British Journal of Anaesthesia 1995; **75**: 441–446

EEG arousal during laryngoscopy and intubation: comparison of thiopentone or propofol supplemented with nitrous oxide

O. H. G. WILDER-SMITH, O. HAGON AND E. TASSONYI

Summary

We studied EEG arousal after laryngoscopy and intubation with standardized bolus induction of anaesthesia. Twenty patients were prospectively allocated randomly to induction with propofol 3 mg kg^{-1} ($n = 10$) or thiopentone (6 mg kg^{-1} ($n = 10$) and 50 % nitrous oxide in oxygen. Neuromuscular block was produced with vecuronium 0.2 mg kg^{-1} given 30 s after induction. Three minutes after induction, laryngoscopy was performed for 60 s, with intubation at 3 min 30 s, and study end at 5 min. Nociception to laryngoscopy and intubation was followed by loss of low (relative delta activity change: thiopentone −30 %, propofol −7 %; $P < 0.05$) and a shift to higher frequency EEG activity (beta activity change: thiopentone +647 %, propofol +61 %; $P < 0.05$). This EEG arousal was greater in the thiopentone group, despite the fact that EEG depression was similar to that produced by propofol before laryngoscopy and intubation. Propofol and thiopentone in combination with nitrous oxide had similar cortical depressant effects, but propofol appeared to depress subcortical nociceptive processing more than thiopentone. While the degree of cortical EEG depression seems less useful for predicting reaction to subsequent nociception, EEG arousal reactions may prove suitable for monitoring intra-anaesthetic nociception and its modulation. (*Br. J. Anaesth.* 1995; **75**: 441–446)

Key words

Intubation tracheal, responses. Anaesthetic techniques, induction. Anaesthetic techniques, laryngoscopy. Anaesthetics i.v., propofol. Anaesthetics i.v., thiopentone. Monitoring, electroencephalography. Anaesthesia, depth.

Detection and assessment of nociception represents one of the present challenges in anaesthetic practice. The most reliable sign, somatic movement, is abolished by neuromuscular block [1]. Other clinical signs of nociception during general anaesthesia such as haemodynamic or autonomic reactions are non-specific, often occurring late and are difficult to interpret [2, 3]. Simple derived EEG variables such as median frequency or spectral edge have been advocated for monitoring "depth of anaesthesia" with limited success [4–6]. They have not proved to be reliable measures for detecting or assessing acute nociception during anaesthesia [7, 8]. Arousal reactions are a phenomenon accepted as accompanying nociception [9]. The EEG, taken as a whole, is well validated for identifying arousal reactions in the non-anaesthetic context [10–14]. It has also been used successfully to identify arousal during anaesthesia [15–17]. So far the EEG has not been used systematically in anaesthesia to investigate the arousal reaction accompanying nociception and its modulation by different anaesthetic agents.

Using laryngoscopy and intubation during bolus induction of anaesthesia as a model of nociception during anaesthesia, we have studied the arousal accompanying nociception in the EEG. We also compared modulation of EEG arousal responses accompanying nociception by two commonly used anaesthetic induction agents, propofol and thiopentone, together with nitrous oxide, at doses accepted as being clinically equipotent [18].

Patients and methods

After obtaining Ethics Committee approval and informed written patient consent, we studied 20 unpremedicated ASA I–II patients undergoing elective surgery. Exclusion criteria included hypertension, neurological disease, drug abuse and chronic analgesic or hypnotic medication. The patients were prospectively allocated randomly to induction of anaesthesia with either propofol or thiopentone.

After cannulation of veins and attachment of monitors, patients were allowed to rest for 5 min. Baseline heart rate, arterial pressure and EEG recordings were performed. After preoxygenation by mask with 100 % oxygen for 3 min, anaesthesia was induced at time $t = 0$ by an i.v. bolus of either propofol 3 mg kg^{-1} or thiopentone 6 mg kg^{-1}, given over 20 s. Simultaneously, nitrous oxide in oxygen (1 : 1, $F_{I_{O_2}}$ measured continuously) was commenced via a mask. Ventilation was assisted or controlled as necessary to maintain end-tidal carbon dioxide partial pressure at 4.0–5.0 kPa throughout the study. At $t = +30$ s, vecuronium 0.2 mg kg^{-1} was given over 20 s. Exactly 3 min after induction, laryngoscopy was performed, always by the same an-

O. H. G. WILDER-SMITH, MB, CHB, MD, O. HAGON, E. TASSONYI, MD, DSC, Department of Anaesthesiology, Geneva University Hospital, 24 rue Micheli-du-Crest, CH-1211 Geneva 14, Switzerland. Accepted for publication: April 22, 1995.

