Monitoring Awareness During Cardiac Surgery

Andreas Fiehn MD, PhD
Department of Cardiothoracic Anaesthesiology, Klinikum Kassel, Moenchebergstr 41-43, 34125 Kassel, Germany

Monitoring Brain Function

In today's anaesthesia, monitoring brain functions is of increasing concern to the anaesthesiologist. Over decades anaesthesiologists have been careful providers of safety for their patients. Attention was focused on haemodynamic stability, pulmonary function, metabolic balance and pain control. However, in the practical operation room settings, the brain seems to be merely a black box. But we have to understand, that to a certain extent we as anaesthesiologist are like gate keepers to our patient's brain, protecting him from harmful effects of anaesthesia.

Brain functions in general can be monitored in the sense of blood flow, oxygen consumption, metabolic, nerve and electrical functions. Different monitors are therefore used for detection of hypoperfusion as in carotid endarterectomy, emboli detection, flow measurements as in neurosurgery, brain protection as in deep hypothermic circulatory arrest and severe head injury, drug control as in long term sedation in ICU or state of hypnosis in anaesthesia.[1,2] Newly invented flow dependent devices as trans cranial doppler (TCD) are more diagnostic than long term monitoring devices. Somatosensory evoked potentials (SSEPs) have shown to be very useful in carotid surgery and spinal cord protection during thoracic aneurysm surgery requiring clamping, but they are also more of diagnostic value. Measurement of cerebral oximetry (INVOS) has certain technical limitations and has not proven to be very reliable or specific. From all these techniques only processed electro encephalogram (EEG) has come to the point of a continuous clinical monitor.

Intraoperative awareness

Our concept and understanding the depth of anaesthesia has changed dramatically since Guedel described the stages of anaesthesia.[3] The semantically and logical questions rising with the term "awareness" as it is used by the anaesthesia community in contradiction to psychologists and memory researchers, leaves us with little hope for more clarity. We have to understand that awareness in general is not synonymous with consciousness and that memory is an ongoing process. Memory itself can basically be divided in to explicit (conscious) type and implicit (unconscious) type.[4-6] To increase our confusion, commercially available monitoring systems are marketed to measure either "depth of anaesthesia", "patient's state of awareness" or "state of hypnosis".

Although intraoperative awareness is a rare event, it concerns about 50% of all patients undergoing surgery. It is a major issue for those who have had previous episode of awareness. Patients can experience from unpleasant after effects as dreams, nightmares, anxiety, up to development of post traumatic distress syndromes.

Recalls or awareness situations are as old as the history of anaesthesia. The first reports of intraoperative awareness can be found in 1908 by Crile who reported the case of a woman who could describe her abdominal operation although it was done "under complete nitrous oxide and oxygen anaesthesia".[7] In 1950 Winterbottom published "Insufficient anaesthesia" in the British Medical Journal and innumerable publications followed.[8] Most of the major textbooks, e.g. Cardiac Anaesthesia by Kaplan, describe that intraoperative awareness occurs only in 1% of the patients, whereas other authors report an incidence of up to 28%. The reported incidence depends on the type of anaesthesia, strength of stimuli, timing and persistence to elicit recall. Using an easy structured interview technique in 617 patients 12-48 hours after the operation, Dowd reported an incidence of 0–7%.[9] In a large serie of patients in Finland, Ranta interviewed 2612 patients, the incidence was found to be 0.3 – 0.4% due to significant smaller doses of isoflurane and propofol.[10] Other authors showed a difference when using interview techniques on the day of operation (smaller incidence) or when used on postoperative day 1–3 and 7–14 and found an incidence of 0.18 % in 11785 patients.[11] In his editorial for Anesthesia&Analgesia Tempe states that only combined efforts by a group of anaesthesiologist, psychologist, and others will resolves some of the mysteries. The incidence of awareness should

Address for Correspondence: Andreas Fiehn MD, PhD, Department of Cardiothoracic Anesthesiology, Klinikum Kassel, Moenchebergstr. 41-43, 34125 Kassel - Germany e-mail: Fiehn@Klinikum-Kassel.de

Annals of Cardiac Anaesthesia 2002; 5: 149–155

Key words: Awareness, Monitoring, Cardiac surgery

be reduced to as low a level as can be, because there is always a risk of posttraumatic neurosis.[12]

The widely accepted definition of anaesthesia is a combination of the state of hypnosis, analgesia, muscle relaxation and vegetative stability. Muscle relaxation and vegetative stability can be easily measured. Up to now analgesia is indirectly measured by vegetative response to surgical stimulus or by the MAC (minimal alveolar concentration) of drugs. Hypnosis in the light state (sedation) can be quantified by sedation scales as the Ramsay or the Modified Observer's / Assessment Scale. These scales are used in many studies, but cannot be used in anaesthesia, due to the lack of response to verbal commands. Besides, this approach provides only a subjective instantaneous assessment of the patients state.

