis. *Intensive Care Med* 2011;37(7):1059-68.

6. Rossanda M, Vecchi G. Determination of cerebral autoregulatory status and pCO2 responsiveness. *Int Anesthesiol Clin* 1979;17(2-3):425-38.

7. Seo H, Kim YK, Shin WJ, Hwang GS. Ultrasonographic optic nerve sheath diameter is correlated with arterial carbon dioxide concentration during reperfusion in liver transplant recipients. *Transplant Proc* 2013;45(6):2272-6.

8. Mavrocordatos P, Bissonnette B, Ravussin P. Effects of neck position and head elevation on intracranial pressure in anaesthetized neurosurgical patients: preliminary results. *J Neurosurg Anesthesiol* 2000;12(1):10-4.

9. Slessarev M, Han J, Mardimae A, Prisman E, Preiss D, Volgyesi G, et al. Prospective targeting and control of end-tidal CO2 and O2 concentrations. *J Physiol* 2007;581(Pt 3):1207-19.

10. Mark CI, Slessarev M, Ito S, Han J, Fisher JA, Pike GB. Precise control of end-tidal carbon dioxide and oxygen improves BOLD and ASL cerebrovascular reactivity measures. *Magn Reson Med* 2010;64(3):749-56.

11. Losasso TJ, Muzzi DA, Cucchiara RF. Jugular venous compression helps to identify the source of venous air embolism during craniectomy in patients in the sitting position. Anesthesiology. 1992 Jan;76(1):156-7.

12. Turner RC, Naser ZJ, Bailes JE, Smith DW, Fisher JA, Rosen CL. Effect of slosh mitigation on histologic markers of traumatic brain injury: laboratory investigation. *J Neurosurg* 2012;117(6):1110-8.

13. Smith DW, Bailes JE, Fisher JA, Robles J, Turner RC, Mills JD. Internal jugular vein compression mitigates traumatic axonal injury in a rat model by reducing the intracranial slosh effect. *Neurosurgery* 2012;70(3):740-6.

14. Stone MB, Tubridy CM, Curran R. The effect of rigid cervical collars on internal jugular vein dimensions. Acad Emerg Med. 2010 Jan;17(1):100-2.

15. Davies G, Deakin C, Wilson A. The effect of a rigid collar on intracranial pressure. Injury. 1996 Nov;27(9):647-9

Hypothesis

Our hypothesis is that there will be a change in *optic nerve sheath diameter (ONSD) with the raised PCO2 and internal jugular venous occlusion*

Objective of study

The main objective of this study is to determine the changes in ONSD with controlled increase in intracranial pressure with hypercapnia and jugular venous occlusion in healthy human volunteers.

Proposed Methodology

The study will be conducted in accordance with guidelines set forth by the University of Toronto, University Health Network Ethics Committee for use of human subjects in research. Ethics board approval will be obtained as well as written consent from each subject.

Study Design

This will be a prospective, non-randomized, observational study.

Recruitment

Healthy volunteers will be recruited by poster advertisement around the hospital. They will be asked to contact Dr. Jigesh Mehta, Research coordinator for the study. His contact number and email will be provided. They will then be screened according to the inclusion and exclusion criteria's to see if they are suitable for the study.

Inclusion criteria

Adult healthy volunteers who are above the age of 18
ASA 1
Body mass index (BMI) less than and equal to 35
Neurologically normal subjects with no symptoms other than occasional non-severe headache

Exclusion criteria

BMI above 35
Lack of informed consent
Language barrier
Medical students and/or anesthesia residents going through the department as part of their rotation
Pregnancy
Frequent migraine headache

Informed Consent

The background of the study, benefits and risks will be explained to the subject and the informed consent form will be signed and witnessed if the subject agrees to participate.