Table 1 Patient characteristics (mean (SD or range) or number). BMI = Body mass index

	Age (yr)	Weight (kg)	Height (cm)	BMI	Sex (M : F)
Thiopentone	30 (20–51)	68.9 (10.1)	174 (8.4)	22.7 (1.8)	6:4
Propofol	38 (27–58)	66.1 (12.6)	167 (12.3)	23.4 (2.8)	6:4

Table 2 Time course of haemodynamic variables (mean (SD)). $t = 0$ is the time at which induction started; all subsequent numbers refer to minutes after $t = 0$. SI = Start of induction, L&I = laryngoscopy and intubation, SAP = systolic arterial pressure, DAP = diastolic arterial pressure, MAP = mean arterial pressure, HR = heart rate. ⋆$P < 0.05$ *vs* control; †$P < 0.05$ *vs* pre-L&I value ($t = 2$–3); ‡$P < 0.05$ *vs* propofol (only control and pre-L&I values tested within groups)

	Control	$t = 0$–1 (SI)	$t = 1$–2	$t = 2$–3	$t = 3$–4 (L&I)	$t = 4$–5
SAP (mm Hg)						
Thiopentone	131.5 (15.7)	130.4 (17.8)	118.8 (18.3)	121. 7 (15.6)‡⋆	129.9 (27.6)	166.1 (21.0)†
Propofol	129.7 (21.5)	130.5 (24.0)	116.3 (16.0)	106.9 (18.7)⋆	131.6 (36.5)†	166.1 (24.7)†
DAP (mm Hg)						
Thiopentone	70.3 (14.9)	73.4 (14.9)	67.8 (13.5)	64.0 (15.9)	74.2 (23.4)	102.9 (12.6)†
Propofol	71.8 (14.9)	73.8 (13.1)	68.3 (17.1)	58.2 (12.9)	84.1 (23.8)†	95.7 (12.3)†
MAP (mm Hg)						
Thiopentone	91.1 (14.4)	93.0 (14.5)	85.9 (13.7)	83.9 (15.1)	93.6 (24.6)	124.0 (13.9)†
Propofol	91.1 (15.5)	93.1 (13.8)	85.6 (16.1)	75.6 (14.1)⋆	101.7 (26.5)†	118.8 (14.7)†
HR (beat min^{-1})						
Thiopentone	75.6 (11.8)	71.9 (14.3)	88.9 (18.5)	94.5 (12.0)‡⋆	87.7 (8.6)‡	95.5 (16.3)
Propofol	73.0 (14.7)	74.2 (16.8)	94.6 (15.7)	79.9 (8.4)	77.7 (12.2)	101.2 (16.9)†

aesthetist, for exactly 60 s. Intubation, which took no longer than 20 s to complete, was done exactly 30 s after the start of laryngoscopy. The study ended 2 min after the start of laryngoscopy and intubation with the introduction of isoflurane. Patients were asked systematically about awareness or other anaesthetic problems at the visit after anaesthesia.

Heart rate, oscillometric non-invasive arterial pressure, end-tidal carbon dioxide concentration, $F_{I_{O_2}}$ and pulse oximetric oxygen saturation were recorded at 1-min intervals starting at induction ($t = 0$) (Merlin Anaesthesia Monitor, Hewlett Packard, Böblingen, Germany). The EEG was recorded continuously (Monisys 91/III neuromonitoring system, Department of Biomedical Engineering, Graz Technical University, Austria) via bilateral Fp1/2-T7/8 cup electrode montages with an Fpz reference. During the control measurement, patients were asked to relax and keep their eyes closed in order to minimize muscle artefact. Electrode impedance was kept below 3 kΩ. Analogue filtering of the signal was not performed, and high- and low-pass digital filters were set at 0.05 Hz and 1.5 kHz, respectively. The raw EEG was displayed continuously to enable removal of artefacts. Any periods of burst suppression in the raw EEG were noted and also excluded. For EEG quantification, Fourier transformation of the dominant hemisphere EEG in 4-s epochs was performed (spectral analysis) and grand means of 1-min epochs, starting at $t = 0$, calculated. The following variables were then determined from the epoch grand means: total EEG power, absolute power in the delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–14 Hz) and beta (14–24 Hz) bands. From these values the relative (band power/total power) activities in each EEG band were calculated.

