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# Monitoring analgesia

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Analgesia (pain relief) amnesia (loss of memory) and immobilisation are the three major components of anaesthesia. The perception of pain, and therefore, the need for analgesia, is individual, and the monitoring of analgesia is indirect and, in essence, of the moment. Under general anaesthesia, analgesia is continually influenced by external stimuli and the administration of analgesic drugs, and cannot be really separated from anaesthesia: the interaction between analgesia and anaesthesia is inescapable. Autonomic reactions, such as tachycardia, hypertension, sweating and lacrimation, although non-specific, are always regarded as signs of nociception or inadequate analgesia. Autonomic monitoring techniques, such as the analysis of heart rate variability, laser Doppler flowmetry, phlethysmographically derived indices and the pupillary light reflex, may help to quantitate reactions of the autonomic nervous system. For the past few years, automated electroencephalographic analysis has been of great interest in monitoring anaesthesia and could be useful in adapting the peroperative administration of opioids. A range of information collected from the electroencephalogram, haemodynamic readings and pulse plethysmography might be necessary for monitoring the level of nociception during anaesthesia. Information theory, multimodal monitoring, and signal processing and integration are the basis of future monitoring.

**Key words:** analgesia; anaesthesia; intraoperative; electroencephalography; bispectral index; entropy; evoked potentials; heart rate variability; plethysmography; pupillary reflex.

## MONITORING ANALGESIA

### Definitions

*Anaesthesia* is a state of unconsciousness induced by a drug. The three components of anaesthesia are *analgesia* (pain relief), *amnesia* (loss of memory) and *immobilisation*, even though some authors have tried to reduced anaesthesia to a lack of perception

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or recall of noxious stimulation.[1] The drugs used to achieve anaesthesia usually have varying effects in each of these areas. Some drugs may be used individually to achieve all three targets, whereas others have only analgesic or sedative properties and may be used individually for these purposes or in combination with other drugs to achieve full anaesthesia. Physiological methods of monitoring must be used to assess anaesthetic depth as normal reflex methods will not be reliable. The major problem is to define what anaesthesia and analgesia really are. In this regard combinations of anaesthetics and analgesics, known as 'balanced anaesthesia', do not help to provide a practical understanding of the concept of depth of anaesthesia paradigm.[2]

*Pain* is one of the most unpleasant sensations in existence, and even in fetal life noxious stimulation causes detectable stress responses. The prevention and treatment of pain are a basic human right, so a better comprehension of the detailed action of analgesics on pain relief is a challenge for the future.[3] There have been many reports on pain research from various fields of medical science, for example physiology, pharmacology, biochemistry and immunology, and the knowledge acquired of the mechanisms of pain perception in the human brain can be directly related to the treatment of pain and the monitoring of pain relief.

Pain is a more complicated sensation than other somatosensory modalities such as touch and vibration, as the degree of feeling can be easily changed by a change in mental state, pain being, by its very nature, subjective. In conscious subjects, pain is greatly affected by the amount of attention paid to and distraction from a noxious stimulus, but this is not the case under sedation or general anaesthesia. Human, as well as animal, studies on pain perception are necessary, but only a relatively small number of the former have been carried out because such studies must be non-invasive. Recently, non-invasive techniques have been developed, such as electroencephalography (EEG), magnetoencephalography, positron emission tomography, functional magnetic resonance imaging and transcranial magnetic stimulation, and the number of reports on pain perception using these techniques has progressively increased over the past 10 years.[4–7]

*Analgesia* is defined by the relief of pain, in other words by absence of pain in response to stimulation that would normally be painful. This definition is subjective because pain is defined by the International Association for Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Pain is a subjective sensation because of this individuality and is also difficult to assess because of the inability to communicate directly about the sensation of pain. Instead, indirect clinical signs of pain are used during anaesthesia. Because of the difficulty in determining when pain is present during general anaesthesia, it is assumed that something that is painful involves reactions of the body that are visible by clinical observation or by monitoring. Analgesia could also be defined by the combination of a stable state and the absence of pain—if the subject were conscious—during and immediately after a painful stimulus.

One of the great paradoxes of analgesia is that, by its very nature, it cannot be predicted because of the perpetual interaction between variations in stimulation and variations in the patient's anaesthetized state. Like anaesthesia, analgesia is a continuum between a perceived absence of pain and maximum pain. Analgesia can be partial and incomplete, and the notion of a threshold of analgesia depends on the state of the patient and is continually under influence of external stimuli.

## Which parameters should be used to monitor analgesia?

### *Individual perception of pain*

This chapter does not aim to consider the auto-evaluation of pain: a discussion of quantitative sensory testing of the nociceptive system in conscious subjects can be found in an article by Dotson.[8] Instead, we will look at methods that could be used in unconscious patients; elucidating the mechanisms underlying pain perception in unconscious subjects could help us to understand analgesia.

