INTRA-OPERATIVE AWARENESS

CENTRAL MADRID SOCIETY OF ANAESTHESIOLOGY AND INTENSIVE CARE

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ERGON
C/ Arboleda, 1. 28220 Majadahonda (Madrid)

ISBN: 84-8473-214-2

Legal Deposit: M-•••••-2006

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Intra-operative awareness. Some considerations by way of introduction

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The "*American Society of Anesthesiologists"*(ASA) approved the document *"Practice Advisory for Intraoperative Awareness and Brain Function Monitoring"* on 25 October 2005. This document is a landmark in the history of anaesthesia in that it highlights the importance of intra-operative awareness and establishes the applications of brain monitors in the measurement of depth of anaesthesia in daily clinical practice.

The Central Madrid Society for Anaesthesiology, Intensive Care and Pain Treatment set up a working party to study intra-operative awareness and neurological function monitoring.

This monograph describes the work of this group with the intention of contributing to continuous medical development in anaesthesiology by updating the current state of knowledge of intra-operative awareness. In the ASA document and in the "Intra-operative Awareness Working Party of the Central Madrid Society for Anaesthesiology and Intensive Care which we present below, the objectives of both commissions were:

- To identify the risk factors associated with intra-operative awareness.
- To describe central nervous system monitoring, which reduces the incidence of intra-operative awareness.
- To design a guide to intra-operative monitoring of brain function in order to help the anaesthetist minimise the incidence of intra-operative awareness

The incidence of intra-operative awareness is 0.1-0.2%, not an insignificant figure, so that as anaesthetists we must assess the risk of intra-operative awareness during general anaesthesia in each patient at the pre-anaesthesia consultation.

Patients with a high risk of intra-operative awareness should be informed of the possibility of this complication.

To reduce the possibility of intra-operative awareness and assess the depth of anaesthesia, we should observe the presence of clinical signs (movement, lacrimation, sweating, etc.), use conventional monitoring (blood pressure, heart rate, respiratory rate, measurement of end-expiratory concentration of inhalational agents, etc.) and use brain function monitors. We should remember that intra-operative awareness may occur in the presence of normal vital signs. Intra-operative awareness may be present without hypertension or tachycardia.

Both documents review the different monitors, but only BIS monitoring has been shown to reduce the incidence of intra-operative awareness, with a decrease of 80%.

The BIS value should be less than 60 during the anaesthetic procedure.

In the document *"Practice Advisory for intraoperative awareness and brain function monitoring,"* it is reported that 69% of anaesthetists surveyed from the American Society of Anesthesiologists and 63% of anaesthetists with the professional grade of consultant agreed with the use of

brain function monitors in patients at risk of intra-operative awareness.

Although the ASA document does not recommend the use of these monitors in all patients, it concludes that the decision to use a brain function monitor should be based in each specific case on the presence of risk factors for intra-operative awareness, which are:

- Previous episodes of intra-operative awareness.
- Presence of opiod tolerance or depressant agents of the central nervous system in the pre-operative assessment.
- Abuse of medicines, addiction to or ingestion of illicit drugs (opioids, cocaine, benzodiazepines, etc.).
- Patients with chronic malignant cancer pain treated with high doses of opioids.
- Previous history of a foreseeable difficulty of intubation and/or ventilation with a face mask.
  - Physical status ASA 4-5.
  - Patients with a poor haemodynamic reserve.
  - Interventions at particular risk for intra-operative awareness (heart surgery, caesarean sections, traumas, emergency surgery).
  - Anaesthetic techniques involving nitrous oxide and opioid drugs.
  - TIVA, total intravenous anaesthesia.
  - Techniques in which the doses of anaesthetic drugs are reduced during paralysis of the patient with neuromuscular blockers.
  - Rapid induction anaesthesia techniques.
  - Use of neuromuscular blockers during anaesthetic maintenance. These drugs may mask the somatic signs of intra-operative awareness. However, the non-use of neuromuscular blockers during surgery does not prevent intra-operative awareness.

The presence of some of these risk factors increases the risk of intra-operative awareness to 1%.

The decision whether or not to monitor brain function may be a similar decision to that of monitoring invasive blood pressure, which depends on the patient, the type of surgery, the technique used, etc., but with the great advantage that these monitors are not invasive.

Similarly, we must stress the need to test our anaesthesia administration systems; vaporisers, infusion pumps, fresh gas flows, etc.

Monitor the end-tidal concentration of the inhalatory agent and record it on the anaesthesia graph every 15 minutes.

In patients treated with beta-blockers, calcium channel blockers and other drugs that alter the physiological and haemodynamic responses we should guard against inadequate anaesthesia, which can give rise to confusion.

Avoid complete neuromuscular block, if possible. Maintain a train-of-four response. Reverse the neuromuscular block before discontinuing administration of nitrous oxide.

Most importantly, however: use adequate concentrations of inhalational and/or intravenous drugs. If endotacheal intubation is difficult, administer an additional dose of inhalational and/or intravenous drug.

A randomized double-blind study evaluated the efficacy of prophylactic administration of midazolam as an anaesthetic co-adjuvant in outpatient interventions with total intravenous anaesthesia. The results indicate a lower frequency of intra-operative awareness in the group given midazolam than in the placebo group.

Two other randomised clinical trials studied anterograde amnesia after administration of midazolam but before induction of anaesthesia. Although both studies demonstrated a decrease in recall in the midazolam groups, consciousness during general anaesthesia and intra-operative awareness were not studied.

The anaesthetists who compiled the document and the members of the American Society of Anesthesiology did not reach a consensus on the use of benzodiazepines or scopolamine in reducing the risk of intra-operative awareness in all patients.

Various randomised clinical trials compared anaesthesia with BIS versus anaesthesia without BIS. In one of them involving 2,500 patients with a high risk of intra-operative awareness, explicit recall occurred in 0.17% of patients in the group monitored with BIS versus 0.91% in the group without BIS ($p < 0.02$).

A comparative, non-randomised study of BIS monitoring versus a historical control group of 12,771 patients found an incidence of explicit recall of 0.04% in the group of patients monitored with BIS versus 0.18% in the historical group ($p < 0.038$).

At present, there are no comparative clinical trials studying the involvement of the use of entropy monitoring, PSI (patient state index), SNAP II, Narcotrend, Cerebral State Monitor or AEP monitor in the incidence of intra-operative awareness.

BIS is the only monitor which to date has proved effective in reducing the incidence of intra-operative awareness. The results of clinical trials with a monitor cannot be extrapolated to other brain function monitors.

The technology of brain function monitoring for the prevention of intra-operative awareness should be available in operating rooms for use in patients with risk factors. Like the recommendations for intra-operative and postoperative monitoring, these monitors are intended to improve the prognosis and reduce the risks of our patients in a global healthcare policy of risk prevention.

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Intra-operative awareness: defining the problem

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Since the beginning of the history of anaesthesia, the possibility that an anaesthetised patient might have intra-operative recall has been a cause for concern[1]. This concern is shared by the patients, to the extent that 54% of people due to undergo surgery are afraid of being conscious during surgery[2].

In the past few years, renewed interest has been shown in the study of intra-operative awareness (IOA) due to the detrimental effects on the patient[3,4] and the legal implications[5].

Before the introduction of surgical anaesthesia, pain and intra-operative recall were frequently associated with surgery. The experiments by Wells and Morton with nitrous oxide and ether opened the way for surgery in an unconscious patient, although anaesthesia was administered superficially and in an uncontrolled form.

In 1937, Guedel described different planes or levels of intensity of the effect of ether. However, with the appearance of neuromuscular relaxants in the 1940s, there arose the possibility that a patient might be conscious and immobile during the operation. This gave rise to various studies on IOA and memory, which have been revisited in recent years as a result of the advances in technology and the development of monitoring [1].

Intra-operative awareness is defined as the state in which the patient has been conscious of events occurring during general anaesthesia and is able to recall them after it has ended. The incidence of IOA is 0.1 to 0.2 %, depending on the studies, i.e. one or two patients for every 1,000 undergoing general anaesthesia[3,6,7].

Patients describe auditory recall, a sensation of suffocation, an inability to move, fear and panic[8]. In 0.01% of patients IOA is associated with pain of the most traumatic kind. Often they express doubts as to whether the experience has actually happened to them. Only 35% report what happened in the operating room, out of doubt as to whether it actually did happen or from fear of being considered mad[9]. 78% of patients who suffer IOA develop psychological disorders[3]. These consist of anxiety, fear, panic attacks, difficulty in concentrating, irritability, insecurity and changes in sleep pattern. In 45% of cases a post-traumatic stress syndrome (PTSD) develops, characterised by anxiety, insomnia, nightmares, depression and a pre-occupation with death and which affect their social behaviour[10]. The long-term consequences have been little studied[4].

From the legal point of view, IOA involves lawsuits for medical negligence and violation of the doctor-patient contract. Claims for IOA account for 1.9% to 12.2 % of claims in anaesthesia[5,11].

MEMORY AND ANAESTHESIA

The term intra-operative awareness describes the presence of explicit memory during anaesthesia[8]. The terms explicit and implicit memory were introduced by Graf and Schacter in 1985(12). Explicit memory is that which requires conscious

effort in order to be retrieved. It refers to the deliberate retrieval of information stored previously.

Implicit memory or unconscious memory develops without requiring recall of the previous learning experience[13]. Thus, we remember stored information without knowing how or when it was learnt. In this way, there may be learning during anaesthesia (implicit memory) without the patient consciously recalling events that happened during the intervention, in other words without intra-operative awareness taking place (conscious or explicit memory)[1].

Controversy surrounds current studies on the development of implicit memory during anaesthesia, possibly due to the lack of standardisation of the type of anaesthesia and the difficulty of studying these two types of memory separately. The circumstances in which implicit memory develops are unclear. Lubke et al. [14] found a correlation between memory and depth of anaesthesia. The most recent articles report that memory activation occurs more frequently with superficial levels of anaesthesia. There is no evidence of its development at levels of deep anaesthesia[15-17]. Another factor associated with learning during anaesthesia is surgical stimulation[18] via a mechanism mediated by the increase in catecholamine concentration. However, there is insufficient evidence to explain this theory.

Implicit memory is studied by learning tests in which information is provided via earphones during anaesthesia (words, phrases or short stories), with questions being asked postoperatively through indirect tests. Explicit memory is studied by means of a postoperative managed interview, which we will describe in detail below. Implicit memory is associated with changes in behaviour produced by previous experiences that are not remembered by the subject. The postoperative psychological impact is not known

Currently, the study of memory during anaesthesia is an open field for investigation. In these pages we focus on the study of intra-operative awareness, in which the anaesthetist plays an essential role in the prevention, detection and early institution of treatment, thus preventing the adverse psychological effects associated with this state.

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Risk factors for intra-operative awareness

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Intra-operative awareness appears to be the result of administration of insufficient anaesthesia to maintain unconsciousness or to prevent memories associated with a stimulus. Information emanating in particular from the American Society of Anesthesiology (ASA) estimates a global incidence of intra-operative awareness of more than 0.1%, representing 1.9% of causes of claims for malpractice[1]. A recent study conducted in seven hospital centres in the United States in 19,575 patients yielded an incidence of intra-operative awareness of 0.13%, excluding dubious cases, and estimates that approximately 26,000 cases of intra-operative awareness may occur annually in that country[1].

Epidemiological studies identify a series of risk factors associated with intra-operative awareness which may be detected in a large group of patients scheduled to undergo general anaesthesia. These factors should be recognised and patients informed pre-operatively of this possibility, without overlooking the fact that any patient, for reasons still not understood, may suffer an episode of intra-operative awareness.

The risk factors may be classified into three groups:

RELATED TO THE PATIENT

- **Sex.** In the study published by Domino et al[2], a three-fold higher number of legal claims for intra-operative awareness was found among women than among men.

  This does not necessarily signify that the incidence of intra-operative awareness is greater in females, although other publications have suggested a similar predominance, evidenced in a greater incidence of dreams in women in the intra-operative period[3]. Although it is not possible to draw definitive conclusions, there are studies that show a more rapid arousal in women after anaesthesia with propofol and alfentanil than in men [4], or also that the plasma levels of remifentanil required to attenuate the haemodynamic response to surgical stimulus in abdominal surgery are greater in women than in men [5], which may ultimately affect the incidence of intra-operative awareness.
- **Age.** Although it is acknowledged that there is a greater anaesthetic requirement in children and adolescent patients, it is not possible to establish a greater risk of intra-operative awareness definitively. A greater incidence of dreams has been described in young patients under general anaesthesia in an outpatient setting, but the relationship between peri-operative dreams and intra-operative awareness is still uncertain(1).
- **Previous history of addiction to alcohol, amphetamines, opioids, etc.** Chronic abuse of these substances increases anaesthetic requirements because of the development of a tolerance to them, predisposing these patients to intra-operative awareness(6, 7).
- **Physical condition and pre-operative medication.** In a recent multicentre study, Sebel and co-workers found an increased risk of intra-

operative awareness in ASA III-V patients undergoing major surgery[1]. A significant number of episodes of intra-operative awareness have also been recorded in patients exhibiting perioperative haemodynamic instability in which the administration of general anaesthetics is reduced or ultimately discontinued in order to prevent their cardiovascular depressant effect. Likewise, those patients receiving previous treatment with antihypertensive drugs, beta-blockers, etc, are prone to suffering episodes of intra-operative awareness as a result of being exposed to underdosing of general anaesthetics in order to prevent or treat episodes of hypotension. These drugs may also mask hypertension and tachycardia, conventionally considered as signs of superficial anaesthesia, although their absence in cases of intra-operative awareness has been demonstrated in various studies[2,8].

- Difficult airway. Difficult intubation was the reason for the occurrence of intra-operative recall in 8% of patients in Domino's analysis[2]. Manipulation of the airway and repeated laryngoscopies after a single dose of an anaesthetic induction agent promote the development of the condition.

RELATED TO THE TYPE OF SURGICAL PROCEDURE

- **Obstetric anaesthesia**. Whereas the incidence of intra-operative awareness in the general population is 0.1-0.2%, in obstetric patients it varies between 0.4 and 1.3% depending on the studies[7]. Contributing factors are rapid sequence induction without opioids to prevent the respiratory depressant effect in neonates and the reduced inspired fraction of inhalational anaesthetics to prevent the tocolytic effect and the consequent haemorrhagic risk of uterine bleeding which they exhibit[10]. The majority of episodes of intra-operative awareness occur in the period between skin incision and foetal extraction, the time of greatest surgical stimulus with lowest anaesthetic concentrations[11].
- **Cardiac surgery.** The incidence of intra-operative awareness in patients undergoing heart surgery is generally greater than that in the general surgical population. Conventionally, the anaesthetic technique in cardiac surgery is based on the administration of high doses of opioids with low doses of hypnotics in order to maintain the greatest possible haemodynamic stability. In a series of 837 patients on extracorporeal circulation, Phillips found an incidence of 1.14% with no differences between the anaesthetic drugs used in patients with and without recall of intra-operative events[12]. Ranta in his series highlighted the young age of patients with intra-operative awareness and emphasised the fact that information to anaesthetists about this complication reduces its incidence from 4 to 1.5%[13]. Finally, Dowd in a study of 617 patients undergoing heart surgery with a balanced technique using continuous administration of an anaesthetic drug before, during and after extracorporeal circulation recorded an incidence of intra-operative awareness of 0.3%, less than in the rest of the studies[14].
- Emergency surgery in multiple trauma patients. Although it is significant that the majority of claims for intra-operative awareness come from patients undergoing elective surgery[2], the haemodynamic instability present in multiple trauma patients involves the frequent underdosing of anaesthetic drugs and therefore increases the probability of intra-operative awareness. However, these patients usually also exhibit hypothermia, hypotension or acute intoxication, all factors which reduce the anaesthetic requirement[15] and protect them from this complication.

RELATED TO THE ANAESTHETIC TECHNIQUE

- **Inhalatory anaesthesia.** Various authors have published articles on the efficacy of relatively low concentrations of volatile anaesthetics in the prevention of intra-operative awareness, although the minimum concentration guaranteeing the absence of intra-operative recall cannot be established definitively, among other reasons because of the additive effect of the

other drugs used (benzodiazepines, propofol, opioids, etc.)[5]. Thus, cases of intra-operative awareness recorded during inhalational anaesthesia techniques appear to be associated generally with mistakes in checking vaporisers (vaporiser vacuum, leaks, etc.) or failure to monitor anaesthetic gases. In the study by Bergman, in 13% of patients exhibiting intra-operative awareness, the cause was related to defects of administration of nitrous oxide or volatile anaesthetics due to malfunctioning of the equipment, in the majority of cases as a result of problems relating to the vaporiser, and it should be pointed out that in almost all cases the inspired and expired concentrations of anaesthetic agent were not monitored[16].

- The techniques of total intravenous anaesthesia based on the administration of hypnotics, opioids and muscle relaxants double or triple the incidence of claims for intra-operative recall[2]. In general, this has been associated with the late institution of the infusion after the induction dose, inadequate dosage regimens and frequently pump failures, disconnection of the system, flow obstruction, etc.
- Administration of neuromuscular relaxants. The use of neuromuscular relaxants has been associated with a greater incidence of intra-operative recall during the maintenance of general anaesthesia[2]. The observation of movement due to the reflex somatic response prior to surgical stimulus, the basis of the concept of minimum alveolar concentration (MAC) of volatile anaesthetic and considered one of the most reliable methods available for detecting intra-operative awareness, cannot be used in patients under the effect of neuromuscular relaxants because the lack of movement contributes to the fact that superficial anaesthesia may pass unnoticed by the anaesthetist. In a study conducted by Sandin in 11,785 surgical patients undergoing surgery under general anaesthesia, the incidence of intra-operative awareness was greater in those patients receiving neuromuscular relaxants (0.18% versus 0.10%). In addition, these patients exhibited anxiety and late neurotic symptoms, a circumstance that did not occur in patients not administered neuromuscular relaxants. Therefore, not only was the incidence of awareness greater, but the symptoms during the awareness and postoperatively were more severe[16].

In general, the risk of intra-operative awareness in this group of patients is determined by various circumstances, not only as the result of an anaesthetic technique based on excessive administration of neuromuscular relaxants during surgical procedures in which lack of movement by the patient is a priority (ophthalmic surgery, neurosurgery, etc), but also because of the prolonged effect of the drug at the end of the procedure, or because of the incorrect administration of neuromuscular relaxants in conscious patients. Errors of administration or identification of intravenous drugs are the most common cause of claims for motor paralysis in an awake patient. Among these drugs, succinylcholine is most frequently associated with incorrect administration instead of a sedative or hypnotic agent in pre-induction or anaesthetic induction[2, 17]. In general, a failure to monitor neuromuscular relaxation is observed in these cases[17].

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Prevention of intra-operative awareness

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Intra-operative awareness is a complication which may occur in the course of general anaesthesia.

The disparity in incidence[1-4] recorded in different studies is principally due to:

- The lack of agreement on its definition.
- The tendency for many anaesthetists to minimise its importance in their own practice[5, 6].
- The absence of reliable methods of detection
- The lack of sufficient properly controlled and randomised studies.

The latter has been difficult for two very different reasons: firstly, because of ethical considerations; and secondly, since the incidence of about 1-2/1000 in the general population appears to be very low [7, 8], an excessively large number of patients (about 50,000)[2, 9] would have to be studied to obtain statistically conclusive results.

However, the incidence of intra-operative awareness varies according to the type of surgery considered, being greatest in obstetrics (0.9-1%), cardiac surgery (1.1-14%) and trauma (11-43%)[10-13]. If the studies are confined to these higher risk groups[14], it is then possible to reduce the size of the sample that needs to be studied (2300 patients)[4, 15].

Why is it so important to have more studies?

In the era of major technological advances, we still do not have a monitoring system that quantifies the depth of anaesthesia and that guarantees unconsciousness during general anaesthesia under all circumstances. There is also no register of actual episodes of intra-operative awareness, or any guide for the anaesthetist in daily practice on the specific decisions that need to be taken in the face of this problem.

Major progress has been achieved in the field of monitoring. In the last few years, the use of end-tidal gas analysers and capnography as well as of computerised administration systems for intravenous anaesthetics that provide estimates of plasma and cerebral concentrations has been widely promoted, and in particular various brain function monitoring systems have been developed. This type of technology is based on the analysis of spontaneous or evoked electrical activity in the cerebral cortex[16-25]. These systems have been available since 1998, although their routine use is not widespread because of certain limitations which they exhibit, economic reasons and inadequate knowledge about them.

Consequently, it is only if we have sufficient information based on reliable studies that we will manage gradually to change anaesthetists' attitudes and design a strategy for preventing the problem, enabling us to establish:

1. A register of cases occurring in each hospital
2. The actual incidence of intra-operative awareness in patients undergoing general anaesthesia and the associated risk factors in our own country. Until now, the data available to us have come from the USA[1] and Anglo-Saxon

[4] (Australia) and Scandinavian countries[26].

3. Medium and long-term follow-up of patients who have experienced intra-operative awareness in order to analyse the consequences, and not only the psychological ones[27, 28].
   According to the results of the few published series, more than half the subjects who experience intra-operative awareness develop some degree of post-traumatic stress syndrome[7, 8]. In almost 50% of these, the symptoms may persist for more than two years[29].
4. Adoption by anaesthetists of a universally agreed policy on the most effective peri-operative preventive measures, so as to provide them with the most extensive and best information to help them take the most appropriate decision for each patient.

A wake-up call about the importance of intra-operative awareness emerged from the conclusions issued in 2004 by the *Joint Commission on Accreditation of Healthcare Organisations*[30].

Until then, little had been published along these lines. There are some not very widely circulated documents, such as those adopted by the *American Association of Nurse Anesthetists (Considerations for Policy Development: Unintended Intraoperative Awareness)*[31], that of the Department of Anesthesiology of the University Hospitals of Cleveland *(Unintended Intraoperative Awareness During General Anesthesia)*[32] *and that of the Canadian Ministry of Health* and Long-Term Care (Ontario) *(Medical Advisory Secretariat about Intraoperative Awareness and Bispectral Index)* [33,34].

Recently, in October 2005, the American Society of Anesthesiologists issued the first and fullest report under the title "Practice Advisory for Intraoperative Awareness and Brain Function Monitoring"[35], which includes a systematic review of the scientific evidence on all preventive, diagnostic and therapeutic measures (as far as possible) of intra-operative awareness. Presumably it will be the basis for other future guidelines.

These recommendations should be reviewed periodically by a group of independent experts in the light of technological advances, systematic reviews of scientific works on the subject, resolutions adopted in national and international forums and the results obtained from the application of all the previous measures.

PREVENTIVE MEASURES

In general, we can classify the different causes that can engender intra-operative awareness into:

I. Those related to the anaesthetic technique and the patient's individual characteristics.
II. Those associated with equipment safety and/or operating defects.

PREVENTIVE MEASURES RELATED TO THE ANAESTHETIC TECHNIQUE

The first preventive measure for minimising the possibilities of occurrence of intra-operative awareness should be to individualise the anaesthetic technique[36] in such a way as to guarantee unconsciousness, amnesia and analgesia, particularly in patients at risk [37].

In many cases, these patients can be identified in the pre-operative consultation. It is therefore necessary to stress the importance of the pre-anaesthetic evaluation, which should include: 1) a detailed clinical history; 2) a complete physical examination; 3) supplementary tests indicated for the individual patient; 4) the type of surgical procedure they will undergo. This information will help us to plan the most suitable type of premedication and anaesthetic technique[37, 38].

Premedication is an essential point. In general, whenever possible and where there is no contra-indication to prevent it, agents with amnesic properties should be used. Regarding which drug should be used, there are numerous studies that demonstrate the anterograde amnesic properties of benzodiazepines, particularly midazolam[39, 40] (superior to those of diazepam and flunitrazepam). The use of other drugs such as ketamine or scopolamine that also exhibit this characteristic is much less widespread and does not enjoy the same support among professionals in the field of anaesthesia, among other reasons because of side-effects, particularly delusions[41, 42]. The same studies warn us that the doses of midazolam used in daily prac-

tice during pre-induction are frequently lower than those that actually produce scientifically proven amnesia.

In terms of anaesthetic technique, although it should be adapted individually, we should not overlook the fact that the majority of publications highlight the better amnesic potential of halogenated inhalatory agents compared to other general anaesthetics[43, 44] whenever they are used in monotherapy at doses ≥ 0.6 MAC. However, some studies demonstrate the possibility of implicit recall even with expired fractions of sevofluorane of up to 1.2%[45].

What implications can this have clinically?

We are not currently in a position to answer this question.

Because of their depressant effect on the level of consciousness and attention, all hypnotics dose-dependently affect the formation of episodic memory of information presented during their administration. Fluctuations in depth of hypnosis, the level of pre-operative stress and surgical stimulation and generally any harmful stimulus facilitate learning phenomena at levels of anaesthesia at which theoretically they should not occur[46]. The potential explanation is that this surgical stimulus raises the levels of plasma adrenaline that appear to activate the neuronal circuits involved in learning. Hence the importance of analgesia.

The actions of intravenous anaesthetics on memory are nowadays the subject of study and debate. In particular, propofol appears to have combined effects on the amygdala, hippocampus and areas of the cerebral cortex related to working memory[47].

As regards the use of neuromuscular relaxants, it is commonly agreed that they affect the need for other general anaesthetics. They should only be used if clinically necessary. Where they are required, they should be titrated carefully, avoiding complete block and constantly monitoring their effect since their inappropriate use can mask the clinical symptoms of intra-operative awareness.

As various studies show, when an "intra-operative recall without painful experience" occurs, the probability of permanent psychological sequelae is minimal[46, 48]. Hence the importance of obtaining adequate analgesia with a multimodal approximation, including the various combinations of techniques and drugs: locoregional anaesthesia/analgesia, opiates, NO_2, NSAIDs, etc.