The data collected were analysed by an observer unaware of the induction agent used. Statistical analysis was performed on the Statistica for Windows software package (Statistica for Windows, Release 4.5, 1993 Statsoft Inc, 2325 East 13th Street, Tulsa, OK 74104, USA). Patient and haemodynamic data are expressed as mean (SD). EEG data, not normally distributed, are given as median (interquartile range). Between-group differences for patient and haemodynamic data were analysed using an unpaired *t* test; within-group haemodynamic differences for control *vs* 1 min before laryngoscopy and intubation, and 1 min before laryngoscopy and intubation compared with 1 min of laryngoscopy and intubation and 1 min after laryngoscopy and intubation were tested by paired *t* test. For EEG variables, between-group testing was carried out using the Mann–Whitney *U* test. Intra-group testing of EEG variables, carried out at the same times as for the haemodynamic variables, was performed using Wilcoxon's paired test. Multiple comparisons were Bonferroni-corrected. $P < 0.05$ was considered statistically significant.

Results

The two groups were similar in characteristics (table 1). There were no problems with the induction scheme used, no patient had an $S_{p_{O_2}}$ less than 97 % at any time, and no patient moved, coughed or bucked with laryngoscopy and intubation. Questioning after anaesthesia did not reveal any episodes of awareness.

Haemodynamic values were generally similar between the groups (table 2), except for heart rate just before and during laryngoscopy and intubation, which was higher in the thiopentone group ($P < 0.01$ and 0.02 *vs* propofol, respectively). Laryngoscopy and intubation resulted in significant increases in arterial pressure in both groups ($P < 0.02$), with only a transient increase in heart rate in the propofol group 1 min after laryngoscopy and intubation ($P < 0.03$).

EEG burst suppression was not seen during the

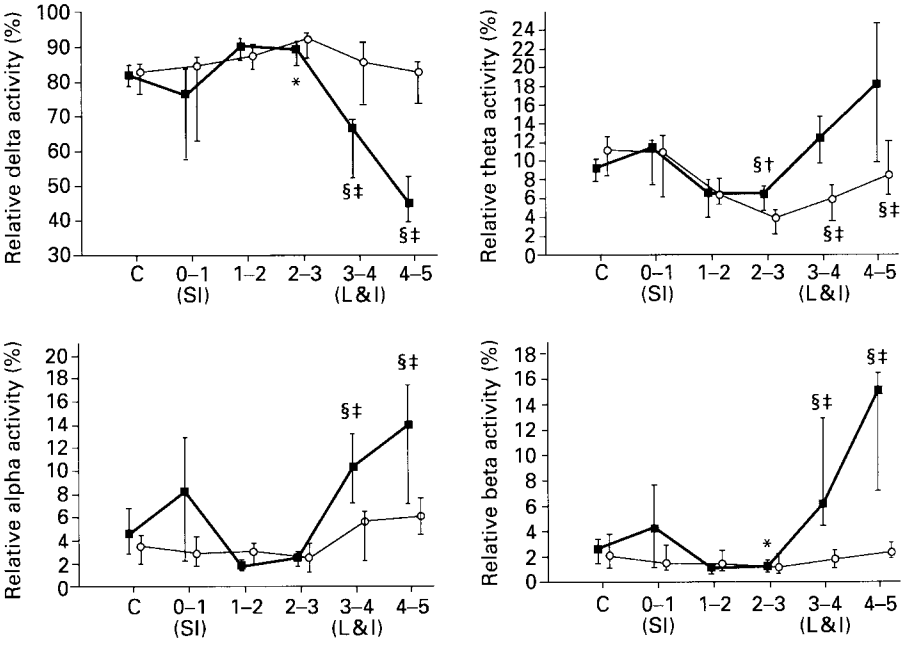

Figure 1 Time course of relative EEG activities. Values are medians and interquartile ranges of relative power in the delta, theta, alpha and beta EEG bands in the thiopentone (■) and propofol (○) groups. *X*-axis: EEG epochs in minutes, with induction starting at 0 min. C = Control, SI = start of induction, L&I = laryngoscopy and intubation. **P* < 0.05 *vs* control in the thiopentone group; †*P* < 0.05 *vs* control in both groups; ‡*P* < 0.05 *vs* pre-L&I value (*t* = 2–3) in both groups; § *P* < 0.05 *vs* propofol.

