Influence of general anaesthesia on slow waves of intracranial pressure

Despina Aphrodite Lalou[1,2]
Marek Czosnyka[1]
Joseph Donnelly[1]
Andrea Lavinio[3]
John D. Pickard[1]
Matthew Garnett[1]
Zofia Czosnyka[1]

[1]Division of Neurosurgery, University of Cambridge Department of Clinical Neuroscience, Addenbrooke's Hospital, Cambridge, UK
[2]National and Kapodistrian University of Athens Medical School, Athens, Greece
[3]Neurosciences Critical Care Unit, Department of Anesthesia, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

Despina Afroditi Lalou
National and Kapodistrian University of Athens Medical School, 72 Voutsina Street, 15561, Athens, Greece
Tel: 0030 2106525174
Fax: 0030 2106521437
Email: alfadt.lalou@gmail.com

Running Title: Are slow waves of ICP suppressed by General Anesthesia?

Abstract

Objective. Slow vasogenic intracranial pressure (ICP) waves are spontaneous ICP oscillations with a low frequency bandwidth of 0.3-4 cycles/min (B-waves). B-waves reflect dynamic oscillations in cerebral blood volume associated with autoregulatory cerebral vasodilation and vasoconstriction. This study quantifies the effects of general anaesthesia (GA) on the magnitude of B-waves compared to natural sleep and conscious state.

Materials and methods. The magnitude of B-waves was assessed in four groups of 30 patients each with clinical indications for ICP monitoring. Normal pressure hydrocephalus (NPH) patients undergoing Cerebrospinal Fluid (CSF) infusion studies in the conscious state (GROUP A) and under general anaesthesia (GROUP B), and hydrocephalus patients undergoing overnight ICP monitoring during physiological sleep (GROUP C) were compared to deeply sedated traumatic brain injury patients with well-controlled ICP during the first night of Intensive Care Unit (ICU) stay (GROUP D).

Results. A total of 120 patients were included. During CSF infusion studies, the magnitude of slow waves was higher in conscious patients (GROUP A: 0.23+/-0.10 mmHg) when compared to anaesthetised patients (GROUP B: 0.15+/-0.10 mmHg; p=0.011). Overnight magnitude of slow waves was higher in patients during natural sleep (GROUP C: 0.20+/-0.13 mmHg) when compared to TBI patients under deep sedation (GROUP D: 0.11+/- 0.09 mmHg; p=0.002).

Conclusion. General anaesthesia and deep sedation are associated with a reduced magnitude of B-waves. ICP monitoring carried out under GA is affected by iatrogenic suppression of slow vasogenic waves of ICP. Accounting for the effects of anaesthesia on vasogenic waves may prevent the misidentification of potential shunt-responders as non-responders.

Key words: b waves, cerebrospinal fluid dynamics, general anesthesia, hydrocephalus

Introduction

Intracranial pressure (ICP) *slow waves*, also called *B-waves*, are spontaneous rhythmic oscillations of the ICP within a low frequency bandwidth of 0.3 to 4 cycles per minute. Slow waves of ICP have been described in healthy individuals, head injury patients and are particularly prevalent in hydrocephalic patients (1, 2).

The physiological and clinical significance of B-waves remains debated and their origin still remains to be conclusively elucidated. The predominant theory postulates a vasogenic origin whereby slow waves of ICP are generated by dynamic changes in intracranial blood volume reflecting autoregulatory cerebrovascular vasodilation and vasoconstriction in response to oscillations in arterial blood pressure (ABP). The vasogenic origin of B-waves would be similar to that demonstrated by Lundberg (3) and Rosner (4) when describing ICP *A-waves* (*plateau waves*). Plateau waves can be observed in patients with exhausted intracranial volume-buffering reserve when a precipitating factor (i.e. hypotension or ICP elevation) results in a critical reduction in cerebral perfusion pressure (CPP) followed by autoregulatory cerebral vasodilatation and increased cerebral blood volume (CaBV) in a form of self-sustaining 'vasodilatatory cascade' (4). Plateau waves can last up to 5-10 minutes and ICP typically plateaus at 40-50 mmHg (i.e. A-waves last longer and have higher amplitude than B-waves). Other theories suggest that B-waves reflect the presence of a brainstem neuro pacemaker controlling cyclical electrical activity changes (5). Because $PaCO_2$ is a potent cerebral vasodilator, B-waves have also been attributed to a crescendo - decrescendo pattern of ventilation (Cheyne - Stokes respiration) (1,5). However, other investigators (6, 7) have showed that artificial ventilation does not affect B-waves, suggesting that cyclical changes in arterial CO_2 are not the exclusive causative factor in B-waves.

