Ocular Microtremor Activity in Comatose Subjects.

C Bolger PhD FRCSi*, S Bojanic BSc FRCS*, J Philips MD FRCSi, N Sheahan PhD,

D Coakley MD MRCPi, J Malone PhD.

Mercer's Institute for Research on Ageing, St James's Hospital, Dublin, Ireland.

*Department of Neurosurgery, Frenchay Hospital, Bristol, UK.

Correspondence to: Miss Stana Bojanic
Room 1,
Academic Centre,
Frenchay Hospital,
Frenchay Park Road,
Bristol, BS16 1LE
UK

Tel: 0117 970 1212 ext 3584.
Fax: 0117 975 3979
e-mail: sbojanic@neurosurgery.demon.co.uk

Confidential

Abstract

Objectives: Ocular microtremor (OMT) is a fine high frequency tremor of the eyes present in all individuals. This tremor has been shown to be related to brain stem function (24) and is abnormal in coma patients (5, 6). This study assesses (i) the potential role of ocular microtremor activity as a prognostic indicator for early mortality in unconscious patients and (ii) the correlation between depth of coma, as measured by GCS and VOR, with OMT activity.

Methods: Thirty non-medical comatose subjects were recruited. OMT activity was measured using the piezoelectric strain gauge technique within the first twenty-four hours of admission. Recordings were repeated if there was a change in the Glasgow Coma Score (GCS). At each recording the GCS was noted and a vestibulo-ocular reflex (VOR) performed. OMT recordings were taken from thirty age and sex matched normal individuals for comparison.

Results: The mean OMT frequency in the normal group was 86.9 Hz (+/- 6), whereas the mean OMT frequency in the coma group was 50.7 Hz (+/-16), $P<0.0001$. In the coma group, seventeen patients survived and thirteen patients died. Ten patients with an initial OMT frequency less than 45 Hz all died. No patients with an OMT frequency less than 45 Hz survived. Linear regression analysis demonstrated a significant correlation between GCS and OMT frequency ($r = 0.82$, $t = 10.34$, $P<0.0001$). There was a significant association between abnormality of VOR and OMT frequency ($P<0.002$).

Conclusion: OMT activity is significantly reduced in comatose subjects and the reduction in activity is related to the depth of come. Serial changes in OMT activity is related to changing clinical status and initial OMT activity is of prognostic significance in the subjects studied.

Key Words: Ocular microtremor (OMT), piezoelectric strain gauge, Glasgow Coma Score (GCS), vestibulo-ocular reflex (VOR).

Introduction.

Considerable research effort in recent years has been directed to the problem of early prognosis in coma. Accurate early prognosis would allow the concentration of expensive, emotionally draining and time consuming therapeutic measures on patients with a real prospect of recovery (8, 10). These considerations have lead to studies evaluating Glasgow Coma Score (GCS) (14), pupillary responsiveness (21), systolic hypotension (17), age (12), intracranial pressure (16) and radiographic findings (32) among others, as factors useful for predicting outcome in coma patients. However, these studies have not had a widespread impact on clinical management of patients, as the likelihood of false prediction is as high as 20%.

Ocular microtremor (OMT) is a small high frequency tremor of the eyes present in all individuals. This tremor is caused by high frequency extra-ocular muscle stimulation which originates in the oculomotor area of the brainstem. (24). However, neural activity from other areas, namely the frontal eye fields (areas 6 and 8) (11), the inferior parietal cortex (23) and cerebellum (20) also influence the oculomotor nuclei. The OMT signal appears as an irregular oscillatory movement with intermittent burst-like components.

Previous studies have shown that OMT activity is slower in patients in coma, with the spectrum of power being shifted to the left (1, 25). In 1977, Coakley recorded OMT activity in 70 unconscious patients. He found a clear relationship between a low initial OMT frequency (<50 Hz) and the occurrence of early death (5). This phenomenon was confirmed by Golda in 1981 (6) and more recently by Michalik in 1987 (15).

At present, the most widely used and accepted measures of depth of coma are the Glasgow Coma Scale and the Vestibular Ocular Reflex. The Glasgow Coma Scale (GCS) was originally described by Jennett and Teasdale in 1974 (7) and is based on giving a score from each of three categories of clinical examination - i.e. best motor response, best verbal response and eye opening. The vestibulo ocular reflex (VOR) is elicited by injecting cold water into the ear and inducing eye movement by exciting the reflex between the vestibular and oculomotor systems (31).

The purpose of our study was to (i) assess the potential role of ocular microtremor activity as a prognostic indicator for early mortality in unconscious patients and (ii) to establish the correlation between depth of coma, as measured by GCS and VOR, with OMT activity.