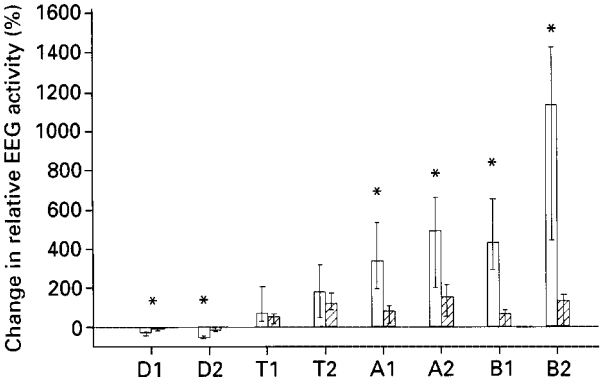

Figure 2 Changes in relative EEG activity with laryngoscopy and intubation (L&I). The changes (*Y*-axis) are given as percentage of relative EEG epoch just before L&I (*t* = 2–3), and are transformed relative EEG activity. Values are medians and interquartile ranges for the thiopentone (□) and propofol (▨) groups. *X*-axis: D = delta, T = theta, A = alpha, B = beta EEG band; 1 = change from the pre-L&I epoch to the epoch during L&I (minutes 3–4), 2 = change from the pre-L&I epoch to the epoch just after L&I (minutes 4–5). **P* < 0.05 *vs* propofol.

study. Figure 1 shows the time course for the relative EEG activities. All relative EEG control and *t* = 0–1 values were similar. Just before intubation, both groups had similar relative EEG activities, except for the lower activity in the propofol group in the theta band ($P < 0.01$). With and after laryngoscopy and intubation, theta, alpha and beta activities were significantly lower, and delta activity significantly higher in the propofol than in the thiopentone group ($P < 0.04$). Induction caused significant decreases in relative theta and beta activities in the thiopentone patients (control *vs* just before laryngoscopy and intubation, $P < 0.02$), while in the propofol group, the increase in delta and decrease in theta activities were significant (control *vs* just before laryngoscopy and intubation, $P < 0.04$). In both groups, laryngoscopy and intubation was associated with significant increases in relative theta, alpha and beta activities, and a significant decrease in delta activity (just before laryngoscopy and intubation *vs* *t* = 3–4 (laryngoscopy and intubation), *t* = 4–5; $P < 0.03$). The *changes* resulting from laryngoscopy and intubation (fig. 2) were significantly larger in the thiopentone group in all but the theta band.

Discussion

In our study, laryngoscopy and intubation were accompanied by a characteristic and reproducible EEG arousal reaction, easily seen in the relative band activities. EEG arousal consists of a loss of delta activity together with increases in higher frequency (theta, alpha and beta) activities and is accompanied by increases in arterial pressure and heart rate. Just before laryngoscopy and intubation, the degree of cortical depression, as assessed by the relative EEG band activities [6, 8, 19], was similar in the thiopentone and propofol groups. The subsequent greater EEG arousal reaction with laryngoscopy and intubation thus suggests poorer subcortical antinociception in the thiopentone than in the propofol group in combination with nitrous oxide.

It might be argued that the EEG arousal reaction can be explained purely on the basis of pharmacokinetic considerations, that is falling effect site concentrations. We consider this unlikely for the following reasons. The EEG, generally accepted as a good reflection of effect site concentrations for

hypnotic agents [4], showed a similar course for relative values for the two groups up to laryngoscopy and intubation. With laryngoscopy and intubation, the EEG courses of the thiopentone and propofol patients, which had been changing only very slowly, changed abruptly and generally in the opposite direction to that seen before laryngoscopy and intubation. In addition, the EEG courses of the two groups diverged abruptly. This EEG behaviour, which supports similar effect site behaviour up to laryngoscopy and intubation, changed markedly with laryngoscopy and intubation, a change difficult to explain on the basis of effect site pharmacokinetics. Finally, we have already seen EEG excitation associated with certain effect site concentrations during induction ($t = 0$–1). Its nature (e.g. slope and maximum) is different from that seen during the EEG excitatory arousal after laryngoscopy and intubation.

