Cerebral monitoring Devices : What we pay For

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Abstract : In this review paper, the authors analyse advantages, pitfalls and economical considerations related to depth of anaesthesia monitoring. They first describe the most widely distributed monitors in Europe, and the physiological basis of each index. The optimal use of those monitors and their demonstrated clinical benefits are detailed, as well as the circumstances that can lead to erroneous information or interpretation. Knowledge of patients and practitioners, as well as beliefs and expectations regarding depth of anaesthesia monitoring are discussed. Finally, the authors give their own opinion regarding the use of depth of anaesthesia monitoring, according to clinical benefit and economical considerations.

Key words : Monitoring ; depth of anaesthesia ; clinical use ; economics.

INTRODUCTION

Several commercially available cerebral monitoring devices are currently capable to provide at the bedside a series of parameters that reflect on line either the physiological or the pathological brain state. They are the most often divided into two categories, the depth of anaesthesia monitors and the monitors used to explore the suffering brain. Some of those monitors have been recently set up thanks to sophisticated new technologies. The cost associated to their use may be high and, in the current context of financial healthcare budget restrictions, their cost-benefit ratio is a matter of great concern. Settling such an important issue requires good knowledge about what is exactly measured by each device, the evidence-based advantages of using those techniques in relation with the patients outcome, in terms of patient care-related cost savings, if any, and, finally about the real cost of their use. In the present review paper, we will address all these points according to available data and restrict the discussion to monitors dedicated to depth of anaesthesia monitoring.

DEPTH OF ANAESTHESIA MONITORS

Depth of anaesthesia monitoring consists in measuring the dose-concentration-response relationship between anaesthetic agents and their main pharmacodynamic effects (1). Because those effects are numerous, the definition of depth of anaesthesia will depend on the considered pharmacodynamic component : the level of wakefulness/ awareness (i.e. the level of hypnosis), the nociceptive-anti-nociceptive balance, the level of muscle relaxation or other components can be considered in that respect. The evaluation of any pharmacodynamic component of anaesthesia by clinical means is poorly sensitive and specific. Signs such as ventilation rate, pupil diameter, eyelash reflex, swallowing reflex, muscular tone, movements, blood pressure, heart rate, tearing, sweating, and response to verbal command are to be checked by the anaesthesiologist at regular intervals but poorly discriminate between the components of anaesthesia. Furthermore, the study of the pharmacodynamic effects of anaesthesia is made complex due to interactions between those effects (e.g. the level of hypnosis is modulated by the level of nociceptive stimulation), variability of pharmacodynamic effects between classes of anaesthetic agents, and interactions between those agents. Hence, several attempts to overcome the problem of poor sensitivity and specificity have led to the development of specific indices designed to monitor a given pharmacodynamic effect of anaesthesia. Most of these attempts were primarily devoted to the hypnotic component of anaesthesia (depth of the hypnotic component of anaesthesia monitors, DHCA monitors). The description of the most widely distributed of them in Europe follows.

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The Bispectral Index™ (Aspect Medical System, Inc.)

The Bispectral Index (BIS™) is the first DHCA monitor introduced on the market, and is probably the most widely used and studied. It ranges between 0 and 100 arbitrary units. It relies on a complex mathematical analysis of the electroencephalogram (EEG). The algorithm extracts several EEG parameters such as the power spectrum, the activity in the b frequency range, the burst suppression activity, the synchronised fast slow activity, and the bispectrum, which quantifies interfrequency phase relationships (2). Each parameter is associated with a factor whose weight depends on the hypnotic level. Schematically, a BIS value between 100 and 60 mainly varies according to the b activity, between 60 and 40 according to the synchronised fast slow activity, between 40 and 20 according to the proportion of quasi-flat EEG activity, and between 20 and 0 according to the suppression ratio. The BIS algorithm has changed from its initial version to improve artefacts rejection and reliability. Fully awake patients have a BIS value above 93. Loss of consciousness usually occurs at 80. A BIS value between 40 and 60 is recommended during anaesthesia (3, 4). This monitor is either available as a separate monitor (Aspect A2000 BIS™ monitor) or as a module that can be part of a Datex-Ohmeda monitor (BIS™ module, Datex-Ohmeda, Inc.). The delay between signal acquisition and the value display on the screen is variable and in the range of 30 seconds, although it has been shortened in the most recent version of the monitor. In the presence of artefacts, this delay can be as long as 60 seconds. The user can choose to smooth the values displayed on the screen over 15 or 30 seconds. The BIS™ provides a signal quality index (SQI) which gives an idea about the number of rejected EEG sequences because of artefacts, and about the reliability of the index at a given time. Several other parameters are available through adequate selection of screen display such as the spectral edge frequency of the EEG or an estimation of the electromyographic activity. An EEG raw tracing can also be displayed on the screen.