Slow waves of ICP have been used as a marker for reduced intracranial compliance and as an indicator of shunt responsiveness in hydrocephalus. The magnitude (or amplitude) of B-waves is inversely correlated with the volume buffering reserve of the intracranial compartment and directly correlated with measured resistance to Cerebrospinal Fluid (CSF) outflow (Rcsf), a reliable parameter describing CSF circulation(8-10). The presence of prominent slow waves has been correlated with clinical improvement after shunting in normal pressure hydrocephalus (NPH) (9,11,12). In the context of severe traumatic brain injury (TBI) the presence of B-waves reflects active vasogenic modulation of cerebral blood flow and is associated with better prognosis (11-12).

Monitoring of ICP is indicated in a variety of clinical settings ranging from conscious, self-ventilating patients, mechanically ventilated patients under general anaesthesia (GA) and during physiological sleep. Anecdotally, we have observed that the slow rhythmic oscillations of ICP often recorded in conscious self-ventilated patients undergoing CSF infusion studies are dampened or absent in patients studied under GA. There have been several studies in the past investigating the relationship between the relative frequency, absolute amplitude, and the morphology of B-waves and different sleep stages (12-14). However, there is no published data quantifying the influence of GA on slow vasogenic ICP oscillations. The wealth of data collected in our lab over the years allows us to quantify and compare B-wave activity during wakefulness, physiological sleep and general anaesthesia in NPH and TBI patients.

Materials and methods

GROUP A and GROUP B consist of two cohorts of 30 non-shunted patients each, undergoing computerised CSF infusion studies for diagnostic confirmation of suspected NPH. Infusion studies are a well-established diagnostic methodology extensively described elsewhere (8,14,16). GROUP A underwent infusion studies in a conscious state in a recumbent position. GROUP B underwent infusion studies under GA. This approach was taken either because the patient was unable to tolerate the diagnostic procedure (which may require up to one hour of monitoring) or as a surgical strategy whereby native CSF dynamics can be assessed preoperatively and, if indicated, shunt insertion, can be performed within the same surgical session (17-19). All patients presented with ventriculomegaly and with at least two elements of Hakim Triad symptoms (urinary incontinence, shuffling gait and memory loss); gait problems were present in all patients. Anaesthesia during the infusion study was induced using propofol, fentanyl and atracurium or vecuronium (20-23) and maintained with either propofol target controlled infusion 3-6 mcg/ml effect site alone or combined with remifentanil 0.05-0.2 mcg/kg/min. Body temperature and CO_2 levels were recorded and controlled at 36-37°C and 4.5-5.0 kPa respectively, as part of standard local practice.

GROUP C and GROUP D consist of two cohorts of 30 age-matched patients each, undergoing overnight ICP monitoring. GROUP C consists of naturally asleep patients investigated for or with a confirmed diagnosis of hydrocephalus, with or without a shunt in place (18, 19, 24). GROUP D consists of patients with ICP monitoring following severe TBI in the absence of intracranial hypertension (mean ICP < 18 mmHg) during the first night of ICU stay (24). These patients were managed with profound sedation according to the NCCU protocol, which includes maintenance of deep sedation with propofol and fentanyl or remifentanil, with or without neuromuscular blockade. We only included patients who had not undergone decompressive craniotomy. Body temperature and CO_2 levels were recorded and controlled at 36-37°C and 4.5-5.0 kPa, as part of standard clinical protocol.

Monitoring and use of recorded signals in TBI patients was approved by the relevant research ethics committee (29 REC 97/291). All hydrocephalus patients were investigated with infusion test or overnight ICP monitoring within the Hydrocephalus Clinic, Addenbrookes Hospital, Cambridge, UK as a part of routine clinical assessment. They all consented for these studies. Digital recordings were analysed anonymously as a part of routine clinical audit.