Study protocol

Ultrasound measurement of ONSD

All volunteers will be fully awake throughout the study and be kept comfortable. The transoccular ultrasound examinations of the ONSD will be carried out using a SonoSite Edge (FUJI FILM SonoSite Inc. US) ultrasound system and a 7-10 MHz linear probe. Two trained investigators will perform investigations on both eyes of all subjects independently without being aware of each other's study results. All patients will be in the supine position and the probe will be gently placed on the temporal part of the closed upper eyelid. Contact with the eye will be gentle at all times and pressure never directly applied on the globe with the probe. A Tegaderm film (Transparent film dressing, 3M Canada) will be applied over the eye to protect the patient from the ultrasound gel applied during sonography. Once the anterior part of the optic nerve is depicted in the transverse/axial plane showing the papilla and optic nerve in its longitudinal course, the ONSD will be assessed 3 mm behind the papilla, as described previously (Figure 3). Each eye will be examined 3 times by each investigator and the mean value of the ONSD will be used for further calculations.

Carbon dioxide Manipulation

The volunteers will don an airtight mask connected to the RespirAct™ sequential gas delivery breathing circuit. The subject will lie supine on a stretcher. Gas will be supplied by a computerized MPET system (RespirAct™). During control conditions, room air will be supplied at flows greater than the subject's minute ventilation. These studies will be done at the subject's baseline end-tidal CO_2 tension (usual range 35 – 40 mmHg). The $PetO_2$ will be fixed at 100 mmHg, a normal $P_{ET}O_2$ for most subjects. We will record baseline values for 120 seconds and then the $PetCO_2$ will be increased to +10 mmHg (Hypercapnia I) from baseline and held for 5 minutes in order to complete ONSD measurements. The venous compression neck collar will then be applied and ONSD measurements will be repeated. Following measurements, the $PetCO_2$ will be returned back to baseline (Figure 1). This sequence will again be repeated increasing the $PetCO_2$ to +15 mmHg (Hypercapnia II) from baseline before returning to baseline. The subject will then have $PetCO_2$ decreased to -10 mmHg (Hypocapnia) from baseline before returning to normal capnia. The study will stop at this point. During each cycle, the $PetO_2$ and $PetCO_2$ will be controlled by delivering mixes of source gases consisting of O_2, air, and blends of CO_2, N_2 and O_2. The speed and accuracy of the RespirAct™ for modulating $PetCO_2$ while maintaining constant $PetO_2$ is shown in Figure 2.

The RespirAct™ system has been used extensively in more than 15 UHN studies. Over 500 spontaneously breathing human subjects have been studied under these approved protocols. Results have been published in abstract and peer reviewed form and a number of Master's and Doctorate Theses at the University of Toronto (Marat Slessarev, Jay Han, Rosemary Regan, Dahlia Balaban, Anne Battisti, Danny Mandell, Hiroshi Sasano). The RespirAct™ is still considered an

investigational device and Health Canada approval will be obtained before beginning the study.

Internal jugular compression using a Neck collar

A custom made collar consisting of two (2 x 3 x 1.5 cm) soft gauze pledgets held over the IJV by an elastic retainer of will be applied around the patient's neck which can be adjusted to the subject's neck circumference using Velcro.(Velcro, US) This will apply only minimal pressure on the neck, which is comparable to wearing a tight dress shirt. In order to confirm the jugular venous occlusion with the neck collar, we will measure the diameter and flow in the IJV using the ultrasound in each subject in both sitting and supine positions with and without collar. Similarly to determine the lowest pressure needed to occlude the IJV, a 100 ml fluid (normal saline) bag which is attached to a pressure manometer will be placed on the subjects' neck below the collar and the minimal pressure at which there is complete occlusion of IJV will be recorded The venous compression neck collar will be applied at each CO2 levels (normocapnia, Hypercapnia I and II and hypocapnia) and ONSD measurements will be measures before and after the collar.