The A-Line Autoregressive Index (Danmeter A/S, Odense, Denmark)

The A-Line Autoregressive Index (AAI™) is obtained through the recording of middle latency auditory evoked potentials (auditory middle latency response, AMLR) consisting in three main peaks Na, Pa and Nb. The amplitude of those peaks decreases and their phase increases with increasing concentrations of hypnotic agents (5). The monitor uses advanced signal processing, namely an autoregressive modelling with exogenous input to extract the signal quickly. AAI™ is defined as the sum of absolute differences in the 20-80 millisecond window of the AMLR (6) and resized into an index ranging between 0 and 100. The delay for obtaining the AAI averages 1.7 seconds (7). The current version of this monitor (AEP-Monitor/2) calculates a composite index based on the AMLR and on parameters of the processed EEG (8). Little is currently known about the clinical significance of this new index. Finally, the combined use of BIS and AAI indices may provide some information about the adequacy of the nociceptive-anti-nociceptive balance during anaesthesia, the BIS serving to target a hypnotic level while the AAI response to a nociceptive stimulation allows the practioner to evaluate the degree of adequacy of the nociceptiveanti-nociceptive balance (9).

The Spectral Entropy of the EEG

The entropy of a system is a measure of the disorder encountered in this system. Shannon first applied this principle to the analysis of a signal (10). The entropy applied to the EEG and to DHCA monitoring relies on the assumption that the EEG of an anaesthetised patient would be more regular (low entropy) than the one of an awake patient (high entropy). The M-Entropy™ module implemented on the S/5™ Anaesthesia Monitor (GE Healthcare, Finland) proceeds to a time domain and frequency domain analysis of the EEG. It first computes a Fourier transform of the signal and generates a power spectrum. The Shannon function is then applied to the power spectrum to obtain a scale-invariant number, independent of the frequency and amplitude scales of the signal. This number is normalised. The length of the time window for entropy calculation varies according to frequencies that predominate in the power spectrum (range : 2- 60 seconds). The window is short for high frequencies and longer for low frequencies (time-frequency balanced analysis). Therefore, numbers will be displayed more rapidly but the delay for obtaining the entropy value will be longer at deeper stages of anaesthesia. The M-Entropy™ monitor has been designed for advanced artefact rejection such as electrocautery, ECG and pacing, eye movements and blinking, as well as movement artefacts. The

analysis is performed on two different frequency ranges, the 0.8-32 Hz band, which predominantly contains EEG signals, and the 0.8-47 Hz band, which includes the frequencies associated to electromyographic activity of facial muscles. Hence, the monitor provides two entropy values, the State Entropy (SE) and the Response Entropy (RE). SE ranges between 0 and 91 and would reflect depth of hypnosis, or the cortical state. RE ranges between 0 and 100 and is thought to reflect the nociceptiveanti-nociceptive balance. In case of nociceptive stimulation and inadequate analgesia, facial EMG activity increases, and RE increases. Therefore, RE is always higher than SE, except when there is no facial EMG activity. In that case, RE and SE are equal. The manufacturer recommends that the hypnotic component of anaesthesia should be adjusted according to SE, which should remain under 60, and that an increase in RE or in the RE-SE gradient should prompt the anaesthesiologist to improve the anti-nociceptive component of anaesthesia (11). However, validation studies are needed to better define the role of RE and RE-SE gradient in appreciating the nociceptive-anti-nociceptive balance (12), and particularly the influence of muscle relaxation on this ability (13).

