Unpublished Paper:
"Non-Invasive Brainstem Monitoring:
The Ocular Microtremor"

Authors:
James Robertson, M.D.
& Shelly Timmons, M.D., Ph.D.

NON-INVASIVE BRAINSTEM MONITORING:

THE OCULAR MICRO TREMOR

Authors:

James Robertson, M.D.

&

Shelly Timmons, M.D., Ph.D.

Affiliations:

Department of Neurosurgery

The University of Tennessee Health Science Center

Memphis, Tennessee, USA

Corresponding author:

James Robertson, M.D.

UT-Neurosurgery

847 Monroe Avenue Suite 427

Memphis, TN   38163

(901) 448-6375

(901) 448-8468

RBeene@UTmem.edu

Key words: Ocular, tremor, monitor, brainstem, non-invasive, coma, brain death.

Running title: Non-invasive brainstem monitoring: The ocular micro tremor

Abstract

The ocular micro tremor (OMT) is mediated by the oculomotor area of the brainstem and is altered in several pathological states, including traumatic brain injury, general anesthesia, brain death, coma, Parkinsonism, and multiple sclerosis. The EYETECT® tremor monitor is a non-invasive means of measuring the frequency and amplitude of this microscopic tremor. It has been clinically tested in these clinical scenarios and has been found to be a reliable means of detecting the depth of anesthesia, and has been useful in predicting outcome in coma and traumatic brain injury patients, and in confirming brain death. This paper reviews the scientific literature on the EYETECT® ocular micro tremor monitor, describes the underlying physiology, and discusses the potential for future studies and clinical use of this innovative technology.

NON-INVASIVE BRAINSTEM MONITORING:

The ocular micro tremor

The ocular micro tremor (OMT) is a well-defined, reliable and easily recorded monitor of brainstem function (1,6,7,8,13,20,21). It was first described as one of the fixational eye movements in 1934 (2). It has a mean amplitude of six seconds of arc. The peak-to-peak rotation involves a displacement of the surface of the eye between approximately 150 and 2000 nm. The tremor is not visible to the naked eye and individuals are unaware of the tiny oscillation. It is caused by high-frequency extraocular muscle stimulation which originates in the ocular motor area of the brainstem (1,7,13). Alterations of this tremor are direct representations of brainstem function at points in time and under adverse conditions. The oculomotor neurons are literally embedded within and surrounded by the reticular formation of the brainstem. These reticular groups of small and large neurons have crossing, ascending and descending fibers that connect with pathways in the brainstem and spinal cord. The ascending reticular activating system is located in the upper pons and mesencephalon (upper brainstem). It projects in multi-synaptic pathways from the mid-pons through the midbrain core to the posterior hypothalamus and intralaminar thalamic nuclei. It is concerned with maintenance of wakefulness. Structures in the lower brainstem have no known effect on wakefulness and are concerned with respiratory and vasomotor control and lower cranial nerve function primarily. Neural activity from other activities outside the brain impinge on the oculomotor nuclei. These include the frontal eye fields, the inferior parietal cortex, and the cerebellum, as well as the output pathways of the vestibular nuclei. These inputs do not suppress the OMT. Historically, OMT has been measured with a probe on the sclera of the open eye using the piezoelectric technique. In 2000, a non-invasive approach was developed by EYETEC®, LLC called the EYETEC® TREMOR MONITOR UNIT. This system provides a method of measuring OMT through the closed eyelid and displaying the measurements in real time on a freestanding monitor. Measurements displayed include the frequency and amplitude of the tremor, the OMT signal form, and frequency trend over time. The mean of OMT peak count frequency in the normal population is 84 Hz.

The tremor is a reliable, physiological phenomenon that has been measured by numerous investigators and correlated with several clinical states. Considerable clinical experience in monitoring this tremor has demonstrated its usefulness in determining the depth of anesthesia, evaluating coma, monitoring level of consciousness in traumatic brain injury, determining brainstem death, and determining early diagnosis of multiple sclerosis. In addition, changes of the tremor have been noted in Parkinsonism (11). The EYETEC® monitor is the only monitor of the brainstem that is non-invasive and clinically proven.