Cardiac anaesthesia, however, is associated with a higher incidence of awareness, compared to other surgical procedures. Possible reasons for this are, the still widely used high opiod based techniques, the almost unpredictable pharmacodynamics of anaesthetics under the extracorporeal circulation especially in the rewarming period and at the time of cessation of bypass, interpersonal and interracial differences in drug reactions, haemodilution, and binding on foreign surface areas.[13] The widely used clinical parameters such as pressure, rate, sweating and tears (PRST Score) within the course of anaesthesia, can not predict episodes of intraoperative awareness and have no scientific background.[14]

System Requirements

Commercially marketed systems should be rated against the description by Sebel for the effectiveness of measuring the depth of anaesthesia.[15] This proposed classification enables us to compare monitor systems.

The ideal monitor should show:

1. A dose dependent relationship with different drugs used in anaesthesia.
2. Measure the depth of anaesthesia during induction as well as during emergence.
3. Detect intraoperative awareness situations.
4. Prevent over dosing and under dosing of anaesthetics.
5. Display malfunction of the system easily.

It should be kept strongly in mind that the scientific method used for the algorithm should be truly validated by a different and accepted scientific method. This algorithm should be published, so it can be critiqued and re-evaluated by different researchers. Reasons for new software releases should be explained freely.

As stated earlier the more clinical signs as the PRST Score[16], the prevention of movements as used in the MAC concept as well as the isolated forearm technique[17] cannot be used to detect either intraoperative awareness or measure the depth of anaesthesia. The main disadvantage in the use of these techniques is that they do not work on paralysed, beta blocked patients or in longer lasting procedures.

EEG

The realisation that the effects of anaesthetics may alter the EEG dates back to the discovery that the brain produces electrical activity. It was Caton in 1875 who, with the use of chloroform, convinced himself, that the waves he recorded from the brain were really of biologic origin.[18] In the earlier 1930's, due to the knowledge of recording small voltages through the skull and the availability of electronic amplifiers, Berger showed the influence of chloroform on the EEG.[19] In 1952 Faulcorner published the correlation between arterial ether concentration in oxygen and in oxygen / nitrous oxide and the depth of anaesthesia based on EEG patterns.[20] Despite these early results, the recording of raw EEG signals in the operating room setting has had many disadvantages. It needed sophisticated knowledge of the neurologist for interpretation, it was time consuming and it distracted the anaesthesiologist's attention. Development of computerised processed EEG with conversion of EEG signals by means of Fast Fourier Transformation (FFT), that provides objective and reproducible information, has made it usable for continuous intraoperative monitoring.

The EEG can be considered to measure the depth of anaesthesia for several reasons. It represents cortical electrical activity derived from summated excitatory and inhibitory postsynaptic activity, which are controlled and paced by subcortical thalamic nuclei. Cerebral blood flow and cerebral metabolism are related to the degree of EEG activity.

Basically the EEG in the awake state shows high frequencies and low amplitudes. Most of anaesthetic drugs change the EEG in the same way, the frequency is reduced and the amplitude is increased. Lower doses of anaesthetics (level of sedation) lead to an increase in the median frequency, maximum strongest in the high frequencies Beta ($\beta 1$ and $\beta 2$) and to a decrease in the Alpha (α) waves. Increasing the dosage of anaesthetics (level of anaesthesia), a decrease in the median frequency and an increase in the amplitude can be seen. The EEG shows mostly Theta (θ) and Delta (δ) activity. The increase over this point will lead to burst suppression and then isoelectric EEG.[21]

Limitation of EEG monitoring is due to the reason that EEG is only able to show cortical alterations. From animal studies we know that variable damage either in patchy or variable degree is mostly seen in depth of the sulci or deeply located structures i.e. the putamen. Also minor changes of the EEG can be found due to alterations by cerebral metabolism (i.e. Isoflurane, Propofol), which is known to alter carbohydrate metabolism such that brain glucose and glycogen levels increase and lactic acid concentration decreases as well as due to change in temperature, $PaCO_2$, and mean arterial pressure.[22]