The Narcotrend™

The Narcotrend™ monitor (Monitor Technik, Germany, and Schiller, Switzerland) is another EEG-based monitor of the hypnotic component of anaesthesia. The development of the algorithm was based on 6 different EEG patterns corresponding to sleep stages, which were further divided into sub stages, leading to a total of 15 stages. Those stages correspond to EEG patterns that can be visually observed during volatile and intravenous anaesthesia (14). The monitor extracts several EEG parameters including spectral parameters, entropy measures, and autoregressive parameters, that best discriminate between those stages. Those parameters are combined into an index ranging between 0 and 100. The monitor displays the value of the index and a letter corresponding to the stage of anaesthesia (A and B_0 = awake, B_{1-2} = sedated, C_{0-2} = light anaesthesia, D_{0-2} = general anaesthesia, E_{0-2} = general anaesthesia with deep hypnosis, F_{0-1} = general anaesthesia with increasing burst suppression). A Narcotrend™ stage D is recommended during surgery. Unlike other monitors, the Narcotrend™ does not require specific sensors and works with simple ECG electrodes.

The Patient State Index™

The PSA 4000™ and SedLine™ monitors (Hospira, USA) are monitors capable of calculating the Patient State Index™ (PSI™) which is also an index of the hypnotic component of anaesthesia, and, hence, of the cortical state. Its value ranges between 0 and 100. The algorithm incorporates a combination of EEG parameters sensitive to changes in depth of hypnosis, but independent of medication combination (15) : power of several EEG frequency bands, symmetry and synchronisation between brain regions, and activity in regions of the frontal cortex are quantified. A specific set of four EEG electrodes and a ground electrode are required.

The SNAP Index™

Among the algorithm developed to calculate indices reflecting the cortical state, the one of the SNAP Index[™] is probably the most simple. The device, implemented on a Personal Digital Assistant system, analyses the EEG upon a large frequency range (from 0.1 to 420 Hz). After a Fast Fourier Transform, it divides the power spectrum into two components, the high-frequency component (80- 420 Hz) and the low-frequency component (0.1- 40 Hz). The high frequency component is scaled to result in values ranging between 0 and 1, and the low-frequency one to values between 0 and 100. The index is obtained according to the following formula : SNAP Index[™] = 100 – (high-frequency X low-frequency) (16), leading to a value ranging between 0 and 100. A value of 50-65 is recommended during surgery (17). Unfortunately, this index still deserves validation studies before recommendation for clinical practice. In particular, the question of the influence of EMG activity and muscle relaxation needs to be clarified.

Other and future monitors

Simplified EEG monitors, such as the M-EEG™ module (GE Healthcare, Finland), are not directly designed to assess a particular pharmacodynamic component of anaesthesia but display several parameters derived from the spectral analysis of the EEG such as the spectral edge frequency (SEF), the median frequency, or the relative power in the frequency bands b, a, q, and d. Those parameters can provide information about the depth of hypnosis, although it has been demonstrated that MEF and SEF are less reliable measures of the

depth of hypnosis than the BIS™ or the Narcotrend™ (18). An advantage of those monitors over those described above is that a larger portion of the scalp is explored. This can be interesting to detect adverse events such as cerebral ischemia during carotid surgery, intracranial aneurysm surgery, or cardiac surgery (19), or the occurrence of some epileptic seizure.

Other devices currently under development are promising. The NeuroSENSE™ monitor (CleveMed, USA) is a monitor of the hypnotic component of anaesthesia. It is based on the quantification of cortical activity using wavelet analysis (20). This device beneficiates from advanced artefact rejection and a short reactive time compared to the BIS. It has still to be validated in clinical practice. The same is also true for the Cerebral State Index (CSI™, Cerebral State Monitor™, Danmeter A/S), the algorithm of which has been developed by using an original statistical approach. The CSI™ integrates parameters derived from the spectral analysis of the EEG, as well as the suppression ratio. It has been demonstrated to be equal to the BIS™ or the AAI™ at discriminating levels of sedation (21). Monitors devoted to assess the adequacy of the nociceptive-anti-nociceptive balance are also under development (22). Most of them are based on measuring the autonomic response to nociceptive stimulation, either the pupil response to light (23), the pulse transit time (24), heart rate or blood pressure variability (25), the skin vasomotor reflex (26), the photoplethysmography pulse wave reflex (27), or a combination of those parameters (28). Finally, it is possible to measure the motor response to nociceptive stimulation using the spinal-H reflex (29).