The most extensive clinical trial using OMT as a monitor during general anesthesia induced by propofol in all patients and maintained with sevoflurane (n=124), isoflurane (n=71) or desflurane (n=11) in nitrous oxide and oxygen confirmed that the frequency of OMT is suppressed by these agents and predicts the response to command at emergence from anesthesia (17). This multi-center trial involving four centers in three countries using continuous closed-eye measurement of the OMT concluded that OMT measured by an automated signal analysis module accurately determined the anesthetic state in surgical patients even during profound neuromuscular blockade and after changes in patient position. Monitoring the depth of anesthesia is clinically important because current estimation of the depth of anesthesia is an inexact science. Autonomic activity (heart rate, sweating, lacrimation) and movement to incision are commonly used as indicators of inadequate anesthesia. However, these clinical signs do not predict the depth of sedation. Anesthesiologists have been cautious in accepting the need for an objective monitor of the depth of anesthesia, as a recent position paper emphasizes (3). In an effort to monitor the depth of anesthesia, EEG-based technologies have been developed for determining the level of awareness and implied depth of anesthesia. The most recent is the inclusion of the spectral index frequency and the bispectral index (BIS). The BIS has been reported as a good general measure of sedation and this monitor is considered clinically to be an overall measure of anesthetic depth; however, there are concerns that these recordings may be affected by specific drugs, certain clinical conditions such as hypoglycemia, and high electromyographic and electrical device interference with the specific models used may occur in unpredictable ways, risking patient awareness of the procedure at BIS levels lower than defined thresholds of unconsciousness(3,16). Nevertheless, BIS monitoring is gaining increased utilization. Kevin, Cunningham and Bolger have reported a comparison of ocular micro tremor and bispectral index recording during sevoflurane anesthesia (18). They concluded that both OMT and BIS decreased at induction and remained depressed during sevoflurane anesthesia. When using response to verbal command to indicate consciousness, OMT showed less overlap between the conscious and unconscious states and more accurately identified patients regaining consciousness after anesthesia. OMT is depressed by intravenous and inhalation anesthetic agents, and recordings can be obtained continuously from a probe placed over the closed eyelid. In adults less than 70 years of age, normal OMT frequency is known to be 84 (SD6) Hz. There are no published OMT data in children. To overcome the effects of age, Parkinson's disease, multiple sclerosis and traumatic brain injury in patients who may be undergoing anesthesia, it appears that a more useful threshold to define unconsciousness may be a percentage reduction from the patient's baseline OMT of 45% (5,18). Clearly, the utility of this monitor in determining the depth of anesthesia holds great potential in comparison with other available methods which include the autonomic signs, EEG, isolated forearm technique, auditory evoked responses, esophageal contractility and surface EMG.

The advent of OMT monitoring in comatose states has revealed a strong correlation between the occurrence of an abnormal OMT record and an abnormal pupillary reflex, again supporting the usefulness of the sensitivity of OMT in determining brainstem dysfunction. Studies at the Burdenko Institute led by A.R. Shakhnovich and J.G. Thomas concerning the prognosis of comatose states induced by brain tumors, arterial and arteriovenous aneurysms of the brain, and patients with traumatic brain injury confirmed that if the level of the ocular motor tremor was not lower than 40-50 Hz., a favorable outcome could be anticipated (1,4,12,19). If there was no ocular motor tremor present, death ensued. They also applied the brainstem auditory evoked responses in evaluating these patients and the results correlated well with the prognostic implications of the OMT, although displaying the seven more or less well-defined peaks with acoustic stimulation of the brainstem auditory evoked response was technically difficult to achieve reliably in these patients. Bolger and Coakley have emphasized the importance of a depressed OMT in predicting outcome in patients with traumatic brain injury and coma (4,13,14). Therefore, the continuous monitoring of OMT in the Intensive Care Unit can become the most sensitive and most easily attainable indicator of brainstem dysfunction. This allows for initial assessment and continuous real time monitoring of any adverse change in the tremor. Current intensive care monitoring includes intracranial pressure monitoring, blood gas determinations, vital signs and neurological observations and, in some centers, cortical localized metabolic and oxygenation measurements. The EEG has little to contribute in continuous monitoring in the brain injured, the comatose, or in intracranial hemorrhagic or mass lesion cases due to the cumbersome requirements for leads and equipment, their interference with frequent imaging, requirement for sophisticated interpretation, and cost.