Methods.

Subjects.

After gaining local Ethics Committee approval and informed consent from the next of kin, thirty non-medical comatose subjects were recruited for study. All subjects were inpatients at the Neurosurgical Intensive Care Unit at the National Centre for Neurosurgery, Dublin. The mean age of the subjects was 46 years (SD+/-23), range 11 to 77. There were twenty-three males and seven females. Thirty age and sex matched normal individuals were recruited for comparison.

Recording Session.

Ocular Microtremor (OMT) activity was recorded using the open eye piezoelectric strain gauge technique (3). This technique has been described in detail elsewhere (28) and provides a reliable estimate of OMT activity (4). Briefly, the piezoelectric transducer was mounted in a Perspex rod and the protruding tip coated with rubber. The subject lay supine wearing a headset. The subject's eyelids were taped apart and the scleral surface anaesthetised with 0.5% Hydroxymethacaine Hydrochloride. The piezoelectric probe was mounted in the headset and gently lowered so that the rubber tip was just touching the scleral surface. Probe placement was judged by visual inspection and by listening to the signal being recorded using audiocassette headphones.

The signal from each probe was then passed to a conditioning unit consisting of a differential amplifier with a 40-dB common mode rejection ratio. The amplification factor is 10. The signal passed from this unit and was recorded on an audiocassette recorder (Sony D3). The record was later played back and analysed on an ECG tape analyser (Reynolds Medical (RM) Pathfinder 3 and RM TP - Thermal Printer).

This system shows a frequency response between 20 - 150 Hz which deviates less than 2 dB from peak response. The system has a signal/noise ratio of >23 dB and the resolution is less than 1% of the dynamic range, or 12 nm.

At least thirty seconds of record was obtained at each recording session. by the same experienced operator (4). During recording the respirator was turned off to minimise the possibility of interference. OMT records were taken within the first twenty-four hours of admission and repeated thereafter if there was a change in the Glasgow Coma Score (GCS). At the time of recording a GCS was calculated for each subject and a vestibulo-ocular reflex (VOR) performed. VOR was tested by injecting 40 mls of ice cold water into each external auditory meatus. The external auditory meatus was inspected using an otoscope prior to injection to exclude possibility of blood or wax blocking the tympanic membrane. While the water was injected a second experienced observer inspected the eyes for movement with the eyelids retracted. The VOR was scored in order of increasing abnormality as nystagmus, conjugate eye deviation, dysconjugate eye deviation and absent.

Analysis of OMT records was performed, independent of clinical data, using peak counting analysis. This provides a good estimate of the high frequency component of any random signal (9, 29), particularly OMT (27). Statistical comparison was performed using the students' t test, linear regression analysis and chi squared test where appropriate.

Results.

OMT records were successfully obtained from all 30 subjects. Three records were obtained from each of 9 subjects and two records obtained from each of 14 subjects, giving 62 OMT records in total. In seven subjects no OMT activity was recordable. In all seven cases the patient satisfied the criteria for brain stem death as defined by the Working Group of the Royal College of Physicians (1995) (22) and were excluded from the study. Thus, there were 55 OMT records and corresponding GCS scores for comparison. VOR was successfully performed in 20 subjects. In the remaining 10 subjects the presence of wax, blood or tympanic membrane perforation prevented the test being reliably performed. The patients were studied during their admission on the Intensive Care Unit and their outcome was graded as regaining consciousness or death.

OMT activity in Coma and Normal Subjects.

OMT records obtained from comatose subjects were significantly different from those of normal subjects. Figure 1 provides and example of a record from a normal subject and a subject in coma, as well as the corresponding linear predictive spectra. The OMT activity is shown to be slower in coma with the spectrum being shifted to the left. The mean OMT peak count frequency in the 30 comatose subjects was 50.7 Hz (SD+/-16), compared to 86.9 Hz (+/-6) in the normal group. This is highly significant, $t = 10.47$, $P<0.0001$.

Frequency and Outcome.

Of the thirty patients studied, a total of 17 survived and 13 died. The mean initial OMT frequency in the survival group was 60.5 Hz (SD+/-2.3) and in the group that died was 37.8 Hz (SD+/-3.9), $P<0.0001$. Of ten patients with an initial OMT frequency less than 45 Hz all died, whilst 7 patients with a frequency greater than 65 Hz all survived. If we take values less than 45 Hz indicating an unfavourable prognosis, then the sensitivity of measuring initial OMT frequency and mortality is 77 % and the specificity is 100%.

Serial Records and GCS.