OPTIMAL USE OF DHCA MONITORS

The optimal use of DHCA monitors requires concomitant knowledge of the concentration of anaesthetic agents at their effect-site, either by using target-controlled infusion systems (TCI) or by monitoring the end-tidal concentration of volatile anaesthetics. To obtain maximum benefit, this type of monitoring should be instituted before induction of anaesthesia. A common way to get rid of the problem related to interaction between anaesthetic agents, which sometimes makes interpretation of index values difficult, is to start the induction of anaesthesia with the anti-nociceptive medications, and ideally to use a TCI system. An effect-site concentration expected to cover the antinociceptive needs related to endotracheal intubation and surgical procedure is chosen. Opioids administrated alone will not affect the value of the index that much (30). Once a steady-state is achieved, the administration of the hypnotic medication can be started. The value of the index at the time of the loss of consciousness may be noted and serve as a reference value throughout the course of anaesthesia. This way of proceeding limits the amount of hypnotic medications given to patients, and may theoretically increase the risk of unexpected awareness. However, it has been demonstrated that this protocol is not associated with intra-operative explicit or implicit memories (31). Thereafter, it is also important to note the effect of muscle relaxation on the recorded index (e.g. a decrease in BIS, or a decrease in RE-SE gradient). Tracheal intubation should be considered as a relatively standardised nociceptive stimulus. The response of the recorded index to that stimulus will provide information about the nociceptive-anti-nociceptive balance (30). The observed response will be the one observed subsequently for each stimulation that is at least as intense, provided that the anti-nociceptive regimen remains the same. An intense response will prompt the anaesthesiologist to increase the target concentration of opioids when he/she expects an intense nociceptive stimulation. In the absence of a specific monitor of the adequacy of the nociceptive-anti-nociceptive balance, it is important to maintain an appropriate anti-nociceptive level, guided by the expected intensity of the nociceptive stimulation. This will limit the risk of titrating hypnotic medications too tightly during episodes of minimal stimulation (e.g. field preparation, patient installation), and observing intense response of the patient, or even awareness, at the beginning of surgery.

DEMONSTRATED CLINICAL BENEFITS

Several demonstrated clinical benefits of DHCA monitors are summarised in Table 1. Most of these advantages have been asserted for the BIS™, and do not necessarily apply for the other monitors. It is now established that using the BIS™ significantly reduces the risk of intra operative awareness (32), particularly in patients at high risk of experiencing such an unpleasant event. A 82% reduction in the incidence has been reported for those patients (33). However, the American Society of Anaesthesiologists Task Force on Intraoperative awareness does not recommend the routine use of DHCA monitors for all patients. According to those

Table 1

Summary of the clinical advantages when using depth of the hypnotic component of anaesthesia monitors combined to an estimation of the effect-site concentration of anaesthetic agents

recommendations, the decision to use a DCHA monitor should be taken on a case-by-case basis by the individual practitioner for selected patients (34). As described above, the optimal use of those monitors combined to an estimation of the effect-site concentration of anaesthetic agents allows individual rationalisation of anaesthetic agent administration, and precludes the anaesthesiologist from over dosage administration (35). Indeed, blinded recordings of BIS™ in patients scheduled to undergo rapid emergence by the anaesthesiologist in charge of their general anaesthesia were in the 30-40 range, corresponding to deep sedation and near burst suppression (4, 32, 33). This is to be pointed out, as a too deep sedation (and hypotension) cumulative prolonged period of time has been reported to be associated with an increased one year mortality (36, 37). Most of the DHCA monitors reduce the amount of hypnotic medications administered to patients, and hasten recovery (35, 38-40). Tightness of titration could even be further improved when closed-loop devices will be available in routine practice (41). Thanks to adequate titration, the incidence of postoperative residual side effects such as drowsiness, dizziness, fatigue, can be reduced (35), as well as the incidence of nausea and vomiting after halogenated volatile general anaesthesia (42, 43). Furthermore, the use of DHCA monitors provides information regarding the adequacy of the nociceptive-anti-nociceptive balance. Considering

all those clinical benefits, the quality of DHCAguided general anaesthesia is undoubtedly improved compared to conventional practice.

CONDITIONS THAT IMPEDE CORRECT INTERPRETATION OF DHCA INDICES

Unfortunately, as with any kind of monitor, several conditions may impede the correct interpretation of DHCA indices (44). Those conditions, that should be known by the user, are summarised in Table 2.