Data analysis

The magnitude of slow waves [SLOW] was assessed using spectral analysis of digitised ICP recordings and calculated as the root of the power of the signal in the frequency bandwidth 0.3 to 4 cycles/min (35-37). Artefacts were manually removed in all groups prior to analysis. In GROUP A and GROUP B, ICP de-trending was performed prior to analysis to minimise the influence of the induced increase in ICP on slow wave activity.

Baseline ICP, intracranial elasticity(16,17), RAP (an index of volume-compensatory reserve) were recorded in all patients as previously described (16,19,24). CSF production and Rcsf were calculated as part of standard CSF infusion studies (16,24). Data were analysed using SPSS version 22.0. Results are presented as mean ± SEM. A one-way ANOVA was used to examine between group differences in examined parameters. Spearman rank correlation coefficient was used to examine the relationship between descriptors of slow waves and CSF compensatory parameters.

Results

Group A and B included age-matched (73+/-7 versus 75+/-8 years) NPH patients undergoing infusion test, in conscious state (GROUP A; N=30) and under GA (GROUP B; N=30). Male to female ratio in both groups was approximately 4:3. Typical ICP time- trends for infusion studies performed in a conscious patient and in a patient under GA are presented in Figure 1A and 1B, respectively. Numerical results for GROUP A and GROUP B are presented in Table 1.

GROUP C and GROUP D included age - matched patients undergoing overnight ICP monitoring for diagnostic investigation of NPH during natural sleep (GROUP C; N = 30; AGE = 23+/-8) and deeply-sedated and mechanically ventilated patients during their first ICU night (GROUP D; N = 30; AGE = 29+/-7 years). Heart rate and respiratory rates in Group C were stable and typical of natural sleep state. Typical ICP time-trends for overnight monitoring recordings in a patient undergoing overnight monitoring for diagnostic investigation of NPH and in deeply-sedated mechanically ventilated patients under GA are presented in Figure 2A and 2B, respectively. Numerical results from the groups of overnight ICP monitoring in hydrocephalus and after TBI are presented in Table 2.

Overall, the average magnitude of slow waves and standard deviations of 10 sec-averaged ICP was lower in the GA patients (Groups B and D) in comparison with conscious patients (Groups A and C). In patients undergoing infusion test, there was no correlation between compensatory reserve and the volume of slow waves. There was no significant correlation between any measures describing the magnitude of B waves and resistance to CSF outflow or elasticity, both in the GA and conscious patient group. The magnitude of B waves was positively correlated with baseline ICP (R=0.48; p=0.0067) but only in conscious patients.

There is a significant difference in the duration of the recording between the 1st (Groups A and B) and the 2nd (Groups C and D) cohort, which was the initial purpose of their formation. The duration of the infusion studies was approximately half an hour, therefore different methodology was used for analysis of Slow Waves. Formally , there is no statistical difference between slow waves in Group A (baseline values, before start of infusion) and C, and respectively B and D (p>0.05).

Discussion

This study quantifies the magnitude by which ICP B-waves are suppressed by GA and deep sedation when compared to conscious state or physiological sleep. These findings provide a reference for further studies and for clinical interpretation of ICP recordings.

So far, studies of B waves, infusion tests and generally studies of CSF dynamics conducted both in animals and in humans are performed in both awake and in a sedated state. The effects of anaesthetic drugs and mechanical ventilation on cerebral physiology have been studied extensively. Propofol has a predictable pharmacokinetic profile and advantageous pharmacodynamic characteristics including profound suppression of cerebral metabolic rate and preserved cerebral autoregulation (26,27). The safety of fentanyl and remifentanil as adjuvants in neuroanaesthesia and neurointensive care is also supported by a large body of evidence (18-21). The impact of neuromuscular blockers on CSF dynamics is negligible (20,21,23). Nonetheless, the current study demonstrates that even propofol-based anaesthesia and sedation are associated with a considerable reduction of approximately 50% in the amplitude of vasogenic waves when compared to wakefulness or natural sleep. The iatrogenic influence is most likely to be multifactorial, with plausible factors being direct pharmacological effect and suppression of cerebral metabolic rate and mechanical ventilation with reduced fluctuation in carbon dioxide (9,11,20). Patients in the TBI group were carefully selected to not have significant intracranial hypertension (ICP<18 mmHg) and their CSF parameters were considered for the first day of their admission. B waves are disturbed and disappear in cases where autoregulation has failed and ICP has risen severely and therefore the difference in slow wave magnitude cannot most probably be due to the TBI itself rather than the fact that patients were sedated. Even though an increase in CaBV has been reported during REM sleep, no significant difference has been reported in the percentage and amplitude of b waves between sleep and wakefulness, in patients groups with non-communicating hydrocephalus and NPH (9,28-30). Our study is consistent with these results in that it shows that it's most probably not natural sleep that causes a decrease in b wave amplitude.