Since the mid 1990's different types of so called "neuromonitors" as the bispectral index (BIS), median frequency (MF), auditory evoked potentials (AEP), 95% spectral edge frequency etc. have been introduced in to clinical practice. Most of them have been critiqued for their limitation of recording only 4 leads or even less, neglecting the fact of topographical feature of the brain. Further disadvantages are that either the mathematical algorithm has not been published, the validation has been done only on an anaesthetised population or the procedure is too complicated for clinical monitoring system.[23] Most of these systems also do not record a high quality of EEG due to the low output impedance amplifiers that are used.

Monitoring Systems Using the EEG

Spectral Analysis of the EEG

Since online raw EEG interpretation is meaningless, most monitor systems are using processed EEG with FFT. Earlier research with the MF and with the spectral edge frequency 95 (SEF 95) – frequencies where 50 % (MF) and 95 % (SEF 95) of the frequencies are below the power of the EEG, have not shown reliable results. SEF 95 and MF have had good correlation with increasing concentrations of volatile anaesthetics. In contradiction to the expectations, both parameters increased in the light state of anaesthesia, showing similar values as in the awake state. A decrease was found only later in deeper state of anaesthesia. Thus resulting in the same SEF 95 and MF values for the awake and light anaesthetised patient.[24,25]

Power Spectrum Analysis of the EEG

Analysis of the EEG power spectrum for measuring the depth of anaesthesia is used in the PSM 2000, SomnoTrack and computer aided quantitative topographical electroencephalometry (CATEEM) (all Medisyst GmbH, Linden, Germany) and the EEG module M-EEG used in Datex-Ohmeda monitoring systems (System 5, Datex-Ohmeda, Helsinki, Finland). The pEEG (Drager AG, Luebeck, Germany) is no longer available.

1. CATEEM

The CATEEM describes the functional changes of the brain by automatic frequency analysis of all 99 (17 real and 82 virtual) electrode position using FFT. The current method (10:20 system), described in 1958, for placement of cortical recording electrodes divides each half of a cerebral hemisphere into quadrants measuring 10%, 20% and 20% of the hemispheric length to locate the position of the electrodes. The results are displayed in real-time, showing the absolute power density (μV2 / Hz) of the real 17 electrodes and a quantitative topographical map using spectral colour scales within the map. The so called mirror mode visualises hemispheric asymmetries, comparing two electrodes to the middle axis. Thereby the more active electrode is reflected by a lighter area, whereas the less active electrode is darker. An automatic high artefact rejection is used as well as the high output impedance amplifier.

Using the CATEEM technology numerous studies in pharmacology research have shown that groups of drugs i.e. sedatives such as propofol and barbiturates increase the beta and alpha activity, whereas benzodiazepines decrease the alpha activity and with neuroleptics only an increase in alpha 1 but not alpha 2 can be found. Same results are shown for different other drugs, stating that drugs leave a "electrical fingerprint" in the brain.[26,27] CATEEM has been used to determine the effect of retrograde cerebral perfusion, in carotid endarterectomy, neurology, anaesthesia and sleep medicine.[28-34]

Spectral Frequency Index (SFx)

In 1998 Dimpfel published the validation of an EEG derived SFx for continuous monitoring of sleep depth in humans.[35] The base for validation of the SFx is the comparison with the conventional sleep staging according to Rechtschaffen and Kales.[36] This staging is an international accepted six score system in sleep medicine, ranging from "awake" through "REM sleep" to "stage 4" reflecting deep sleep.

Background for the SFx is the knowledge about the correlation between biochemical transmitters and changes of frequency content of potentials. Three systems – the norepinephrine system, the glutamate system and the GABA ergic system control sleep. The net balance of these transmitters are reflected in the theta, beta 1 and beta 2 frequencies. Loss of norepinephrine control results in increase of theta activity, loss of glutamatergic control in an increase of beta 1 activity. Enforcement of GABA-ergic activity results in a decrease of beta 2 frequencies. The EEG derived formula of the absolute electrical power theta (θ) + beta 1 (β1) / beta 2 (β2) reflect the changes