Artefacts from surrounding electrical devices

The operating theatre is crowded with a number of electrical devices. Their use may contaminate the EEG tracing and artificially modify the EEGderived index. The most perturbing one is the electrocautery. The use of this device usually prevents the monitor to acquire reliable EEG signal and therefore to calculate an index value. Otherwise, electrocautery can also artificially increase the value of the index. Advanced artefact rejection systems reduce the importance of this problem for some of the available monitors (M-Entropy™, PSArray^{2™}, NeuroSENSE™) (20, 45, 46). Other devices such as atrial pacers, warming blankets, endoscopic shavers or electromagnetic systems can also cause troubles (44).

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Table 2

Summary of different conditions which may impede correct interpretation of DHCA index values. Adapted from Dahaba (44)

Inter and intra individual variability

It is sometimes not easy to cope with the interindividual variability of the recorded indices. For example, awake baseline values can be highly variable from one subject to another (47). Similarly, the same anaesthetic regimen will not necessarily lead to the same DHCA value in two different patients, and the index response to a given nociceptive stimulation can also differ. This can be attributed to inter-individual differences in skull impedance, audition, genetically-determined EEG amplitude, sensitivity to nociceptive stimulation, and probably other factors. The best way to overcome this problem is to work on an individual basis rather than using absolute reference values. As mentioned above, observing individual baseline values and the individual profile of the index during induction of anaesthesia is very important in that respect. Intra individual variability of the value of a DHCA index does exist. Indeed, the same index recorded on two

different sites in the same patients may have different values (48).

Interactions between anaesthetic agents

Single drug general anaesthesia is rare. Practitioners often use a cocktail of medications designed to encounter hypnotic, anti-nociceptive, muscle relaxation and autonomic modulation needs. All those medications have specific properties. They may influence the DHCA value either directly or through drug interactions.

As opposed to the well established relationship between DHCA index and effect-site concentration of hypnotic medications, opioids alone poorly influence the value of that index. This is also true under general anaesthesia with propofol alone in the absence of nociceptive stimulation (49, 50). When a nociceptive stimulus is applied, the value of the DHCA index associated with the absence of

movement in the majority of patients depends on the hypnotic-anti-nociceptive combination. Schematically, this threshold value will be higher when the opioid concentration is high and the hypnotic concentration low than in the inverse situation (opioid low and hypnotic high) (50).

Paradoxical increases in BIS™ have been reported following abrupt increases in halothane or isoflurane in the inspired gases (51-53). This effect is not observed with sevoflurane and may be due to specific EEG patterns induced by those agents at clinical concentrations. Therefore, monitoring the depth of hypnosis using BIS during halothane or isoflurane anaesthesia may lead to inadvertent overdosage of these medications (44).

Ketamine administered alone at a dose sufficient to produce unresponsiveness does not reduce BIS[™]. When administered during sevofluranesufentanil anaesthesia, ketamine has been demonstrated to paradoxically increase BIS™ and entropy (54), and the amplitude of the AMLR (55). This drug is acknowledged as a dissociative anaesthetic with excitatory effects on the EEG, that could explain those paradoxical changes (2). Similarly, nitrous oxide does not affect BIS™ and entropy value when administered alone or under general anaesthesia in the absence of nociceptive stimulation, but does decrease BIS™ when that stimulation is present (56). Although having a similar mechanism of action as ketamine and nitrous oxide, that is inhibiting N-methyl-D-aspartate receptors, xenon does not have the same effects on DHCA indices. It decreases the BIS™ and the AMLR in a concentration-dependent manner (57).

The degree of muscle relaxation may influence the value of the DHCA index by two mechanisms. Muscle relaxation by itself decreases muscle-generated sensory inputs to the brain, and hence the level of arousal (58). Depending on the frequency band included in the calculation algorithm, EMG activity may also be a determinant factor of the DHCA value. It has been shown to falsely elevate BIS™ value (59-61). The effects of neuromuscular blocking agents on DHCA monitoring probably depend on the background anaesthetic level, and may be less marked at deep levels of anaesthesia. Indeed, in those circumstances, central afferentation and EMG activity are depressed by anaesthetic agents. This would explain why it has been reported that antagonism of neuromuscular block but not muscle relaxation affects the depth of anaesthesia (62). Muscle relaxation has also been demonstrated to attenuate the RE and RE-SE response to nociceptive stimulation (13).