There is a relationship between the pain system and the motor, sensory and autonomic systems. Alterations to these systems, for example in a child with a significant neurological impairment, can have a profound and unique impact on the pain experience and analgesia.[9] Likewise, hypoalgesia in borderline personality disorders may primarily be due to altered intracortical processing similar to that seen in certain meditative states: there is no general impairment of the sensory-discriminative component of pain, no hyperactive descending inhibition, and no attention deficits revealed by laser evoked potentials.[10] There are also gender differences in pain perception[11–13], which might be of clinical relevance in morphine titration.[14] These differences could be explained by a more pronounced descending inhibitory control.[15] Nevertheless, there is no difference in desflurane minimum alveolar concentration (MAC) between young men and women.[16]

### *Clinical variation in the perception of analgesia*

Both the Ramsay Sedation Score and the Observer's Assessment of Alertness/Sedation Scale include response to pain in their graduated scales, reflecting an abolition of conscious pain perception.[17,18] The Cardiac Analgesic Assessment Scale is a postoperative pain evaluation instrument used in children after cardiac surgery, providing more information than a visual analogue scale completed by an observer.[19] Studies performed with anaesthetic personnel show that no variable was considered entirely specific for either intraoperative pain or depth of anaesthesia. Changes in breathing rate and volume, blood pressure, heart rate and lacrimation, as well as the presence of moist and sticky skin, were given higher scoring values as indicators of pain than as indicators of depth of anaesthesia.[20]

### *Movement and minimum anaesthetic concentration*

Under general anaesthesia, movement in response to painful stimulation is the end-point classically used to assess the potency of anaesthetic agents. Withdrawal reflexes are tailored to produce the most appropriate movement according the site at which the noxious stimulus is applied, as flexors or extensors could act as the primary movers. Areas from which a reflex can be sensitised closely match those from which the reflex itself can be evoked, providing the spinal cord is intact.[21] The principal site of response to nociceptive stimulation is spinal[22], and the interaction between analgesia and anaesthesia is inescapable.

### *Interconnection between haemodynamics and nociception*

Somatosympathetic reflexes have been characterised for more than 30 years[23], but the exact interaction between systems is still being researched because relationships are complexes.[24,25]

Some neurones from the rostral ventrolateral medulla have spinally projecting axons, and their responses to noxious mechanical, thermal and/or electrical stimulation have been shown to be accompanied by increases in arterial pressure in anaesthetised rats. In humans with spinal cord transection above vertebral level T5, profound elevations in systolic blood pressure and pulse pressure were induced by bladder distension: the authors noticed a decrease in heart rate in three of seven patients.[26] A baroreflex mechanism may explain hypertensive hypoalgesia. At rest, arterial baroreceptors are stimulated during the systolic upstroke of the pressure pulse wave. Stimulation of the baroreceptors by natural increases in blood pressure during the systolic phase of the cardiac cycle was associated with dampened nociception.

There are also interactions between angiotensin and pain perception. Untreated hypertensive subjects showed a reduced perception to painful stimuli when compared with normotensive individuals. A significant reduction in both pain threshold and tolerance was observed during enalapril or losartan treatment.[27] Hypertension diminishes pain perception, and the electrical stimulation of vagal afferent nerves (cardiopulmonary baroreceptors) suppresses nociceptive responses. In addition, both a pharmacological elevation of blood pressure and vascular volume expansion produce anti-nociception.[28]

### *Autonomic reactions*

Autonomic reactions, such as tachycardia, hypertension, sweating and lacrimation, have usually been regarded as signs of nociception or inadequate analgesia, heart rate being less consistent than blood pressure response. Isoflurane used as a sole agent is unable to suppress haemodynamic reactions (blood pressure and heart rate) to painful stimuli.

The lack of motor response is not an accurate predictor of the ability of an agent to depress haemodynamic reactions[29], but haemodynamic responses after noxious stimulation such as laryngoscopy or tracheal intubation are still considered to be the responses which are easiest to interpret during anaesthesia.[30] Motor or haemodynamic responses to nociceptive stimuli could, a posteriori, serve to adapt the dosage of hypnotic or analgesic agents, and heart rate variations have been used to automatically amend remifentanil target-controlled infusion during general anaesthesia.[31] Tentative measures for standardisation have been proposed by Evans, using the PRST (blood Pressure, heart Rate, Sweating, Tears) score of responsiveness (Table 1).

Stimulation of the sympathetic system in response to noxious stimulus is, however, not always the case. Parasympathetic stimulation can occur, with opposite responses (Table 2).

Different types of pain can lead to particular reactions. For example, the mesenteric Pacinian corpuscle is the baroreceptor that probably initiates the vasomotor reflexes in skin and muscle[32] during abdominal pain.