PREVENTIVE MEASURES RELATED TO THE PATIENT

As we have already mentioned, a focused and detailed clinical history will enable us to identify patients at greatest risk of intra-operative awareness, i.e. patients with:

- A history of previous episodes of awareness.
- A history of use of drugs that can mask the vegetative response to stress before surgical stimulation, such as β-blockers[49] and calcium antagonists.
- A history of abuse of psychotropic drugs and/or opioid derivatives and patients receiving treatment for chronic pain or drug-dependent patients.
- A history of alcoholism.
- Patients with limited haemodynamic reserve[50], in other words patients who because of their concurrent disease are considered ASA IV/V with severely impaired cardiovascular and pulmonary function[37].
- Extreme age[51-53].

The type of surgery and the circumstances in which it is performed can also imply an increased possibility of suffering intra-operative awareness:

- Cardiac surgery[54].
- Caesarean section[50,55].
- Emergency surgery[50].
- Multiple trauma patients[37].
- Transplants
- Special anaesthetic circumstances: rapid sequence induction, airway manipulation[56], difficult intubation, etc.
- Morbid obesity[57].

Until very recently, probably because of the low recorded incidence, the legal repercussions of intra-operative awareness were minimal[58]. However, this situation is changing as medical quality controls and patients' level of requirements

and demands increase. Claims for this problem in the United States have already reached 1.9% of the total of those filed for "anaesthesia-related causes"[59].

Despite agreeing on the definition of risk groups, it is not they who most often file claims for this problem. According to a database kept in the USA by Domino KB *(Closed Claims Analysis)*[60], it is female patients between the ages of 40 and 60 years, ASA I-II and scheduled for elective surgery who complain most. This brings us to the need to undertake an exhaustive analysis of the cases occurring in our area and their comparison with the rest of the groups.

There is no uniform agreement among experts on the benefit of informing patients beforehand of the possible risk of intra-operative awareness, although it seems that in the latest reviews on the subject the majority agree on the need to do this pre-operatively[30, 35] whenever possible, weighing up the level of anxiety which this may generate.

One simple and not very widely applied measure for assessing the patient's degree of satisfaction and the early detection of possible cases of intra-operative awareness and the prevention of their sequelae would be the establishment of a protocolised postanaesthetic visit undertaken between the first and third day after surgery. Each centre should compile its own records of incidents from the information obtained.

PREVENTIVE MEASURES RELATED TO MONITORING

Intra-operative monitoring should combine the various procedures available to us, which include:

- Clinical monitoring: pupil reflexes, eye opening, movements, response to verbal stimulus and commands, sweating, breathing pattern, lacrimation, tachycardia and hypertension and the forearm tourniquet test. These clinical parameters display obvious limitations in quantifying the depth of hypnosis but continue to represent the first stage in assessing the patient[61].
- Internationally agreed standard conventional monitoring, to include: electrocardiogram, non-invasive measurement of blood pressure, pulse oximetry, expired gas analyser, capnograph and peripheral nerve stimulator when neuromuscular relaxants are used. Whenever possible, body temperature measurement is recommended [35, 62, 63].
- Brain function monitoring: this is a particularly controversial point. For a large majority of experts, the routine use of "depth of hypnosis" monitors designed to evaluate the effect of anaesthetics on brain activity only appears justified, at least at the present time, in patients at risk[64, 65].

It is certain that they still exhibit major limitations because of various factors that distort the recording of brain activity and ultimately the quantified depth of anaesthesia[66-69]. It is to be hoped that in the near future commercial companies will improve their respective models to resolve these problems.

However, in general, the advantages that they offer - good correlation with the concentration of anaesthetic drugs, indirect estimation of the level of analgesia, ease of use and simplicity of interpretation, optimisation of consumption of drugs, resources and surgical time, etc. - show them to be superior to the "classic" detection systems[70-75] and appear sufficient to support their use in daily practice. The shortage of controlled studies evaluating them continues to be the main problem.

However, the question remains: what solid evidence is necessary to support the use of this type of monitoring? In accordance with the opinion expressed by the President of the American Society of Anesthesiologists, E.P. Sinclair[76], other monitors such as pulse oximetry have been adopted without sufficiently justified scientific evidence and yet their usefulness is never questioned nowadays. 69% of the members of the A.S.A. *(American Society of Anesthesiologists)* consulted agree with the opinion that the rational use of brain function monitors reduces the possibility of intra-operative awareness in at risk patients [35].

Nevertheless, this "still" does not justify their inclusion in compulsory routine monitoring and their use should be considered on an individual basis.

No monitor guarantees that intra-operative

awareness will not occur nor replaces the presence and clinical vigilance of the anaesthetist during the anaesthetic procedure.

PREVENTIVE MEASURES RELATED TO SAFETY

Nowadays, general anaesthesia can be considered a "safe" procedure. If we compare the current mortality statistics directly attributable to anaesthesia with those from the last 20 years (0.5-10 with a mean of 7.12/10000 cases) [77, 78], the improvement is obvious [79].

Despite this, a series of critical incidents still occurs with variable consequences for the patient's morbidity and the judgement which he or she makes of the quality of the anaesthetic procedure[80-82]. One of these adverse events is the possibility of intra-operative awareness.

After considering the individual factors of certain patients that cause them to be considered "at risk" for this complication, the next stage is to act on another of the most frequent causes of avoidable anaesthesia-related critical incidents (83): errors of drug administration and defects in systems or circuits[84, 85].

Systematic and repeated testing of the correct functioning of the anaesthesia apparatus, respirator, respiratory circuits and vaporisers before each procedure by a supervisor, who in the final instance will be the anaesthetist, is considered compulsory, paying particular attention to circular systems in which low flows are used and all material that the anaesthetist considers to be customary[86].

Likewise, the patency of the patient's intravenous accesses, the infusion lines and the intravenous drug administration pumps and systems must be checked, choosing systems with the best safety profile and the most accurate control devices from among those available in order to prevent disconnections or obstructions. This inspection is not limited to the pre-induction period, but should be performed periodically in prolonged interventions or in those in which access to the patient is restricted.

The correct labelling of the medications should also be checked, with precedence being given to the use of prefilled syringes where possible.

These safety measures have been shown to be most effective when they are established as a routine practice, following a predefined systematic checking protocol that is known to all the members of the team participating in the anaesthetic procedure (anaesthetist, house officers, anaesthetic nurse, etc.) [86].

Finally, comment on the use of earplugs in the patients' ears as a preventive measure

PREVENTIVE MEASURES RELATED TO PERSONNEL

Like the measures relating to safety, a series of simple and easily applied measures should be included that impact on potentially "avoidable" causes of intra-operative recall, but which we frequently forget to put into practice.

As the auditory capacity is one of the last faculties to be abolished, comments about the patient, their disease, prognosis and physical characteristics, particularly if they are pejorative, should be avoided in the operating theatre during the procedure and particularly in the period of anaesthetic induction and eduction when the depth of hypnosis is more variable.

A quiet environment should be provided without unnecessary, excessive noise, using an appropriate tone of voice.

All personnel involved should be informed and trained to recognise and manage the problem of intra-operative awareness if it is suspected and familiarised with the handling of the different items of equipment used by the anaesthetist and with the depth of hypnosis monitors which each centre possesses. This will require an additional effort on the part of the team.

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Diagnosis of intra-operative awareness. Monitoring of anaesthetic depth

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The current incidence of intra-operative awareness (IA) ranges between 0.1-0.2%(1), 10 times less than that recorded 20 or 40 years ago[2, 3]. This tenfold reduction is very probably due to the greater awareness of anaesthetists and the application of the measures to prevent IA already mentioned in this publication.

How can the anaesthetist detect the occurrence of IA? Unfortunately, there are few clinical signs of IA, which explains the prevalence of this anaesthetic complication. With the introduction of muscle relaxants in the 1940s, two of the most important clinical signs disappeared: respiratory rate and depth and degree of muscle relaxation, as well as movements in response to pain. Among Guedel's classic signs, only pupil diameter offers the vague possibility of ascertaining the degree of depth. In addition, the clinician can infer the level of anaesthesia from haemodynamic reactivity: increase in heart rate and blood pressure - or reflex bradycardia due to vagal stimulation - in the case of insufficient anaesthesia, and the opposite if the level of anaesthesia is excessive. Together with this, there is the occurrence of sweating and lacrimation, also a consequence of insufficient anaesthesia. Unfortunately, the vegetative signs are very imprecise: pain is not the same as depth of anaesthesia; and a large proportion of the population is also taking medications that attenuate this expressivity (ß-blockers for example), not to mention those that can be used during the anaesthetic procedure. The inferral of anaesthetic depth from haemodynamic stability often results in an anaesthetic overdose in elderly patients or those with a concurrent disease, even if everyone is aware that there is a poor correlation between blood pressure, heart rate and anaesthetic depth.

Given this paucity of symptoms, *is there a reliable monitor for detecting IA?* The response, currently, is yes. In fact there are three monitors of anaesthetic depth that can help us to diagnose the existence of IA:

- EEG Bispectral Index Monitoring. BIS (Bispectral index) Aspect Medical Systems, Newton, MA.
- Measurement of Evoked Auditory Potentials. AAI (Alaris Auditory Evoked Potentials Index) Danmeter, Odense, Denmark.
- EEG Entropy Monitoring. S/5 Entropy Module, Datex-Ohmeda, Helsinki.

These monitors determine the degree of anaesthetic depth by different procedures, as has already been described in the section on physical principles. Both BIS and the entropy module obtain their information from the spontaneous EEG. In the case of BIS, the degree of synchronisation between EEG components of different frequencies is studied, including high frequencies (α/β wave ratio) and the burst suppression ratio. The entropy module examines the degree of irregularity in the EEG signal and its predictability. The greater the order and predictability, the less the entropy and the greater the hypnotic depth. The AAI does not

study the spontaneous EEG, but measures the auditory potential evoked by a known acoustic signal generated by the apparatus itself through the headsets placed on the patient, deducing the hypnotic depth from the change in these potentials.

The three monitors translate the level of hypnotic depth into an adimensional number between 0-100. There is a direct correlation between this digit and the patient's degree of hypnotic depth. We can see this in brief for the BIS monitor:

BIS number	*Degree of consciousness*
100	Conscious patient
88	Relaxed patient
60	Borderline consciousness/ unconsciousness
40	Adequate hypnotic depth
20	Excessive anaesthetic depth (overdose)

Not only does the number provide valid information in isolation, it also indicates a trend. For example, an increase from 40 to 55, coinciding with surgical stimulation, would indicate the appropriateness of increasing the anaesthetic dosage.

The entropy module has adopted the same scale as the BIS with a recommended anaesthetic range of between 40 and 60, while the AAI, with a different graduation, has a recommended range of between 20 and 45.

The reliability of the BIS, which appeared in 1992, has been more than demonstrated. There are two relevant studies: that of Ekman et al.[4] who compared a prospective group of 4945 patients monitored by BIS, with another pre-existing historical group of 7826 patients without any neurophysiological monitoring. The group using BIS obtained a 78% reduction in IA; the other study, known as B-Aware, is a multicentre, prospective, randomised, double-blind study that compared two high-risk groups: one of 1225 subjects monitored by BIS and another of 1238 without any monitoring. The respective incidence of IA was 0.17% in the BIS group versus 0.91% in the control group. This then assumes a reduction of 82% in the group managed by BIS[5]. In May 2004 the BIS database contained approximately 8,700,000 cases of anaesthesia, with 103 cases of possible IA. Of the 49 confirmed cases, 46 had BIS figures > 60.6. We should also point out that two cases of IA have been published with BIS values less than 60[7,8], although in one of these there are doubts as to the correct collection of the data[9].

The other monitors, of auditory potentials and of entropy are not supported by clinical studies to the same extent as the BIS. None of them have such extensive statistical series, which are necessary for such an uncommon event. Many of the studies correlate the efficacy of BIS with AAI[10,11]; or the efficacy of BIS with the entropy module[12]; or all three with one another[13,14]. There are doubts as to whether the statistical results obtained with the BIS can be extrapolated to other monitors of anaesthetic depth. In view of the fact that the algorithms of the different monitors are empirical and differ from one another, some authors are of the opinion that each one must be tested individually for its statistical validity[15].

Is it necessary to include a monitor of anaesthetic depth in the optimal monitoring of general anaesthesia, even if the incidence of IA is 0.1-0.2%? The acceptance of an IA monitor is perhaps based not only on its quality but also on the importance which anaesthetists attribute to IA. Its incidence is not excessively high, but its consequences are, representing the complication of anaesthesia that generates the greatest dissatisfaction among those who have suffered it[16] and being one of the great fears of general anaesthesia; not to mention the repercussions which it may have in the long-term, such as post-traumatic stress syndrome, which can occur in up to 78% of those who have had IA[17]. Proof of its importance is that, despite its low incidence, it accounts for up to 12.2% of causes of litigation against anaesthetists[18]. Therefore, it seems reasonable to recommend the use of some monitor of anaesthetic depth, at least in interventions with a high risk of IA. In addition, these types of monitors enable the dose to be adjusted to the patient's needs, allowing a better and more rapid anaesthetic recovery[17,19,20]. Finally, there are published stu-

dies that correlate excessive hypnotic depth (BIS < 40) with greater long-term mortality[21,22].

On 25 October 2005, the A.S.A. published its "*Practice Advisory for Intraoperative Awareness and Brain Function Monitoring*". Systematic monitoring of hypnotic depth is not recommended here; the use of these monitors is at the individual discretion of the doctor in those cases where he or she considers it appropriate.

ACTION IN THE EVENT OF INTRA-OPERATIVE AWARENESS

IA occurs when the supply of anaesthesia is less than the patient's requirements. Therefore the first thing to be done is to deepen the level of anaesthesia as rapidly as possible, and a benzodiazepine can also be administered because of its amnesic potential[23]. Immediately after this we should check that everything is working correctly, as the majority of cases of IA are the result of an error in the administration of the anaesthetic[24,25], e.g. due to vaporiser malfunction. If everything is found to be correct, it should be accepted that the patient has high anaesthetic requirements and greater hypnotic depth provided. In this case once again the ideal situation is to have a monitor of anaesthetic depth.

There are two other situations in which IA occurs with greater frequency: one is prolonged intubation, in which the need to repeat the administration of the induction agent should be borne in mind, and the other is precipitated emergence from anaesthesia with the patient still relaxed (monitoring of neuromuscular blockade). Finally, care should be taken in respect of savings in benzodiazepines when seeking a quicker recovery in the day surgery patient [26].

In all patients in whom intra-operative awareness is known or suspected to have occurred, all the mechanisms of postoperative care discussed later in these guidelines must be implemented to attenuate the psychological consequences that awareness can cause.

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Detection of intra-operative awareness

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PRELIMINARY REQUIREMENTS

- The Anaesthesia Department is responsible for training and instructing health care professionals in the use of consciousness monitoring systems before their clinical application.
- Consciousness should be monitored during the whole process of general anaesthesia, from induction to awakening.
- Interpretation of the data provided by the consciousness monitor must always be done on the basis of clinical criteria and by analysing the remainder of the variables at the same time(1-3). Data provided by the consciousness monitor should be interpreted in the clinical context taking into account all the other clinical signs.

POSTOPERATIVE FOLLOW-UP OF PATIENTS UNDERGOING GENERAL ANAESTHESIA

- The possible existence of intra-operative awareness should be investigated in all patients [4-6], including children.
- The basic screening tool must be a specific interview which in many recent studies[2,7] followed the Brice model, however this is not without its critics[9]. This is a structured interview which is associated with a minimum risk of generating pseudomemory and which includes the following scientifically validated questions:
  - What is the last thing you remember before going to sleep?
  - What is the first thing you remember on waking up?
  - Do you remember anything between going to sleep and waking up?
  - Did you dream during the procedure?
  - What was the worst thing about your operation?

Numerous variants of this interview have been described, most of them complementing it[10-15]. These highlight the occurance of memories, of which pain or the inability to move are the most unpleasant for the patient, but also those related to the recall of noises, voices, specific words, touch, visual sensations, discomfort in the throat, and questions about the duration or the patient's sensation of anxiety, dreams and nightmares. The patient's degree of satisfaction is also noted, the consequences of the surgery and the change in the patient's attitude to anaesthesia. Interviews conducted after the detection of clear evidence of awareness are far more exhaustive.

The first interview must be performed in the Post-Anaesthetic Care Unit[17-22] or in the Day Hospital before the patient's discharge, while in those patients who are taken directly from the operating room to the Intensive Care Unit/Resuscitation/Critical Care Unit the interview can be conducted in the unit as soon as the patient is awake.

A second interview must be undertaken bet-

ween days 1 and 7 after the general anaesthesia and this can be done by the anaesthetist concerned or a nurse, either face to face with the patient or by telephone as part of a routine postoperative evaluation.

∑ The medical team and all medical staff must maintain a sympathetic attitude towards those patients who complain spontaneously of an experience of intra-operative awareness; these complaints may be expressed somewhat belatedly.

∑ If a positive response is obtained in any of the interviews held or if there is a spontaneous report, it must be assumed to be an incident of intra-operative awareness during general anaesthesia. The patient must be assured that their complaint has been noted and the whole team must be alerted to empathise with the patient.

∑ All positive responses must be reported to the Anaesthetic Department and the Patient Care Department for follow-up.

PAEDIATRIC PATIENTS

Children are potentially more easily influenced the younger they are, although all of them can be influenced to a certain extent. Induced reports are usually more bizarre and the degree of suggestion increases with the number of interviews. The first interview is usually the most accurate, although it does not always serve to detect the episode. In the study by Davidson, three interviews were performed, which increased the probability of detection and of suggestion.

Screening interview on the first day

- Were you worried, concerned or frightened before your operation?
- How worried, concerned or frightened were you?
- What is the last thing you remember before the operation?
- How did the anaesthetist put you to sleep?
- What is the first thing you remember after the operation?
- While you were having the operation, did you dream, feel or hear anything?
- Were you sore after the operation?
- How much did it hurt?
- What did you least like about having an operation?
- What did you most like about having an operation?
- Did anyone tell you what the operation would be like?
- Was the operation how you had been told?
- How do you feel about the operation?
- Would you like to have known more details?

Questions asked by parents on days 3 and 30

- What is the last thing you remember before the operation?
- How did the anaesthetist put you to sleep?
- What is the first thing you remember after the operation?
- While you were having the operation, did you dream, feel or hear anything?

MANAGEMENT OF AN EPISODE OF INTRA-OPERATIVE AWARENESS

- The anaesthetist in charge will be responsible for detecting and managing each case of intra-operative awareness.
- If a case of intra-operative awareness is reported, an anaesthetist must interview the patient as soon as possible, take a detailed description of the episode and determine whether it is consistent with intra-operative awareness (confirmed), possible intra-operative awareness, or intra-operative dreams. It must be recorded in the patient's record.
- If a case of unintended intra-operative awareness has occurred, apologies must be made to the patient, assuring them that they are being taken seriously. The medical staff immediately responsible, such as the surgeon, nurse or primary care doctor, must be informed.
- If possible, an explanation of the aetiology of the episode must be offered to the patient, for example the clinical causes preventing the anaesthesia from being deepened.
- The possibility of referring the patient to other medical experts, such as mental health experts, to assess the patient and minimise the possible

consequences must also be considered.

- All patients who have suffered an episode of intra-operative awareness must be guaranteed the possibility of continuous access to hospital resources if late after-effects appear. A contact address will be given to them and they will be called 2 and 3 months after the procedure.

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Intra-operative awareness in children. Incidence, risk factors and prevention

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Intra-operative awareness (IA) has for many years been an underestimated anaesthetic complication in adult patients and to an even greater extent in children. Interest in this subject has currently been revived to the extent that the *American Society of Anesthesiologists* (ASA) has recently issued an *"advisory"* on intra-operative awareness and brain function monitoring in the adult patient. The social alarm generated by the publicity that has been given to some cases of IA in the media in countries such as the United States, a better understanding of the incidence and risk factors from the publication of new studies on the subject and the development of technology that enables us to know the depth of anaesthesia, increasing the means available to the anaesthetist to avoid IA, help give this anaesthetic complication and its prevention the importance it deserves.

For many years there has been a debate as to whether premature neonates need anaesthesia for surgery[1]. The greater risk of haemodynamic instability, cardiac arrest and adverse effects associated with anaesthesia in neonates and infants led anaesthetists to refuse anaesthesia or minimise the doses during surgery in this population group[2-6]. Some years later, it was found that the response to stress in neonatal cardiac surgery was exaggerated compared to that in adults and that it was also associated with an increase in intra- and postoperative complications, such as sepsis, metabolic acidosis or disseminated intravascular coagulation, and mortality[7]. It was also found that administration of hypnotic and analgesic drugs reduced morbidity and mortality[8-9]. The long-term consequences of prolonged and repetitive pain in the neonatal period include changes in sensibility and in the processing of pain, as well as defects of nervous, cognitive and behavioural development manifested during infancy. On the basis of these findings on the development of the response to pain and stress, the use of postoperative anaesthesia and analgesia is routine in critically ill surgical neonates and surgery without anaesthesia has come to be a medically and socially unacceptable practice. Very recently, the paradigm of the anaesthetised infant has been called into doubt by studies in laboratory animals in which it was shown that blockade of NMDA receptors with drugs such as nitrous oxide or ketamine[10] and the use of other commonly employed anaesthetics such as isoflurane or midazolam[11], anticonvulsants and ethanol can cause an increase in apoptotic neurodegeneration in the developing brain[12]. These neurodegenerative changes in numerous areas of the brain are associated with memory and learning deficits and have been associated with the use of these drugs in the absence of pain, so that it appears that both surgery without anaesthesia and anaesthesia without surgery can be harmful to the developing brain.

We can define an "anaesthetised brain" as one that is incapable of having self-awareness or subsequent recall. This definition is useful conceptually, but the difficulty lies in knowing when the

patient is unconscious and amnesic and what doses of anaesthetic are needed to achieve this. It should be borne in mind that this dose will vary in the presence or absence of pain. There are different dimensions in what can be considered IA and the published articles do not always agree on their objective when they come to define it. Thus, some authors endeavour to determine which patients have conscious recall of what happened in the operating room (explicit memory), while others try to discover whether the patient has self-awareness during surgery, even if subsequently they do not recall anything consciously. This can be determined by Tunstall's isolated forearm technique(13), which consists in placing a cuff on the patient's arm that prevents the muscle relaxant from reaching the hand, so that if the patient is conscious they can respond to our orders and demonstrate this by movement of the hand. There is another group of patients who, although they do not exhibit self-awareness or posterior recall, can process the unpleasant events that occur during surgery unconsciously and this can cause behavioural changes subsequently (implicit memory). Implicit memory is assessed by postoperative tests or the observation of changes in behaviour.

The peri-operative experience and hospitalisation in themselves have repercussions on the emotional well-being of children in 16-54% of cases. This variability depends on the definition of behavioural change and the follow-up time given to the child. The most common consequences are anxiety, nocturnal crying, enuresis, fear of separation and tantrums, and the methods to avoid this include premedication, inhalational induction, pre-operative preparation programmes, musical therapy, presence of the parents, acupuncture, etc. It is therefore difficult to know what the most stressful aspects of hospitalisation and surgery are and in this context it will be difficult to measure the effects of a hypothetical and infrequent event such as IA.

Extrapolating the data obtained from studies of IA in adults would be inappropriate because of the differences in anaesthetic technique, pharmacology and the different psychology of development of the child. However, articles published on children are very sparse. In 1973, McKie[14] published a study of 202 children aged 7-14 years in whom a high incidence of IA was found (5%). He then used the Liverpool anaesthetic technique based on the administration of nitrous oxide and a muscle blocker without inhalational or intravenous anaesthetics. Some years afterwards other studies did not find IA using a similar anaesthetic technique, but the number of patients studied was much smaller and they were only given one postoperative interview[15-16]. Since then a clinical case has been published[17], a study conducted in paediatric intensive care[18] and some articles designed with other objectives and with very small samples in order to detect IA, but which concluded that this was not present[19, 20]. The most complete study of IA in children was published very recently[21], involving a sample of 864 patients aged 5-12 years in whom postoperative conscious recall was evaluated in three interviews conducted over a period of one month. Twenty-eight suspected cases of IA were found, of which 7 cases where considered as true awareness, which assumes an incidence of 0.8% using current anaesthetic techniques. This incidence is high in comparison with that found in adults (0.1-0.2%). We will try to unravel below some of the factors that might affect this greater incidence.

CAUSES OF INTRA-OPERATIVE AWARENESS

The causes of IA in children are similar to those in adults, but are affected by the specific characteristics of the paediatric patient. It has been shown in adults that, as might appear logical, IA occurs most frequently in patients receiving lower doses of anaesthetics[22]. The type of surgery can affect the frequency of IA. It can be more frequent in ambulatory surgery because of the possible reduction in the dose of anaesthetic to prevent postoperative complications and obtain arousal and discharge. Likewise in cardiac surgery, because of the pharmacological and pharmacodynamic changes caused by the extracorporeal circulation which are more accentuated in children. Rewarming is one of the moments of greatest risk given that the metabolism of the brain increases, as has been

shown by the reduction in saturation by cerebral oximetry or the increase in the bispectral index figures[23]. The incidence of IA due to errors in the labelling or administration of drugs, carelessness, failures of anaesthetic equipment or communication and fatigue can be assumed to be similar to those in adult patients, where it has been found that 4.4% of errors in the administration of drugs cause intra-operative awareness[24] or that 1.9% of complaints for anaesthetic reasons were for IA, including 18 cases of muscle paralysis with the patient awake[25]. The anaesthetic technique also affects the incidence of IA. Thus, it has been shown that the nitrous oxide-opiate-muscle relaxant technique is associated with a greater frequency of IA[25], as well as the use of a short-acting induction agent with a slow-onset muscle relaxant which can cause a high incidence of IA at the time of laryngoscopy and intubation[26]. This is the technique most commonly used in paediatric patients when intravenous induction is performed in view of the fact that succinylcholine is avoided as far as possible in paediatric anaesthesia because of the greater incidence of bradycardia. However, the principal induction technique in paediatrics is inhalational sevoflurane, with or without nitrous oxide, which when administered at high concentrations can permit a sufficient depth of anaesthesia in the patient to allow laryngoscopy and intubation of the patient without the use of neuro-muscular blocking agents (NMB). Not only have these muscle blockers been shown to be a factor in increasing the incidence of IA, but also patients who suffered IA under the effect of NMB experienced pain, anxiety and delayed neurosis, as opposed to those who were not relaxed[27]. In paediatric anaesthesia, NMB are used less frequently than in adults and it is possible that this, among other factors, influenced the absence of development of anxiety or behavioural changes in children with IA in Davidson's study[21]. The severity of the patient's condition determined by the classification of physical status of the *American Society of Anesthesiologists* (ASA) affects the incidence of IA[28], as does haemodynamic instability, which frequently induces us to reduce the dose of anaesthetic, as has been shown in multiple trauma patients[29]. Both adult[30, 31] and paediatric[18] critical patients exhibit a very high incidence of recall of dreams, nightmares and hallucinations, and recall of pain, paralysis, a noisy environment, the presence of the endotracheal tube, mechanical ventilation and the impossibility to communicate is common.