Specific clinical conditions

Several particular clinical conditions may also modify DHCA values. Hypothermia and hypoglycaemia decrease BIS™. Low BIS™ values have been reported in patients with Alzheimer dementia, cerebral palsy, genetically determined low voltage EEG and in the post-ictal phase of seizures (44). Cerebral ischemia and cardiac arrest produce a sudden decrease in BIS™ of high amplitude (63-66). Finally, in the absence of cerebral ischemia, carotid clamping may be associated to a paradoxical transient increase in BIS™, particularly in patients with poor contralateral blood supply to the brain (67).

AGREEMENT BETWEEN DIFFERENT INDICES

Comparison of measurement techniques can rely on the calculation of their respective correlation coefficients or prediction probability values with pharmacokinetic or pharmacodynamic parameters. In that way, each technique is evaluated on its own behalf and its global performance is compared with that of others (47, 49). The vast majority of DHCA indices do perform well in assessing depth of hypnosis as estimated by clinical scores of sedation. They also correlate well with the effect-site concentration of anaesthetic agent and between each other. However, high correlation between two measures does not necessarily mean good agreement. Hence, although correlating well, differences of more than 20 units between BIS™ and SE have been reported to occur frequently (68). The agreement between two measures can be good in a given clinical situation (e.g. the awake state) and poor in another (e.g. at the time of the loss of consciousness). Discrepancies between measures can be due to scales differences, or related to the site of recording, to differences in calculation algorithms and delays to obtain the value, as well as in shapes of the relationship between a given DHCA index and the hypnotic level. Finally, EMG activity can also differently affect the value of the compared indices. Therefore, DHCA indices can not be used interchangeably and specific reference values should be defined for each of them.

PATIENTS AND PRACTITIONERS KNOWLEDGE AND EXPEC-**TATIONS**

As demonstrated in an Australian study, the problem of awareness is often underestimated by

the anaesthesiologists, especially the more senior ones, although many of them have already experienced a patient with awareness (69). Before the efficacy of DHCA monitoring in preventing intra operative awareness had been demonstrated, sceptical anaesthesiologists were claiming that they were prepared to use DHCA monitoring more widely if it was demonstrated to reduce the incidence of awareness. The future will tell us if this assertion is true. The patient's knowledge about the problem of awareness is weak. Only half of the patients have already heard about awareness, mainly through the media. Many patients are anxious about it but few would pay for a proven awareness monitor. The propensity of willing to pay depends on the perceived risk and on the occurrence of a previous awareness episode (70). However, patients still assign an intrinsic base value for the possibility of awareness (71) and some studies highlight the lack of information and knowledge both of patients and anaesthesiologists. On the other hand, some practitioners are not convinced that DHCA monitors are valuable and should be used to reduce the risk of intra operative awareness during general anaesthesia (34).

COST-BENEFIT ESTIMATION

The average cost of DHCA monitors is high, and, at the present time, approximates 8000 Euros. Furthermore, disposable specific sensors are purchased at a cost approaching 16 euros per unit. If turnover of the stock is not fast enough, those sensors can be rapidly out of date and become unusable. There is no real difference between one type of monitor or another in terms of cost (45, 46). Cost saving when using those devices is not easy to evaluate. Although reducing the amount of anaesthetic agents given to patients and hastening recovery, the cost savings associated to these advantages do not exceed the supplementary costs associated to DHCA monitoring when the procedure is short (72- 74). However, improvement of the quality of anaesthesia and prevention of awareness are not money quantifiable at an individual scale.

CONCLUSIONS

DHCA monitors are certainly interesting tools. They undoubtedly improve the quality of anaesthesia if they are used in the right way. This requires a good knowledge of the information they

can provide, and of their limitations. When using them, anaesthesiologists must know that the total cost of anaesthetic management will increase, particularly for short procedures. Future research will highlight other advantages linked to their use, particularly in the domain of intra operative awareness prevention, nociceptive-anti-nociceptive balance appreciation, development of closed-loop systems, and prevention of the risks associated to a too deep anaesthesia.

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