Chronotropic and inotropic responses to the noxious stimulation caused by laryngoscopy or surgical stimulation can be effectively suppressed by beta-receptor blockade[33], and esmolol leads to analgesia and a reduction in cardiovascular responses to pain in the non-sedated rat.[34] Esmolol does not attenuate the heart rate response to sternotomy but does attenuate the increase in blood pressure in patients receiving chronic beta-blocker therapy.[35] Perioperative esmolol administration during anaesthesia reduced the intraoperative use of isoflurane and fentanyl by 25%, decreased haemodynamic responses and reduced morphine consumption by 30% for the first 3 postoperative days in patients undergoing a hysterectomy.[36]

**Table 1.** Evans' PRST score.

| Clinical signs | Conditions | Score |
|---|---|---|
| Systolic arterial pressure (mmHg) | < Control + 15 | 0 |
| | < Control + 30 | 1 |
| | > Control + 30 | 2 |
| Heart rate (beats per minute) | < Control + 15 | 0 |
| | < Control + 30 | 1 |
| | > Control + 30 | 2 |
| Sweating | None | 0 |
| | Skin moist to touch | 1 |
| | Visible beads of sweat | 2 |
| Tears | No excess of tears in open eye | 0 |
| | Excess of tears in open eye | 1 |
| | Tears overflow closed eye | 2 |

Vagal afferent nerves are thought to mediate autonomic responses evoked by noxious mechanical or chemical oesophageal stimuli, and participate in the perception of pain originating from the oesophagus. The fibres involved in this mechanism include both A and C fibres.[37] Sesay et al have evaluated electrocardiographic (ECG) spectral analysis during surgery on the cerebellopontine angle. Vagal reactions were defined as a decrease in heart rate or an increase in HF of more than 10% of the pre-stimulus value.

**Table 2.** Responses of major organs to autonomic nerve impulses.

| Organ | Sympathetic stimulation | Parasympathetic stimulation |
|---|---|---|
| Heart | Increased heart rate $\beta_1$ (and $\beta_2$) | Decreased heart rate |
| | Increased force of contraction $\beta_1$ (and $\beta_2$) | Decreased force of contraction |
| | Increased conduction velocity | Decreased conduction velocity |
| Arteries | Constriction ($\alpha_1$) | Dilatation |
| | Dilatation ($\beta_2$) | |
| Veins | Constriction ($\alpha_1$) | |
| | Dilatation ($\beta_2$) | |
| Lungs | Bronchial muscle relaxation ($\beta_2$) | Bronchial muscle contraction |
| | | Increased bronchial gland secretions |
| Eye | Dilatation of pupil ($\alpha$) | Constriction of pupil |
| | Contraction of sphincters ($\alpha$) | Increased lacrimal gland secretions |
| Liver | Glycogenolysis ($\beta_2$ and $\alpha$) | Glycogen synthesis |
| | Gluconeogenesis ($\beta_2$ and $\alpha$) | |
| | Lipolysis ($\beta_2$ and $\alpha$) | |
| Kidney | Renin secretion ($\beta_2$) | |
| Bladder | Detrusor relaxation ($\beta_2$) | Detrusor contraction |
| | Contraction of sphincter ($\alpha$) | Relaxation of sphincter |
| Uterus | Contraction of pregnant uterus ($\alpha$) | |
| | Relaxation of pregnant and non-pregnant uterus ($\beta_2$) | |
| Submandibular and parotid glands | Viscous salivary secretions ($\alpha$) | Watery salivary secretions |

This monitoring permits the detection of intraoperative vagal reactions earlier than is allowed by the conventional monitoring of heart rate[38], as could be seen during a study of hysteroscopy.[39] The vagus nerves supply the guinea-pig oesophagus with nociceptors in addition to tension mechanoreceptors.[37] Susceptibility to vasovagal reactions after a noxious stimulus may be associated with individual differences in baroreflex sensitivity.[40]

*Monitoring the cardiac autonomic system: heart rate variability.* Cardiac autonomic function is estimated by heart rate variability measures and is expressed in the time domain as the mean of R–R intervals for normal heart beats and the standard deviation of all normal R–R intervals. The spectral analysis of heart rate variability allows a continuous, non-invasive quantification of cardiac autonomic function, pure vagal activity being assessed by high-frequency power (0.15–0.4 Hz). Low-frequency power (0.04–0.15 Hz) reflects both parasympathetic and sympathetic control.