Of great importance is the clinical determination of brainstem death. Clinically, brainstem death is determined by the absences of pupillary response to light, corneal reflex, motor response with painful stimuli to both trigeminal distribution and the periphery, gag response, cough reflex, oculocephalic reflex, vestibular-ocular reflex, and failure of the apnea test. In addition, the patients must be free of medication and have a normal core temperature. The declarative diagnosis of brainstem death in patients correlating the usefulness of OMT has been reported by Bolger and Coakley (10,13,14). This salient study followed the criteria for determining clinical brainstem death in 32 patients. In 28 patients, the initial clinical assessment confirmed the diagnosis of brainstem death and no OMT activity was present. In three patients failing to show the criteria for complete brainstem death, OMT was present but when brainstem death was clinically diagnosed, it disappeared. A single patient with bacterial cerebritis did not demonstrate this correlation but it is well-known that encephalitis may cause the determination of clinical brainstem death to be difficult. Presently in the United States, the determination of clinical brainstem death is essentially that reported by Bolger with the addition of two straight-line electroencephalograms (EEGs) twelve to twenty-four hours apart or failure of arteriography to show entrance of the contrast into the cerebrum or the failure of nuclear brain scanning to show activity of the isotope inside the head since the pressure inside the head is usually so severe as to prevent entrance of contrast or isotope. A recent critique of ancillary tests used in determining brain death noted that the clinical examination is essential in declaring brainstem death. The EEG is not definitive and the evoked potentials (SSEPs and BAERs) pose a technical challenge and are limited to highly restrictive anatomic pathways (22). However, ancillary confirming tests are often required to support the diagnosis of brainstem death and are mandatory for young children (22). The most accurate of the current ancillary tests are those of brain perfusion, e.g., arteriography and isotope brain scan. These tests most often require the patient to be transported, sometimes in hemodynamically unstable states, require specialized personnel oftentimes at off-hours, are costly, and take significant amounts of time to complete. The ideal ancillary test of brainstem death should be readily available, easily applied, reliable, safe and cost effective. The portable bedside and simple technique of using OMT to determine brainstem death fulfills these criteria. OMT has not been tested in patients under 18 years of age, but is expected to be reliable. This early determination of brainstem death is expected to replace the use of expensive cerebral perfusion tests and enhance organ donation capabilities for transplantation, but will prevent the expensive and prolonged intensive care of the clinically brain dead patient.

In summary, with the advent of OMT allowing non-invasive monitoring of the brainstem, the clinician will have for immediate clinical application this proven objective measurement of a physiologic monitor in altered clinical states.

Dr. James T. Robertson is an investor in EyeTect LLC.

REFERENCES

1. Abakumova LY, Shakhnovich AR, Thomas JG. An investigation of the correlation between abnormal patterns of ocular microtremor and an abnormal pupil reflex in neurological patients. *Journal of the Neurological Sciences,* 26; 469-477, 1975.

2. Adler FH, Fliegelman M. Influence of fixation on the visual acuity. *Arch Ophthalmol,* 12; 475, 1934.

3. American Society of Anesthesiologists' Task Force on Intraoperative Awareness Alert (press release). Practice Advisory for Intraoperative Awareness and Brain Function Monitoring. Oct. 25, 2005.