Another factor to be borne in mind is interindividual variability[32], as some patients may have greater requirements for drugs for various reasons. Age affects the minimum alveolar concentration (MAC) of inhalational anaesthetics, which is greatest in the first month of life and decreases with age[33, 34]. In addition to requiring a higher concentration of inhalatory anaesthetic, neonates and infants are more sensitive to the haemodynamic changes that these produce[35], exposing them to the risk of sub-MAC concentrations being used. The pharmacokinetics of intravenous anaesthetics have not been determined completely in children, but the requirements are also greater than in adults[36].

MONITORING OF ANAESTHETIC DEPTH IN CHILDREN

There is limited inter-subject variability in the response to inhalatory anaesthetics so that the end-expiratory (EE) concentration can be used to predict adequate anaesthetisation of the patient better than with intravenous drugs administered on the basis of pharmacokinetic models, which might not be applicable to all individual patients and even less so to children. However, monitoring of the EE concentration of inhalational anaesthetics in small children is much less reliable than in adults

Neurophysiological monitoring of anaesthetic depth, which has been shown in adults to reduce the incidence of IA[37-39], requires greater evaluation in paediatric patients and possibly calibration to adapt it to the developmental characteristics of the infant brain. The bispectral index (BIS), which has been the most extensively studied in children, has a similar behaviour in older children to that in adults [40], but in those aged under 6 months or 1 year the significance of the BIS is less clear and should be interpreted with caution as the BIS algorithm is based on the electro-encephalogram of adult patients and may not been applicable to young paedi-

atric patients in whom the maturation of the brain and the formation of synapses is still ongoing. In accordance with Bannister's findings[41], children under 6 months of age require a lower concentration of sevoflurane in nitrous oxide to achieve the pre-established BIS figures, similarly to the study by Davidson [42] who obtained lower values in a group of infants than in older children in monitoring BIS prior to emergence from anaesthesia with sevoflurane combined with penile block for circumcision. After induction and during recovery from sedation with 2% sevoflurane in the absence of nociceptive stimulus, we found significantly lower values in the group of children less than 6 months of age than in the remainder, in spite of the fact that the MAC decreases with age[43]. Recently, other authors have found that age in itself is a factor that affects the BIS and that there are differences in the behaviour of the BIS in 6-month-old and 12-year-old children compared to adults. Increasing concentrations of sevoflurane, 2-3%, are followed by reductions in BIS, however when increased to 4% a paradoxical elevation is observed in BIS values[44]. Despite these limitations, and taking into account the special characteristics of the paediatric patient, the methods of monitoring hypnosis may also be useful in this population in specific cases, as described in the corresponding section of this book.

PERCEPTIONS, EMOTIONS, FEELINGS, REACTIONS AND CONSEQUENCES OF INTRA-OPERATIVE AWARENESS (IA)

Only 35% of patients with IA inform their anaesthetist. Auditory perception, the sensation of paralysis and pain are common findings, capable of causing feelings of anxiety, fear, occasionally building up to panic, powerlessness, helplessness and defencelessness, which can cause long-term psychological consequences such as sleep disorders (dreams, nightmares), anxiety or post-traumatic stress syndrome, although this is uncommon and occurs with greater frequency in patients who have suffered pain[45-49].

From the child's perspective, the relevance of intra-operative awareness can be different since the expectations, fears and ways of dealing with stressful events are also different. The definitions of consciousness and the processes of memory formation are complex and disputed, even among adults, and even less is known of the processes of memory formation in neonates and infants. Explicit memory is generally better in adults, but implicit memory which affects behaviour in the absence of conscious recall can be as good in children as in adults. It has been shown that pain causes changes in behaviour in neonates, although probably, in the absence of pain, hearing the conversation that takes place in the operating theatre does not cause them any harm. Infants and children up to 2 years of age are stressed by separation from their parents and, in the absence of pain, IA is probably stressful in a similar way. Preschool children, who attribute fantastical explanations to their experiences, schoolchildren or adolescents with their concern about integrity and body image can be particularly vulnerable groups. Children probably have less developed psychological defence mechanisms for coping with the situation. Nevertheless, the psychological impact on children is unknown because of the scarcity of studies on this subject[50].

DETECTION OF INTRA-OPERATIVE AWARENESS IN CHILDREN

Physiological signs, such as haemodynamic, respiratory and muscle changes or autonomic nervous system activity fail to indicate cognitive changes, although they have been used in relaxed critical patients in the form of a scale to evaluate sedation[51]. These signs have a better correlation with the subcortical component of anaesthesia (antinociception, immobility, autonomic stability) than with the cortical (unconsciousness, amnesia). Neurophysiological methods of monitoring anaesthetic depth (BIS, entropy, evoked potentials, etc.) are the only ones that can be helpful in detecting IA in the operating theatre but require greater evaluation in the paediatric patient.

Conscious recall is evaluated after surgery by separate interviews over time, so that they have no value for clinical purposes, only scientific ones. In children, there are difficulties of suggestibility and

truthfulness in their testimonies, making this unviable below the age of 5-6 years, an age which even for the evaluation of pain or sedation in intensive care requires physiological or behavioural scales. It is important that the questionnaire should be adapted to the child's language and also that it should not be administered by the parents, for whom it is more difficult to detect IA since they do not know the perceptions experienced during this complication and also they can suggest or trivialise their children's memories. Details such as who undertakes the interview with the child, the language used or when it is conducted can cause the incidence of IA obtained in different publications to vary from 0.8% in the study by Davidson[21] to the alarming percentage of 6.3% found by Iselin-Chaves(52). The response to stimulation by Tunstall's isolated forearm technique is considered by many to be the technique of choice for determining self-consciousness during anaesthesia, but is not useful in clinical practice. It has been found to be better correlated with the methods of monitoring anaesthetic depth (BIS) than with haemodynamic variables, which are better correlated with conscious recall[53]. IA can be underestimated if conscious recall alone is considered, since only 17% of paediatric patients experiencing IA during scoliosis surgery and only 25% of the 66% who had a positive isolated forearm test during deep sedation up to a BIS of 60-70[53] are capable of recall[54].

PREVENTION OF INTRA-OPERATIVE AWARENESS (IA)

For the time being there is insufficient scientific evidence to draw up a clinical guide or standards for the prevention of IA. In October 2005, the ASA published an *"Advisory"* on intra-operative awareness and monitoring of brain function(55), based on a review of the available literature, expert opinions and interviews among its members. This document, as the authors point out, *is not intended to be applied during the peri-operative treatment of paediatric patients*. It is applicable to procedures undertaken under general anaesthesia, excluding sedation in the operating room or in intensive care, and considers only self-awareness during anaesthesia and explicit recall, excluding the formation of implicit memory.

Measures to prevent IA start in the pre-operative anaesthetic consultation when the severity of the patient's condition is determined according to the ASA classification and risk factors such as drug addiction, treatment of chronic pain with high doses of opiates, or a previous anaesthetic history of intra-operative awareness or difficult intubation can be detected. In these patients with a greater risk of IA and in those due to undergo cardiac surgery, caesarean section, multiple trauma patients or those due to receive a total intravenous anaesthetic technique with monoxide-opiate, as well as in cases of muscle relaxation, the patient must be informed of the possibility of IA. In the pre-induction phase of anaesthesia, it is recommended that protocols for checking the anaesthetic apparatus and other equipment should be followed to ensure that the required quantity of drugs is administered. With this in mind, the correct functioning of the venous accesses, infusion pumps and connections should be checked. It is recommended that midazolam is administered as prophylaxis of IA only in selected patients and, given that there is no scientific evidence of its utility in preventing recall, administered after the unexpected recovery of consciousness during surgery; the decision to administer it must be taken individually in each specific case. When the patient reports recall of intra-operative events, details must be obtained to identify the causes and document the case. We must also offer the patient psychological assistance.

As regards intra-operative monitoring of anaesthetic depth, a multiple approach is recommended, which includes clinical techniques such as the detection of reflex or voluntary movements and conventional monitoring (ECG, BP, HR, end-expiratory analysis of inhalational anaesthetics, capnography), which is more important, where possible, in cases in which MB are used. At present there is insufficient scientific evidence to justify the routine use of monitors of anaesthetic depth, even in patients at greater risk of IA. The use of this monitoring should be evaluated by the anaesthetist in each individual case and applied in selected cases.

These considerations that are applicable to the

adult patient should be borne in mind by the paediatric anaesthetist, who should adapt them to his own practice according the specific characteristics of children in the course of their development.

CONCLUSIONS

Intra-operative awareness also occurs in paediatric patients and probably with a higher incidence than in adults. Because of the difficulty of evaluating it, studies in children are very rare and its consequences unknown. Despite the scarcity of data available to us at present, it seems necessary to make an effort to prevent IA in paediatric patients by all available means, including the application and adaptation of methods of monitoring anaesthetic depth which are showing promising results in adults.

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Depth of hypnosis monitoring systems in paediatrics

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Although modern systems of monitoring hypnosis and, more questionably, anaesthetic depth are genuinely useful in adults, neurological maturational development in children passes through stages that are difficult to classify. Therefore extrapolation of the results from adults to the youngest subjects is a complex matter and, among them, we cannot consider the neonatal or infant stage as being the same as that of the oldest children or of those of intermediate ages. It is sufficient as an example just to take a five-year-old child; we all know, even though there are few literature references, the differences in intellectual integration present when trying to understand the surgical, and even more so the anaesthetic, process in these cases. And when talking of maturational development - in this case the physical, not the intellectual - we all perform anaesthesia in 12-year-old children who have the physical development of an adult and 16-year-old children with a physical development similar to or less than that of someone aged less than 12 years. If such inter- and intrapopulation variations exist from the purely organic or physical point of view, how can these not be present in psychoneurological development? It is therefore a matter of observation and above all of clinical experience to know how to handle each case individually and to adapt to the specific conditions of each "child" patient when approaching the monitoring of hypnotic depth in anaesthesia. Even more complex is the approach to preventing implicit and/or explicit memory in these cases, particularly when the development of the corticothalamic pathways and the subthalamic nuclei is at a different level of maturation depending on each case.

Although, for anthropological reasons, all healthy individuals are born with the functions that are dependent on the paleo-encephalon active, it is the neo-encephalon and the higher structures derived from it that undergo the interaction of the neuro-endocrine, metabolic and immune system associated with contact with the immediate circle and environmental factors, thus engendering cognitive, integrational and intellectual development. It is therefore a multimodal concept, as in almost all medical aspects, and requires us to analyse it to consider whether or not there is conscious perception, in any of its forms, in children during the anaesthetic procedure.

Numerous systems have been developed, almost all dependent on and derived from brain electrical activity (cortical and subcortical), in an attempt to identify, through various mathematical algorithms, the level of perception or, where applicable, the depth of hypnosis in subjects undergoing general anaesthesia. For the reasons mentioned previously, extrapolating these systems to the paediatric population in its various processes of organic developmental is almost impossible. However, not everything is so difficult and we must not abandon this path in the face of the eventualities that have arisen. Sometimes the combination of different systems and multimodal analysis of the numerous variables presented to us helps to establish whether some or all the systems are valid for our purpose of monitoring hypnotic depth in children.

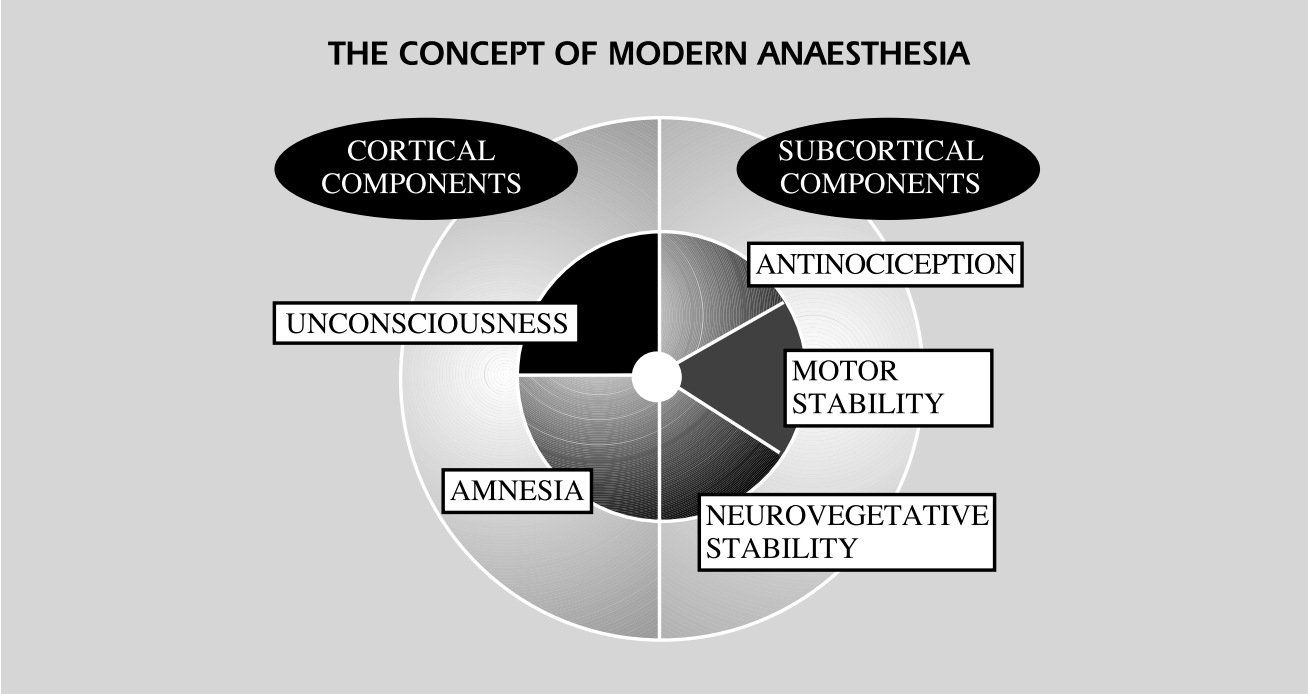

Figure 1. Components of adequate anaesthesia.

Although we are approaching a purely speculative field in many cases, we intend to talk about the correlation or lack of correlation of the data in the different systems in relation to children by attempting to use as a basis other indirect systems that also help us to observe the level of perception of the anaesthetic procedure.

We are increasingly aware of the fact that monitoring hypnotic depth or the level of perception during anaesthesia, at least in children, requires the need to analyse numerous variables in combination. We should not abandon the idea that, although the separation of autonomic response from conscious perception during anaesthesia has already been demonstrated[1], at least in children the response of certain systems to different kinds of stimuli during anaesthesia continues to play an important role in the assessment of their perception. Thus, changes in heart rate, the occurrence of sweating or piloerection, to a lesser extent - because it depends much on age and the development of the sympathetic nervous system - blood pressure, and even changes in *end-tidal* CO_2 - although this is disputable -, continue to alert the anaesthetist to the possibility of conscious perception during the general anaesthetic state.

Without therefore abandoning indirect monitoring systems, various systems of detection of hypnotic depth have been developed in the concept of modern anaesthesia which could be useful in their application to children.

Traditionally, anaesthesia was visualised using the diagram of a triangle, with hypnosis, analgesia and relaxation at its vertices. However, this chart overly simplified anaesthesia, in addition to which new theories have developed and complicated the concept of anaesthesia.

The diagram has now been transformed (see Fig. 1) into a circle whose halves include the cortical and subcortical components of anaesthesia. Among these, consciousness and amnesia are included in the cortical component, and antinociception, immobility and autonomic stability in the subcortical component.

The cortical components of anaesthesia refer to the effects of anaesthetic drugs on the brain, particularly in the cerebral cortex, where the cognitive processes take place.

The term unconsciousness has been taken, in the conceptual sense, to indicate one of the components of anaesthesia. Thus, many of the traditional terms have been tried, although they were

not always entirely correct. Some of these terms are "consciousness", "insomnia", "hypnosis" and "depth of anaesthesia." In the purely anaesthetic context, the term consciousness has been defined as a state of knowledge or perception of the outside world [2]. Thus, unconsciousness would be determined by the absence of this perception.

Many investigators see in the loss of consciousness the principal component of general anaesthesia and, therefore, a large part of scientific and research energy has been directed to studying anaesthesia on the basis of this component. Given that the loss of consciousness is a cortical component, one of the most obvious indicators of levels of loss of consciousness are some of the neurophysiological measurements of cortical brain activity. Specifically, the processed electro-encephalogram in all its forms (EEG) and auditory evoked potentials (AEP) have been proposed for this purpose.

Vesselis et al.[3] demonstrated that the sedative and amnesic effects of anaesthetic drugs are, in reality, two different phenomena. This explains how Glass et al.[4] demonstrated that amnesia always occurs at a lower concentration of anaesthetic drugs used than loss of consciousness.

In studying amnesia, or the absence of recall, we must remember that there are two classes of memory: explicit and implicit. The first refers to conscious recall of actual events. Therefore, when it is considered that the patient is conscious during anaesthesia, explicit memory plays a fundamental role. Implicit memory is that to which the conscious mind has no access. However, it has a major influence on human behaviour. Lubke et al. have also shown that the formation of a part of memory can occur even during adequate anaesthesia[5, 6]. As we shall see below, the so-called reverberation circuits intervene in this type of memory.

The subcortical components of anaesthesia also play a role of utmost importance. They are responsible for maintaining autonomic stability, immobility and antinociception.

Antinociception is the inhibition of the nociceptive process of the nervous system mediated by analgesia. The establishment of complete antinociception is crucial to obtaining adequate anaesthesia.

Another of the objectives of general anaesthesia is to ensure that the patient does not make involuntary movements during anaesthesia. Thus, muscle relaxation may be considered a component of adequate anaesthesia and, even if this is highly disputable, there are interventions that necessitate neuromuscular relaxation. The appropriateness of using relaxant drugs that act on the motor end plate is however disputed.

As Rampil[7] points out, the motor response of an anaesthetised patient does not appear to be a cortical phenomenon but is initiated in the spinal cord This is why, if an anaesthetist interprets an unexpected movement of the patient as indicative of inadequate hypnosis, he may be making a major error since this is an incorrect interpretation.

Autonomic or neurovegetative stability is a further component of adequate anaesthesia. Sudden haemodynamic changes can be indicative of nociception, signalling that something in the anaesthetic process is inadequate. Circulatory stability is therefore crucial and anaesthetised patients with a compromised cardiovascular system require precise adjustments in the administration of drugs.

However, it does not appear very orthodox to talk of adequate anaesthesia if we then omit other components that are present in the process of the surgical procedure and which, directly or indirectly, also intervene in the conceptual basis of the anaesthetic practice, such as the maintenance of internal haemostasis for the development of adequate anaesthesia. The functioning of the organs and basically the respiratory system responsible for tissue oxygenation should be included in the concept of adequate anaesthesia within the subcortical components. In this respect, the monitoring systems for maintaining gases in the respiratory mixture administered to patients and their elimination are vital for understanding the levels of tissue oxygenation, cell metabolism and the probable state of anaesthetic depth. The administration of anaesthetic gases and vapours in the respiratory mixture supplied requires us to know their partial pressures in the anaesthetic circuit, the alveolar territory and ultimately the brain or, better, the central nervous system (CNS). Knowing the partial pressures, we can obtain their concentrations, and

using multiples of the minimum alveolar concentration (MAC) we can control the depth of anaesthesia by way of increasing hypnotic depth and/or abolishing integration of nociceptive stimuli of greater or lesser intensity.

Current control and monitoring systems are highly developed and are based on very contrasting techniques. Thus, the haemodynamic profile is studied by invasive or non-invasive techniques. Among these, there is very little discussion about their functioning and the degree of certainty in their measurements. Nevertheless, science continues to evolve in its attempt to perfect and improve these systems and above all to replace those invasive methods by others less harmful to the patients, with the same or greater reliability.

Modern methods of monitoring pressures, vascular resistances, cardiac output, metabolism and clearance of substances, etc., by infrared spectrum detectors or systems of dilution of substances such as lithium[8] and by spectrophotometers using laser technology have meant that other methods have fallen into disuse because of their aggressiveness and complexity in terms of their attachment and use. However, from these we have learnt the rationale for many functions and we can apply their principles to other non-invasive experimental systems that are unknown at present.

Monitoring of the degree of neuromuscular relaxation, like the previous form of monitoring, is perfectly developed and although the current tendency is not to use substances that act on the motor end plate where possible, achieving immobility by other methods, existing monitoring systems based on electrical neurostimulators meet the need for control with very high reliability.

It is accepted that systems for monitoring anaesthetic gases and the respiratory mixture as well as pressure and airflow are highly reliable protective measures in the complex methods used for measurement and analysis. However, we should not forget that science is not infallible and we must continue to perfect our analysis models since the lack of knowledge of alternatives, the technical impossibility of their application or an excess of confidence in what has been amply tested may cause us to obtain errors - although in most cases without clinical repercussions - which we wish to forget in an attempt to continue to progress in the investigation of other models and other areas of which we are mostly or entirely unaware and which also form part of adequate anaesthesia.

Spirometry of the patient provides a visual tool for improving ventilation in anaesthesia and critical care. It helps prevent and diagnose problems with the ventilator and endotracheal tube (or airway masks) by displaying various loops and curves. The information is generated from the pressures, volumes and flows measured in the patient's airways, which are integrated with other parameters on the monitoring screen in the form of qualitative and quantitative information.

The term capnometry is used to define the numerical measurement of the maximum and minimum values of the CO_2 concentration during a respiratory cycle, while the term capnography refers to the graphical recording of the CO_2 concentration during the respiratory recording. The capnograph used in clinical practice is an instrument that displays both parameters, numerical value and graphical recording[9].

Capnography provides safe, non-invasive, continuous and economic information. Together with the pulse oximeter, it is the monitor that had the greatest impact in anaesthetic practice in the last decade of the previous century. It is considered a standard for intra-operative monitoring by scientific societies[10, 11].

However, despite the widespread systematic use of these devices throughout the world, we cannot guarantee that the measurements they take are absolutely true.

The quality of anaesthesia has become one of the primary aims of peri-operative management. As a result of the new surgical techniques and the continuous changes in patient care needs, it is increasingly more essential to find a rapid, simple and safe management of general anaesthesia. In this respect, a broad spectrum of pharmacological actions must be used. These include not only analgesia and hypnosis, but also the suppression of somatic and autonomic responses to the nociceptive stimulus[12].

When a given analgesic or anaesthetic dose is

administered, the ultimate aim is to obtain a given clinical effect. Therefore, a specific therapeutic concentration of the drug, a specific site of action and a specific receptor are required. It is characteristic that each anaesthetic individually produces its pharmacological spectrum of action. According to the traditional concept of drug administration, it may be necessary, in an ideal anaesthetic state, to adjust the dose to obtain the clinical components separately[4]. With the aim of achieving the highest levels of safety, the anaesthetist must always optimise the administration of a number of drugs, titrating them progressively to obtain specific therapeutic effects. For this reason, a theoretical knowledge of the conceptual components of anaesthesia is necessary.

In 1847, Plombey[13] was the first to classify the depth of anaesthesia in three characteristic stages: intoxication, excitation (both conscious and unconscious) and deep level of narcosis. In 1937, Guedel[14] defined four anaesthetic stages for ether, based on respiratory, haemodynamic and ocular signs and muscle tone (somnolence, psychomotor agitation, hypnosis and coma). In 1942, when neuromuscular relaxants were introduced into clinical practice, reports began to circulate on intra-operative awareness. In 1954, Artusio[15] divided Guedel's first stage into three different levels: the first in which the patient does not experience amnesia or analgesia; the second in which the patient experiences complete amnesia but only partial analgesia; and the third in which the patient exhibits complete amnesia and analgesia.

The classical clinical signs and the known stages were relevant when anaesthetics such as ether, cyclopropane or chloroform were used. With the appearance of other volatile anaesthetics, these became disputable and with the combination of opioids and other drugs, they lost their importance. The appearance of modern monitoring systems provides information that has caused the old concept of anaesthesia to disappear.

Classical anaesthesia was based on the unitary theory of narcosis with a non-specific mechanism of action in which the anaesthetic, any anaesthetic, occupied critical hydrophobic loci in the central nervous system. It was assumed that one anaesthetic could freely replace another and, in the event of their combination, the resultant effect would be the sum of both[16].

In the classical concept of anaesthesia, the state of general anaesthesia was considered a multifactorial phenomenon, caused by a single confused mechanism. In an attempt to group all general anaesthetics with a different chemical structure under a common hypothesis, a non-specific mechanism was assumed.