Numerous studies of ischaemic heart disease have used this method, demonstrating the clinical significance of heart rate variability analysis. An acute noxious stimulus appears to produce an increase in respiratory-related sympathetic heart rate control and a significant decrease in respiratory-related parasympathetic control in adults and infants. Stressful events during the heel-prick procedure in newborn infants[41] or painful stimuli in children[42] could be evaluated by this method. With increasing age, the sympathetic and parasympathetic changes appear to be less intense but more sustained.[43] Limitations of this method are artefact detection and the necessity for a long enough period of signal sampling. Wavelet analysis could be helpful with this indication.[44]

*Skin vasomotor reflexes*

Testing the skin vasomotor reflexes (SVmR) by laser Doppler flowmetry is a recognised method of measuring peripheral dysautonomia and can detect an impairment of the reflex control of fingertip blood flow in both diabetes mellitus and leprosy.[45] The reflex control of fingertip blood flow is assessed by measuring the reduction in laser Doppler flowmetry induced by a deep inspiratory gasp, a cold challenge of immersing the contralateral hand in cold water or electrostimulation of the ulnar nerve. Patients with diabetic neuropathy had resting laser Doppler flowmetry levels significantly lower than those of the uncomplicated group and showed a substantial impairment of both the inspiratory gasp and cold challenge reflexes.[46]

A sympathetic vasoconstrictor reflex is induced by noxious stimulation: laryngoscopy alone and intubation with laryngoscopy significantly reduced skin blood flow.[47] Shimoda et al evaluated SVmR in response to laryngoscopy. A decrease in SVmR amplitude to less than 0.1 u before laryngoscopy is associated with blood pressure stability. SVmR amplitude and systolic blood pressure changes showed a significant linear correlation.[48]

SVmR is also useful to estimate objectively the level of somatosensory block induced by regional anaesthesia.[49,50] Shimoda et al demonstrated that the level of current that induced the SVmR was proportional to the depth of anaesthesia induced by sevoflurane, and that the duration of electrostimulation (i.e. painful increase) was correlated to the magnitude of the SVmR.[51] Thus, the SVmR could be helpful in the objective assessment of nociception and anti-nociceptive effects in individual cases. These authors also investigated the SVmR and haemodynamic responses to the

insertion of an intubating laryngeal mask airway and found that the most stressful period was removal of the airway.[52]

Nakahara et al determined the MAC of anaesthetic that blocked the SVmR to surgical incision (MACBVR) for sevoflurane in 37 patients.[53] They found that the MACBVR contribution to the total anaesthetic MAC multiple was 1.75 MAC for sevoflurane alone and 1.43 MAC when 50% nitrous oxide was used. There was no relationship between the amplitude of the reduction in skin blood flow and any changes in haemodynamic variables. Owing to its resistance to chronic ischaemia, the SVmR is preserved in chronically ischaemic limbs with non-diabetic, atherosclerotic peripheral arterial disease.[54]

Neuropeptide Y participates in sympathetically mediated cutaneous vasoconstriction.[55] Owing, however, to the cost of the device to measure its level, this technique is used only in research.

### *Plethysmography*

*Plethysmogram amplitude*. Sustained pinching of the interdigital webs of the hands of human volunteers induced a tonic reflex vasoconstriction in the stimulated hand with a rather slow adaptation rate and no signs of habituation between trials. Step increases in the pinching force in the course of a stimulus were reflected by a decrease in amplitude of the plethysmogram.[56] This reflex occurred at a spinal level but could be inhibited by the cerebral hemispheres.[57] Skin incision is followed by a clear sympathetic vasoconstrictor response in the plethysmographic signal, and suppression of the photoplethysmographic pulse wave reflex to a nociceptive stimulus has also been found to predict a reduced haemodynamic response to tracheal intubation.[58]

The pulse wave reflex may be a better predictor than other variables. In another study, the best variables for logistic regression classification in movers versus non-movers at incision appeared to be response entropy, instant RR and plethysmogram notch amplitude. Plethysmogram notch amplitude was measured as the distance from the baseline to the lowest value of the notch (Figure 1).[59] Nevertheless, arterial pressure was not incorporated into the variables studied.

*Pulse transit time*. PTT was originally measured by recording the time interval between the passage of the arterial pulse wave at two consecutive sites. More recently, for ease of measurement, the electrocardiographic R or Q wave has been used as the starting