4. Bojanic S, Bolger C. Ocular Microtremor (OMT): A useful indicator of outcome in coma? Presented at the 1st workshop of Neurosurgery, Neuroanesthesia and Critical Care Medicine. Dec., 1998.

5. Bojanic S, Simpson T, Bolger C. Ocular microtremor: A tool for measuring depth of anaesthesia? *Brit J Anaesth,* 86(4); 519-522, 2001.

6. Bolger C, Sheahan N, Coakley D, Malone J. High frequency eye tremor: Reliability of measurement. *Clin Phys Physiol Meas,* 13(2); 151-159, May, 1992.

7. Bolger C, Bojanic S, Sheahan NF, Coakley D, Malone JF. Ocular microtremor in oculomotor palsy. *J Neuro-Ophthalmol,* 19(1); 42-45, 1999.

8. Bolger C, Bojanic S, Sheahan NF, Coakley D and Malone JF. Dominant frequency content of ocular microtremor from normal subjects. *Vision Res,* 39(11); 1911-1915, June, 1999.

9. Bolger C, Bojanic S, Sheahan N, Malone J, Hutchinson M, Coakley D. Ocular Microtremor (OMT): A new neurophysiological approach to Multiple Sclerosis. *J Neurol Neurosurg Psychiatry,* 68(5); 639-642, May, 2000.

10. Bolger C, Bojanic S, Phillips J, Sheahan N, Coakley D, Malone J. Ocular microtremor in brainstem death. *Neurosurgery,* 44(6); 1201-1206, June, 1999.

11. Bolger C, Bojanic S, Sheahan NF, Coakley D, Malone JF. Ocular microtremor in patients with idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry,* 66; 528-531, 1999.

12. Bolger C, Bojanic S, Sheahan NF, Coakley D, Malone JF. Effect of age on ocular microtremor activity. *J Gerontol A Biol Sci Med Sci,* 56(6); M386-390, June, 2001.

13. Coakley D. <u>Minute Eye Movement and Brain Stem Function.</u> CRC Press, Boca Raton, FL. 1983.

14. Coakley D, Thomas JG. The ocular microtremor record and the prognosis of the unconscious patient. *Lancet,* 1(8010); 512-515, March 5, 1977.

15. Coakley D, Thomas JG. The ocular microtremor record as a potential procedure for establishing brain death. *J of Neurol Sci,* 31; 199-205, 1977.

16. Dahaba AA. Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. *Anesth Analg,* 101(3); 765-773, 2005.

17. Heaney M, Kevin LG, Manara AR, Clayton TJ, Timmons SD, Angel JJ, Smith KR, Ibata B, Bolger C, Cunningham AJ. Ocular microtremor during general anesthesia: Results of a multicenter trial using automated signal analysis. *Anesth Analg,* 99(3); 775-780, Sept., 2004.

18. Kevin LG, Cunningham AJ, Bolger C. Comparison of ocular microtremor and bispectral index during sevoflurane anaesthesia. *Brit J Anaesth,* 89(4); 551-555, 2002.

19. Shakhnovich AR, Thomas JH, Dubova SB, Milovanova LS. The prognosis of the outcome of comatose states. *Resuscitation,* 8; 243-255, 1980.

20. Sheahan NF, Coakley D, Hegarty F, Bolger C, Malone J. Ocular microtremor measurement system: Design and performance. *Med Biol Eng Comput,* 31(3); 205-212, May, 1993.

21. Sheahan NF, Coakley D, Bolger C, O'Neill D, Fry G, Phillips J, Malone JF. Sources of variance in ocular microtremor. *Physiol Meas.* 15; 101-106, 1994.

22. Young G, Lee D. A critique of ancillary tests for brain death. *Neurocrit Care,* 1(4); 499-508, 2004.