Risks

1. **Carbon dioxide**

The physiologic stresses of Co2 manipulation on this proposal can be considered minimal. The higher $PetCO_2$ required will not exceed 60 mmHg nor will this change be sustained for long (10 minute intervals). The lower level of $PetCO_2$ is frequently seen with exercise. This range of $PetCO_2$ is physiological and is experienced repeatedly by most people over a regular day. Hyperventilation with hypocapnic $PetCO_2$ is common in day-to-day living (anger, excitement, running). Taking sedatives (alcohol) or even normal sleep can be associated with a PCO_2 of ~ 50 mmHg.

2. **RespirAct ™**

The inhaled gases used in this study are supplied by a computerized MPET system. During control conditions, room air will be supplied at flow greater than the subject's minute ventilation. The subject will be monitored continuously for heart rate, depth of sedation and saturation by pulse oximetry by an attending physician (neurosurgery/ICU or anesthesia). When there is any concern about the subject's condition an alarm button on the RespirAct™ will deliver 100% oxygen to the subject as an extra safety feature. The re-breathing circuit can be easily removed from the subject's face.

Theoretically, CO_2 manipulation can cause further impairment of perfusion in areas with low flow and poor reactivity, by a "steal phenomenon" – flow would be diverted to areas of preserved reactivity during stimulation. In spite of this theoretical possibility this seems to be exceedingly uncommon even in patients with

severe chronic ischemic conditions such as Moyamoya, where the cerebrovascular reactivity is frequently tested with CO_2 manipulation and acetazolamide, and more recently at the Toronto Western Hospital, using the RespirAct™ (several protocols are currently approved by the UHN REB). As well, it is anticipated that the majority of our subjects studied will be young and otherwise healthy.

The device has built in safety features and alarms. For example,

- All source gases contain at least 6 % oxygen to limit the level of hypoxia to a safe and asymptomatic level in case of an error or technical problem with implementing the desired blend of gases
- The blender has a "dead man's switch" that defaults to 100% oxygen at 12 L/min if there is any loss of communication between the blender and the computer such as "hanging up" of the software or computer, loss of power to computer or blender, any one of a series of pre-set alarm conditions are met.
- The RespirAct™ has a large red button that if pushed switches the gasses to 100% oxygen allowing fast and easy intervention in case of any problematic issue.
- The gas delivery circuit has a rubber button with a handle accessible to the subject that if pulled immediately opens the circuit and provides the subject with room air.
- In addition to being monitored by a physician, the RespirAct™ continuously assesses a series of subject and hardware parameters to assure that they stay within pre-set safe limits. Some of these are:
    - Subject parameters:
        - Respiratory rate
        - Peak expired CO_2 concentration
        - inspired CO_2 concentration
        - expired O_2 concentration
        - inspired O_2 concentration
        - apnea time
    - Blender parameters
        - Delivered flow of each gas is equal to the demanded flow
        - Internal pressures and temperatures
        - Proper functioning of gas flow controllers and switches

The RespirAct™ been used in about 500 cases at the Toronto Western Hospital in patients with significant impairment of the blood supply to the brain without undue effect or complication.

3. Neck Collar and Jugular compression

The physiological effect jugular venous compressions used in this study are minimal and the brief period of jugular occlusion is similar to the effects produced

by straining, coughing and heavy lifting. Neck collar will apply only minimal pressure on the neck, which is comparable to wearing a tight dress shirt and a tie.

4. **Ultrasound**

   There are no risks with the use of ultrasound. Orbital ultrasound is routinely done in all patients coming for cataract and retinal surgery at Toronto Western Hospital. Around 30 patients undergo transorbital ultrasound every day at UHN. Ultrasound Gel can be cold on contact with skin.

Data collection

Data collected will include:

- Volunteer demographics
- Medical history
- Vital signs- Heart rate, non-invasive blood pressure and cardiac output, oxygen saturation, end-tidal Co2 levels.
- Optic nerve sheath diameter at normocapnia, 2 levels of hypercapnia and hypocapnia.
- Internal jugular vein diameter and flow in supine and Siting position with and without the neck collar.
- The minimal pressure needed to occlude the IJV.