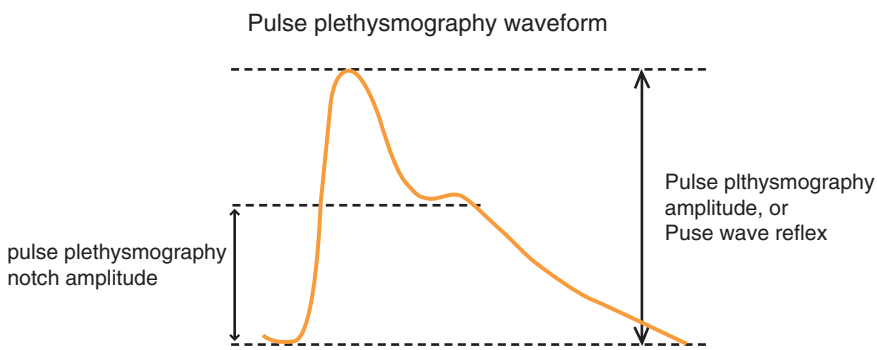


**Figure 1.** Parameters measured from the pulse plethysmography waveform.

point as it approximately corresponds to the opening of the aortic valve. This 'new' pulse transit time (rPTT), the interval between ventricular electrical activity and the arrival of a peripheral pulse waveform, has been used to detect changes in autonomic tone and in inspiratory effort. Noxious stimulation can affect this parameter: during anaesthesia, rPTT decreased by an average of $43 \pm 25$ ms in response to endotracheal intubation but did not vary in response to the insertion of laryngeal mask airway or to a surgical stimulus.[60] This measure does not seem suitable, but further studies are needed.

The major problem with SVmR and plethysmography-derived measures is that skin blood flow is profoundly influenced by not only pathological states, but also thermoregulatory state, age and emotional stress.[61–63]

*Pupil*

Iris activity reflects physiological reactions to different sensory stimuli, resulting in a variation in pupil size. As such, pupillometry is a method that can provide valuable data concerning the functioning of the autonomous nervous system.[64] Pupil size reflects the interaction between the sympathetic and parasympathetic divisions of the autonomic nervous system and can be used to evaluate brainstem function in comatose patients.[65] Noxious stimulation and the cold pressure test dilate the pupil—pupillary reflex dilatation (PRD)—in both unanaesthetised and anaesthetised humans.[66] In the absence of anaesthesia, dilatation is primarily mediated by the sympathetic nervous system. In contrast, under anaesthesia, pupillary dilatation in response to noxious stimulation or desflurane step-up is mediated principally by inhibition of the midbrain parasympathetic nucleus, although the exact mechanism remains unknown.[67] PRD is not present in organ donors (Yang). In addition, esmolol does not block PRD in anaesthetised volunteers.[68]

Pupillary size and reactivity have long been a critical component of the clinical assessment of patients with or without neurological disorders.[69] Neuromuscular blocking drugs do not alter the pupillary light reflex.[70] Infrared pupillary scans have been used extensively as an objective measure of pupillary reflexes during pharmacological studies on human subjects.[71] Women show greater pupillary dilatation than men, this gender difference in pain perception being beyond voluntary control and reflecting low-level sensory and/or affective components of pain.[11] Pupillometry has served to assess the bioavailability of rectal and oral methadone in healthy subjects[72], as well as, for example, the influence of age or cytochrome P4503A activity on the acute disposition and effects of oral transmucosal fentanyl citrate.[73,74] Pupillometry is also able to quantify the extent and time course of the effects of morphine-6-glucuronide.[75] Similarly, the pharmacodynamics of epidural alfentanil, fentanyl and sufentanil have been studied with this method.[76,77]

Dynamic pupillometry with automatic recording has recently been developed.[78,79] PRD is measured using an ophthalmic ultrasound biomicroscope (Oasis Colvard Pupillometer) or video-based pupillometer (Procyon video pupillometer, FIT 2000, videoalgoscan). The pupillary response to noxious stimulation induced by electrical fingertip stimulation was investigated in volunteers by Chapman et al.[80] These authors found that PRD began at 0.33 seconds and peaked at 1.25 seconds after the stimulus. PRD increased significantly in peak amplitude as the intensity of the stimulus increased.

Larson et al showed that alfentanil exponentially impaired the PRD, decreasing the maximum response amplitude from 5 mm at 0 ng/ml, to 1.0 mm at 50 ng/ml, and to 0.2 mm at 100 ng/ml.[81] In contrast, alfentanil administration had no effect on

the pupillary light reflex. Dilatation of the pupil in response to a noxious stimulus is a measure of opioid effect, and this stimulus-induced pupillary dilatation may be used to evaluate the analgesic component of a combined volatile and opioid anaesthetic. The relative variations of PRD (+233%) are more sensitive than those of heart rate (+19%) or arterial pressure (+13%) after an electrical stimulus (65–70 mA, 100 Hz) has been applied to the skin of the abdominal wall.[68] During anaesthesia, PRD allows an estimation of the sensory level during combined general/epidural anaesthesia in adults.[82] The supraspinal effects of epidural fentanyl can be assessed during general anaesthesia using infrared pupillometry, maximum suppression being 70±15% for the epidural route and 96±3% for the intravenous route.[83] In children, a PRD of 0.2 mm is sensitive to the loss of analgesia.[84] PRD during anaesthesia is not initiated by slowly conducting C fibres, and fentanyl at 3 μg/kg depresses the reflex.[85] During propofol anaesthesia in healthy patients, the fall in PRD is a better measure of the progressive increase in effect of a remifentanil concentration up to 5 ng/ml than are haemodynamic measures or the bispectral index (BIS). Pupil dilatation in response to 100 Hz tetanic stimulation decreased progressively from 1.55 (0.72) to 0.01 (0.03) mm as remifentanil concentration increases.[86] Similar responses have been found also in children by Constant et al.[87]

Quantitative pupillary measurements can be reliably obtained during anaesthesia with newer pupillometers. Continuous improvements are seen in the flexibility and recording capacity of pupillometers, and they are used in an increasing number of medical fields, including anaesthesiology.