The problem with the classical concept of the anaesthetic state became apparent with the appearance of neuromuscular blocking drugs, opioids and barbiturates, which were increasingly combined with volatile anaesthetics. In 1957, Woodbridge[17] studied the anaesthetic drugs of the time and defined anaesthesia as a procedure which included four components.

1. Sensory block of afferent nerve impulses.
2. Motor block of efferent impulses.
3. Reflex block of the respiratory cardiovascular and gastro-intestinal tract
4. Mental block, sleep and unconsciousness.

In this classification, each drug could be used to obtain a specific effect. However, no effort was made to define the methods by which each of these components was classified. In 1986, Pinsker[18] sent a letter to the editor of a reputed anaesthesia journal in which he postulated three components for the concept of anaesthesia: paralysis, unconsciousness and attenuation of the response to stress. In this theory, any drug or combination of drugs endowed with reversibility of these three conditions could be used in anaesthesia.

In 1987, Prys-Roberts[19] incorporated a new aspect, the perception of pain. If pain was considered as a "conscious perception of the nociceptive stimulus", then "a state of anaesthesia" could be defined as unconsciousness induced by drugs in which the patient would never perceive pain. According to this theory, surgery causes nociceptive stimuli with the result of a series of somatic (pain or movements), autonomic and haemodynamic responses that could be modified by different drugs.

Kissin[12, 16] extended and improved the concepts

and fundamentally contributed to the definition of anaesthesia. He proposed that a broad spectrum of pharmacological actions induced by different drugs could be used to create a state of general anaesthesia. These pharmacological actions could include analgesia, anxiolysis, amnesia, unconsciousness and somatic, motor and cardiovascular suppression, as well as the hormonal responses subsequent to the surgical stimulus. He also emphasised that the spectrum of effects constituting the state of general anaesthesia and the multiple components of anaesthesia could not be understood from a single anaesthetic action. The spectrum assumes separate pharmacological actions even if anaesthesia is produced by a single drug.

In order to confirm the theories and the principals of our understanding of anaesthetic depth, it was clear that we required more scientific information about the interaction of the combinations of anaesthetic drugs of clinical relevance.

In 1998, an editorial appeared in which Glass[20] discussed the interaction of hypnotics and opiates in obtaining two principal points in general anaesthesia, loss of consciousness and inhibition of movements as a response to the surgical incision of the skin. He suggested that the interaction between hypnotics and opiates might explain the loss of consciousness and lack of response to the incision of the skin. This would at all events not be a continuum in the increase of anaesthetic depth, but two separate phenomena.

Combining his observations, Glass proposed the following hypothesis on general anaesthesia: a process which requires a state of cerebral unconsciousness, produced primarily by volatile or intravenous anaesthetics. If only unconsciousness is obtained, the nociceptive stimuli must be inhibited by acting on higher centres where arousal reflexes might be produced. These inhibitory effects could be obtained by the action of opiates at specific receptors in the spinal marrow. Alternatively, local anaesthetics might be used to block peripheral nerves. In the case of volatile anaesthetics, concentrations exceeding the minimum alveolar concentration (MAC) could be administered to obtain a similar effect on the spinal marrow. Special effects could be obtained by specific therapeutic agents. For example, in the case of neuromuscular blockade, neuromuscular relaxants could be used.

In summary, the anaesthetist currently needs to know the specific effect of each drug and its pharmacological interactions. Monitoring of the effects of drugs during anaesthesia is possible using specific monitoring techniques, which help achieve a high therapeutic quality.

In general anaesthesia, muscle paralysis considerably complicates the evaluation of the level of consciousness. In addition, the classical clinical signs for adjusting the level of anaesthesia, blood pressure and heart rate, may in exceptional cases not be reliable. On the other hand, the pharmacokinetic model is not very precise when individualised in each patient, and even less so in children; the concepts of minimum alveolar concentration (MAC) of inhalational anaesthetics or another ED50 may exhibit substantial interindividual variability. Therefore, the only objective way of optimising anaesthesia is the pharmacodynamic measurement of the anaesthetic effect (Fig. 2).

The brain is the target organ of all hypnotic drugs. The anaesthetist can monitor the hypnotic component of anaesthesia by measuring its effect through electrical brain activity (electro-encephalogram, EEG). Some characteristics of the spontaneous EEG or auditory evoked potentials (AGP) may indicate the state of the brain during anaesthesia[21, 22]. In this way, the recording of the waves emanating from the brain assumes particular relevance in the analysis.

Particular efforts have been made to identify the useful information obtained from the EEG and to transform it into a readily comprehensible form, even at the expense of excessive simplification. Although many clinicians would like to have a measurement of hypnosis as simple as a “yes” or a “no”, unfortunately the reality is much more complex.

During the administration of hypnotic medication, a numerical value derived from the EEG can be obtained, which is adjusted to the depth of hypnosis. Undoubtedly, in this kind of observation, the determinations would be simplified to such an extent that without doubt we would lose other va-

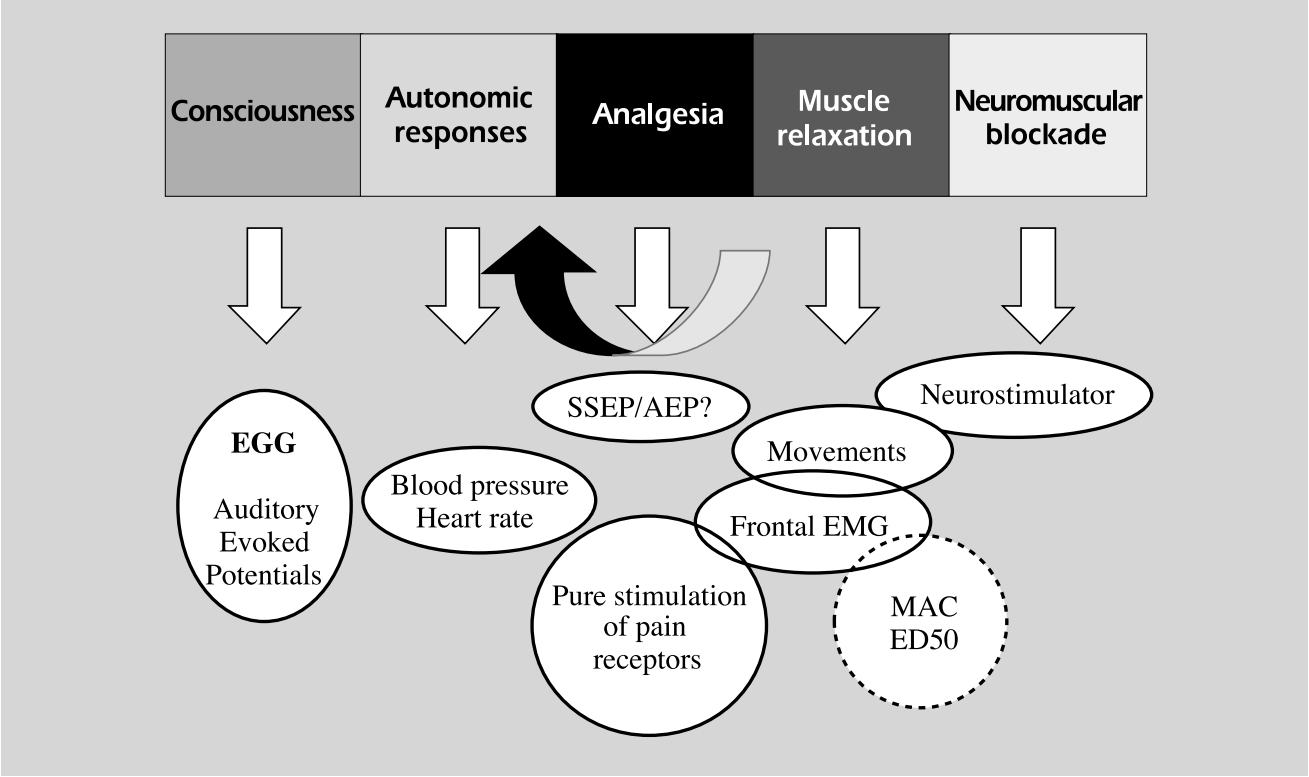

Figure 2. The concept of modern anaesthesia can be based on a group of parallel effects; theoretically, each of them can be monitored by special techniques. (SSEP: Somatosensory Evoked Potentials; AEP: Auditory Evoked Potentials; EEG: Electro-encephalogram; EMG: Electromyogram; MAC: Minimum Alveolar Concentration; ED50: Median effective dose)

lid information derived from the EEG, making the final result unusable. A single number might only give us an estimate of the degree of hypnosis, but would not offer any predictive value about changes in the patient's conditions.

There is an additional point that deserves special mention. When the information derived from the EEG or hypnosis monitors is compared with clinical signs such as withdrawal movements or elevation of heart rate and blood pressure, we might be inclined to think that all this indicates nociception. These findings may have very little to do with consciousness. Therefore, monitoring systems that have been designed to measure the degree of hypnosis, and only that, do not have the capacity for prediction in respect of other central components involved in the anaesthetic process. There are no monitors of movement, frequency or other aspects that indicate nociception.

Peter Glass and his colleagues studied memory, degree of sedation (OAA/S) and the levels of the bispectral index derived from the EEG during sedation with isoflurane, propofol, midazolam or alfentanil in healthy volunteers[4]. They demonstrated that, by increasing the concentrations of isoflurane, midazolam or propofol, memory disappeared in conjunction with falls in BIS. The probability values of predicting loss of consciousness from the BIS were within a range of 0.89 to 0.98. In the study, the probability of any recall for BIS values of 60 was extremely low. This study provided a firm scientific basis for BIS monitoring when hypnotic drugs are used. Later, Johansen et al.[23] concluded that the true benefit of BIS monitoring is obtained only when its values during surgery are maintained between 50 and 65. Nowadays, when the value of BIS monitoring is known, it is accepted that it helps the clinician to administer the hypnotic medication, avoiding unnecessary overdosing or underdosing of the drug. An overdose might be indicated by BIS values of less than 40-50 and conversely an underdose would display values above 60-65.

The monitoring of hypnosis reduces the con-

sumption of drugs during the maintenance of anaesthesia, a fact which has been described with various hypnotics and two or more monitoring systems in numerous publications (between 13 and 15% decrease for propofol according to the system used) [24-27].

Hypnotic monitoring reduces the immediate recovery time by titrating the hypnotic medication. The first to demonstrate this was Gan et al.[24] who found a response to commands with propofol in four minutes in the monitored group; Song et al.[25] using volatile anaesthetics obtained orientation in monitored patients two to three minutes before that in the unmonitored group. These data were confirmed subsequently by others[26]. It was shown that, in addition to reducing the time to arousal and recovery, the same also applied to the time spent in the recovery room by patients who had been monitored with these systems[28].

There is also evidence of the reduction in hospitalisation costs of patients. Johansen and Sigl[29] undertook an interesting study of costs correlated with patients whose hypnosis was monitored.

Not all studies, however, demonstrate effective improvements with EEG monitoring. Sometimes an incorrect interpretation of the traditional criteria of depth of anaesthesia have meant that, conversely, the use of hypnotics is increased. When hypnosis is monitored, the subcortical components of inadequate anaesthesia (autonomic nervous system signs, motor responses) might not be considered as involved in awareness.

The studies designed to elucidate accidental awareness have assumed particular relevance. If an increase in the quantity of drugs used in anaesthesia occurs when patients are monitored with the systems mentioned, or if there is an increase in episodes of awareness, the standards of clinical practice in the anaesthesia department concerned might be analysed critically.

Even if the consumption of hypnotic drugs is not the principal factor in the use of a hypnosis monitoring system, they might be useful for patients individually. When the hypnotic concentrations of the drugs are adjusted according to individual needs, the side effects of the drugs can be minimised. A study by Nelskylä et al[30] demonstrated the reduction in post operative vomiting in patients monitored by BIS.

Thus, hypnosis monitoring offers many advantages for modern anaesthesiology and many studies indicate a potential for new applications for these systems. There are major clinical aspects that demonstrate their importance for the future. Firstly, hypnotic monitoring enables clinicians to have a better understanding of the concept of modern anaesthesia, based on a group of parallel effects, each one of which can ideally be monitored (Fig. 2). Secondly, the use of the EEG as a measurement of anaesthetic effect might interest anaesthetists in other applications of peri-operative monitoring of brain function.

In line with what we have said previously, the current concept of anaesthesia includes both the cortical components of unconsciousness and amnesia and the subcortical components of antinociception, immobility and neurovegetative stability. Until now it was thought that progressively larger doses of anaesthetic were required to achieve each of these states. We now know that this does not necessarily apply to sevoflurane[31].

The neurophysiological theory of "anaesthetic cascade"[32] explains the action of anaesthetics in the cortex in suppressing the state of vigilance. This can be summarised in six basic steps: the reduction in cerebral flow reduces the stimulus of the ascending reticular activating system (RAS) on the thalamus and cortex; in turn, the RAS also reduces activity on the limbic system and prefrontal cortex, giving rise to the blockade of both retrograde and anterograde memory; a further reduction in RAS activity suppresses the inhibition which this exerts on the reticular nucleus of the thalamus, blocking the thalamocortical pathways, particularly the system of diffuse projection via the GABAergic pathways, thus producing an increase in theta waves. This results in turn in blockade of the thalamocortical reverberations and therefore a reduction in perception, so that the parietofrontal pathways are uncoupled, reducing gamma activity and consciousness. The prefrontal cortex is depressed, reducing waking activity, with the result that the delta and theta waves are increased (thus increasing hypnosis) [31-33].

To obtain depression of the motor neuron in

the anterior horn of the spinal cord and therefore immobilisation, a greater concentration of anaesthetic is required than for the process of suppressing vigilance. However, this is not applicable to halogenated anaesthetics. Recent studies conducted with sevoflurane by Matute et al. suggest inhibition mediated by this gas of both nociceptive and non-nociceptive spinal cord reflexes at anaesthetic concentrations, contributing substantially to immobility during surgery. In publications by the same author, the action of sevoflurane is described as a marked reduction in accumulative depolarisation and a reduction in the reflex potential of the anterior horn of the spinal cord comparable to the reductions described by Silviotti et al.[34] for morphine[35-37].

Reminiscent of the type of waves which can be found after decomposition of the EEG by a fast Fourier transform[38], we observe that the waves that correspond to this power are beta type waves and gamma loops whose origin according to Thompson and Varela (and others)[39-42] has been seen possibly to play an important role in perception. In fact, a so-called "sustained reverberations" system has been proposed, according to which there are some thalamocortical loops which combine all the disperse fragments of perception in the cortex in the form of unified perception, which would be equivalent to the concept of consciousness. According to this model, information emanating from an exogenous stimulus and the relevant information obtained through previous experiences would converge via anatomically distinct systems in layers 1 and 5 of the cerebral cortex, corresponding to the pyramidal neurons. Studies conducted in vitro[40] involving the generation of direct electrical stimuli demonstrate that pyramidal neurons act as comparators, detecting coincident stimuli in time in the synapses of layers 1 and 5. In this way, a direct stimulus of the neuronal body or a stimulus of a thalamic (ventrobasal) relay nucleus produces moderate activation in layer 5 of the corresponding sensory cortex. Direct stimulation of the apical synapses or of a non-specific nucleus of the diffuse projection system (central lateral) reduces cortical activation of layer 1. When both synapses (apical and somatic) coincide or the ventrobasal relay nucleus plus that of the centrolateral diffuse projection are stimulated simultaneously, or in another way when exogenous and endogenous stimuli coincide, the corticosteroid discharges increase considerably and gamma activity is detected in the cortical regions in which this coincidence has taken place. This form of feedback of the corticosteroid pathways ends by uniting the different fragments distributed through the cerebral cortex, producing a reverberation in the form of corticothalamic loops whose frequency is equal to 25-50 Hz. This is supported by the study conducted by Rosen et al[43] in which it is shown that painful or non-painful finger movements or the position of a phantom limb primarily activate the contralateral part of the motor cortex corresponding to the cortical area of the limb (unconscious motor perception) and also the lateral part of the cerebellar lobe. However, painful movements stimulate somatosensory areas and lateral areas of the left "insula" and, bilaterally, the posterior ventrolateral nucleus of the thalamus. This suggests that the insula and the thalamus can involve critical neuronal pathways in the processing of pain relating to the experience which, associated with the feedback from the corticothalamic loops, produce integration of the pain in the cortex during deep hypnosis.

Many of the observations of an elevation in values reflected in the monitoring systems derived from the EEG (BIS, entropy, etc.) might imply that this increase does not occur as a consequence of superficialisation due to lack of hypnosis and that the events that occur there are more related to the appearance of pain (nociceptive events) correlated with a parallel elevation of heart rate for each event, which would be consistent with what is described by Wheeler P et al.[44] and Sleigh et al.[45].

Sevoflurane has been used as an analgesic bolus, which might cause a certain degree of controversy as it might be thought that the mechanism of action of halogenates would tend more to cause a motor block and, at higher doses, a corticosubcortical afferential block than a sensory block. However, studies by Matute et al.[35-37], which highlight the nociceptive inhibition of the spinal reflexes, the reduction in accumulative depolarisation and the decrease in reflex potential of the anterior horn

of the spinal cord, similarly to the effect of opiates, associated with the excellent haemodynamic control of sevoflurane in the surgical response to stress, demonstrate the existence of a purely spinal component of the anaesthesia. On the other hand, and just to note this clinical fact, Uchida et al.[39] describe how a progressive suppression of gamma activity in the hippocampus is observed in electro-encephalographic recordings taken in epileptic patients as the concentration of sevoflurane is increased, which is associated with the disruption of the NMDA-dependent integrator processes by antagonism or neuronal modulation of the NMDA receptor channels (Campagna et al.[46]). In this way, the previously mentioned mechanism of thalamo-subcortical re-entry and of pyramidal cortical dendrites is blocked. Thus the somatosensory areas and lateral areas of the left "insula" and, bilaterally, the posterior ventrolateral nucleus of the thalamus are inhibited and hence the processing of pain relating to the experience (sustained reverberation systems) and associated with the non-feedback of the corticothalamic loops; there would therefore be no integration of pain by the cerebral cortex.

All that has just been described highlights the complexity of the anaesthetic act and the monitoring of the different aspects in its process. Analysing just one of these aspects separately is, at the least, an excessively compromised simplification. We should therefore integrate the various facets that we currently monitor, particularly in the early stages of life, if we wish to consider adequate anaesthesia. Only by performing a multimodal analysis of the monitored organic responses will we be able to approximate to a safe and desirable anaesthetic depth, in which the patient has a sufficient degree of hypnosis, blocking perception and therefore implicit and explicit recall, especially that resulting from the nociceptive effect, without adverse autonomic, endocrine/metabolic and immune responses, and with a sufficient degree of immobility for the ease of conduct of the surgical procedure.

Numerous systems have been developed to prevent the occurrence of intra-anaesthetic awareness or recall which have been shown to be relatively useful in adults and doubtful at the least in children, basically because of the difficulty associated with the development of reliable studies in this respect. However, we must admit that, although we are still at the beginning of the development of these systems, we can now observe their usefulness in the prevention of intra-operative awareness. We shall mention below those which exhibit more scientific and technical relevance and finally those with which there is more clinical experience. However, we must not forget that, when talking of children, their integration with the other systems of conventional monitoring is necessary, apart from those relating purely to cognitive function, whether implicit or otherwise. We will not cease to reiterate the importance of analysing all the different aspects of the data obtained from monitoring, integrating them holistically in an attempt to explain the events that can occur during the anaesthetic process.

Since the appearance of the electro-encephalogram (EEG) and subsequently the processed EEG and the initial concepts derived from its understanding, much has evolved in its application to clinical anaesthesia. The great majority of monitoring systems of hypnotic depth are based on the development of algorithms of greater or lesser complexity derived from the processed EEG signal (Fig. 3).

The electro-encephalogram (EEG) is the recording of electrical activity of the neurons that make up the layer of parietal cells of the cerebral cortex or superficial layer. The ionic interchange between the cytoplasm and the extracellular medium in the neurons that constitute this area of the central nervous system is responsible for the occurrence of electrical activity. It represents the synchronised postsynaptic electrical potentials in the dendrites oriented in the same direction, perpendicular to the cortical surface[47]. The voltage produced must pass through all the anatomical formations until it reaches the metallic electrodes that capture the signal (meninges and cerebrospinal fluid, cranium, subcutaneous cellular tissue and skin). Filtration is performed from the electrodes - in real time or retrospectively - and the signal received is amplified and collected for analysis.

The system of production of action potentials or postsynaptic potentials in the CNS is determined

by the activation of neurotransmitters. There is an extensive transmission network of the components of the central (CNS) and peripheral nervous system, based on intercommunication by means of neurotransmitter molecules which act as connecting nexuses or messengers between millions of synapses that govern brain functions. The neurotransmitters released by a neuron interact with receptors of one or more others, modifying the permeability of their membrane to the different ions; an ion flux is therefore induced which changes the electrolyte equilibrium and finally the voltage (potential difference) existing in the neurons. The production of an inhibitory or excitatory phenomenon or both depends on the nature of this change, the cell structure or the different receptors stimulated and this will represent depolarisation or hyperpolarisation of the cell membranes, facilitating blockade or transmission of the nerve impulse. The EEG is the graphical representation of the spontaneous electrical activity of the cerebral cortex, representing an equilibrium between the excitatory and inhibitory potentials of the parietal cells and to a much lesser extent of the glial cells[40]. We now know from positron emission tomography that the electrical changes reflected in the EEG are due to modifications in neuronal metabolism and that they correspond to the individual's clinical state[49].

The signal is characterised by the presence of wave forms with different frequencies, phases and amplitudes; it is about 100 times less than that recorded in the electrocardiogram and has an amplitude of between 0 and 100 μV. It can be obtained from different zones of the cortex depending on the positioning of the electrodes. The first description of the EEG as a recording of cortical electrical activity was given by Richard Caton in 1875 in animals[50]. In 1929, Berger started to use it regularly, publishing his results in which he described the electro-encephalographic effect of drugs such as scopolamine, cocaine, morphine and barbiturate derivatives[51, 52].

The placement of the electrodes follows an established order according to an international system known as 10/20 and for normal continuous recording 8 or 16 pairs of electrodes are attached (8 channels per hemisphere plus those for reference). The impedance must be reduced by correct placement of the electrodes, must be measured and be less than 50 Ohms (Ohm), usually between 5 and 10 Ohm. They can be configured in a bipolar form in that the electrode of each channel has its own reference, or referentially in that all the electrodes have the same reference.

The amplitude of the signal detected is very small and must be amplified (100,000 times), after which it is filtered to eliminate artifacts (ECG, EMG, electrocautery etc), discriminating the frequencies between 0.5 and 30 Hz.

The processed signal is displayed in the form of waves with certain specific parameters:

- **Frequency:** number of waves per unit of time, measured in cycles per second or hertz (Hz).
- **Amplitude:** height of the wave measured in microvolts (μV).
- **Phase angle:** angle formed by the start of the wave with the iso-electric line measured in degrees (° of circumference which the sinusoid displaces in the time from the start of the wave).
- **Regularity and rhythmicity**.
- **Reactivity:** response which the wave presents to sensory stimuli.
- **Localisation:** discrimination of the focal or general origin of a given wave.
- **Duration:** time during which the tracing is maintained (for a wave).
- **Degree of symmetry.**

Traditionally, the waves are classified according to the predominant frequencies measured in hertz (Hz), grouped into the following distinct bands:

- **Beta** (β) waves from 13 to 45 Hz, of low voltage, subdivided into β1 (13-30 Hz) and β2 (30-45 Hz); they appear in the waking state with eyes open, in a situation of alertness or full activity of higher functions.
- **Alpha** (α) waves from 8 to 13 Hz, dominant in the occipital cortex, and in the remainder of the cortex when the eyes remain closed.
- **Theta** (θ) waves from 4 to 7 Hz, appear when there is a certain cortical depression, as in the

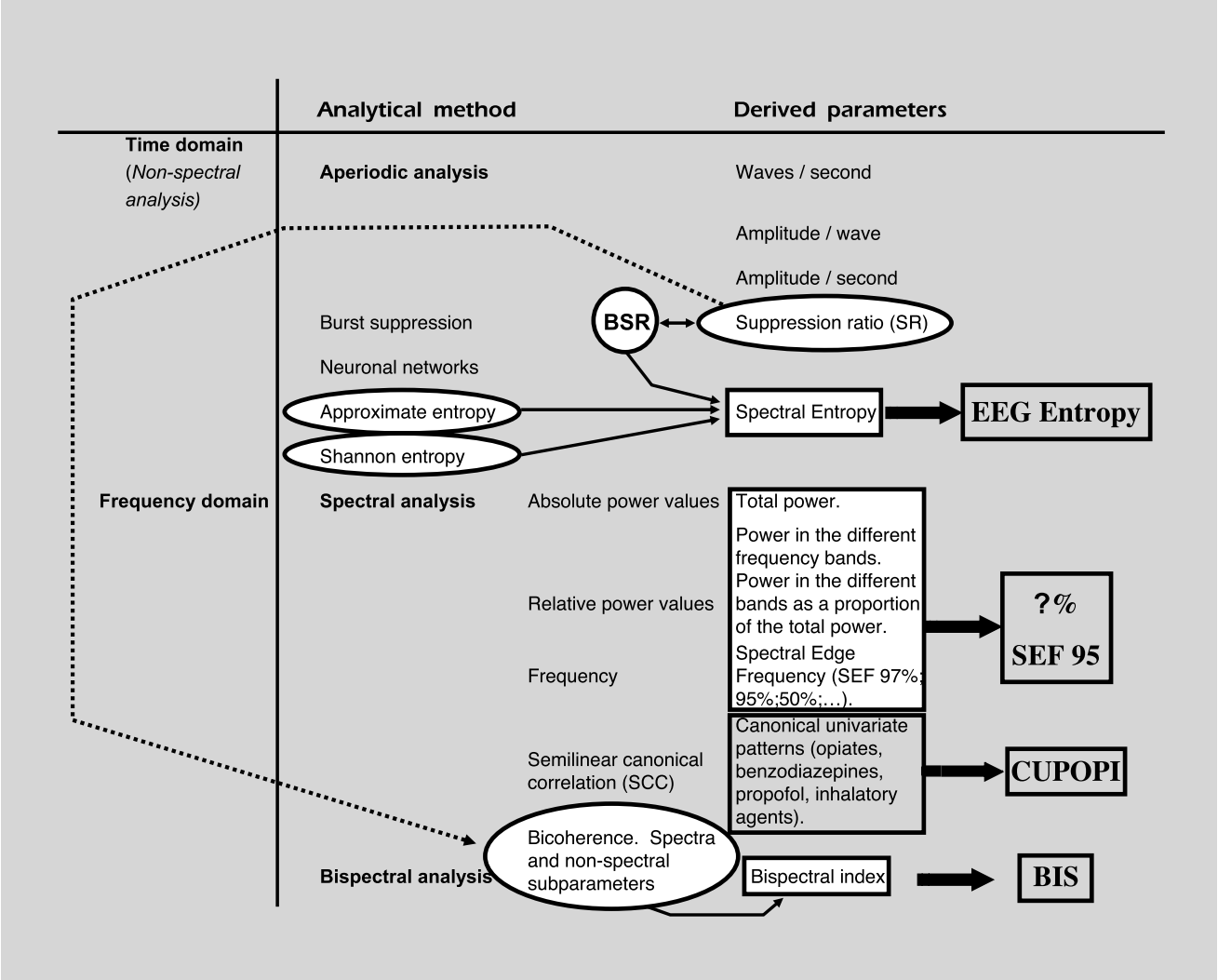

Figure 3. Summary of the principal methods of analysis of the EEG signal. BSR: Burst Suppression Ratio, CUP: Canonical Univariate Parameter; SEF95: 95% spectral edge frequency; %δ: relative power of the delta band; CUPOPI: Canonical Univariate Parameter for opiates; BIS: Bispectral Index (table adapted from Gambús, Shafer)(70).

state of drowsiness and in specific pathological situations.