We chose a thiopentone to propofol dose ratio accepted as being clinically equipotent for bolus induction [18]. This was confirmed by the similar relative EEG course before laryngoscopy and intubation for the two groups. To ensure clinically and ethically acceptable induction conditions, we had the choice of using nitrous oxide supplementation with the propofol or thiopentone doses stated, or using higher doses. We decided on nitrous oxide supplementation with the doses stated because it was closer to clinical practice and associated with fewer overall side effects. While the results reflect the interaction between the induction agent and nitrous oxide, the *differences* between the groups can be considered to reflect differences between propofol and thiopentone, as both groups received the same concentrations of nitrous oxide under similar conditions.

A higher than usual vecuronium dose was used in order to achieve complete neuromuscular block reliably in the required 2.5 min. This is important not only from clinical considerations and to avoid EEG artefacts, but also because it has been suggested recently that active muscle movement caused by noxious stimulation in light anaesthesia is associated with EEG activation resulting from activation of muscle stretch receptors [20]. This cerebral response is attenuated by neuromuscular block [20].

Absolute EEG values in anaesthesia are highly dependent on initial EEG state and type, and vary considerably according to the anaesthetic drug(s) used [7, 12, 15, 21]. To allow statistical comparisons of EEG between groups, particularly regarding degree of cortical depression, normalization in the sense of relative EEG activity, that is absolute activity in an EEG band/total absolute EEG activity, is generally used [22, 23]. Our discussion of EEG results is thus based on relative EEG values. The 1-min duration of the EEG epoch grand means was chosen to permit detection of significant EEG effects after events while maintaining acceptable temporal resolution. Other studies of noxious stimuli in anaesthesia have successfully used similar methods of EEG analysis [15, 16].

We have found only one study of the interaction between laryngoscopy and intubation and EEG. Rampil and Matteo [24], studying patients induced with varying doses of thiopentone, fentanyl, lignocaine, droperidol and suxamethonium, found a significant correlation between EEG spectral edge values before laryngoscopy and intubation and systolic arterial pressure response to laryngoscopy and intubation. There was no correlation for heart rate or diastolic pressure.

Few studies have addressed the effect of nociceptive stimuli during anaesthesia on the EEG [15–17]. In two topographical EEG studies, Kochs and colleagues [16, 17] demonstrated that surgical stimulation during standardized fentanyl-supplemented isoflurane–nitrous oxide anaesthesia was associated with increases in delta and decreases in alpha activities, that is 'paradoxical' or inhibitory arousal. These results are in contrast to ours, which consisted of a "classical", excitatory EEG arousal reaction, that is loss of low frequency (delta) activity and increased high frequency (alpha, beta) activity [6, 16, 17, 19]. Bimar and Bellville [15], studying patients under a variety of anaesthetics, noted both classical and paradoxical arousal reactions in the EEG with surgical stimulation. Both types of EEG arousal reactions are also well documented in association with non-nociceptive and nociceptive sensory stimulation either awake [10] or during sleep or coma in humans [11, 12] and animals [13, 14].

Both excitatory and inhibitory arousal responses to pain have been described in the literature [25, 26]. Nociception from deep structures (viscera, joints, muscle) generally elicits inhibitory arousal, while superficial nociception (skin, mucous membranes of body orifices) is associated with excitatory responses. The factors determining the type of EEG arousal in response to nociceptive stimulation in anaesthesia have not been investigated specifically. However, the observation that the "superficial" nociception (mucosa) of laryngoscopy and intubation in our study is associated with a predominantly excitatory response, taken together with the finding of inhibitory arousal in the studies of Kochs and colleagues [16, 17], which involved "deep" nociception (muscle and viscera), suggests that similar principles apply to EEG arousal during anaesthesia. In addition to the location of nociception, other factors in the anaesthetic setting may include EEG topography [16, 17, 23] or degree of cortical depression just before the stimulus [13, 14, 16, 21, 23]. For topography, arousal is best seen in a frontal EEG montage [16, 23], as in our study: the more depressed the cortex, the higher the likelihood of paradoxical arousal [13, 14, 16, 27]. In our study the depth of anaesthesia achieved was less than that in the studies of Kochs and colleagues [16, 17], favouring a classical arousal reaction.