The limitations of this method are that droperidol and metoclopramide constrict the pupil and block the pupillary dilatation brought about by nociceptive stimuli, whereas ondansetron does not. Larson recommends that when pupillary diameter measurements are used to gauge opioid levels during experimental conditions or during surgical anaesthesia, antiemetic medication acting on the dopamine D2 receptor should be avoided.[88] Clonidine also modifies the central norepinephric control of pupillary function.[89] Autonomic neuropathies and spinocerebellar degeneration syndromes are strongly associated with pupillary abnormality, both at rest and in tonic conditions, and may disturb monitoring.

### *Ocular microtremor*

Ocular microtremor is a physiological tremor whose frequency is related to the functional status of the brainstem. It is suppressed by propofol and sevoflurane in a dose-dependent manner. Sevoflurane and ocular microtremor accurately predict response to verbal command.[90] Ocular microtremor may be a useful monitor of depth of hypnosis, but further studies are needed despite encouraging results in the evaluation of preoperative analgesia.[91]

### *Spontaneous EEG*

The effects of noxious stimulation on the EEG have long been studied to monitor cerebral function.[92] The basic EEG responses to noxious surgical stimulation have not been clearly defined, which has been a major factor limiting the clinical use of the EEG to monitor anaesthesia.

*Bispectral index.* The BIS is a statistical index involving the weighted average of three subparameters that analyse the phase and frequency relations between the component

frequencies in the EEG.[93] It changes with increasing concentration of anaesthetic agents and is correlated with sedation scales. The BIS correlates well with the hypnotic component of anaesthesia but predicts movement in response to surgical stimulation less reliably, especially when different combinations of hypnotic and analgesic drugs are used. Use of the BIS has been shown to prevent awareness in at-risk patients.[94]

Early studies with the BIS show that it could be a useful predictor of whether patients will move in response to skin incision during anaesthesia with isoflurane/oxygen or propofol/nitrous oxide and no opioid.[95,96] Leslie et al[97] have compared several parameters in 10 propofol-anaesthetised volunteers and determined their prediction probability of movement. The BIS (PK = 0.86), 95% spectral edge frequency (PK = 0.81), pupillary reflex amplitude (PK = 0.74) and systolic arterial blood pressure (PK = 0.78) did not differ significantly from those of a modelled propofol effect-site concentration (PK = 0.76). In a study of 60 unpremedicated adults[98], a BIS of 60 separated patients responding to laryngeal mask airway insertion from non-responders ($P = 0.006$), with a sensitivity of 68% and a specificity of 70%. Movement response was not predicted by cardiovascular changes. Sebel et al, in a multicentre study, pointed out that, when opioid analgesics were used, the correlation to patient movement became much less significant, so that patients with apparently 'light' EEG profiles could not move or otherwise respond to incision. Therefore, the adjunctive use of opioid analgesics confounds the use of BIS as a measure of anaesthetic adequacy when movement responses to skin incision[99] or to another noxious test[100] are used.

BIS and sevoflurane end-tidal concentration are reliable guides to the depth of sedation, with prediction probability values of 0.966 and 0.945, respectively, but not to the adequacy of anaesthesia for preventing movement.[101] In a same way, Doi et al[102] have shown that the auditory evoked potential (AEP) index discriminated between movers and non-movers with a prediction probability of 0.872. BIS, spectral edge frequency and median frequency could not predict movement at laryngeal mask airway insertion in patients anaesthetised with propofol and alfentanil. The addition of remifentanil to propofol affected the BIS only when a painful stimulus was applied.[103] Moreover, remifentanil attenuated or abolished increases in BIS and MAP after tracheal intubation in a comparable dose-dependent fashion.

In another study with sevoflurane[104], the prediction probability values for AEP index, BIS and sevoflurane concentration for sedation score were 0.820, 0.805 and 0.870, respectively, indicating a high predictive performance for depth of sedation. AEP index and sevoflurane concentration successfully predicted movement after skin (prediction probability 0.910 and 0.857, respectively), whereas BIS did not (prediction probability 0.537). Despite these limitations, BIS might be a useful clinical monitor for predicting patient movement to command during the intraoperative wake-up test in scoliosis surgery[105], particularly when controlled hypotension is used and haemodynamic responses to the emergence of anaesthesia are blunted.