Data Analysis

A paired t test will be used to compare the following changes in ONSD

- Normocapnia (baseline Pco2) to hypercapnia (baseline+10 mmHg)
- Normocapnia (baseline Pco2) to Hypercapnia (baseline+15mmHg
- Normocapnia (baseline Pco2) to hypocapnia (baseline -10mmHg)
- Neck collar ON and OFF at each Co2 levels.

Sample size

Since this is a preliminary study to evaluate the effect of hypercapnia and hypocapnia and IJ compression on ONSD, only a small sample is required. We intend to enroll 15 subjects in this initial phase. Given the fact that the CO_2 manipulation technique using the RespirAct™ is a new method developed at the University of Toronto and not yet widely available, the lack of information in the literature regarding its utilization for this purpose is obvious. We believe that this small sample will be sufficient to demonstrate the feasibility of the test and set the stage for larger studies.

Project Feasibility

We anticipate no difficulty in obtaining 15 volunteers to participate in this study. The RespirAct™ gas blender used for CO_2 manipulation has been installed at 10 sites including John's Hopkins, University of Colorado, Duke University, University of Nottingham, University of Montreal, University of Texas, and McGill University. The device has a proven track record with regard to clinical implementation.

Figures

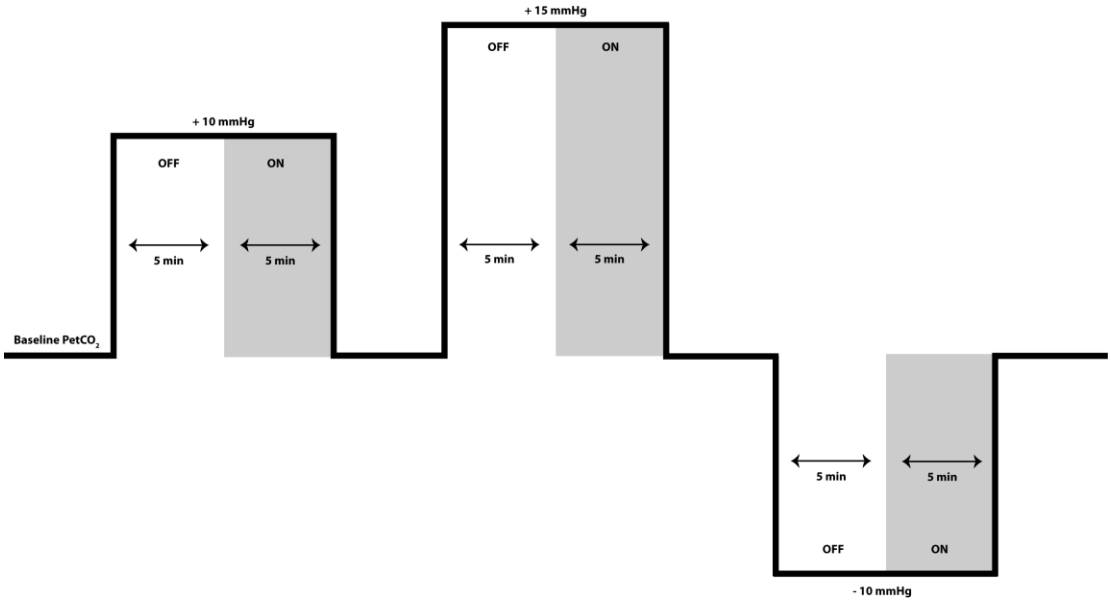

Figure 1: Experimental protocol demonstrating target $PetCO_2$ levels with measurements being performed both while the venous compression collar is off and then subsequently applied.