Serial records were obtained in 23 subjects. Three records were obtained from 9 subjects and two records from 14 subjects, giving 32 record comparisons. Of these an increase in OMT frequency was seen in 22 cases and a decrease in frequency in 10 cases. In those cases with an increase in tremor frequency, this corresponded to an increase in GCS in 21 cases and a decrease in one case. In all 10 cases with a drop in OMT frequency between records this corresponded with a fall in the GCS (Chi-squared = 27.78, $P<0.001$). Table 1.

Fifty-five records were available for comparison with GCS. Linear regression analysis demonstrates a significant correlation between GCS and OMT frequency ($r = 0.82$, $t = 10.34$, $P<0.00001$). This is shown in Figure 2.

OMT activity and VOR.

VOR was performed in 20 patients and results compared with OMT frequency. The number of subjects in each category of VOR result was compared using chi-squared analysis with the number of subjects with an OMT frequency greater than or less than 50 Hz. This demonstrates a significant association between abnormality of VOR and OMT frequency (chi-squared = 15.6, $P<0.002$).

Discussion.

In this study, abnormal OMT records were found in all 30 unconscious patients. The overall mean peak count frequency was significantly lower in the coma group when compared with the normal control group (P<0.0001). Similar findings have been observed in previous studies of OMT records of unconscious patients (25, 6) Shakhnovich and colleagues (26) studied the OMT records of 43 patients with loss of consciousness. They graded the microtremor frequencies into nine levels, and they found a close correlation between the frequency of OMT and the degree of disturbance of unconsciousness. There was a clear relationship between low initial OMT frequencies and an unfavourable prognosis for regaining consciousness, whilst high frequencies, in contrast, carried a better prognosis. This study re-affirms these findings. In particular, our ten patients with an initial OMT frequency of less than 45 Hz died, whereas all patients with an initial frequency greater than 65 Hz survived.

A recent study by Liu and colleagues (13) has defined a grading system based on findings on Computer Tomography Scans (CT) that correlate changes of the brainstem and its perimesencephalic cistern in severe head injury with outcome. The poorer grades, defined by a deformed brain stem with density changes, correlated well with a poor outcome in these patients. The extent of brain stem damage is an important determinant in relation to recovery and survival from coma (30). As OMT activity is an indicator of the functional state of the brain stem (24) the use of the OMT record in the prognosis of the comatose patients would seem feasible.

In seven of the patients studied, there was no activity shown on initial OMT records. At the time of OMT recording, all these patients satisfied the criteria for brain stem death as defined by the Working Group of the Royal College of Physicians, 1995 (22). It may be possible that another potential role of the OMT record is in establishing brain stem viability or death.

This study also identifies a significant correlation between depth of coma, as determined with GCS and VOR, and OMT frequency. In individual patients changes in depth of coma are also strongly correlated with changes in OMT activity. It is well established that the maintenance of consciousness is dependent on continued activity in the brain stem reticular activating system and the degree and duration of coma directly correlate with the extent of brain stem damage (18). Coma in humans is most commonly due to damage to the brain stem reticular formation (19). It is these studies that have stimulated the interest in developing objective methods of determining the extent of brain stem damage in comatose subjects, in order that a reliable prognosis may be given for individual cases.

The best methods, including clinical tests are those which most closely relate to brain stem function (2). At present, the test of eye reflexes provides one of the most important indicators of coma prognosis (2) and we have shown a significant association between abnormality of VOR and OMT frequency.

In conclusion, we have found that OMT activity is significantly reduced in comatose subjects and the reduction in activity is related to the depth of coma. Serial change in OMT activity is related to changing clinical status and initial OMT activity is of prognostic significance in the subjects studied. The methods employed for measuring ocular microtremor activity are easily employed and portable. These findings lead us to believe that OMT analysis has a potential role in predicting the prognosis of unconscious patients.

References.

1. Abakumova L.Y, Shakhnovich A.R, Thomas J.G: An investigation of the correlation between abnormal patterns of ocular microtremor and an abnormal pupil reflex on neurological patients. **J.Neurol Sci 26:**469, 1975.

2. Bates D: Defining prognosis in medical coma. **JNNP 54(7):**569-571, 1991.

3. Bengi H, Thomas J.G: "Three electronic methods for recording ocular tremor". **Med Biol Eng 6:**171-178, 1968.

4. Bolger C, Sheahan N, Coakley D, Malone J: High frequency eye tremor: Reliability of Measurement. **Clin.Physics and Physiol.Measure. 13(2):**151-159, 1992.

5. Coakley D, Thomas J.G: The ocular microtremor record and the prognosis of the unconscious patient. **Lancet 1:**512.

6. Golda V, Petr R. Cermak F, Rozsival V, Sverak J: Ocular microtremor and the level of vigilance. **Sb.Ved.Pr.Lek.Fak.** Karlovy Univer. Hvada, Kralow **24:**77, 1981.