There are, however, various limitations of the BIS. Vivien et al pointed out the fact that the fall in BIS following the administration of myorelaxant was significantly correlated to the BIS.[106] During fentanyl-induced muscular rigidity, BIS recordings reflect EMG variations. When assessing BIS in the absence of neuromuscular blockade, it is necessary to evaluate the effect of the electromyelogram (EMG) on the BIS before making conclusions about depth of sedation. Fentanyl-induced rigidity appears to be a dose-related phenomenon that an EMG variable of BIS 3.4 is able to quantify.[107] It must be borne in mind that BIS is primarily a sedation monitor.

*Entropy*. Entropy is a quantitative measure used to determine the disorder or randomness in a closed system, in the sense of thermodynamic/metabolic processes or the increasing molecular disorder in a structure, according to Boltzmann's definition of entropy ($S$) $S = k \ln(\Omega)$. The second law of thermodynamics states that the entropy (and disorder) increases as time moves forward. Shannon has extended this concept to information theory and defines entropy in terms of a discrete random event $x$, with possible states $1,\ldots,n$ as:

$$H(x) = -\text{Sum}_i(p(i)\log(p(i))).$$

There are multiple ways in which to compute the entropy of a signal: in a time domain, as approximate entropy[108,109] or as Shannon entropy.[110] In the frequency domain, spectral entropy may be computed; this is the case for the Datex-Ohmeda Entropy Module, a new EEG monitor designed to measure depth of anaesthesia.[111] The monitor calculates a 'state entropy', computed over the frequency range 0.8–32 Hz, and a 'response entropy', computed over the frequency range 0.8–47 Hz. The difference between the response and state entropies is a reflection of the high-frequency activity of the EEG, and includes by nature some EMG-frequency components.

Some studies with this monitor have now been published. It appears that it has the same lack of sensibility as the BIS when analgesics drugs are used, for example with ketamine[112] or nitrous oxide.[113] An elevated difference between response entropy and state entropy is related to a significant increase in state entropy, blood pressure and heart rate, response entropy during painful stimulation is seen more often in patients anaesthetised with 0.8% compared with 1.4% isoflurane. Response entropy more probably reflects the frontal EMG and may be useful to identify inadequate anaesthesia and patient arousal during painful stimulation.[114]

Vanluchene et al[115] compared state entropy, response entropy and BIS when measuring loss of response to verbal command (LOR(verbal)) and noxious stimulation (LOR(noxious)) during propofol infusion with and without remifentanil. BIS, state entropy and response entropy all detected LOR(verbal) accurately, but BIS performed better at 100% sensitivity. The sensitivity/specificity for the detection of LOR(verbal) decreased for all methods with increasing Ce(REMI). LOR(noxious) was poorly described by all measures. Future studies are needed to elucidate the role of response entropy in terms of analgesia monitoring.

*Evoked EEG*. Animal and human cerebral evoked potentials have been employed for years in pain research to describe pain perception physiology and to test the effectiveness of various analgesics.[116,117] More recently, positron emission tomography has revealed significant changes in pain-evoked activity within multiple cerebral regions, particularly the anterior cingulate cortex.[118] Subdivision of the anterior cingulate cortex into an anterior non-specific attention/arousal system and a posterior pain system explain the interaction between alertness and pain.[119]

*Mid-latency AEPs* are small changes noted on the EEG that are caused by discrete auditory stimuli. AEPs are more sensitive to pain stimuli than are spectral features of the spontaneous EEG[120] or BIS.[102] The A-Line Auditory Evoked Index (AAI) is a unique device commercially available for depth of anaesthesia monitoring. Values of the index range between 0 and 100, but there is a wide variation in the awake values and a considerable overlap of AAI values between consciousness and unconsciousness, suggesting that further improvement of the AAI system is required.[121,122]

Unlike AEPs, because of the variability in latency and the difficulties of repeating stimulation, *somatosensory evoked cerebral potentials* are analysed by calculating the spectral power in selected frequency bands and frequency percentiles from the spontaneous EEG segment preceding each somatosensory stimulus. Late cortical somatosensory evoked potentials response parameters are calculated from the respective post-stimulus EEG segments.

Spectral analysis of the late cerebral (later than 80 milliseconds) components of the potential evoked by painful somatosensory stimuli reveals a stimulus-induced increase of power in the low frequencies—delta and theta. The pre-stimulus:post-stimulus relationship of the delta waves was found to be the most sensitive measure for monitoring the cerebral bioavailability of meperidine.[123] Under halothane anaesthesia, late somatosensory evoked potentials and haemodynamic responses in response to painful electrical stimuli are abolished by fentanyl.[124] The same authors showed that the analgesic effect of low-dose ketamine (0.25 and 0.5 mg/kg) could be quantified by somatosensory evoked potentials, especially by a dose-dependent decrease of the long-latency N150-P250 somatosensory-evoked late cortical response.[125]

Laser-evoked potentials are nociceptive-related brain responses to activation of the cutaneous nociceptors by laser radiant heat stimuli. The cost of the technique is the major limitation to its development.