In their studies, Kochs and colleagues concluded that deeper anaesthesia resulted in more attenuation of the arousal response to nociception [16, 17]. In common with others [6, 8, 19], they found that deeper anaesthesia was associated with more relative delta and less relative higher frequency (alpha, beta) activities. Using these classical EEG criteria of degree of cortical depression, our thiopentone and propofol groups had similarly deep anaesthesia just

before laryngoscopy and intubation. Despite this, the thiopentone group experienced a greater EEG arousal reaction with laryngoscopy and intubation. This not only suggests that the subcortical block of nociceptive input provided by propofol was more effective than that provided by thiopentone, but also illustrates the difficulties in predicting the response to nociception from the degree of cortical depression before the stimulus, particularly between different drugs.

The similar EEG changes resulting from induction of anaesthesia with thiopentone or propofol in our study correspond to those described by others [28–31]. We have found no studies directly comparing the effects of thiopentone and propofol on the EEG in humans. However, our results are in agreement with the study of Tomoda and colleagues [32], who found that thiopentone and propofol had similar simple CNS depressant effects on supratentorial electrical activity in cats.

The increases in arterial pressure and heart rate with laryngoscopy and intubation during propofol or thiopentone induction have been observed previously [33] and changes in our study are comparable with those described.

We conclude that while propofol and thiopentone combined with nitrous oxide had similar depressant effects on cortical function in the absence of nociceptive stimulation, propofol provided better depression of subcortical nociceptive processing than thiopentone. Thus hypnotic and antinociceptive equipotency of anaesthetic drugs did not necessarily coincide. While the degree of EEG cortical depression only seems of limited use for predicting reactions to subsequent nociception, the EEG arousal reactions themselves may prove suitable for studying intra-anaesthetic nociception and its modulation.