found with the noradrenergic alpha 2-agonist medetomidine, which produce tremendous dose and time dependent specific increases in comparison to pre drug theta power. Together with the observation that other sedative drugs increase beta 1 power and that beta 2 power is decreased during human sleep, this formula is background for the Sfx. Since then the SFx has been used in many studies for determination of sedation after coronary bypass surgery, induction and depth of anaesthesia with various anaesthesia regimens as sufentanil, propofol, balanced anaesthesia with fentanyl and inhalation agents. In 6 single blinded, randomised multicenter trials – including propofol, midazolam and opiods as reference drugs in comparison with a new drug, LK 544 (ethanolamin derivate), the SFx showed superior quality.[37-38] The SFx is scaled from 0 - 100% awake, where > 85 % is awake. The SFx follows temperature changes and also reflects zero line EEG under deep hypothermic circulatory arrest.

2. PSM 2000

The PSM 2000 is using the same technology as the CATEEM. It is a touch screen monitor, displaying the SFx as well as a hemisphere index. This index reflects the mirror mode as stated above. With the hemisphere index, hypoperfusion during cardiac procedures as well as in carotid surgery can be detected, keeping in mind that only cortical processes will be monitored.

3. Somnotrack

The Somnotrack with the so called Hypnax Technology is using 5 electrodes, positioned in an elastic, reusable EEG cap. Electrodes are using comparison between C3 (left) and C4 (right) hemisphere. The Hypnax is scaled from 0 to 100 %. According to the company suggestions a Hypnax of > 85% is awake, 70 – 80 % light sleep, 40-70 % deep sleep, < 40 % comatose. The Hypnax is a modified SFx, where evaluation still has to be done.

4. EEG-Modul M-EEG

This technology is only made for implementation into the Datex-Ohmeda Monitor system 5 (Datex Ohmeda, Finland). It uses a 4 channel EEG, which displays MF, SEF and burst suppression. It is also combined with AEP and BIS. A similar module using 4 channel EEG as well as BIS has been introduced to the market recently by Drager and Marquette (Drager, Germany) for use in their monitor systems Solar. Till now there is not much experience with this M-EEG module.

Personal clinical experience in cardiac anaesthesia as well as in studies over the last 3 years has shown that the system is easy to use, cost effective and reliable. To compare the costs between the BIS, hardware cost are comparable, where the single use probes of the BIS cost 18 EUR and the reusable EEG cap for about 500 recordings cost 150 EUR. This gives a single use cost factor off 0.3 EUR with the CATEEM or PSM 2000.

Non-linear, Chaotic Multivariant EEG

In contradiction to the linear EEG measurements with spectral or power analysis the technology used in BIS, Narkotrend, Entropy or the Patient State Index is based more on a chaotic approach. The details of the different mathematical formulae and technology cannot be discussed here.

1. BIS

The Bispectral Index (Aspect Medical Systems Inc. and SpaceLabs Medical Inc. USA) is based on a multivariant, statistical Analysis taking in to account the EEG, "Power" frequencies, bispectral analysis of the biocoherence, ß-activation, Quazi-suppression and burst suppression as well as so called hypnotic index. For details of the technology the reader is referred to the article by Rampil, but one has to keep in mind that the company never released the formula.[39] Even if the BIS is the most studied value in the sense of hypnotic effect or as a monitor of awareness, the results are quite confusing. In comparing studies on the BIS it is important to take the software version in to consideration, i.e. the software 1.1 is using movements due to surgical stimulation, whereas the software 2.0 and higher is accounting loss of consciousness as well as intraoperative awareness. Except one large scaled multicenter study (300 patients) using the BIS software version 1.1. there are no large studies with the higher software versions, especially no studies are undertaken in cardiac surgery. BIS is a dimensionless number from 0 to 100. The exact definition when a patient is deeply asleep and is not endangered by awareness is still under debate. The major points of criticism are: additive anaesthetic and analgesic potency of nitrous oxide could not be measured,[40] in Xenon anaesthesia verbal command were followed on a BIS < 50,[41] ketamin as well as opiods are not reflected by the BIS,[42-44] there being some case reports on intraoperative awareness even with a BIS of 47[45,46] and out of personal experience temperature changes are reflected poorly by the BIS. Out of studies with concepts of postoperative sedation, we know that the BIS only poorly reflected the state of sedation.[47-50] All these points seem to show that BIS is not a totally reliable monitor for detecting awareness. Besides, the cost of the single use sensors with 18 EUR / piece is enormous compared with 0.3 EUR using

a reusable EEG cap, which cost 150 EUR and can be used about 500 times. However, it should not be stated that this monitor is useless, its the only marketed monitor with FDA approval but its limitations should be kept strongly in mind.