## Monitoring analgesic administration

The computer administration of opioids by target-controlled infusion contributes to the monitoring of analgesia.[126,127] Real-time displays of intravenous anaesthetic concentrations and effects could significantly enhance intraoperative clinical decision-making by a visualisation of pharmacodynamic relationship between hypnotics and analgesics.[128]

## Titration of opioids during noxious events

The majority of clinical studies have focused on the BIS. Brocas et al showed that an alfentanil bolus of 15 μg/kg markedly reduced the increase in BIS values, blood pressure and heart rate observed immediately after tracheal suction, whereas there are differences in Ramsay scores.[129] Godet et al showed that maintenance of anaesthesia predominantly with propofol and a low dose of remifentanil, administered in accordance to the BIS, was associated with a greater stability in perioperative haemodynamics.[130] Likewise, sufentanil effect-site concentrations adjusted on BIS values and variations could achieve good haemodynamic tolerance.[127] In cardiac patients, titration of propofol using the BIS allows a significant reduction in propofol consumption, with only minor effects on the stress response in these conditions.[131]

## Considerations of stability

Analgesia is a stable state seen both during and after a noxious stimulus. One of the questions of importance here is the definition of stability. For example, a system is stable if it can maintain equilibrium after stimulation, and adequate analgesia could be defined in terms of resistance to change. In control theory, stability characterises the reaction of a dynamic system to external influences. Likewise, haemodynamic stability is often defined by a lack of variation between 20% under or upper reference heart rate

or arterial pressure. This percentage is guided by experience and can be changed if a more stable state is required. Absolute or relative percentages of variation, coefficients of variation, standard deviations and ranges are parameters available to describe stability. Variations in statistical significance are not always of great clinical use. Analgesia is a temporal state and must always be topped up against a background of duration and intensity of stimulation.

## CONCLUSION

If information collected from the EEG response entropy, heart rate and pulse plethysmography of anaesthetised patients is combined, a significantly improved classification performance (96%) between movers and non-movers to skin incision is achieved compared with discrimination using any single variable alone. This suggests that a combination of information from different sources may be necessary for monitoring the level of nociception during anaesthesia.[59]

Pupillometry seems to be a promising generalised tool, but we must aware of being too enthusiastic towards it because there are commercially available analgesia monitors who no longer still exist.[132] Many candidate signs are available for analgesia monitoring (Table 3). But whatever the latest monitors are like[133,134], they will never be able to predict whether the depth of analgesia is sufficient for the next painful surgical stimulus:

**Table 3.** Different parameters available for monitoring analgesia.

| | Parameter to be monitored |
|---|---|
| Clinical scales | PRST score |
| | Sedation scores |
| Effect of pain | |
| Sympathetic system | Direct microneurography |
| | Heart rate variability |
| | Spectral analysis of heart rate |
| | Low-frequency/high-frequency power ratio |
| | Arterial blood pressure |
| | Skin vasomotor reflexes: laser Doppler flowmetry |
| | Plethysmogram amplitude, notch amplitude |
| | Pulse transit time |
| Ventilation | Respiratory rate |
| Pupil | Pupillary reflex dilatation |
| Brainstem | Ocular microtremor |
| Spinal | Movement |
| Cerebral | Response entropy |
| | Auditory evoked potentials |
| | Somatosensory evoked potentials |
| | Spectral analysis of late cerebral potential components |
| | Bispectral index |
| Action of analgesics | Plasma concentration |
| | Theoretical concentrations with target-controlled infusions |
| | Secondary effects: heart rate, respiratory rate |
| Action of anaesthetics | End-tidal concentrations of inhaled anaesthetics |
| | Theoretical concentrations of intravenous drug |

they can only monitor the anaesthetic state at the time of measurement, and the balance between excitation and responsiveness. Anaesthetists must always consider their experience ahead of any technique for monitoring the depth of analgesia.

Multiparametric approaches are probably the best way to deal with monitoring analgesia.[135] Like Kutas and Federmeier[136], we could say that a combination of measures—old and new, central and peripheral—will ultimately provide the greatest power to resolve the questions we hope to answer, using all the physiological measures at our disposal, in our quest to understand the nature of the relationship between mind and body, between analgesia and anaesthesia.

**Research agenda**

- characterise the mechanisms of pain perception
- characterise the mode of action of analgesics
- characterise individual variations in and intervariability of events related to noxious stimuli
- develop plethysmography-derived and pupillary reflex indices
- include the pharmacodynamics of hypnotics/analgesics in EEG automated depth of anaesthesia systems
- develop data-fusion systems and multimodal monitoring of analgesia

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