References

1. Edmonds HL jr, Yli-Hankala A, Heine MF, Tsueda K, Strickland TJ jr. Anaesthetic adequacy, surface EMG and quantitated EEG. *Acta Anaesthesiologica Scandinavica* 1993; **37** (Suppl 100): 102–104.
2. Prys-Roberts C. Anaesthesia: A practical or impractical construct? *British Journal of Anaesthesia* 1987; **59**: 1341–1345.
3. Hug CC jr. Anesthesia monitoring. In: Miller RD, ed. *Anesthesia*, 2nd Edn. New York: Churchill Livingstone, 1986; 411–463.
4. Bührer M, Maitre PO, Hung OR, Ebling WF, Shafer SL, Stanski DR. Thiopentone pharmacodynamics. I. Defining the pseudo-steady-state serum concentration-EEG effect relationship. *Anesthesiology* 1992; **77**: 226–236.
5. Long CW, Shah NK, Loughlin C, Spydell J, Bedford RF. A comparison of EEG determinants of near-awakening from isoflurane and fentanyl anesthesia: spectral edge, median power frequency, and delta ratio. *Anesthesia and Analgesia* 1989; **69**: 169–173.
6. Schwilden H, Schüttler J, Stoeckel H. Closed-loop feedback control of methohexital anesthesia by quantitative EEG analysis in humans. *Anesthesiology* 1987; **67**: 341–347.
7. Drummond JC, Brann CA, Perkins DE, Wolfe DE. A comparison of median frequency, spectral edge frequency, a frequency band power ratio, total power, and dominance shift in the determination of depth of anaesthesia. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 693–699.
8. Hung OR, Varvel JR, Shafer SL, Stanski DR. Thiopentone pharmacodynamics: II. Quantitation of clinical and electroencephalographic depth of anesthesia. *Anesthesiology* 1992; **77**: 237–244.
9. Jänig W. Pain and the sympathetic nervous system pathophysiological mechanisms. In: Bannister R, Mathias C, eds. *Autonomic Failure*, 3rd Edn. Oxford: Oxford University Press, 1992; 231–251.
10. Berger H. Über das Elektrenkephalogram des Menschen. *Archive der Psychiatrie* 1931; **101**: 452–469.
11. Schwartz MS, Scott DF. Pathological stimulus-related slow wave arousal responses in the EEG. *Acta Neurologica Scandinavica* 1978; **57**: 300–304.
12. Evans BM. Patterns of arousal in comatose patients. *Journal of Neurology, Neurosurgery and Psychiatry* 1976; **39**: 392–402.
13. Prince DA, Shanzer S. Effects of anaesthetics upon the EEG response to reticular stimulation. Patterns of slow synchrony. *Electroencephalography and Clinical Neurophysiology* 1966; **21**: 578–588.
14. Moruzzi G, Magoun HW. Brain stem reticular formation and activation of EEG. *Electroencephalography and Clinical Neurophysiology* 1949; **1**: 455–473.
15. Bimar J, Bellville JW. Arousal reactions during anesthesia in man. *Anesthesiology* 1977; **47**: 449–454.
16. Kochs E, Bischoff P, Pichlmaier U, Schulte am Esch J. Surgical stimulation induces changes in brain electrical activity during isoflurane/nitrous oxide anesthesia. *Anesthesiology* 1994; **80**: 1026–1034.
17. Bischoff P, Kochs E, Droese D, Meyer-Moldenhauer WH, Schulte am Esch J. Topographisch-quantitative EEG-Analyse der paradoxen Arousalreaktion. *Der Anaesthesist* 1993; **42**: 142–148.
18. Naguib M, Sari-Kouzel A, Seraj M, El-Gammal M, Gomma M. Induction dose-response studies with propofol and thiopentone. *British Journal of Anaesthesia* 1992; **68**: 308–310.
19. Schwilden H, Stoeckel H. Quantitative EEG analysis during anaesthesia with isoflurane in nitrous oxide at 1.3 and 1.5 MAC. *British Journal of Anaesthesia* 1987; **59**: 738–745.
20. Lanier WL, Iaizzo PA, Milde JH, Sharbrough FW. The cerebral and systemic effects of movement in response to a noxious stimulus in lightly anesthetized dogs. Possible modulation of cerebral function by muscle afferents. *Anesthesiology* 1994; **80**: 392–401.
21. Li CL, Jasper H, Henderson L. The effect of arousal mechanisms on various forms of abnormality in the electroencephalogram. *Electroencephalography and Clinical Neurophysiology* 1952; **4**: 512–526.
22. Dumermuth G. Numerical spectral analysis of the electroencephalogram. In: Rémond D, ed. *Handbook of Electroencephalography and Clinical Neurophysiology, vol. 5A.* Amsterdam: Elsevier, 1973; 33–60.
23. Tinker JH, Sharbrough FW, Michenfelder JD. Anterior shift of the dominant EEG rhythm during anesthesia in the Java monkey: correlation with anesthetic potency. *Anesthesiology* 1977; **46**: 252–259.
24. Rampil IJ, Matteo RS. Changes in EEG spectral edge frequency correlate with the hemodynamic response to laryngoscopy and intubation. *Anesthesiology* 1987; **67**: 139–142.
25. Bandler R, Shipley MT. Columnar organization in the midbrain periaqueductal gray: modules for emotional expression? *Trends in Neuroscience* 1994; **17**: 379–389
26. Samso E, Farber NE, Kampine JP, Schmeling WT. The effects of halothane on pressor and depressor responses elicited via the somatosympathetic reflex: a potential antinociceptive action. *Anesthesia and Analgesia* 1994; **79**: 971–979
27. Kaada BR, Thomas F, Alnaes E, Webster K. EEG synchronisation induced by high frequency midbrain reticular stimulation in anesthetized cats. *Electroencephalography and Clinical Neurophysiology* 1967; **22**: 220–230.
28. Rosner BS, Clark DL. Neurophysiological effects of general anesthetics. II. Sequential regional actions in the brain. *Anesthesiology* 1973; **39**: 59–81.
29. Schwilden H, Stoeckel H, Schüttler J. Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans. *British Journal of Anaesthesia* 1989; **62**: 290–296.
30. Yate PM, Maynard DE, Major E, Frank M, Verniquet AJW, Adams HK, Douglas EJ. Anaesthesia with ICI 35868

monitored by the cerebral function analysing monitor (CFAM). *European Journal of Anaesthesiology* 1986; **3**: 159–166.
31. Frank M, Maynard DE, Tsanaclis LM, Major E, Coutinho PE. Changes in cerebral electrical activity measured by the cerebral function analysing monitor following bolus injections of thiopentone. *British Journal of Anaesthesia* 1984; **56**: 1075–1081.
32. Tomoda K, Shingu K, Osawa M, Murakawa M, Mori K. Comparison of CNS effects of propofol and thiopentone in cats. *British Journal of Anaesthesia* 1993, **71**: 383–387.
33. Lindgren L, Yli-Hankala A, Randell T, Kirvelä M, Scheinin M, Neuvonen PJ. Haemodynamic and catecholamine responses to induction of anaesthesia and tracheal intubation: comparison between propofol and thiopentone. *British Journal of Anaesthesia* 1993; **70**: 306–310.