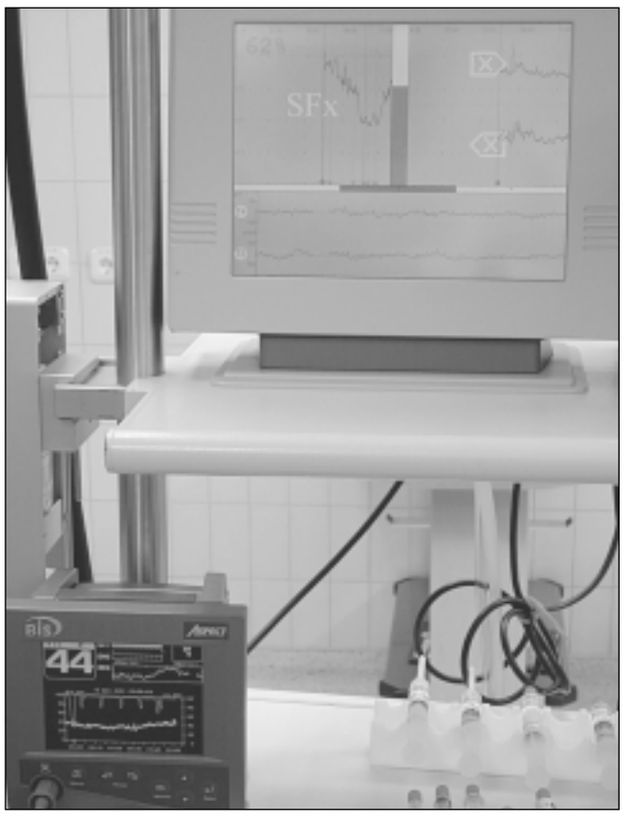

Fig 1. Picture comparing graph on PSM 2000 and BIS CABG surgery, intermittent cross clamping technique, balanced anaesthesia, note temperature drifts on PSM 2000 – no drift on BIS.

2. Narkotrend

Using the anaesthesia classification of Kugler[51] from A to F and subclassification of B, C and D to a total of 13 stages reflected by the EEG the Narkotrend (MT Monitor Technik Inc., Germany) uses 4 electrodes on the frontal, temporal and occipital area. It displays the anaesthesia classification A – F, where D and E are adequate anaesthesia and F reflects very deep stages with burst suppression. In elderly patients a decrease of Delta (δ) activity is seen in stages D and E, reflecting the limited need of anaesthetics. The user can choose to display the Cerebrogram (A-F), on-line EEG, power spectrum, two quantile of the power spectrum (MF, SEF 95%) or a 2 channel EEG comparing both hemispheres.

Unpublished data (personal communication) from more than 5000 patients in a multicenter trial have shown good and reliable results.

3. Entropy

The Entropy is a very new non linear statistical parameter describing the order of chaotic data i.e. the EEG.[52] Regarding the entropy, the EEG is not a summation of sinus waveforms but a chaotic, non-linear system. Algorithm used are the approximative entropy and the Shannon Entropy[53] and the spectral entropy.[54] Induction as well as emergence of anaesthesia could be detected by the spectral entropy as well as the apporximative and the Shannon entropy. Published data of single centre and small number studies are available, they are promising but cannot be evaluated yet. A commercially available monitor is under construction by Datex-Ohmeda.

4. Patient State Analyzer

The PSA 4000 (Physiometrix, USA) is using a so called Patient State Index (PSI), based on a processed EEG and variable resolution electromagnatic tomography (VARETA) studies for evaluating the impact of anaesthetic agents on the various regions of the brain.[55] The monitor has been introduced to the market in 2001 and has not yet been given the FDA approval. It is not available outside the USA. No large scale studies are yet published, but it seems to be a promising approach as it uses more than the frontal cortex information that is used by the BIS.

Auditory Evoked Potentials

The complex auditory evoked potential (AEP) have been studied in memory research as well as for measuring depth of anaesthesia. Mainly the midlatency potential (MAEP, 15-100 ms) are used for this purpose, they show a high intra and interindividual stability. Thorton et al described in a group of patients under halothane, etomidate and propofol anaesthsia that most of the anaesthetics increase the latency and decrease the amplitude in a dose dependent manner.[56-58] Late latency auditory evoked potentials (LLAEP 100-1000 ms) are already in the awake state very variable and cannot be used for measuring the depth of anaesthesia.