Our results indicate that ICP dynamics are suppressed by GA. Both the average magnitude of slow waves and standard deviation of mean ICP (10 second averages) were significantly lower in patients under GA than in those who were conscious. Baseline ICP is known to correlate with slow wave power of ICP probably reflecting the fact that increasing ICP is associated with decreasing intracranial compliance and increased power of slow waves. However in this study, baseline ICP was not significantly lower under GA. This suggests that factors other than mean ICP must be contributing to the decrease in magnitude of slow waves in the anesthetised or sedated state (20-23,25) The lower amplitude in the GA group may be associated to lower brain metabolism rate implicating lower Cerebral Blood Flow (CBF). This could be supported by the fact that production of CSF was significantly lower in the GA group. (18,19) The most convincing physiological substrate of B-waves consists of autoregulatory changes in cerebrovascular tone in response to cyclical changes in arterial blood pressure and/or cerebral metabolic demand. This would in turn be reflected in changes in ICP proportional to the amount of changes in CaBV and inversely proportional to intracranial compliance. Interestingly, intracranial elasticity did not differ between groups(16,17). The Resistance (R) to the CSF outflow was found significantly higher in the GA group (group B). This was most probably a derivative of patient selection, since GA infusion studies involve patients with severe clinical features and most likely to be a candidate for CSF shunting procedures (24). Although alternative markers of CSF circulation are nowadays more prominent (25), the resistance to CSF outflow is still a convenient index used in NPH. Moreover, there is no biological substrate supporting a link between the anaesthetised state and higher resistance to CSF reabsorption.

Slow waves in ICP are thought to be related to phasic alterations in CaBV. Being vascular phenomena, these slow waves of ICP could be related to slow waves in ABP, the strength of cerebral autoregulation, slow waves in vasoactive mediators (such as arterial CO2) or could be related to primary intracranial vascular events via neurovascular coupling. (1-3,26,27) Therefore, interpretation of the physiology by which GA decreases slow wave ICP power is complex. Arterial CO2 is a potent vasodilator and therefore slow variations in arterial PCO_2 could account for changes in CaBV and ICP. Coherent changes in CO2, CBF and ventilation have been described in situations such as central sleep apnoea (26,27). Whether such ventilation changes could account for the observed differences is unknown. GA induced alterations in slow wave ABP power could account for changes in slow wave ICP power. Slow waves in ABP are transmitted to the cerebral vasculature according to the presence and strength of autoregulation. (9,12,13) GA under stable and well – controlled conditions has been shown to not influence the ABP power or cerebral autoregulation. (22,30)

The clinical implications of quantifying the influence of anaesthesia and deep sedation on slow waves of ICP may be of particular relevance in the context of diagnostic workup of hydrocephalic patients as the magnitude of slow waves is used to identify shunt responders and to indicate surgery in patients with a diagnosis of NPH (8,9,30-32). ICP monitoring carried out under GA or in sedated patients is affected by iatrogenic suppression of slow vasogenic waves of ICP. Accounting for the effects of anaesthesia on vasogenic waves may prevent the misidentification of potential shunt-responders as non-responders.