7. Teasdale G, Jennett B: Assessment of coma and impaired consciousness. A practical scale. **Lancet ii:**81-84, 1974.

8. Jennett B, Teasdale G, Braakman R: Predicting outcome in individual patients after severe head injury. **Lancet 1:**1031-1034, 1976.

9. Kedem B: Spectral analysis and discrimination by zero-crossings. **Proc IEEE 74:**1477-1479, 1986.

10. Knaus W.A, Wagner D.P, Draper E.A: The APACHE III prognostic system: Risk prediction of hospital mortality for critically ill hospitalised adults. **Chest 10:**1619-1636, 1991.

11. Leichnetz G.R, Spencer R.F, Smith D.J: Cortical projection to nuclei adjacent to the oculomotor complex in the medial dienmesencephalic tegmentus in the monkey. **J.Comp.Neurol 228:**359-387, 1984,

12. Luerssen T.G, Klauber MR, Marshall LF: Outcome from head injury related to patient's age. **J Neurosurg 68:**409, 1988.

13. Lui H.M, Tu Y.K, Su C.T: Changes of brainstem and perimesencephalic cistern: dynamic predictor of outcome in severe head injury. **J of Trauma 38(3):**330-333, 1995.

14. Marshall L.F, Gautille T, Klauber M.R: The outcome of severe closed head injury. **J Neurosurg 75:**S28, 1991.

15. Michalik M: Der okulare Mikrotremor -ein Indikator fur den functionellen Zustand des Hirnstammus. **Psychiatr.Neurol.Med.Psychol.Beih 29:**196-204, 1987.

16. Miller J.D, Becker D.P, Ward J.D: Significance of intracranial hypertension in severe head injury. **J Neurosurg 47:**503, 1977.

17. Miller J.D, Becker D.P: Secondary insults to the injured brain. **J R Coll Surg Edinb 27:**292, 1982.

18. O'Leary J.L, Cohen L.A: The reticular core. **Physiol. Rev. 38:**243, 1958.

19. Plum F, Posner P.B**: Diagnosis of stupor and coma,** Philadelphia: Davies F.A, 1972.

20. Precht W. Cerebellar influences of eye movements. **Basic Mechanism of Ocular Motility,** Pergannon Press, Oxford: Lennerstrand G, Bach P, Rita Y, 1978.

21. Price D.J, Knill-Jones R: The prediction of outcome of patients admitted following head injury in coma with bilateral fixed pupils. **Acta Neurochir Suppl 28:**179, 1979.

22. Royal College of Physicians: Criteria for the diagnosis of brain stem death. **Journal of the R Colleg. of Physicians of London 29(5):**381-382, 1995.

23. Sakata H, Shibutani H: Spatial properties of visual fixation neurones in posterior parietal association cortex of the monkey. **J Neurophys 43:**1654-1672, 1980.

24. Shaknovich A.R, Thomas J.G: OMT as an index of motor unit activity and of the functional state of the brain stem. **J. Physiol.238:**36P, 1975.

25. Shakhnovich A.R, Thomas J.G: Microtremor of the eyes of comatose patients. **EEG and Clin Neurophys.42:**117-119, 1977.

26. Shakhnovich A.R, Thomas J.G, Dubova S.B et al: The prognosis of the outcome of comatose states. **Resuscitation 8:**243-255, 1980.

27. Sheahan N: Ocular microtremor measurement technique and biophysical analysis. **PhD Thesis**, T.C.Dublin, 1991.

28. Sheahan N.F, Coakley D, Hegarty F, Bolger C, Malone J: Ocular microtremor measurement system: design and performance. **Med&Biol.Eng&Comp.31:**205-212, 1993.

29. Smith J.D. **Vibration measurement and analysis.** Butterworths, London, 1989.

30. Snyder B.D, Gurnnit R.J et al: Neurologic prognosis after cardiopulmonary arrest IV. Brain stem reflexes. **Neurology 31(9):**1092, 1981.

31. Teasdale G, Smith J: Eye movements and brain stem dysfunction. **Neurol.Neurosurg.Psychiatric 32:**822, 1975.

32 Toutant S.M, Klauber M.R, Marshall L.R et al: Absent or compressed basal cisterns on first CT scan: Ominous predictors of outcome in severe head injury. **J Neurosurg 61:**691, 1984.

Figure 1: Example of an OMT record from a normal subject and a subject in coma, with the corresponding linear predictive spectra. The overall mean peak count frequency is reduced in the coma subject with the power spectra shifted to the left.

Figure 2: Glasgow Coma Score (GCS) versus Ocular Microtremor Frequency (Hz).