- **Delta** (δ) **waves** from 0.5 to 4 Hz, which appear in the state of physiological or non-physiological hypnosis, particularly in the occipital cortex; this implies a clear reduction in higher functions; it is characteristic of slow wave deep sleep.
- For some authors there is another group of so-called **gamma** (γ) waves, corresponding to those frequencies greater than 45 Hz that usually coincide with those derived from muscular or cardiac electrical activity or from external artifacts. There are genetic alterations which are manifested in the absence of waves in any specific band(83).

In a normal, healthy, awake, resting subject with their eyes closed, α frequency waves predominate; a predominant pattern of α (occipital) and β (frontoparietal) fast rhythms is displayed, with the presence of only 5-10% slow rhythm waves. The transition from a conscious state to deep sleep shows a clear occipital transition from α rhythms to δ rhythms and a global slowing of the remainder of the cortex.

There are other patterns, in addition to the typical ones, with a characteristic significance and morphology:

- **Spikes:** transient wave of between 20 and 70

msec duration ≤ 1/12 of a second) which differ and stand out from the previous activity.

- **Spike-and-wave complexes:** complexes formed by double waves in which the first has a duration **≤ 1/12** sec and the second **1/5-1/2** sec.
- **K complexes:** these are displayed as a wave with a large-amplitude initial component followed by a high-frequency activity of approximately 2 seconds' duration. They appear in induced superficial hypnosis or in physiological sleep, usually as a result of an auditory stimulus. They may be spontaneous, sporadic or transient[54].
- **Paroxysms or bursts:** These appear suddenly. They are seen as a group of waves that are clearly different from the previous pattern in amplitude, frequency and phase. Among these should be distinguished **multispike-wave complexes** [complexes formed by various spikes (≤ 1/12 sec.) followed by a wave of 1/5-1/2 sec] and **burst suppression complexes**, which appear as a result of a substantial reduction in cerebral metabolism and can be seen after administration of high doses or concentrations of anaesthetic drugs, episodes of severe cerebral ischaemia, severe metabolic changes and brain trauma. They usually indicate a poor prognosis and, depending on the presentation, are a probable sign of brain death. They are depicted as alternating periods of high amplitude electrical activity (multispikes between 8 and 12 Hz) with iso-electric periods (± 5 mV y > 0.5 sec) considered as electrical silence.
- **Spindle:** waves originating in sleep in the central frontoparietal region with a frequency of 14 Hz and an amplitude of <50 μV.
- **Rolandic μ rhythm:** waves related to cognitive activity and intentional movement. Having a frequency of between 7 and 11 Hz shared with the α rhythm, but their cortical localisation is in a more rostral region (it is recalled that the α rhythm is usually occipital). The μ rhythm is attenuated with voluntary movements of the contralateral extremity, while the α rhythm in anterior regions of the cortex decreases on opening of the eyes)[55, 56].
- **λ waves:** lambda waves originate in the occipital region, are sharp (> 50 μV), always have a positive sign and are related to eye movements.

There has been much discussion about the rhythmic activity of the EEG. There are nevertheless neurons with intrinsic pacemaker activity, widely distributed throughout the CNS - cortex, thalamocortical connections, thalamic reticular nucleus, etc. - that exhibit voltage-dependent changes in membrane ion conductance cyclically. The cyclical activity is reflected in the cerebral cortex in fluctuations that appear on the EEG. These "pacemaker" cells are the origin of the majority of afferents of the terminal cells and their relationship with the changes that regulate the level of consciousness has been known for some time[57].

There appears to be complex mechanisms of homeostatic balance involving the participation of the brainstem and high-density areas of cortical processing, with the involvement of all the known neurotransmitters are involved in regulation[57-59]. We know at least two α rhythm pacemakers, one in the cortex itself, particularly occipital, and the other thalamocortical, which projects throughout the cortex.

The activity of the intracortical and thalamocortical connections involved in the processing of information, which are the origin of the β band, are detected in awake subjects in particular in the frontoparietal region[57], hence the importance given to this band in intra-anaesthetic awareness and in the configuration of mathematical algorithms of hypnosis monitoring (the appearance of a high β band ratio implies a tendency to awareness).

The deepest layers of the cortex together with a group of so-called oscillatory thalamic neurons are the origin of δ activity in aroused subjects. The efferents of the ascending reticular activating system inhibit this thalamic activity (δ), while the hippocampus-septum-cortex pathway is a source of θ activity. Two types of δ activity have been identified, **polymorphic** or corticothalamic and **monomorphic** or subcortical. The reticular thalamic nucleus, on the other hand, mediated by γ-aminobutyric acid (GABA), the principal inhibitory

neurotransmitter, is capable of hyperpolarising the thalamocortical neurons and slowing their α electrical activity[60].

Deafferentation of cortical neurons might give rise to a slow δ type activity. It has been shown that lesions of the grey substance do not produce slowing, whereas lesions in the white substance and thalamic regions cause slowing with distinct δ rhythms[61].

Since the studies by Berger, the EEG has been used as a diagnostic tool of neurological disorders and at the end of the 1930s the first publications appeared relating the effect of anaesthetic drugs to changes in the electro-encephalographic tracing[62]. Other authors dedicated works to the study of the effects of anaesthetic drugs on neurophysiological signals[60]. One of the high points of their clinical applications in anaesthesiology is the description by Bickford and Faulconer in 1950 of a series of surgical interventions involving a system of automatic control of the continuous intravenous administration of barbiturates, using the EEG as a system of quantification and adjustment of the effect[63]. Subsequent technological developments have enabled the use of this diagnostic tool to be extended and in the last few years the increased presence of microprocessors in monitoring systems as well as the use of computers in biomedicine has made it possible to adapt the complex tasks of analysis and calculation so that these are assumed by computers.

Given that the signal of the "raw" EEG, which is determined by the difference in electrical potentials between different points of the cerebral cortex, is taken as a basic value, it should be explained that the quantity of information this provides is so great that it would be almost impossible to analyse it if its study were not simplified by the mathematical processing of the fast Fourier transform algorithm(38), which breaks down the signal formed by multiple frequencies into its basic frequencies so as to obtain a spectrum of frequencies. The frequencies between 1 and 4 hertz (Hz) constitute the delta (δ) band, those between 5 and 9 Hz the theta (θ) band, those which appear between 9 and 13 Hz the alpha (α) band, and the frequencies between 13 and 32 Hz (for some authors up to 45 Hz) constitute the beta (β) band. We thus have the quantified EEG and can establish various important concepts such as "spectral power" or quantity of frequencies obtained at one point in the observation; the "spectral edge frequency" (SEF) which determines a cut-off point within which a defined percentage of the total power of the spectrum of frequencies is to be found; we thus obtain the so-called SEF 95 or spectral edge frequency comprising 95% of the total spectrum of frequencies (95% of the total power of the processed EEG), the "delta wave percentage" understood as the relationship between the "total delta power" and the "total power of the processed EEG" expressed as a percentage (this value is key in anaesthesia because it is this frequency band which is predominant in the parietotemporo-occipital region in obtaining deep hypnosis); etc.

All EEG signal monitoring systems take the fast Fourier transform[38] as a basis for analysis and even if the calculation algorithm of the bispectral index (BIS) has not been completely defined (it has not been published in its full extension), Rampil[21] describes the basic concept of its analysis as phase coupling in the measurement of the extent and variation of the phase in the series of the spectral frequency analysis [phase correlation between the waves obtained (frequencies, amplitude and phases - bicoherence -)].

Another of the properties of sinusoidal waves is the phase, in other words the angle defined by the starting point of the wave form relative to the origin. By analysing and integrating the phase, it is possible to determine the degree of harmonisation that may exist between two wave form and therefore to define relationships, including non-linear ones, between the waves. This makes it possible to evaluate the coherence between wave forms. The bispectral index is a parameter derived empirically from the measurement of coherence between components of the quantitative electro-encephalography of the frontal lobe and can be considered a measurement of the hypnotic effect of anaesthetics in the cerebral biophase.

The relationships between the neuronal impulses are probably not simple and do not exhibit a linear correlation. The distribution of the amplitudes in the spectrum does not follow a normal distribution and it is probable that, just as there are

non-linear relationships between neurons, so these are reflected in non-linear relationships between different wave forms. Bispectral analysis makes it possible to quantify both deviations from normality and non-linear relationships of the quadratic type, in other words when a dependent variable is the result of squaring each of the values of the independent variable. Therefore, the bispectral analysis makes it possible to quantify the interaction between all the components constituting the EEG signal, including the phase of the sinusoid[64]. It includes the possibility of characterising the interdependences that probably exist between the EEG waves.

The bispectral index in its current version is a conglomerate of subparameters extracted from the EEG following the application of a time domain analysis, spectral analysis and bispectral analysis, modulated so as to correlate them optimally with the concentration of hypnotic administered and also with the clinical responses associated with hypnosis. These responses are the presence or absence of consciousness, the different levels of sedation or the capacity or otherwise to develop memory at different concentrations of hypnotic drugs. This is an indicator whose value ranges from 100 to 0. Values close to 100 are associated with consciousness and absence of hypnotic effect; values close to 0 would indicate the maximum depression induced by hypnotics, the value being independent of the hypnotic drug used. It is considered that below 50 the probability that the patient is conscious is minimal[65].

Entropy is a physical concept relative to the quantity of disorder of a system. It was defined on the basis of the second principle of thermodynamics given by Clausisus in the 19th Century from which it is inferred that "the variation in Thermodynamic Entropy of an adiabatic - closed - system is the relationship between the temperature and the energy released in the form of heat transferred to the molecules." It tends to increase with time and is the measurement of disorder (chaos) of the system. The concept was refined by Boltzman, defining it as the product of a constant "K" by the logarithm of the number of independent microstates available for a system. Shannon defined the concept of "logical entropy" in his mathematical theory of communication[66] and considered the measurement of dispersion, variation or diversity of the data in a series. Recently, this theory was applied by Johnson & Shore[67] to the spectral power of any signal. Confining ourselves to the EEG and applying Shannon's normalised theory, entropy might measure for us the possible statistical regularity of the EEG signal and also would reflect the flow of intracortical information[68]. Thus, the changes in the EEG pattern from irregular to more regular as the patient loses consciousness are interpreted as a reduction in EEG entropy.

In view of the fact that the complexity of the EEG is correlated with the level of brain activity, various algorithms based on the concept of entropy can be applied as descriptors of the EEG signal. The spectral entropy[69] which analyses the disorder in the frequency space - domain - (knowing the frequency content of the EEG) and the approximate entropy of Kolmogorov-Sinai, which analyses the disorder in the time space - domain - is based on the knowledge of the previous signal to predict the EEG signal.

If the concept of entropy is applied to the brain, the premise is that when the mind is active (conscious stage), the state of the brain is more complex. Given that the EEG signals reflect the underlying state of brain activity, this is reflected in greater relative "irregularity" or complexity of the EEG signal data or, put a different way, a low level of order. When the state of consciousness is gradually lost (for example, in anaesthetic induction), brain function decreases and its signals become more ordered and regular. The logical result is to consider these changes to be reflected in the EEG signals with a relative reduction in irregularity or complexity of the data obtained depending on the electrical signal or, put a different way, an increase in the global order will be produced (conscious state).

In terms of anaesthesia, the references appear to indicate that the EEG signal data contain more order, less irregularity and a lower entropy at high concentrations of any anaesthetic drug, in other words a greater depth of anaesthesia, than at lower concentrations

Figure 4. Representation of the circle of Willis and Doppler insonation

(more disorder and irregularity and less entropy).

The possible success and utility of this monitoring system in paediatric anaesthesia is due to the fact that entropy is a measurement with an invariable scale, independent of the scale of frequencies and amplitudes of the signal. We know that the absolute frequencies of the EEG rhythms vary from one patient to another and therefore those techniques which use defined measurements in terms of an absolute frequency scale can experience a large interindividual variability.

As mentioned previously, an essential component of adequate anaesthesia is haemodynamic stability. It would therefore be absurd not to monitor the parameters that define this concept as part of the monitoring of anaesthetic depth. Heart rate and blood pressure provide us with a rich source of information which, combined with the previous monitoring systems mentioned, can help us to understand the events that occur in these systems. These variables associated with the monitoring of end-tidal CO2 help provide information about cerebral blood flow which can be measured directly within the CNS (brain) by non-invasive techniques. The determination of cerebral blood flow and its clinical application can provide clearer information about the existence or otherwise of cerebral metabolic changes (due to a number of reasons) or a greater or lesser degree of hypnotic depth.

The transcranial Doppler (TCD) is a non-invasive technique for monitoring the cerebral blood flow velocity in the principal intracranial arteries, particularly the arteries of the circle of Willis (Fig. 4).

It is a relatively simple, economic, non-invasive, portable technique that does not emit radiation and provides us with continuous monitoring of the cerebral haemodynamics. It requires training and experience, patience and a correct knowledge of the anatomy of the intracranial vessels.

The generation of images by ultrasound is based on the emission of waves with different frequencies and the reception of the acoustic echo produced by the reflection and dispersion of these waves in the tissues[71, 72].

TCD is based on the Doppler effect, described by Johann Doppler in 1842, according to which when an ultrasound (US) beam of determined frequency (Fo) reflects off a point in movement (in this case, the erythrocyte), the wave frequency received differs from that transmitted. This change in frequency (ΔF) is proportional to the velocity of the erythrocytes (V) and also depends on the angle of incidence between the US beam and the blood vessel (θ), the emission frequency of the transducer (Fo), and the transmission velocity of sound in the medium (C)(72).

$$\Delta F = 2 \bullet Fo \bullet V / C \bullet \cos \theta \rightarrow DF = V \bullet \cos \theta$$

Given that the emission frequency of the transducer and the medium are constant, ΔF depends only on the cosine of the angle θ (of the vessel) and the cerebral blood flow velocity that we wish to discover. This formula is used to calculate the blood flow velocity to be determined from the

changes produced in the Doppler frequencies.

Once received, the signal is processed to give us a new audible signal and a visual image (the Doppler velocimetry wave). A series of values are quantified from this wave, such as peak systolic flow velocity (Vs), end-diastolic flow velocity (Vd) and mean flow velocity (Vm).

The intensity of the signal is proportional to the cosine of the angle of insonation so that the maximum velocity is obtained when the angle of insonation is 0° and is in line with the arterial flow. Therefore, the highest velocity obtained is the one we evaluate, as this is the one obtained with the best angle of insonation.

The mean velocity is calculated automatically and can be increased by an absolute elevation of cerebral blood flow (CBF) or by a reduction in the area or section of the vessel studied, according to the formula:

$$CBF = V \bullet \text{area of the vessel}$$

If the arterial diameter remains constant, the CBF is proportional to the recorded velocity.

Vm can be reduced after a stenotic region or absent if there is occlusion of the vessel without the collateral circulation.

Certain indices can be calculated from these Vs, Vd and Vm values which show the haemodynamic behaviour at the point of study. These points are the resistance index (RI) and the pulsatility index (PI):

$$IR = \text{Systolic velocity (Vs)} - \text{Diastolic velocity (Vd)} / \text{Systolic velocity (Vs)}$$

$$IP = \text{Systolic velocity (Vs)} - \text{Diastolic velocity (Vd)} / \text{Mean velocity (Vm)}$$

Conceptually, pulsatility can be described as the degree of variability of the velocities over the cardiac cycle. The relative difference of velocities depends essentially on the vascular resistances of the brain. The most widely used index is the PI, which reflects the peripheral resistances distal to the region of tissue irrigated by the vessel under study. These indices are independent of the angle of insonation(73).

The morphology of the curve also provides information.

An increase in PI occurs due to an increase in cerebral vascular resistance (CVR) secondary to an increase in intracranial pressure (ICP) or hypocapnia, although in some cases it can be due to cardiac changes (aortic insufficiency) or bradycardia. A decrease in PI is due to a decrease in CVR in vessels that have arteriovenous malformations or vasodilatation distal to stenosis.

The technique is performed using an ultrasound apparatus consisting of an emitter-receiver pulsed at 2 MHz which allows insonation of the depth required.

There are three routes of access for the study: the transtemporal route, the transorbital route and the transforaminal.

The first task involves localising the "cranial window" that allows the US beam to enter. The most important are:

- **Transtemporal:** most frequently used. Localised in the depression of the temporal squama, above the zygomatic arch, anterior and superior to the tragus, at approximately the height of the external canthus of the eye. It enables the middle cerebral artery (MCA), the internal carotid artery (ICA) and the posterior cerebral artery (PCA) to be identified.
- **Transorbital:** rarely used. In the direction of the midline with the eyes closed, with a transducer of 3-7 MHz at minimum power. It enables the ophthalmic artery (AO) and the internal carotid artery (ICA) to be identified.
- **Transforaminal** (through the foramen magnum): with the patient's head flexed, the probe is positioned medially, 1-2 cm below the palpable margin of the occipital bone, in the direction of the occipital foramen. It enables the vertebral artery (VA) and basilar arteries (BA) to be identified.
- **Transfontanellar:** in neonates and infants with a permeable anterior fontanelle, it enables the anterior cerebral artery (ACA) to be identified.

The second step is to identify the different intracranial arteries and optimise the signal detected. For this, the following criteria must be taken into account:

- Window used and direction of the probe.
- Insonation depth, represented by the distance between the surfaces of the transducer and the insonated vessel, measured in mm.
- Direction of flow. If the blood flow of the artery being investigated is directed towards the transducer, the recording will be positive relative to the baseline; if the artery displays a flow away from the transducer, it will be negative in relation to the zero flow line
- Outline and morphology of the curve.
- Response to compression of the carotid artery.

The MCA provides us with better information about the global cerebral blood flow[74]. It is also the easiest to locate and the one which exhibits the least inter-assessor variability. Insonation is performed through the transtemporal window. It is localised at a variable depth of between 30-60 mm with a direction of flow towards the transducer (positive). It must be studied from its most peripheral position to the point of bifurcation, taking the maximum obtained as the value. A gentle and rapid compression of the homolateral primary carotid artery confirms its localisation by revealing a reduction in the systodiastolic amplitude followed by a physiological increase when the compression is released.

If the study is continued at a greater depth (45-70 mm) a biphasic wave will be obtained corresponding to the bifurcation of the ICA into the MCA and the ACA. The flow in the ACA will be away from the transducer (negative).

At greater depths (55-80 mm), and with the probe pointing backwards, signals will be obtained from the PCA. It is important to be aware that the measurements obtained from a specific vessel can vary between individuals or over time in the same subject because of the technique used by different assessors.

The mean velocities and the indices of the different arteries have been quantified by different authors in adults and children[71-73], with differences being found in relation to age. In the first 20 days, the flow velocity experiences a rapid increase with higher velocities in neonates of greater weight and gestational age. This increase continues more slowly, reaching peak values between five and seven years of age which are three to four times higher than at birth. From the age of 6 years onwards, the values start to decrease slowly to 70% of the maximal values at the age of 18 years.

The resistance index is highest in the neonate (between 0.69-0.72), falling in the first year of life to values of 0.55-0.6 and remaining practically constant until adulthood. The pulsatility index (PI) also has higher values in the neonate (between 1.1-1.2), falling from the age of three months to 0.9 and from one year of age it is between 0.75-0.85 [75, 76].

The velocities which we detect, if the diameter of the vessel remains constant, will depend on the CBF. Therefore, all those physiological factors that modify the CBF (age[75, 76], PA Co2, PO2, haematocrit[79], blood pressure[80], temperature[81], sleep[80, 81], **level of consciousness**[82], circadian rhythm[79], **anaesthesia**[83-88], etc.) will affect the mean velocities and the resistance indices. From a practical viewpoint, the two most important factors are **Pa CO_2** and the **haemodynamic situation**.

Pa CO_2 is considered the most important factor in the regulation of vascular tone and CBF. In moderate hypocapnia (Pa CO_2: 30-35 mmHg) Vd and Vm decrease slightly with an increase in the resistance and pulsatility indices (RI and PI). If Pa CO_2 is less than 30 mmHg, Vs is also affected. Hypercapnia increases Vd disproportionately in relation to Vs, decreasing the RI.

In a stable haemodynamic situation, CBF remains constant over a wide range of mean arterial pressures (cerebral autoregulation)[89]. Outside this range, or in patients with a loss of cerebral autoregulation, the fall in blood pressure produces a reduction in cerebral blood flow and mean velocities (Vm).

PO_2 affects CBF to a lesser extent, an increase in CBF occurring in severe hypoxaemia.

Haematocrit, the main factor responsible for blood viscosity, is affected in inverse proportion to CBF velocity.

The level of consciousness has a prominent effect on the CBF, particularly in the infant, as marked increases are occasionally observed in velocities on arousal [71-73].
The existence of different patterns of cerebral blood flow have been described in the anaesthetic process with the use of different drugs[83-87] and although there is a certain correlation with electrical brain activity[80-82], studies comparing the patterns of change of monitoring systems such as entropy and BIS with transcranial Doppler have yet to be conducted.

When TCD is performed, the following data must be recorded for its correct interpretation: age, Pa CO_2, PO_2, blood pressure, temperature, administration of inotropic agents, administration of central nervous system (CNS) depressant drugs, ventricular drainage or leakage of cerebrospinal fluid (CSF) and ICP.

The changes in cerebral haemodynamics are reflected in the pattern obtained in the Doppler sonography.

The most characteristic patterns are:

- **High resistance pattern (→Vm, →PI):**
  This is characterised by low mean velocities and a high pulsatility index. A change in the sonogram is highly indicative, revealing a rapid increase and decrease in the systolic component, each differentiation in systole and diastole, and an increase in the difference between the maximum systolic value and end-diastolic velocity (Vs>>>Vd).
  Causes: Reduction in cerebral perfusion pressure (CPP), generally due to an increase in ICP as a result of oedema, space-occupying lesion or hydrocephaly.
- **High velocity pattern (→Vm, PI normal or →):** characterised by a high mean velocity; PI can be normal or decreased. On the sonogram there is less difference between the maximum systolic peak and the end-diastolic velocity, which is increased.
  Causes: given that the Vm obtained depends on the CBF and the area of the insonated vessel **(Vm = Q / vessel area),** the increase in Vm can be due to an increase in CBR (hyperaemia) or a decrease in the calibre of the vessels (vasospasm or vasculitis).
  a) **Hyperaemia** occurs in situations of hypercapnia, rebound after hypoxic-ischaemic or traumatic insult and in infectious processes. In general, in hyperaemia Vm remains below 120 cm/sec; the pattern is usually symmetrical and loss of the dicrotic notch is common.
  b) The increase in Vm due to a reduction in the calibre of the vessel occurs in **vasospasm** secondary to a subarachnoid haemorrhage or to a reduction in the calibre of the vessel in vasculitis (tuberculous meningitis), or in the case of stenosis observed in sickle cell anaemia. In vasospasm, the velocities are usually above 120 cm/sec. with values even greater than 200 cm/sec., indicating severe vasospasm, which may be asymmetrical. **Lindegaard's index** is used to differentiate vasospasm and hyperaemia, which is obtained as the quotient of the mean velocities detected in the extracranial MCA and ICA. If the value is greater than 3, the calibre of the vessel is considered to be reduced.

Special mention should be made of evoked potentials (EP), which evaluate sensory function (acoustic, visual, somatosensory) and its pathways by means of induced responses to a specific, known and normalised stimulus[90].

The signal is captured by contact or needle electrodes situated in specific normalised localisations of the scalp or other parts of the body. The placement of the electrodes on the scalp, dorsal spine, plexus, nerve, etc., both for stimulation and for recording, as well as the characteristics of the stimuli, are determined by anthropometric criteria and specific techniques defined according to the guidelines *"Standards of clinical practice for recordings of evoked potentials (EP)"*[91] and the "International 10/20 System of the IFSECN" guidelines[92] with their corresponding revisions.

The responses obtained are evaluated against a normal group specific to each laboratory.