1. AEP Monitor

The so called AEP monitor (Alaris Medical Systems, USA) is using a AEP index. This index is supposed to predict movement, response to verbal command, implicit and explicit memory.[59] Due to certain mathematical calculations (ARX modelling) short latency of 2-6 sec can be displayed. A so called "A-line ARX Index" (AAI) is calculated from the MAEP, which is a dimensionless

number from 100 – 0. The AAI from 100 – 60 is rated as awake, 60 – 40 sedation, 40 – 30 light anaesthesia and < 30 adequate anaesthesia. No major studies are yet published with these AAI.

Conclusions

Patients undergoing cardiac anaesthesia belong to a group which is highly succeptible to experience awareness. Monitors for detecting intraoperative awareness should be easy to use, reliable and cost effective. As highly qualified professionals in the medical field we should question our drive for even more simple monitors, in this way ending treating only numbers. Neuromonitoring offers a vast field for research and anaesthesiologists should play a leading role due to our aim of delivering best care to the patients. Large scale multicentre studies should be conducted to compare different monitors as well as to find strategies to minimise the risk to our patients.

References

1. Lopez JR. Intraoperative neurophysiological monitoring. *Int Anesthsiol Clin* 1996; 34: 33-54
2. Cantelmo NL. Cerebrovascular monitoring during carotid endarterectomy. *Stroke* 2000; 31: 1799-1801
3. Guedel AE. Third stage of anaesthesia: a sub classification regarding the significance of the position and movements of the eyeball. *Am J Surg (Anest Suppl)* 1920; 34: 53-57
4. Graf P, Schachter DL. Implicit and explicit memory for new associates in normal subjects and amnesic patients. *J Exp Psychol (learn Mem Cogn)* 1987; 13: 501-518
5. Payne JP. Awareness and its medico legal implications. *Br J Anaesth* 1994; 73: 38-45
6. Lubke GH, Kerssens C, Phaf H, Sebel PS, et al. Dependence of explicit and implicit memory on hypnotic state in trauma patients. *Anesthesiology* 1999; 90: 670-680
7. Crile G. Crile George, an autobiography. Philadelphia JB Lippincott 1947; pp 197
8. Winterbottom LH. Insufficent anaesthesia. *Br Med J* 1950; 1: 247
9. Dowd NP, Cheng DC, Karski JM, Wong DT, Munro JA, Sandler AN. Intraoperative awareness in fast track cardiac surgery. *Anesthesiology* 1998; 89: 1068-1073
10. Ranta SO, Laurila R, Saario J, Ali-Melkkila T, Hynynen M. Awareness with recall during general anesthesia: incidence and risk factors. *Anesth Analg* 1998; 86: 1084-1089
11. Sandin RH, Enlund G, Samuellson P, Lennmarken C. Awareness during anaesthesia : a prospective case study *Lancet* 2000; 355: 707-711
12. Tempe DK. In search of a reliable awareness monitor. *Anesth Analg* 2001; 92: 801-4
13. Tempe DK, Siddiquie RA. Awareness during cardiac surgery. *J Cardiothorac Vasc Anesth* 1999; 13: 214-219
14. Evans JM, Frazer A, Wise CC, Davies WL. Computer controlled anesthesia, Computing in Anesthesia and Intensive Care. Edited by Prakash O. Boston, Martinus Nijhoff, 1983, pp 279-291
15. Sebel PS. Can we monitor depth of anesthesia? *Anesth Analg* 2001; 92 (Suppl): 94-98
16. Evans JM. Patients experiences of awareness during general anaesthesia. In: Rosen M, Lunn JN (Ed): Consciousness, awareness and pain in general anaesthesia. Butterworth, London, 1987: 18-34
17. Tunstall ME. Detecting wakefulness during general anaesthesia for Cesarean section. *Br Med J* 1977; 1: 1321
18. Caton R. The electrical currents of the brain. *Br Med J* 1875; 2: 278
19. Berger H. Ueber das Elektroenkephalogramm des Menschen. *Arch Psychiatr Nervenkr* 1929; 87: 527-570 (German)
20. Faulconer A Jr. Correlation of concentration of ether in arterial blood with electroencephalographic pattern occurring during ether oxygen and during nitrous oxide, oxygen and ether anaesthesia of human surgical patients. *Anesthesiology* 1952; 13: 361
21. Clark DL, Rosner BS. Neurophysiologic effects of general anesthetics: I. The electroencephalogram and sensory evoked responses in man. *Anesthesiology* 1973; 38: 564-580
22. Shapiro HM. Anesthesia affects upon cerebral blood flow, cerebral metabolism, electroencephalogram, and evoked potentials, in Miller RD (ed) Anesthesia, vol 2 (ed 2) New York NY, Churchill Livingstone, 1988; pp 1249 – 1288
23. Gajraj RJ, Doi M, Mantzaridis H, Kenny GN. Analysis of the EEG bispectrum, auditory evoked potentials and the EEG power spectrum during repeated transitions from consciousness to unconsciousness. *Br J Anaesth* 1998; 80: 46-52
24. Schwender D, Daunderer M, Klasing S, Finsterer U, Peter K, et al. Power spectral analysis of the electroencephalogram during increasing end-expiratory concentration of isoflurane, desflurane and sevoflurane. *Anaesthesia* 1998; 53: 335-342
25. Struys M, Versichelem L, Mortier E, et al. Comparison of spontaneous frontal EMG, EEG, power spectrum and bispectral index to monitor propofol drug effects and emergence. *Acta Anaesthesiol Scand* 1998; 42: 628-636
26. Zickmann B, Boldt J, Schindler E, Wulf K, Dapper F, Hempelmann G. Topographic electroencephalometry following anaesthesia induction with ketamine-midazolam. *Anaesthesist* 1994 43 (Suppl 2): S59-67
27. Bischoff P, Drogemeier K, Scholz J, Nahm W, von Knobelsdorff G, Schulte am Esch J. Electrphysiologic arousal raections during sufentanil / isoflurane anaesthesia. *Anaesthesiol Intensivmed Notfallmed Schmerzther* 1998; 33: 88-95 (German)
28. Dimpfel W, Spueler M, Nickel B. Dose and Time dependent action of morphine, tramadol and flupirtine as studied by radioelectroencephalogarphy in the freely behaving rat. *Neuropsychobiology* 1988; 20: 164-168
29. Dimpfel W. Dizocilpine (MK801), ketamine and phencyclidine: low doses affect brain field potentials in