Limitations of the study

Using TBI as a comparison group can have its limitations, even though as mentioned above we tried to exclude most possible confounding parameters of disturbed CSF dynamics in those patients. We have noted a significantly higher in Rcsf in the NPH patients whose infusion study was performed under GA. This could be a derivative of patient selection (studies under GA are probably performed in patients with worse symptoms). CBF was not assessed in any patient group and therefore cerebral vasodilation and CBF fluctuations cannot be confirmed with the current study. Similarly, ABP was not measured, to compare slow waves in arterial pressure between conscious/anaesthetised patients. It was not within the purpose of the study to compare CSF and slow wave dynamics with the use of different types of anesthetics. The problem of choosing the right anesthetic has been addressed by the literature and other research groups with a tendency to indicate that it is best to use propofol with or without remifentanyl than inhaled anesthetics for CSF dynamics studies. The main focus and point of this study is to assess slow wave magnitude, however propofol and/or remifentanyl were the only anesthetics used. Even though it is reasonable to assume that there may be a dose-dependent association between the depth of anaesthesia and the suppression of vasogenic ICP waves we are unable to explore this question with the dataset available. While there may be considerable within-group heterogeneity in the anaesthetised and sedated group, there still remains a consistent and statistically significant difference in the magnitude of vasogenic waves in patients undergoing infusion studies under general anaesthesia when compared to patients undergoing infusion studies in the awake state. Finally, previous studies have found that the amplitude of b waves probably increases during REM sleep, although results remain contradictory. In such case, REM sleep could account for another possible interpretation of the difference between Groups C and D. However, it was not possible to neither compare awake patients with long – term monitoring with naturally asleep patients nor determine and select the REM sleep phase.

Further studies need to be performed to confirm these findings and provide better insight on how to interpret slow wave analysis derived from anesthetised patients.

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Table 1 Infusion test and slow wave analysis results from the first two groups; conscious patients with NPH (Group A) and under GA (Group B). NPH: Normal Pressure Hydrocephalus, GA: General Anesthesia, ICP: Intracranial Pressure, CSF: Cerebrospinal fluid

	Conscious patients (Group A)	Under GA (Group B)	p
Age [years]	73+/-7	75+/-8	
Male/female ratio	~4:3	~4:3	
Power of slow waves [mm Hg]	0.23+/-0.16	0.15+/-0.11	<0.0023
Standard deviation of thirty 10 sec averages of ICP [mm Hg]	1.41+/-0.24	0.61+/-0.28	<0.0001
Baseline ICP [mm Hg]	9.56+/-4.1	5.04+/-3.87	NS
Amplitude of Pulse wave [mm Hg]	1.82 +/-1.7	1.91+/-1.41	NS
Resistance to CSF outflow [mm Hg/(ml/min)]	13.6+/-5.2	19.5+/-11.1	0.011
Elasticity [1/ml]	0.17+/-0.14	0.22+/-0.17	NS
Production of CSF [ml/min]	0.30+/-0.21	0.21+/-0.28	0.022

Table 2 CSF dynamics & slow wave analysis results from the second cohort groups (conscious patients with overnight ICP monitoring (Group C) & sedated TBI patients (Group D). CSF: Cerebrospinal Fluid, ICP: Intracranial Pressure, TBI: Traumatic Brain Injury

	Conscious patients (Group C)	Sedated patients (Group D)	p
Age [years]	23+/-8	29+/-8	
Male/Female ratio	~2:1	~2:1	
Magnitude of slow waves [mmHg]	0.196+/-0.13	0.11+/-0.091	0.0024
Standard deviation of thirty 10 sec averages of ICP [mm Hg]	1.42+/-0.64	0.71+/-0.42	<0.0001
Mean ICP [mmHg]	7.7+/-4.9	13.6+/-5.91	0.001
Pulse amplitude of ICP	3.21+/-1.18	3.41+/-1.43	NS
RAP index	0.44+/-0.17	0.3+/-0.18	0.045