EP are recorded on magnetic tape, with valid segments for processing being monitored at all times. The selection of the analysis time depends on the phenomenon being explored and the type of EP. The responses obtained can be presented as graphs of direct expression of the analysis of the signal.

They can be studied for various supplementary investigations to the clinical diagnosis and for monitoring in anaesthesia and critical care, and are divided into[90, 93-96]:

- Visual pathway, which in the broad sense involves procedures for investigating the optical pathway and include the evaluation of the physiology and pathophysiology of the retina by electroretinogram (ERG) and electro-oculogram (EOG), and that of the optic nerve, visual pathways and visual cortex by Visual Evoked Potentials (VEP) in the specific sense.
  - Electroretinogram (ERG). This is a recording by means of electrodes of the response of the retina to a normalised light stimulus. It serves to evaluate the functional integrity of the retina and, more specifically, of the rods, cones or both photoreceptor systems.
  - Electro-oculogram (EOG). This is a recording by means of special electrodes of the voluntary oculomotor activity in following a mobile light stimulus in a set of investigations (Ganzfeld) which must be repeated under photopic and scotopic conditions (previous appropriate adaptations) to obtain Arden's index. It is an indirect measurement of the function of the pigmentary epithelium.
- Visual Evoked Potential (VEP). This is the recording in the scalp of the electrical potential produced in response to a normalised light stimulus and represents the mass response of the cortical visual areas. It is used to evaluate the functional integrity of the visual pathway.
- Auditory Evoked Potentials (AEP). These are the recordings - by means of electrodes - of the response to a normalised acoustic stimulus. They are used to determine the functional state of the auditory nerve, brainstem, thalamus and primary auditory cortex and as a method of objective evaluation of hearing.
  Depending on the response we are studying, which differs in its chronological relationship to the stimulus, they can be divided into: short latency or brainstem AEP (BAEP) - between 1 and 12 msec-, midlatency AEP - between 12 and 50 msec - and long latency AEP - greater than 50 msec.
- Somatosensory Evoked Potentials (SEP). These are recordings of the electrical potentials generated principally by the coarse fibres of the somatosensory pathway in the central and peripheral portions of the nervous system in response to a reproducible stimulus.
  They can also be divided according to their chronological relationship with the stimulus into: short latency SEP which are produced in the first 50 milliseconds and which are the most constant and therefore the most widely used clinically, midlatency SEP and long latency SEP with much greater variability, making their clinical use more difficult.
- Long latency endogenous evoked potentials - cognitive potentials - (P300) (EEP). These are generated in the cerebral cortex by an infrequent stimulus which is presented randomly according to the "odd-ball paradigm" and used as a measurement of cognitive function. Depending on the stimulus used, there are visual (VEEP), auditory (AEEP) or somatosensory (SEEP) EEP and Contingent Negative Variation (CNV).
  EP monitoring has different clinical uses, primarily in ICU; for the functional evaluation of the different sensory pathways in comatose patients or those with severe neurological/muscular changes; and in the operating theatre to define in situ the integrity or otherwise of the different sensory pathways involved in each type of intervention and to monitor the depth of anaesthesia.
- Multimodal evoked potentials (MMEP). This involves the exploration of various sensory pathways in the same patient.
- Evoked potential mapping (EPM). This is the graphical recording on a diagram of the scalp

of the response produced at different points in the cortex to the different stimuli mentioned above, analysed and presented according to a scale of power of the responses. It requires a specific signal analysis programme and somewhat different recording conditions (larger number of recording electrodes and channels or amplifiers).

At present, many centres use evoked potentials routinely to monitor the auditory system, particularly when hearing is at risk due to an otological or neurosurgical procedure on the cerebellopontine angle or when there is a risk of lesion in surgery of the posterior fossa or aneurysm of the vertebrobasilar system. A sound of short duration can be recorded from the internal ear, the auditory nerve and the pathways through the brainstem and cerebral hemispheres. The time which the sound takes to reach the tympanic membrane and the electrical activity from each of these structures can be recorded as follows: for the inner ear immediately, the auditory nerve 1.5 milliseconds, the brainstem 2.5 milliseconds and the cerebral hemisphere 10 milliseconds.

Auditory evoked potentials can be used in tumours of the pontine angle to prevent damage to hearing due to the fact that monitoring can alert the surgeon at the earliest opportunity to any change that might indicate a deterioration in the patient's hearing.

They can also be used in combination with sensory evoked potentials to detect brainstem ischaemia during surgery on an aneurysm or a basilar arteriovenous malformation. The loss of potentials is a reliable indicator of a poor prognosis. Unfortunately, these techniques fail to detect ischaemic events significantly in about a quarter of patients.

General anaesthesia has aroused discussion about the effect on the auditory evoked potentials, however there appears to be a need for an explanation of what is a correct analyser of anaesthetic depth[93, 97-99]. They are good indicators of the balance between the destabilising effect of the surgical stimulus and the depression induced by anaesthetic overdose[100] and midlatency auditory potentials can be a very useful indicator of the state of hypnosis during anaesthesia[101]. At standard concentrations or doses, inhaled anaesthetics, propofol, opiates, benzodiazepines and ketamine do not have a depressant effect on the waves that abolishes the predictive value of the system[102-105].

Visual EP obtain signals emanating from the retina that reach the occipital cortex and which are recorded by electrodes placed on the scalp in the occipital region. The stimulus during anaesthesia is administered by means of light emitted by glasses or contact lenses. This monitoring can be used in surgery of lesions around the optic chiasma. The sensitivity is limited and there may be a lesion of the optic chiasma without appreciable changes in the evoked potentials, in addition to which visual evoked potentials are very sensitive to anaesthesia[106], temperature and blood pressure, so that this type of monitor is not specific to visual acuity and has not been shown to be of use in warning of the risk of intra-operative lesions.

Somatosensory EP are an electrical response recorded in the contralateral somatosensory cortex to a spinal stimulus emanating from a peripheral nerve. The function of a peripheral nerve, the spinal cord (posterior column), the brainstem, the medial lemniscus and the contralateral somatosensory cortex can be evaluated. The somatosensory evoked potentials can be used to detect a lesion in a specific area of the spinal marrow by evaluation of the waves generated at the cortical level and can also act as a non-specific indicator of adequate oxygen transportation to the brain. The waves generated by the evoked potentials have two important components that must be considered: latency and amplitude.

Latency is measured in multiseconds and has to do with the time elapsed between the stimulus and the occurrence of the peak. This can be short (less than 40 msec), intermediate (40-120 msec) or long (120-500 msec). Short latency potentials are generated when the site of the stimulus is local. Latency is affected by the intensity of the stimulus and other factors. Prolongation of latency is usually abnormal.

Amplitude: measured in microvolts, is positive (P) or negative (N) depending on its polarity and is variable but sensitive to abnormalities. In clini-

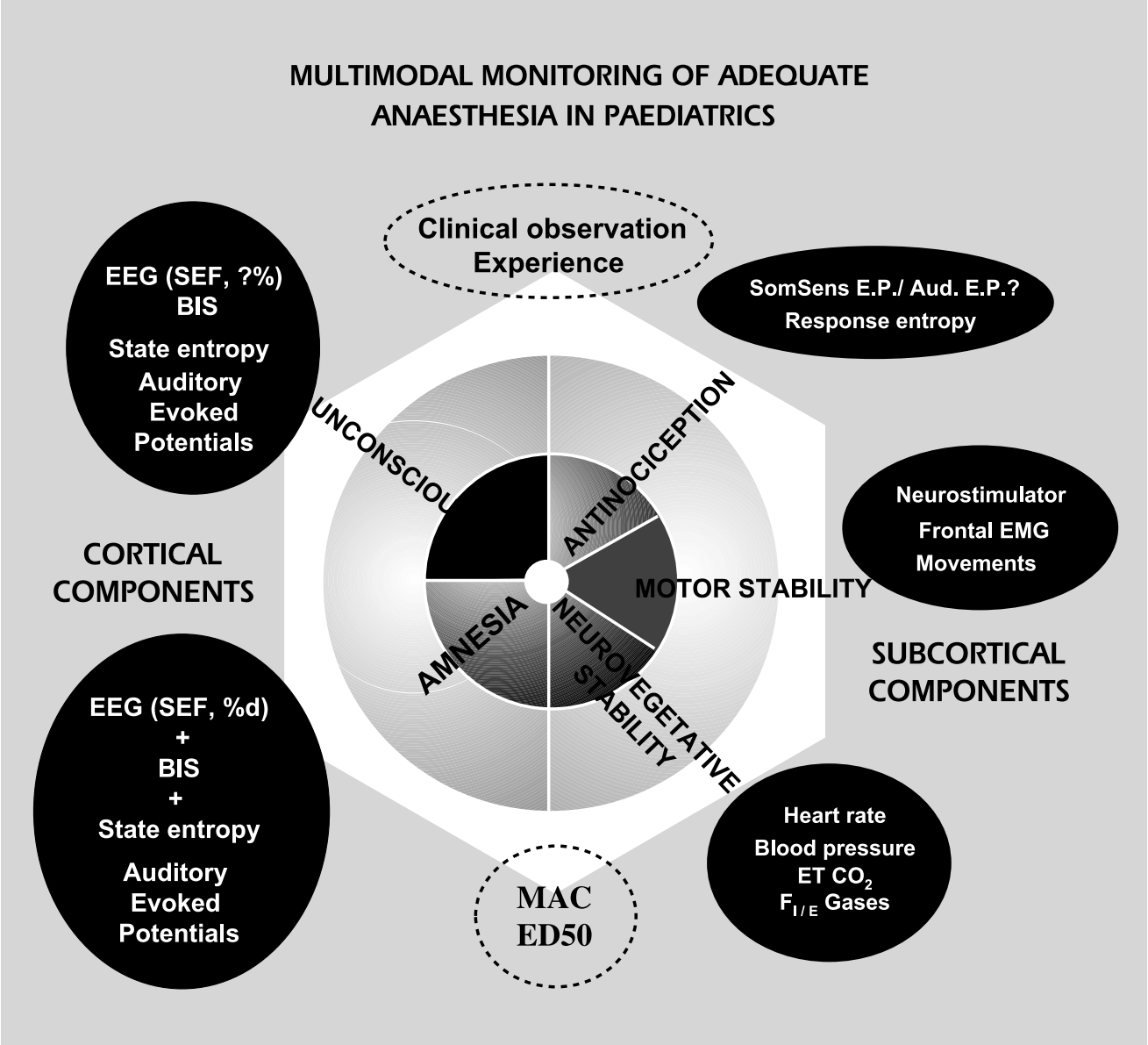

Figure 5. Preventing IOA in paediatric anaesthesia depends on inter- and intrapopulation factors and one or more of the monitoring systems can give the warning signal. The absence of other data and clinical observation will provide the key. (EEG: electro-encephalogram; SEF: spectral edge frequency; %δ: relative power of the delta band; BIS: bispectral index; EMG: electromyogram; MAC: minimum alveolar concentration; ED50: median effective dose; ET CO2: end-tidal CO2 fraction; FI/E Gases: inspired/expired fraction of gases; E.P.: evoked potentials).

cal practice, the median, ulnar, posterior tibial and peroneal nerves among others are stimulated individually. The impulse is recorded via the spinal nervous pathway and the scalp. On some occasions, and where possible, a caudal peripheral nerve is stimulated at the site of surgery for monitoring and a second peripheral nerve rostral to the site of surgery to have a control pattern without neurosurgical responses. Although anaesthetics affect the generation and transmission of evoked potentials, suppression of muscular artifacts with the use of muscle relaxants and the possibility of being able to use stimuli of greater intensity in the anaesthetised patient allow the rapid production of waves that are reproducible, even if they differ from those found in the conscious patient. In an anaesthetised

patient with evoked potentials in the median nerve it is possible to obtain a characteristic wave at the cervical level of N 14 (negative, with a latency of 14 msec). In the scalp, the characteristic of the wave is N20 and P23. If there is an attenuation of the recording in the scalp without any effect on the signal at the cervical level, this suggests a lesion of the brainstem, while if there is attenuation at the cervical level this suggests a lesion of a peripheral nerve or the cervical plexus.

Monitoring of the median nerve for the upper extremity and the posterior tibial nerve for the lower extremity can be used simultaneously. Stimulation of the posterior tibial nerve produces a response that can be monitored in the popliteal fossa, lumbar column and somatosensory cortex(107). Sensory evoked potentials can be obtained in the spinal cord by application of electrodes in the epidural space. The electrodes are positioned under fluroscopic control and are used for direct stimulus of the spinal cord. This has the advantage that they are subject to less depression as a result of the use of general anaesthesia. This technique is used during surgery of an aortic aneurysm when narrowing of the aorta can produce ischaemia in the peripheral nervous system.

The diagnostic criteria for evaluating changes in waves intra-operatively have been difficult to define. Using an average conventional technique, changes in latency of 6 to 15% and a reduction in amplitude of 45 to 50% can occur without changes in postoperative neurological function. In order to reduce the difficulty of determining whether a change in wave morphology is due to surgical or anaesthetic manipulation, changes in anaesthetic concentration and the injection of hypnotic boluses must be avoided during risk periods.

In general, sensory evoked potentials are resistant to anaesthetic-induced depression(108). Intravenous drugs generally have a moderate effect in the initial part of the wave and allow an adequate generation of the wave for rapid evaluation. Barbiturates such as thiopental 5 mg/kg cause moderate or no reduction in amplitude and a moderate increase in latency. Propofol does not cause changes in amplitude and produces an increase in latency. Surprisingly, etomidate produces an increase in wave amplitude (between 200 and 600%) and also an increase in latency. This increase in the wave size has been used clinically to highlight an abnormal small wave and thus enable it to be monitored, which otherwise would not be possible. The anaesthetic gases including nitrous oxide produce dose-dependent depression of the wave[109].

In spinal surgery, scoliosis is one of the main indications for evoked potential monitoring [110, 111]. During scoliosis surgery in specialist centres there may be a lesion of the spinal cord in up to 1.7%, which may result from compression or traction of the spinal marrow, direct trauma from the instrumentation or intra-operative vascular insufficiency.

In motor EP, the somatosensory signals travel primarily along the posterior column of the spinal cord and the lateral portion of the brain stem. A lesion in another region of the spinal marrow or the brain stem, particularly in the efferent pathways, might not be detected by sensory evoked potentials. Motor evoked potentials are promising in intra-operative neurophysiological monitoring which does not involve sensory pathways. However, experience is still limited for them to be established as standard.

In conclusion to the discussion of the complex subject of anaesthetic monitoring in paediatrics, we should highlight various relevant data based on the existing literature, which moreover is still sparse but which contains studies that are worth mentioning[112, 113]. This is due in particular to the enormous difficulty engendered by studies of the different populations included in the excessively broad spectrum of what is generally known as “paediatrics”.

Although many monitoring systems of adequate anaesthesia have been developed, the majority of them of a reliability and sensitivity that is beyond all dispute and extensively tested, the area relating to hypnosis and conscious or unconscious perception of surgical stimuli continues to be a subject for further study. Although hypnotic monitoring is quantifiable by BIS and almost certainly by EEG entropy and other systems in adults and its use is recommended as standard by scientific

societies[114] for the prevention of intra-anaesthetic awareness in risk situations, this still does not appear to be the case in children[115, 116], as there is marked intergroup variability and the systems do not exhibit reliability in children under one year of age [117, 118]. Nevertheless, until we have other safer systems and/or we can perfect or validate the existing ones, we should not abandon the available hypnotic monitoring [119] which, at all events, can on many occasions reveal events of relevance in the anaesthetic process.

As we have mentioned from the beginning, the integration of the different systems of monitoring the various components of adequate anaesthesia, combined with the known systems of hypnotic monitoring, help the professional to ascertain the behaviour of the "child" patient in the anaesthetic process. Similarly, we should not forget that clinical observation by the good professional should also be supplemented by the insight provided by monitoring to obtain adequate anaesthesia.

We propose the diagram of an anaesthetic monitoring algorithm in paediatrics which should help us bear in mind the various factors involved in adequate anaesthesia. A change in one or more of the factors being monitored should alert the anaesthetist to the possible development of intra-anaesthetic awareness in the absence of other clinical data that might be suggestive of this (Fig. 5).

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Physical and mathematical principles of monitoring hypnosis

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ELECTRO-ENCEPHALOGRAM (EEG)

This involves recording the electrical activity emanating from the cerebral cortex via electrodes attached to the scalp. The post-synaptic potentials generated in the cortical pyramidal cells constitute the basis for this recording. Non-specific thalamic centres have been identified as the probable EEG pacemakers. The centres receive stimulation from the reticular substance and their asynchronous firing pattern is reflected in the characteristic random appearance of the EEG. The normal EEG wave is characterised by a small amplitude (20-200 μV) and a variable frequency (0-50 Hz).

The most important studies relating to the effect of anaesthetic drugs on the EEG began around 1950. One of the fundamental characteristics enabling its use in this area is that the changes in signal occur gradually in relation to the dose of the different anaesthetics used. These changes are characterised generally by an increase in amplitude, a slowing of frequency and the appearance of periods of silence. The quantification of these changes by means of mathematical algorithms and statistical analyses has made it possible to incorporate EEG-derived parameters calculated in real time in monitoring the degree of hypnosis during anaesthesia.

EEG signal processing

In current monitors, the analogue signal of the EEG emanating from the cutaneous electrodes is amplified and digitalised to facilitate its electronic processing. The analogue signal collected is "sampled" at regular intervals (sampling frequency expressed in Hz or number of samples per second) so that each wave is defined by a succession of specific positive or negative values depending on the moment of sampling[1].

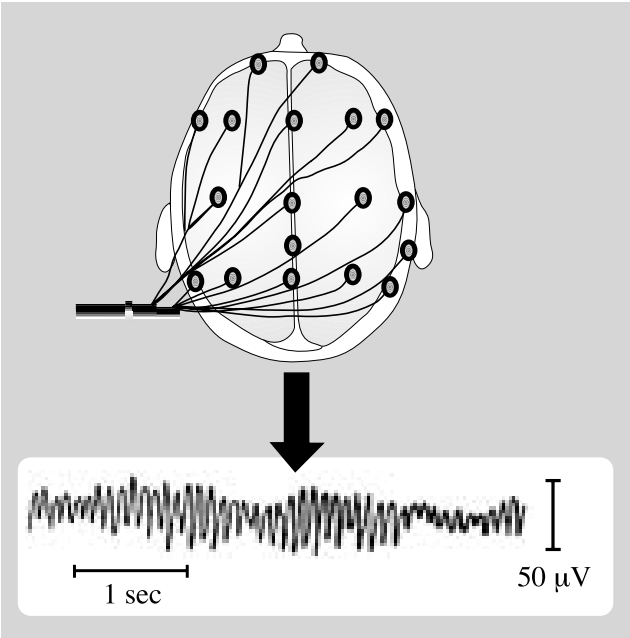

Figure 1. Electro-encephalogram

The sampling frequency is essential when obtaining a reliable digitalised signal since according to Shannon's theorem it must be greater than twice the maximum frequency of the analysed signal.

The maximum frequency of the EEG signal has for a long time been taken as 30 or 40 Hz; however, a frequency of 70 Hz is more realistic[1].

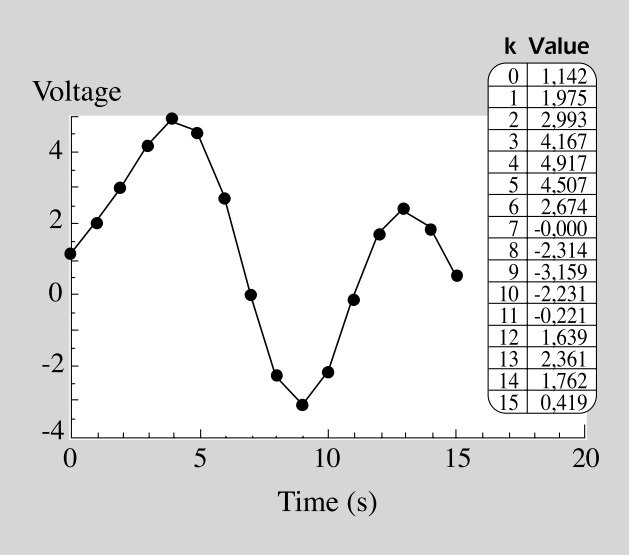

Figure 2. EEG signal processing

If the sampling frequency is small, there is the risk of incorrectly converting a rapid analogue wave into a slow digitalised wave ("flattening" or "aliasing" phenomenon).

After digitalisation, the signal is subjected to a process of artifact recognition. Artifacts that are produced by signals that have exceeded the dynamic range of the amplifier, such as the use of the electric bistoury, can be identified, but the epoch (finite divisions of time of the recording during which the analysis is performed) will have to be rejected since the original data cannot be reconstructed.

Other artifacts can be eliminated from the contaminated signal and the resultant "filtered" signal can be used for the subsequent analysis. These types of artifacts include those which have a signal with a frequency greater than those of the EEG waves, such as electromyographic activity or the signal of the alternating electrical current (50 or 60 Hz). Other artifacts with a frequency within the frequency range of the EEG waves, such as the ECG and artifacts produced by rotary pumps (during extracorporeal circulation), can be eliminated in that they are recognized by their regularity. Other contaminants that are also detectable are interferences produced by the peripheral nerve stimulator or those emanating from an evoked potential stimulator. In conscious or slightly sedated patients, eye movements and blinking create a slow undulatory activity that can be recognised.

Mathematical processing of the EEG

The digitalised and filtered signal is prepared for mathematical processing by different types of analysis. The statistical analysis of the EEG signal is complex to perform since it involves a non-deterministic signal, in other words it is not possible to predict exactly the future values of the EEG. However, it is a stochastic signal, which means that some statistical characteristics of the EEG are predictable (the future values can be predicted only on the basis of an amplitude probability distribution observed previously in the signal). In addition, the EEG signal does not have a Gaussian distribution so that, in order to be able to perform comparisons, non-parametric tests must be used, the ECG signal must be transformed into another with a normal (Gaussian) distribution, or higher order spectral statistical techniques must be used. Transformation of non-Gaussian data by taking their logarithm is often all that is required to enable the EEG to be analysed as a normal distribution. However, logarithmic transformation is not a complete panacea, and when statistical comparisons of the quantified EEG are performed, the data must be examined to check the supposition of a normal distribution(1).

Time domain analysis

The EEG can be considered as an alternating voltage composed of many small undulations (simple sinus waves) superimposed on one another. The time-related changes in voltage can be treated statistically by two types of analysis: a strict statistical analysis and an *"ad hoc"* analysis.

Historically, the first intra-operative applications of EEG analysis used various parameters derived from the descriptive statistical analysis over time: electrical power of the EEG, total digital power, the trio of derived parameters described by Hjorth: activity, mobility and complexity, the crossover frequency (of the iso-electric line of zero

voltage) and Demetrescu's aperiodic analysis derived from the previous parameter. None of these parameters is currently used in the analysis of the EEG signal(1).

The *"ad hoc"* analysis is based on the morphology of the EEG wave and is used to detect burst suppression (BS) patterns defined as periods greater than 0.5 seconds in which the EEG voltage does not exceed approximately ± 0.5 μV and the burst suppression ratio (BSR) is the fraction of an epoch in which the EEG is "iso-electric" (does not exceed ± 0.5 μV).

Analysis in the frequency domain

An alternative approximation to the time domain analysis consists of the examination of the activity of the EEG signal as a function of frequency.

The EEG signal can be processed mathematically and transformed into a set of waves of different frequencies by a Fourier analysis (based on Fourier's theorem: any form of complex undulation which varies arbitrarily in time can be decomposed into the sum of simple sine or cosine waves).

Each simple sinusoidal wave is defined by three components: amplitude (expressed in μV) corresponding to the voltage between the equilibrium point and the maximum voltage, frequency (expressed in Hz), which corresponds to the number of cycles per second, and finally the phase angle, which reflects the starting point of the wave.

The Fourier analysis (FA) generates a spectrum of frequencies which is a simple histogram of amplitudes (or phase angles) as a function of frequency[(1)]. The best way of understanding what the FA does is to compare the EEG with white light which passes through a crystal prism, creating a rainbow (or spectrum). Each colour of the light represents a frequency and the luminosity of the colours the amplitude of each frequency [(1)].

To obtain the spectrum of frequencies of the EEG signal, a discrete Fourier transform is applied [(2)], which transforms the original values x(ti) sampled at times ti into an equal number of complex numbers X(fi) corresponding to the different harmonics of frequency fi:

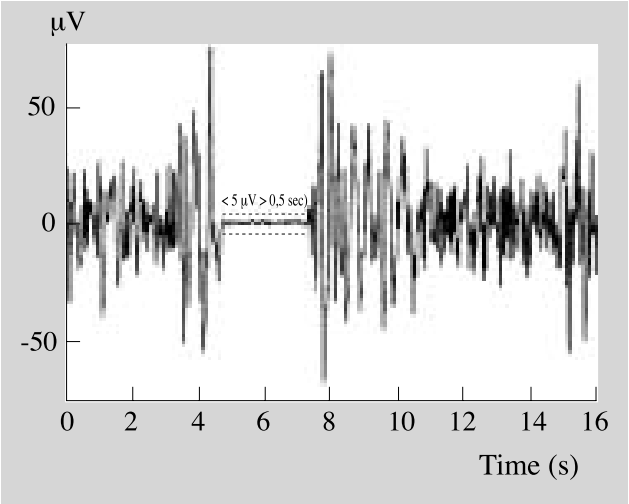

Figure 3. Frequency domain analysis.