the freely moving rat in the same way as activation of dopaminergic transmission. *Psychopharmacology* 1990; 101: 317-323
30. Schober F, Dimpfel. Relation between psychometric test and quantitative topographic EEG in pharmacology. *Int J Clin Pharmacol Ther Toxicol* 1992; 30: 428-430
31. Wozniak G, Dapper F, Zickmann B, Gehron J, Hehrlein FW. Selective cerebral perfusion via innominate artery in aortic arch replacement without deep hypothermic circulatory arrest. *Int J Angio* 1999; 8: 50-56
32. Rolz L, Wolter S, Klee B, Schontube E. Possibilities of classification of topographically distributed neurophysiological multi-channel data. *Int J Clin Monit Comput* 1996; 13: 27-34
33. Entholzner E, Mielke L, Pichlmeier R, Weber F, Schneck H. EEG changes during sedation with gamma-hydroxybutyric acid. *Anaesthesist* 1995; 44: 345-350 (German)
34. Entholzner E, Schneck HJ, Harghasser S, Hipp R, Tempel G. Electroencephalographic demonstration of central nervous system effects of different premedication regimens. *Anaesthesist* 1994; 43: 431-440 (German)
35. Dimpfel W, Hofmann HC Schober F, Todorova A. Validation of an EEG deprived spectral frequency index (SFx) for continuous monitoring of sleep depth in humans. *Eur J Med Res* 1998; 3: 453-460
36. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. D.C. 20014, DHEW Publication No. (NIH) 204, U.S. Government Printing Office, Washington 1968; 12p
37. Soltesz S, Silomon M, Biedler A, Kleinschmidt S, Benak J, Molter GP. Gamma-hydroxybutyric acid ethanolamide (LK544). The suitability of LK544 for sedation of patients in intensive care in comparison with midazolam. *Anaesthesist* 2001; 50: 323-328 (German)
38. Renz D, Dimpfel W, Schober F, Karliczek GF. Bedeutung des Spektralen Frequenzindex (SFx) zur Quantifizierung der Schlaftiefe während der Narkoseeinleitung. *Acta Anaesth Helvetica* 1999; 2: 9-11
39. Rampil IJ. A primer for EEG signal processing in anesthesia. *Anesthesiology* 1998; 89; 980-1002
40. Coste C, Guignard B, Merigaux C, Chauvin M. Nitrous oxide pevents movement during orotracheal intubation without affecting BIS value. *Anesth Analg* 2000; 91: 130-135
41. Goto T, Nakata Y, Saito H, et al. Bispectral analysis of the electroencephalogram does not predict responsiveness to verbal command in patients emerging from xenon anaethesia. *Br J Anaesth* 2000; 85: 359-363
42. Sakai T, Singh H, Mi WD, Kudo T, Matsuki A. The effect of ketamine on clinical endpoints of hypnosis and EEG variables during propofol infusion. *Acta Anaesth Scand* 1999; 43: 212-216
43. Suzuki M, Edmonds HL, Jr, Tsuede K, Malkani AL, Roberts CS. Effect of ketamine on bispectral index and level of sedation. *J Clin Monit Comput* 1998; 14: 373