Figure 1
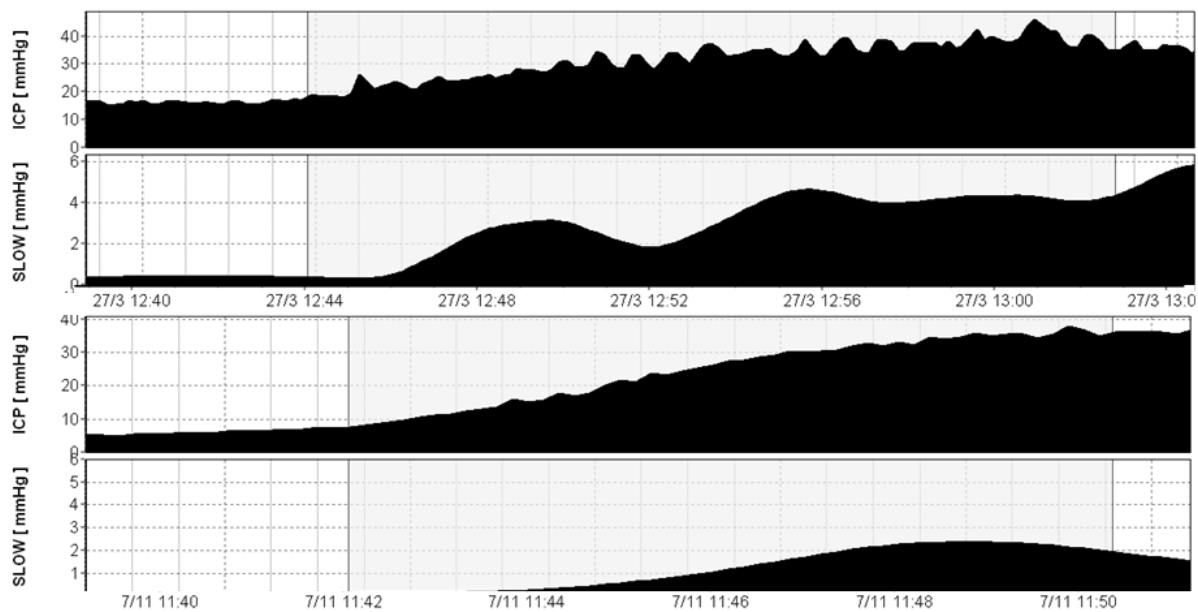
Typical infusion study performed in conscious patient (Group A) with ICP oscillations visible (upper) and Patient under GA (Group B), where ICP oscillations almost completely disappear (lower). ICP: Intracranial Pressure GA: General Anesthesia SLOW: magnitude of slow waves

Figure 2
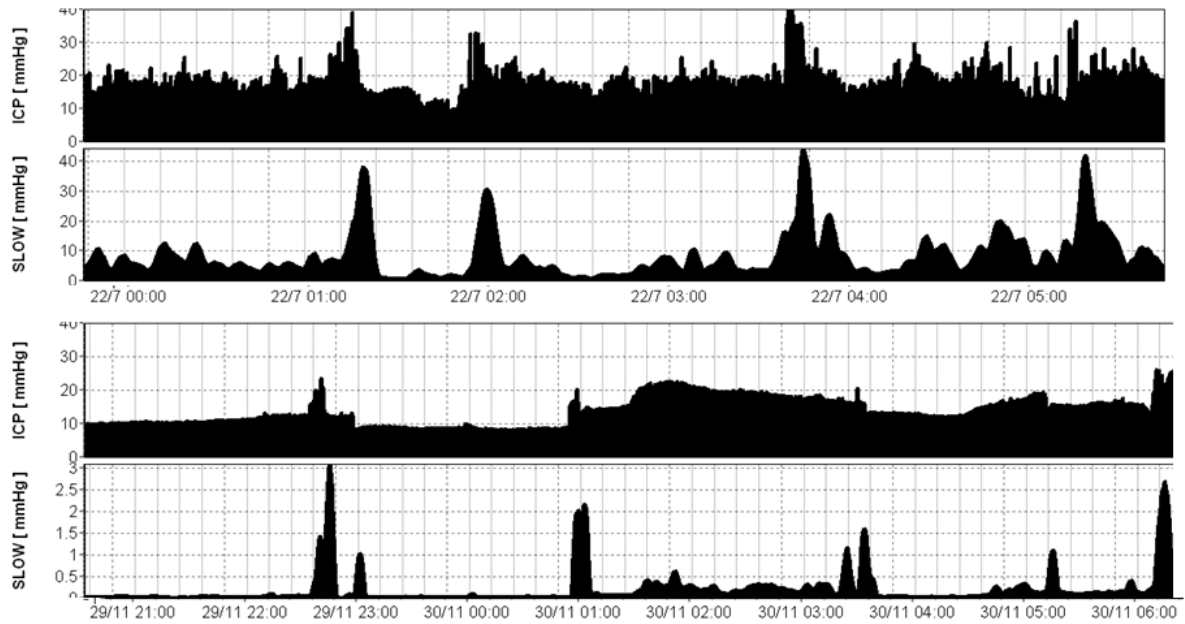
Overnight ICP monitoring in conscious patient (Group C) [upper] and monitoring of TBI patient (Group D) [lower]. ICP: Intracranial Pressure TBI: Traumatic Brain Injury SLOW: magnitude of slow waves