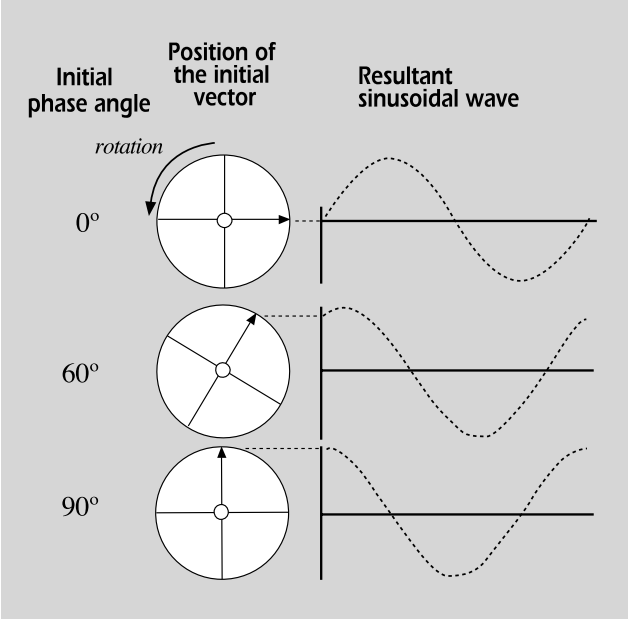

Figure 4.

$$X(f_i) = \sum_{t_i} X(t_i) e^{-i2Df_i t_i}$$

The complex numbers, as the result of the Fourier transform X(fi), are characterised by having two components, the real part and the imaginary part, and in fact are vectors whose extreme is known as a complex affix. The real part of the vector is the projection on the real axis (horizontal axis in the graphical representation), while the imaginary is the projection of this vector on the imaginary axis i (vertical axis in the graphical representation).

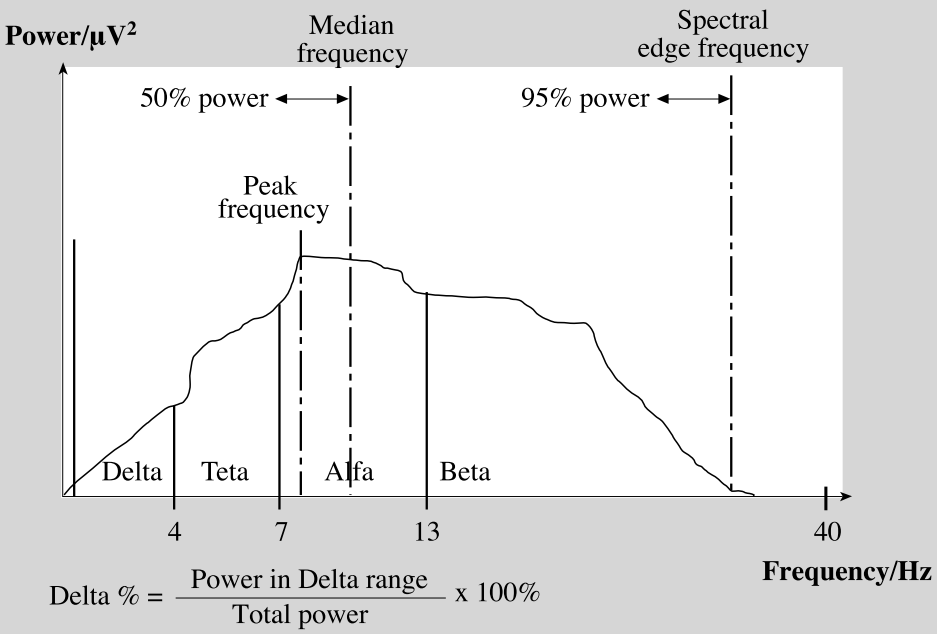

Figure 5.

An example of a complex number would be (+3) + (+4)i, where (3) is the real part and (4)i is the imaginary part, i being equal to the square root of - 1. In the same example, the conjugate of (3) + (4)i is (3) + (-4)i and the opposite (-3) + (-4)i.

In clinical monitors, the EEG is broken down into its frequency spectrum by Cooley and Tukey's fast Fourier transform (FFT) since this algorithm allows an efficient computation of the digitalised data.

The quantitative analysis of the signal obtained by FFT makes it possible to identify generic patterns known as bands and each of these is defined by a range of frequencies: δ = 0.5-3.5 Hz, ϕ = 3.5-7.0 Hz, α = 7.0-13.0 Hz, β = 13.0-30.0 Hz and β2 = 30.0-50.0 Hz.

From the Fourier transform X(fi) of the initial signal x(ti), the spectrum power P(fi) is calculated, squaring the amplitudes of each X(fi) element of the Fourier transform.

$$P(f_i) = X(f_i) * X\hat{}(f_i)$$

where X^(fi) is the conjugate of the complex number obtained X(fi) and * denotes multiplication(2).

A number of parameters can be derived from the power spectrum: total amplitude or power (TP), band amplitude or power, relative band amplitude or power, peak power frequency (PPF), mean power frequency (MPF), spectral edge frequency (SEF), 90 or 95% spectral edge frequency (SEF 90 or 95%) and increased δ quotient. There are other parameters which combine the time analysis with the spectral analysis, such as the spectral edge frequency compensated by the burst suppression ratio (BcSEF = SEF (1- BSR/100)).

Bispectral analysis

While the phase spectrum produced by the Fourier analysis measures the phase of the frequencies obtained in relation to the start of the epoch, the bispectrum measures the phase correlation between the different frequencies obtained.

The physiological significance of the relationship between wave phases is uncertain. In a simplistic model, the greater the phase relationship, the fewer the number of EEG "pacemaker neurons" and under anaesthesia this will be associated with deeper states of hypnosis. The bispectral analysis

enables the Gaussian sources of noise to be suppressed, increasing the signal to noise ratio of the non-Gaussian EEG, and is able to identify non-linear situations which can be important in the signal generation process.

The bispectrum quantifies the relationship between the different sinusoidal components of the EEG. Specifically, the bispectral analysis examines the relationship existing between the sinusoids at two primary frequencies and a modulation component at one frequency equal to the sum of the primary frequencies. The bispectrum B(f_1, f_2) is calculated by multiplying three complex values, the value of the primary frequencies f_1 and f_2 by the value of the conjugate of the modulation frequency ($f_1 + f_2$).

$$B(f_1, f_2) = |XB(f_1) * X(f_2) * X^{\wedge}(f_i + f_2)|$$

where X^ (f_1 + f_2) is the conjugate of the complex value of the modulation frequency and * denotes multiplication. The bispectrum incorporates information about the spectral power and the phase[1].

This product is the core of the bispectral analysis: if in each frequency of the triplet (fi , f_2 and fi + f_2) the spectral amplitude is large (there is some sinusoidal wave for this frequency) and if the phase angles for each of the three frequencies considered are aligned, the final product will be large. Conversely, if one of the sinusoidal components is small or absent, or if the phase angles are not aligned, the product will be small[5].

The unique set of frequency combinations for calculating the bispectrum is a space in a triangular wedge that compares frequency with frequency. The possible combinations outside the space do not need to be calculated because of the symmetry (B(f_1, f_2) = B(f_2, f_1) and because the range of possible modulation frequencies (f_1 + f_2) is limited to frequencies less than or equal to half the sampling frequency[5].

The bispectrum is expressed in microvolts cubed (μV3) since this is the product of three sinusoidal waves, each one with an amplitude (in microvolts). The bispectrum can be normalised and the bicoherence obtained, which is a number varying between 0-1 in proportion to the degree of phase coupling in the frequency triplet concerned.

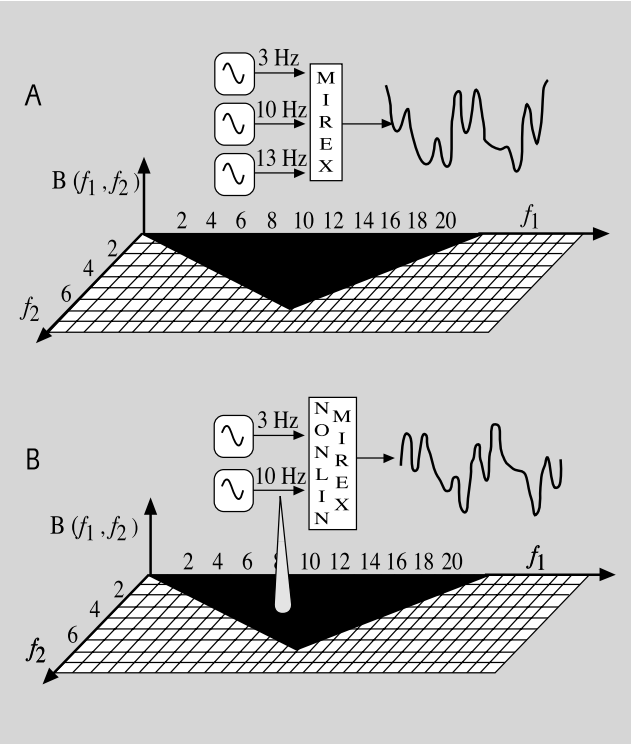

Figure 6.

Indices derived from the quantitative EEG

Bispectral index (BIS)

In the particular case of the BIS (Aspect Medical Systems, MA, USA), the digitalised EEG is filtered to exclude high and low frequency artifacts and divided into 2-second epochs. Each epoch is compared with an ECG model and if pacemaker spikes or ECG signals are detected, they are eliminated from the epoch and the lost data are estimated by interpolation. Eye blinking is detected but epochs contaminated with this artifact are rejected. The EEG baseline is analysed and the contaminating voltage due to low frequencies (low frequency noise from the electrodes) is eliminated.

The BIS (bispectral index) is an empirically derived index that is dependent on the measurement of the "coherence" between the components of the quantitative electro-encephalogram. Because it is

an empirical parameter, it lacks a neurophysiological substrate. BIS provides us with an average of the state of hypnosis/sedation in the last 30 seconds and is not capable of predicting future events.

The calculation of the BIS is based on four basic subparameters of the processed EEG:

In calculating the BIS, two *"ad hoc"* measurements are used based on the morphology of the EEG wave: burst suppression ratio and QUAZI suppression index.

Burst suppression ratio

The burst suppression (BS) pattern is defined as periods greater than 0.5 seconds in which the EEG voltage does not exceed approximately ± 0.5μV. The burst suppression ratio is the fraction of the epoch (2-second period of analysis) in which the EEG is "iso-electric" (does not exceed ± 0.5 μV).

QUAZI suppression index

The QUAZI suppression index was designed to detect the presence of burst suppression patterns in the presence of "errant" baseline voltage. QUAZI incorporates information about slow waves (< 1.0 Hz) derived from the spectral analysis and serves to detect burst suppression activities superimposed on these slow waves which may contaminate the original BSR algorithm by exceeding the established voltage criteria for defining electrical silence. With this derived index, it is possible to detect certain periods of suppression which would not have been detected with the strict criteria of electrical silence (± 0.5 μV) imposed by the definition of the burst suppression ratio.

Relative beta ratio

The parameter derived from the frequency analysis used by the BIS is the relative β ratio, which is defined as log (P30-47Hz/P11-20Hz), in other words the logarithm of the quotient between the sums of the spectral power or energy (wave amplitude expressed as square voltage or power) of two frequency bands: a high frequency band included within the β2 spectrum = 30-47 Hz and another of low frequency = 11-20 Hz (which is included within the two classic spectra α = 7-13 Hz and β = 13-30 Hz).

SynchFastSlow

The parameter derived from the bispectral analysis used for the BIS is SynchFastSlow, defined as log (B0.5-47 Hz/B40-47 Hz), in other words the logarithm of the quotient of the sum of all the peaks of the bispectrum in the range from 0.5 to 47 Hz and the sum of the bispectrum in the range from 40 to 47 Hz.

The BIS number is obtained from the weighted sum of the four subparameters analysed: BSR, QUAZI suppression index, relative beta ratio and SynchFastSlow, to which a multivariate statistical analysis is analysis and which are combined using a non-linear function(1).

The particular mixture of subparameters in version 3.0 of BIS is derived empirically from a prospectively collected database, which includes the EEG and other sedation scales and which represent approximately 1500 administrations of anaesthetics (~5,000 hours of recording) in which a large variety of anaesthetic protocols were used.

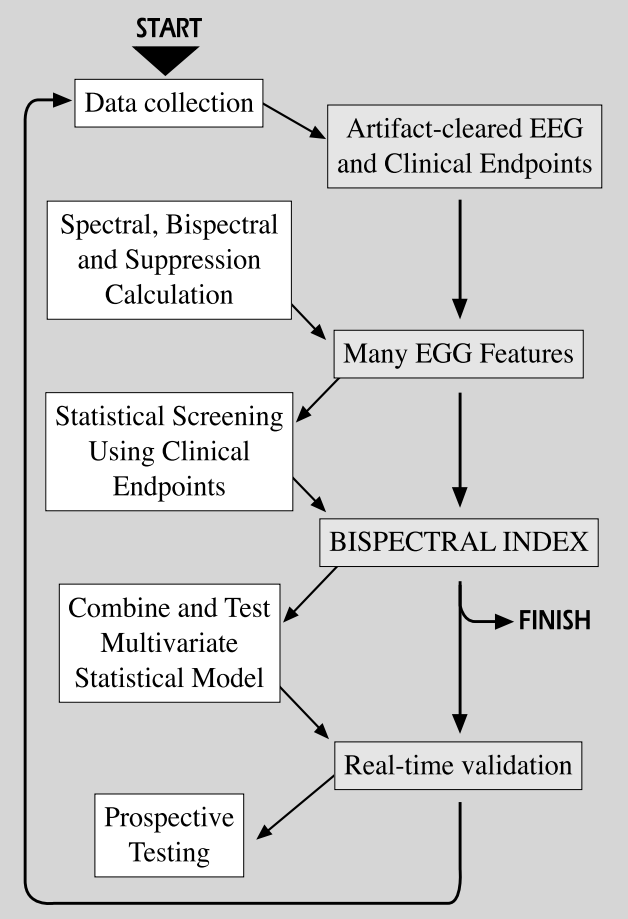

Figure 7.

Each of these subparameters has been chosen to represent a specific range of anaesthetic effect better. SynchFastSlow is better correlated with the responses during moderate sedation or superficial anaesthesia. This subparameter also correlates well with the state of activation of the EEG (excitation phase) and during surgical levels of hypnosis. The relative beta ratio is the dominant parameter in the BIS calculation algorithm during superficial sedation. The BSR and the QUAZI index detect deep anaesthesia.

A scale was developed from version 3.0 of BIS correlating the bispectral index with the degree of sedation/hypnosis.

Bispectral index scale

100	Patient awake
70-100	Mild to moderate sedation. Eduction
70	Little probability of recall
60-70	Mild hypnosis. Mild anaesthesia
60	Limit of unconsciousness
40-60	Moderate hypnosis. Adequate anaesthesia
0-40	Deep hypnosis
0	Iso-electric EEG

PSI (Physiometrix, MA, USA)

With the loss and recovery of consciousness, there are changes in the EEG that indicate that certain brain structures do not fire in unison and certain regions can be inhibited or disinhibited at different times. The PSA 4000® monitor has been developed to provide a multidimensional view of the brain and during its development the information obtained from the different areas of the brain was taken into account to develop an algorithm that could be sensitive to all anaesthetics during all stages of the surgical procedure. In fact, the frontal and posterior regions of the brain change at different times during induction and the recovery of consciousness.

The PSI (Patient Status Index) is an empirical index derived from the quantified EEG. The algorithm which the PSI calculates was developed from three databases[3].

The electrophysiological database of the Brain Research Laboratory (BRL) of the School of Medicine of New York containing approximately 20,000 electro-encephalograms (in processed and raw format) collected from normal subjects and psychiatric, neurological and surgical patients. On the basis of this database, the statistical descriptors necessary to establish the normalisation of the age-dependent distributions of numerous quantitative measurements extracted from all these traces were determined. The normalised quantitative measurements are characterised by a high degree of reliability, specificity, sensitivity and significantly high replicability in tests-retests, and the absence of ethnic or cultural deviation. The BRL database also served to determine the characteristics of the artifacts contaminating the EEG signal and to develop the algorithms necessary for the identification and exclusion of artifacts in real time.

The electro-encephalographic database of a large population of patients anaesthetised with general anaesthesia, using a wide variety of anaesthetics and administered according to usual clinical practice. In each case, the characteristics of the ECG process were extracted under predetermined conditions and in predefined states. These characteristics (approximately 2500 per session) include spectral and bispectral measurements of power and coherence and were used to create a new documented database of the state of consciousness. This new database was explored systematically to identify the subset of characteristics that change invariably with deepening levels of sedation-hypnosis and loss of consciousness and which revert on the recovery of consciousness. The candidate measurements were explored additionally using a multivariate analysis to establish mathematically the classifying functions that estimate the most probable level of consciousness. The classifying functions were evaluated retrospectively to correlate them with the depth of sedation-hypnosis defined by the anaesthetist administering it.

The third database was derived from the EEG traces obtained in 64 procedures in healthy volunteers administered various anaesthetics incrementally (variations of 0.1 MAC until loss or recovery of consciousness). The parameters of the quantified EEG and the clinical scales of this database

were used to calibrate the PSI.

To establish the PSI, a 4-channel EEG is recorded using a specific matrix of electrodes. The position of the active electrodes is: 2 anterior (FP1 and FPZ1), one in the central midline (CZ) and another in the posterior midline (PZ), the earth is connected to the electrode in position FP2 and the references to electrodes located in the mastoids coupled to one another. The signals are sampled with a frequency of 2500 Hz per channel and passed through a bandpass filter of 0.5 to 70 Hz where they are decimated into 250 samples per second per channel in accordance with Nyquist's theorem

The EEG signals are processed using a series of artifact detection algorithms for the identification of artifact-free EEG epochs. An additional algorithm detects the pattern of suppression of the EEG, excluding these data from subsequent analysis algorithms, and these are used to compute the suppression ratio. This ratio can be monitored on the PSA 4000® monitor screen and included in computing the PSI.

When periods of 2.5 seconds of artifact-free EEG are detected, the data contained in 1.25-seconds epochs are transformed into frequency and into power sub-bands including delta, theta, alpha, beta, gamma and total power (0.5-50 Hz).

A series of parameters is derived from the frequency-transformed data for incorporation in the discriminant algorithm (recorded algorithm). These parameters include:

- Gradient of absolute power between the frontopolar and vertex regions in the gamma frequency band.
- Changes in absent power between the mediofrontal and central regions in the beta frequency band and between the mediofrontal and parietal regions in the alpha band.
- Total spectral power in the frontopolar region.
- Mean frequency of the total spectrum in the mediofrontal region.
- Absolute power in the delta band in the vertex.
- Relative power in the slow delta band in the posterior region.

All the parameters used in computing the PSI are transformed (logarithmic transformation) to obtain normality (Gaussian distribution), an essential step to enable multivariate statistics to be used in computing the PSI. Each parameter is transformed into a standard score (Z score) relative to its distribution in a specific reference state and expressed as a probability of deviation from this state. The Z score is a calculated value indicating how many standard deviations a specific value is away from its corresponding mean and is calculated as follows:

$$\text{Puntuación Z} = \frac{X - \overline{X}}{\delta}$$

where X is the value to be scored, X is the mean and δ the standard deviation. The Z score is used to compare series with different means and standard deviations.

The values of these Z scores are those entered for the constant renewal of the PSI value. The PSI is the relationship of the probability that the observation belongs to the reference state to the sum of probabilities that the observation belongs either to the reference state or to a different level of hypnosis.

Finally, two functions modulate the PSI algorithm and these functions are sensitive to the suppression ratio and sudden changes in the level of sedation. To ensure optimum sensitivity, these modulatory functions are self-normalised relative to the patient's baseline.

The PSA 4000® monitor has an additional screen which displays four EEG channels with diagnostic quality to check that each EEG channel has a good signal. The PSA 4000® can be connected at any time, but it is recommended to do so before anaesthetic induction since it is sensitive to the changes in the EEG that occur during the loss of consciousness. If it is started halfway through an anaesthetic case, the PSI number does not appear immediately since it requires a period of 40-60 seconds for the system to equilibrate with the patient.

The PSI number is renewed internally every 1.25 seconds and every 2.5 seconds on the monitor

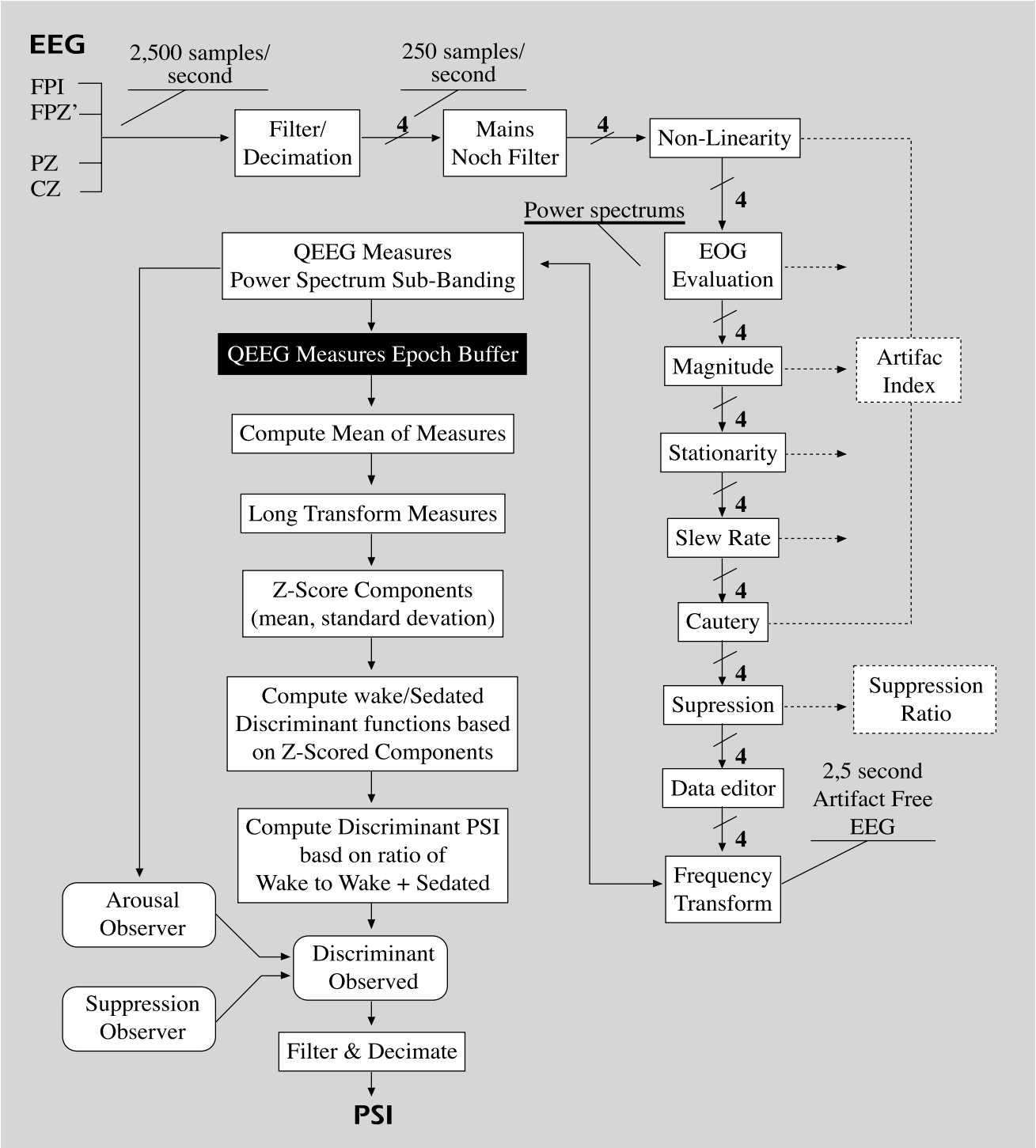

Figure 8.

screen. The PSI tendency is renewed every 6.45 seconds on the monitor screen. The PSA 4000® monitor is approved by the FDA for clinical use in humans, but is only marketed in the USA. The processed EEG sub-parameters used and the mathematical process combining them in order to calculate the PSI are secret.

The PSI scale ranges from 0 to 100 like the BIS scale. 0 represents the absence of cerebral activity and 100 represents absolute consciousness. The level of adequate anaesthesia is within the range 25-50; in this PSI range, no intra-operative recall was detected in the group analysed during surgery.

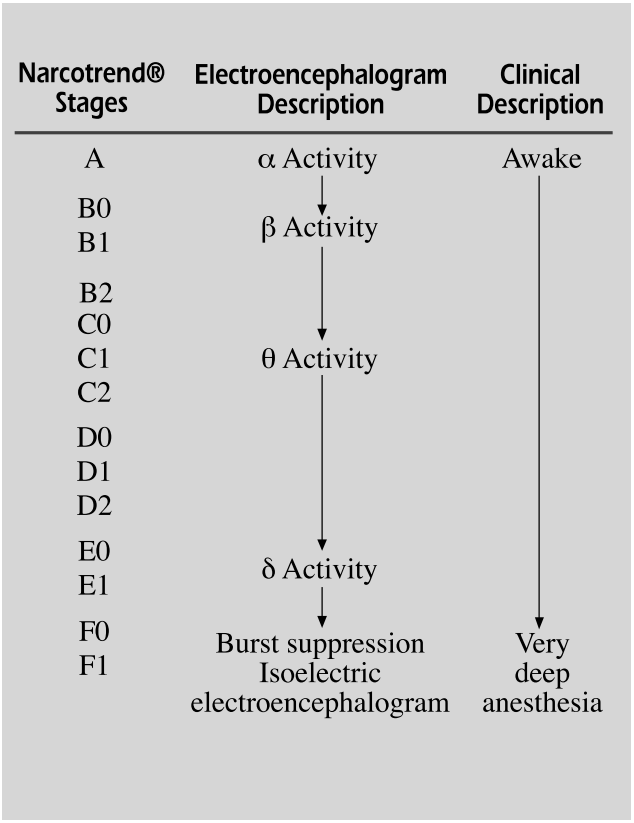

Figure 9.