44. Lehmann A, Zeitler C, Thaler E. Isgro F, Bold J. Comparison of two different anesthesia regimens in patients with aortocoronary bypass grafting surgery: sufentanil-midazolam and remifentanil-propofol. *J Cardiothorac Vasc Anesth* 2000; 14: 416-420
45. Mychaskiw G, Horowitz M, Sachdev V, Heath BJ. Explicit intraoperative recall at a bispectral index of 47. *Anesth Analg* 2001; 92: 808-809
46. Guignard B, Chauvin M. Bispectral index increases and decreases are not always signs of inadequate anesthesia. *Anesthesiology* 2000; 92: 903
47. Lehmann A, Zeitler C, Thaler E. Isgro F, Bold J. Comparison of two different anesthesia regimens in patients with aortocoronary bypass grafting surgery: sufentanil-midazolam and remifentanil-propofol. *J Cardiothorac Vasc Anesth* 2000; 14: 416-420
48. Walder B, Suter PM, Romand JA. Evaluation of two processed EEG analyzers for assessment of sedation after coronary artery bypass grafting. *Intensive Care Med* 2001; 27: 107-114
49. De Deyne C, Struys M, Decruyenaere J, Creuplandt J, Hoste E, Colardyn F. Use of continuous bispectral EEG monitoring to assess depth of sedation in ICU patients. *Intensive Care Med* 1998; 24: 1294-1298
50. De Deyne C, Struys M, Decruyenaere J, Creuplandt J, Hoste E, Colardyn F. Use of continuous bispectral EEG monitoring to assess depth of sedation in ICU patients. *Intensive Care Med* 1998; 24: 1294-1298
51. Kugler J. Elektroenzephalographie in Klinik und Praxis. Thieme, Stuttgart, New York 1981 (German)
52. Bruhn J, Ropcke H, Hoeft A. Approximate entropy as an electroencephalographic measure of anesthetic drug effect during desflurane anesthesia. *Anesthesiology* 2000; 92: 715-726
53. Bruhn J, Lehmann LE, Roepcke H, Bouillon TW, Hoeft A. Shannon entropy applied to the measurements of the EEG effects of desflurane. *Anesthesiology* 2000; 93: A265
54. Vietro-Oja H, et al. Entropy of the EEG signal is a robust index for depth of hypnosis. *Anesthesiology* 2000; 93: A264
55. John ER, Prichep LS, Kox W, et al. Invariant reversible qEEG effects of anesthetics. *Conscious and Cogn* 2001; 10: 165-183
56. Thorton C, Heneghan CP, James MF, Jones JG, et al. Effects of halothane or enflurane with controlled ventilation on auditory evoked potentials. *Br J Anaesth* 1984; 56: 315-323
57. Thorton C, Heneghan CP, Navaratnarajah M, Bateman PE, Jones JG, et al. Effect of edomidate on the auditory evoked response in man. *Br J Anaesth* 1985; 57: 554-561
58. Thorton C, Konieczko K, Jones JG, Jorden C, Dore CJ, Heneghan CP. Effect of surgical stimulation on the auditory evoked response *Br J Anaesth* 1988; 60: 373-378
59. Schwender D, Dawnderer M, Klaising S, Mulzer S, Finsterer U, Peter K. Monitoring intraoperative awareness. Vegetative signs, isolated forearm technique, electroencephologram, and acute evoked potentials. *Anästhesist* 1996; 45: 708-721 (German)