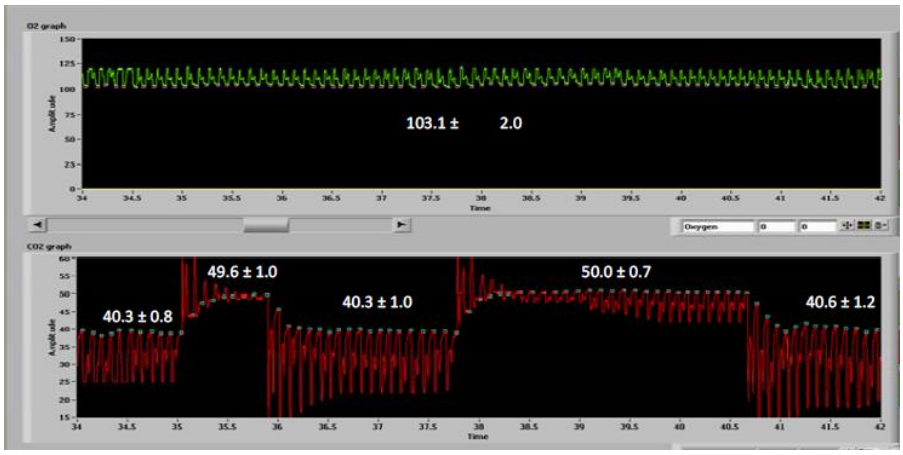

Figure 2: An experiment of end-tidal CO_2 ($PetCO_2$) manipulation using MPET (RespirAct™). Please note the stable O_2 levels and the precision control of $PetCO_2$ levels.

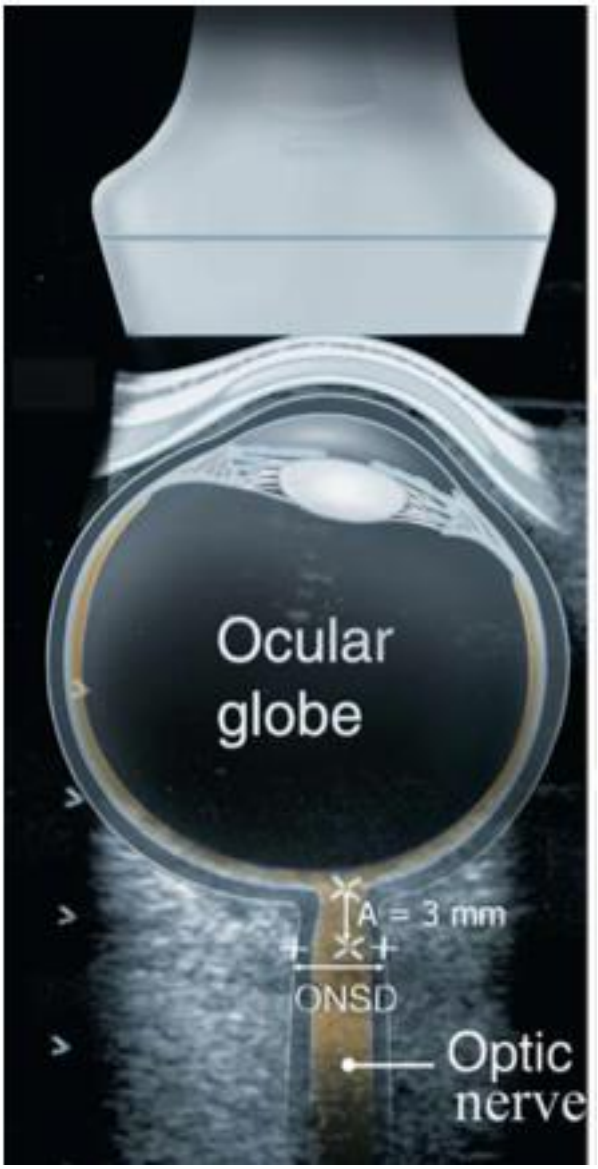

Figure 3: Two-dimensional ocular sonography. A diagram showing the ultrasound probe, the ocular globe and the optic nerve with the optic nerve sheath diameter (ONSD) which was measured 3 mm behind the papilla using an electronic caliper (A X LONG measure) and an axis perpendicular to the optic nerve (B + LONG measure).