Narcotrend index

The Narcotrend® monitor (MonitorTechnik, Bad Bramstedt, Germany) presents a classification of the EEG obtained from certain processed EEG parameters to which a multivariate statistical analysis is applied[4-6]. The EEG signal is classified on the basis of the scale proposed by Krugler, which varies from stage A (awake) to stage F (very deep narcosis). Apart from this classification, a numerical index ranging from 0 to 100 is also presented, which has been adjusted so that the ranges of the Narcotrend® classification stages correspond to the BIS values [6].

State and response spectral entropy (Datex-Ohmeda, GE)

Entropy describes the irregularity, complexity or absence of predictability of the characteristics of a signal such as the stochastic signals of the EEG. In information theory, entropy was defined initially by Shannon and Weaver in 1941[7] and was applied subsequently by Johnson and Shore in 1984 to the spectral power of the signal[8].

Spectral entropy has the advantage that the contribution to the entropy of a range of particular frequencies can be separated explicitly. For an optimum response time, the calculations are performed on a window of varying duration according to the frequency considered.

The concept of spectral entropy derives from an information measurement known as Shannon's entropy[2].

Various steps are required to calculate the spectral entropy for a given epoch of the EEG signal in a given frequency range [f_1, f_2]. To obtain the frequency spectrum of the EEG signal, a discrete Fourier transform is applied as explained in the time domain analysis of the EEG signal. The spectral components X(fi) can be evaluated using an effective computational technique known as a fast Fourier transform (FFT). The power of the spectrum P(fi) is calculated from the Fourier transform X(fi) from the initial signal x(ti).

The spectral power is normalised subsequently. The normalised spectral power Pn(fi) is computed by establishing a normalisation constant Cn such that the sum of the normalised spectral power in the frequency range [f1, f2] is equal to one:

$$\sum_{f_1=f_1}^{f_2} P_n(f_i) = C_n \sum_{f_1=f_1}^{f_2} P(f_i) = 1$$

The spectral entropy corresponding to the frequency range [f_1, f_2] is calculated[2] as a sum (Shannon function):

$$S[f_1, f_2] = \sum_{f_1=f_1}^{f_2} P_n(f_i) \log\left(\frac{1}{P_n(f_i)}\right)$$

This entropy value is normalised (SN) for a range between 1 (maximum irregularity) and 0 (complete regularity), by dividing the value by a factor, log (N[f_1, f_2]), where N[f_1, f_2]: is equal to the total number of frequencies contained in the

$$S_N[f_1, f_2] = \frac{S[f_1, f_2]}{\log (N\ [f_1, f_2])} = \frac{1}{\log (N\ [f_1, f_2])} \sum_{f_1 = f_1}^{f_2} P_n(f_i) \log \frac{1}{P_n(f_i)}$$

range [f_1, f_2]:

In the real-time analysis of the signal, the values of the non-digitalised EEG signal x(ti) are sampled at a frequency of 400 Hz. The shortest sampling window is equal to 1.92 s = 768 samples per epoch and the longest duration 60.16 s = 24064 sample values per epoch. The largest epoch is used only for frequencies below 2 Hz. For frequencies between 2 Hz and 32 Hz, epochs of intermediate duration are used. The window below 2 s is used for frequencies between 32 Hz and 47 Hz(2).

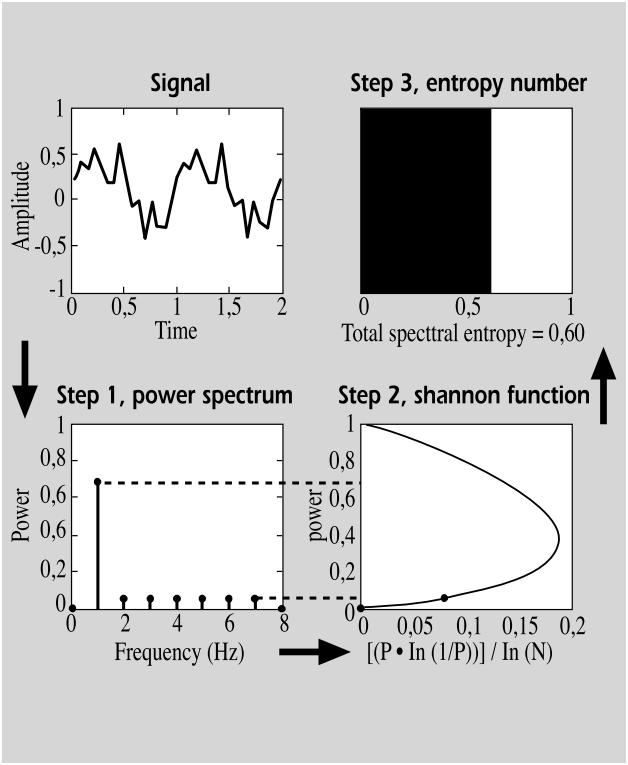

Figure 10.

Two types of entropy are depicted in the entropy monitor: state entropy (SE) which concerns the range of frequencies between 0.8 Hz and 32 Hz and which is assumed to be the dominant frequency range of the EEG, and response entropy (RE) which analyses a frequency range between 0.8 Hz and 47 Hz and which includes the two dominant frequency spectra of the EEG and EMG(2). These two entropy parameters have been normalised so that RE is equal to SE when the spectral power of the EMG (sum of spectral power in the frequency range between 32 Hz and 47 Hz) is equal to zero, so that the normalisation of the entropy defined previously will be reflected in the way mentioned above.

Consequently RE varies between 0 and 1, while SE varies between 0 and log(N[0.8 Hz, 32 Hz])/log(N[0.8 Hz, 47 Hz]), i.e. a value below 1. The two entropy values coincide when the spectral power between 32 Hz and 47 Hz is zero, while when there is EMG activity the spectral components between 32 Hz and 47 Hz differ significantly from zero and RE is greater than SE(2).

When burst suppression patterns appear, the part of the signal containing the suppression is treated as a perfectly normal signal with zero entropy, while the part containing the bursts is analysed as a normal EEG signal. For the detection of burst suppression patterns, a special technology described by Särkelä and co-workers is applied(9). When these patterns are detected, an epoch of 1 minute duration is used to be able to quantify the relative quantity of suppression, which is calculated with a parameter known as the burst suppression ratio (BSR), which is the percentage of epochs of 0.05 s which have been computed as suppression in the last 60 s.

To facilitate the reading of the values obtained in the original entropy formulas, which vary between 0 and 1, they are transformed into a scale of whole numbers between 0 and 100. As a relatively large portion of the original mathematical entropy scale is within a range in which hypnosis is considered excessively deep and the more interesting range of adequate hypnosis and consciousness is within the range between 0.5 and 1, this transformation has been performed using a non-linear function. The function used is a polynomic func-

$$SE = S_n\,[0{,}8\ Hz, 32\ Hz] = \frac{S\,[0{,}8\ Hz, 32\ Hz]}{\log\,(N[0{,}8\ Hz, 47\ Hz])} = \frac{\log\,(N\,[0{,}8\ Hz, 32\ Hz])}{\log\,(N\,[0{,}8\ Hz, 47\ Hz])} = \frac{S\,[0{,}8\ Hz, 32\ Hz]}{\log\,(N\,[0{,}8\ Hz, 32\ Hz])}$$

$$RE = S_N\,[0{,}8\ Hz, 47\ Hz] = \frac{S\,[0{,}8\ Hz, 47\ Hz]}{\log\,(N\,[0{,}8\ Hz, 47\ Hz]}$$

tion of various segments of the spline type characterised by the fact that they are continuous, as are their derivatives of any order. This function used has different slopes in various segments, being greater in the range of clinical anaesthesia and in the waking zone. On this scale, RE ranges between 0 and 100 and SE between 0 and 91 (2).

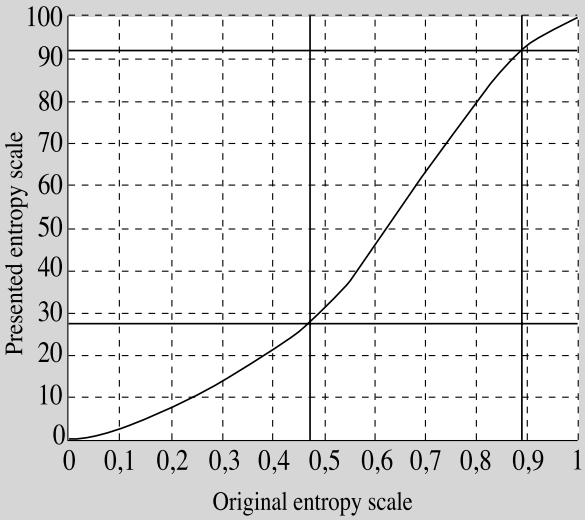

Figure 11.

Auditory evoked potentials (AEP)

AEP are the response to an auditory stimulus transmitted from the cochlea to the cerebral cortex. It is EP that have proved to be most useful in evaluating the depth of hypnosis6. The stimulus produces a succession of waves characterised by peaks and troughs which are generated at more or less specific anatomical sites and which can be recorded by electrodes attached to the scalp and forehead. Depending on the time that elapses from the stimulus being produced until the responses are obtained, AEP are divided into brainstem auditory evoked potentials (BAEP), midlatency auditory evoked potentials (MLAEP) and long-latency auditory evoked potentials (LLAEP).

The early cortical response, also known as midlatency, appears from 8 to 60 milliseconds (ms) after the acoustic stimulation is produced. This portion of the AEP exhibits gradual dose-dependent changes in form with various anaesthetic drugs. As the anaesthetic depth increases, the signal flattens and the Pa and Nb latencies increase(6).

AEP signal processing

Any signal defined as s, recorded from an EEG monitor with surface electrodes, consists of three components:

$$s = EEG + EMG + noise$$

The EEG is the component that originates in the brain, the EMG is the spontaneous activity of the facial muscles and the head, and noise is any interference with the signal that may occur from movements, electrical artifacts, electrodes or errors in the quantification of the analogue to digital conversion. Despite the fact that modern apparatuses have different types of filters that eliminate noise fairly acceptably, AEP have to be separated from the remainder of the signals gathered by the electrodes. One of the characteristics of EP is that the signals have a fixed relationship to the stimulus. This makes it possible to differentiate them from random signals to the stimulus, such as EEG or EMG. On repeating the stimulus a specific number of times, the non-synchronised signals cancel one

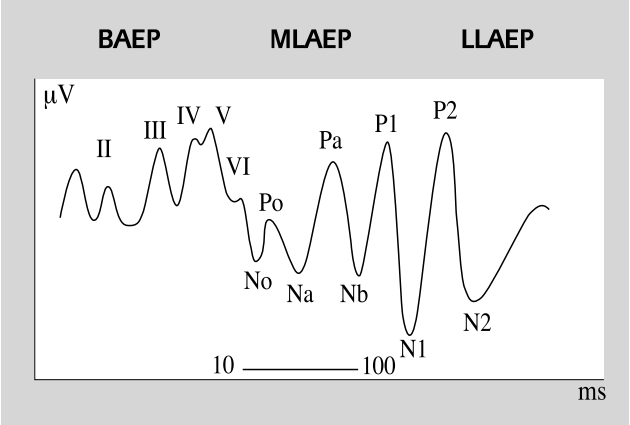

Figure 11.

The relationship between the AEP signal and "noise" is known as the signal to noise ratio (SNR) and is expressed by the mathematical formula:

SNR ≈ Estimation of synchronous EP / Asynchronous noise estimation

The smaller the SNR, the poorer the estimation of the EP. An SNR of about 1 implies an EP that is not different from the noise, either because there is no EP or because the measurement is of poor quality. Conversely, the higher the SNR, the better will be the signal.

The low amplitude of AEP is a very important problem in the operating theatre setting, where the use of electrical equipment generating a large amount of interference is common. To avoid this, modern teams use amplifiers and filters with special characteristics and automatic systems to identify and eliminate artifacts and interference.

Usually a mathematical model for averaging the signals, known as moving time averaging (MTA), is used to extract the EP. The first AEP measurement systems were based on the repetition and superimposition of traces produced with ink or photographic paper. In the 1950s and then the 1960s, electronic and subsequently digital systems were developed, enabling the averages of the EP traces to be obtained. The MTA method consists in repeating the stimulus a specific number of times, usually between 256 and more than 2000. The responses synchronised with the stimulus are averaged and improve the quality of the signal relative to the non-synchronised noise in a value proportional to the square root of the number of repetitions or means performed[10].

The MTA method is very robust, but has the disadvantage that it requires a relatively long time to update the signals, which may range from 30 seconds to several minutes depending on the number of repetitions. For this reason, more rapid methods have been developed but with an equal estimation of EP.

The AutoRegressive model with eXogenous input (ARX) extracts the AEP in a shorter time. This type of mathematical model was developed in the technology used to improve night vision in helicopters, where a stable image had to be obtained rapidly from the infrared camera, distorted by the vibrations of the apparatus. In a similar way, AEP signals were affected by the EEG and EMG, so that they had to be processed to obtain an AEP of good quality and in the shortest possible time. Cerutti[11] described the application of the ARX model to the extraction of physiological signals, obtaining visual EP with a single scan. Jensen et al[12] applied the ARX model to obtain AEP with a few sweeps. As the amplitude of AEP is less than that of visual EP, the authors found that they obtained a good quality signal with 15 sweeps.

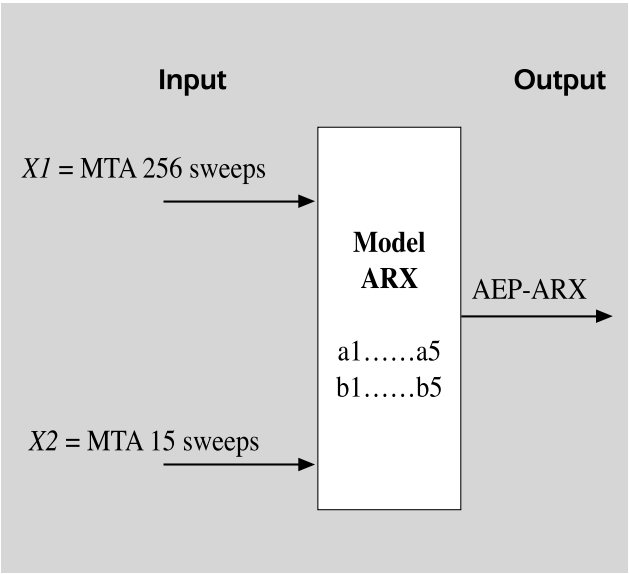

Figure 12.

The ARX model consists of the combination of two MTA signals synchronised with the stimulus, one with 256 or more sweeps and the other with a few sweeps that are updated continuously. For the exogenous input X1, the slow estimation of AEP with little noise is entered. For the input X2 the signals of the last 15 sweeps are input, but with more noise. The AEP output modelled by ARX (AEP-ARX) combines common elements of both MTA (linear combination of the common peaks in the two inputs) so that the output is rapid and with little noise.

The principal advantage of the model is that it can detect changes very rapidly as they are produced in the 15 scan input, but with much less noise than a MTA average of only 15 sweeps would have had.

The principal disadvantage is that if any signal is synchronised with the stimulus it will be identified as an EP, even if it is not, so that the quality of the filters used to isolate AEP from the remainder of the signals is very important(13).

Clinical indices derived from the AEP

Once the AEP signals are obtained, identifying the changes that occur during anaesthesia may be very difficult. To resolve this, various indices have been defined which evaluate automatically the AEP signals and make it possible to quantify the patient's level of hypnotic depth. McGee et al[14] quantified the AEP waves by measuring the area of a successive peak and trough so as to convert it into a single number, but this exhibited great variability. Schwender and co-workers applied the Nb latency as a measurement of loss of consciousness. Thornton et al[15] defined an index based on the second derivative of the AEP in the period 30-70 ms after the stimulus.

AEPindex

The first clinically validated index, the AEPindex, was described by Mantzaridis and Kenny in 1997[16]. These authors studied the AEP evoked by clicks of 1 ms duration at a rate of 6.9 Hz and at 70 dB above normal hearing level. They reconstructed the AEP waves using the MTA method, averaging 256 sweeps in a window of 144 ms duration, the sampling frequency of the EEG being 1778 Hz. The AEPindex was obtained empirically and is a mathematical derivative which indicates the waveform and is defined as the sum of the square roots of the absolute difference between two successive segments of the AEP wave separated by 0.56 ms in a calculation window that begins at the time of the auditory stimulus and continues until 144 ms after the stimulus. The mathematical description that calculates the AEPindex would be as follows:

$$\text{AEPindex} = k \sum_{i=1}^{255} \sqrt{\left| Vi - Vi + 1 \right|}$$

Where V1…V256 describes an AEP curve as and when it has been stored in the memory of the computer used. The scale constant k is equal to 0.25 and has been determined empirically so that the AEPindex is about 100 in totally awake volunteers. The units of this constant are reciprocals of the square root of voltage as the index does not have any units. The square root of the absolute differences between two successive points of the curve separated by 0.56 ms are used instead of the absolute difference to increase the resolution of the algorithm in the lowest frequencies and amplitudes[17].

This index is calculated every 3 seconds. When the patient is awake, the AEPindex is approximately 80-90 and during surgical anaesthesia between 30-40. During awakening, the AEPindex increases, but does not reach (values slightly below), the previous values of the awake patients. This index correlates well with the clinical levels of the OAAS scale after administration of propofol[17].

AAI1.5 index

The AEP-ARX-Index version 1.5 (AAI1.5) defined by Jensen et al (12) is calculated in a window between 20 and 80 ms after the auditory stimulus, in which the changes in latency and amplitude of AEP are evaluated as the sum of the ab-

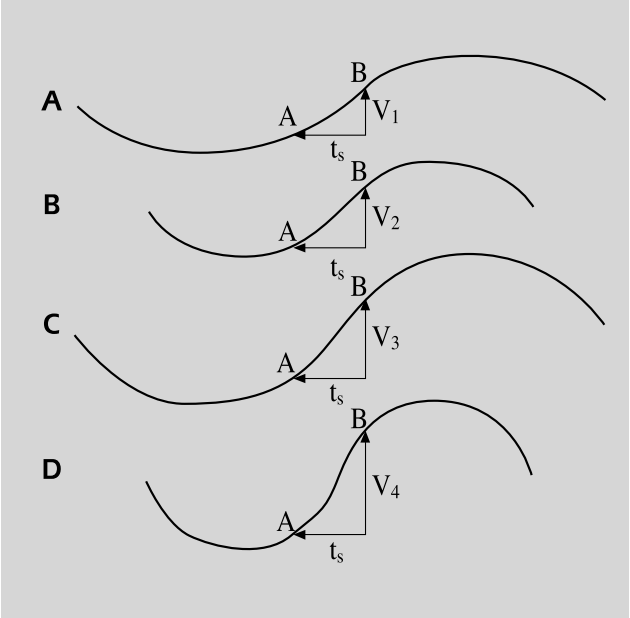

Figure 13.

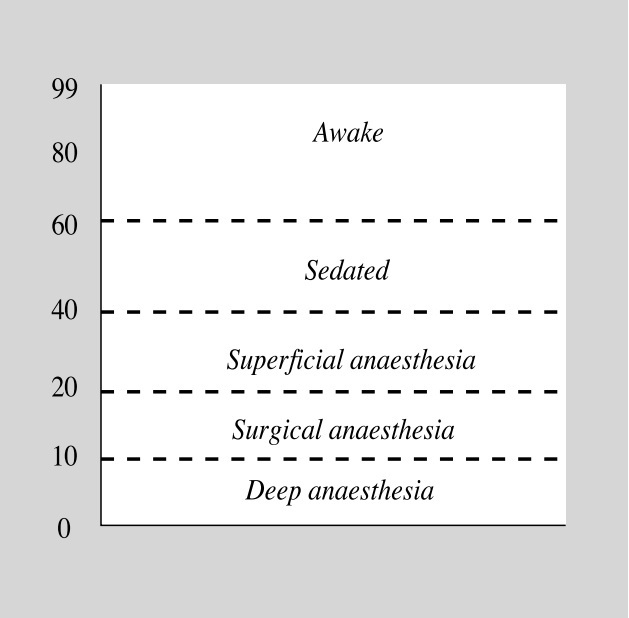

Figure 14.

solute differences in this window, which is done according to a propietary formula. The length of the calculation window between 20 and 80 ms is defined so as not to include BAEP signals or auricular muscle artifacts in the first 20 ms, nor the LLAEP signals at the other extreme.The AAI1.5 expresses the dimensions of amplitude and time in a single dimension, which is represented numerically and graphically on the A-line® monitor screen (Danmeter A/S, Odense, Denmark). The monitor extracts the MLAEP every 80 ms, calculates the index and displays it on the screen every second. The data are obtained continuously, but the delay which the monitor generates in processing and updating them is 6 to 10 seconds, depending on the signal quality, since poor quality signals are discarded. A diagram for obtaining the AAI1.5 algorithm.

AAI 1.6 Index

The A-Line“ ARX Index, version 1.5 (AAI 1.5) incorporated in the A-Line“ monitors (Danmeter A/S, Odense, Denmark) does not correlate well with the propofol effect site concentration (Ce PROP) when anaesthetic levels are excessive, as detected by the increase in the suppression patterns[18]. At high levels of hypnotic depth, the amplitude of the unprocessed (raw) MLAEP waves is reduced (and the latency increased) so that they are practically a straight line, limiting their discriminant power. The new A-Line“ ARX Index, version 1.6 (AAI 1.6) composite index which varies between 0 and 100 uses three different sources of information[18]. The first is an ARX which extracts information from the raw MLAEP waves when the signal/noise ratio (SNR) is high. When the MLAEP waves are reduced to a flat line, then SNR becomes so small that a valid calculation of AAI is impossible. At this time, the information from the electro-encephalogram will determine the calculation of the AAI 1.6. Finally, when burst suppression is detected, this information becomes the most important factor in the calculation of this composite index. The mathematical expression of the AAI 1.6 index is as follows:

The AAI 1.5 is the result of the ARX model, E 30-47 Hz and E 10-20 Hz the results of the analysis of the potency of the spectrum of the raw electroencephalogram using high and low frequencies respectively, BS is the percentage of burst suppression patterns detected during the last 30 seconds. In this expression k0, k1 and k2 depend on the SNR, the detection of iatrogenic artifacts (which are translated into a signal quality index) and the intensity of the auditory stimulus[18].

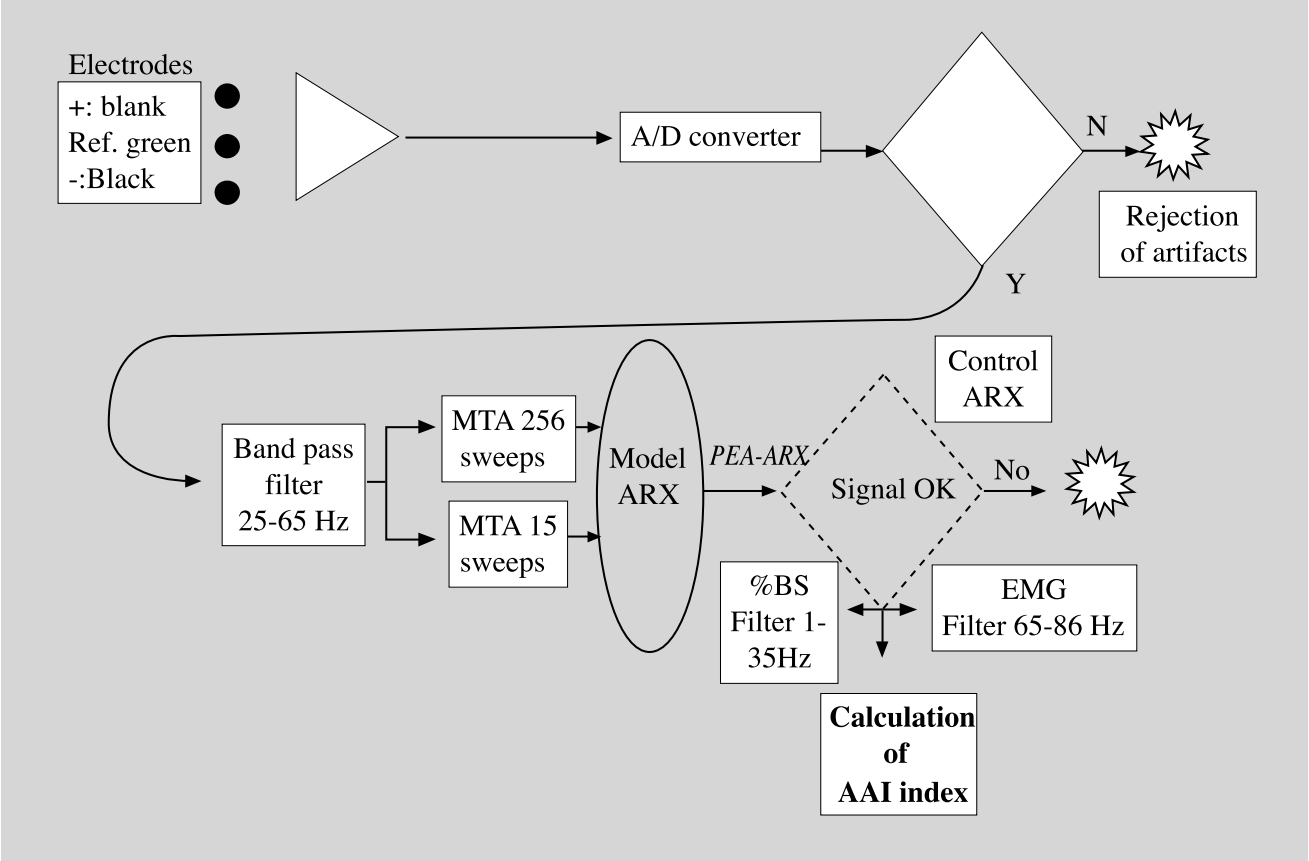

Figure 14.

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