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REVIEW ARTICLE

Evoked responses in anaesthesia

C. THORNTON AND R. M. SHARPE

The aim of this review is first, to provide the clinical anaesthetist with a sufficient background regarding evoked responses, and second, to present current research in this sphere, thereby allowing an appraisal to be made of the usefulness of evoked potentials in the clinical setting. We shall consider: (1) the background, including the origins of the various evoked response components and the technical and subject related factors which should be considered when using evoked responses; (2) potential clinical applications: (a) as a monitor of awareness and depth of anaesthesia/sedation; and (b) for the assessment of nociception and pain.

Background

Evoked responses are derived from the electroencephalogram (EEG) in response to auditory, somatosensory, nociceptive and visual stimuli. These evoked responses are obvious candidates for investigation as they reflect the *functional integrity* of specific peripheral and central nervous system (CNS) regions in humans. The changes that occur in the evoked responses allow anaesthetists to assess the effects of the drugs that they are administering on the target site, namely the brain, *in vivo*. Consequently, interest in evoked response monitoring in the three speciality areas of clinical anaesthesia (general anaesthesia, intensive care and pain assessment), has increased considerably in the past 10–15 yr. This review explores the potential usefulness of evoked responses in fulfilling these aims, based on an understanding of the research in these areas.

PRODUCTION OF THE EVOKED RESPONSE

Many types of stimuli evoke a response in the EEG. To extract the response from background "noise", signal averaging is necessary to produce an "averaged" evoked response. Modern techniques digitalize EEG waveforms for a specified time after the stimuli and add them together. The response to the stimulus emerges and background noise which occurs randomly with respect to the stimulus is therefore cancelled out. These techniques require the stimulus to be applied at a known and precise point in time. This is straightforward for auditory, visual, electrical and laser stimuli, but less so for mechanical stimuli.

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ORIGINS OF THE EVOKED RESPONSE

Different evoked responses reflect different functional or anatomical areas of the brain. The auditory, somatosensory and laser evoked responses waveforms are shown in figures 1, 2 and 3, respectively.

The auditory evoked response (AER) waveform with its series of peaks and troughs represents the passage of electrical activity from cochlea to cortex. Figure 1 shows 11 waves generated by a sound stimulus given at the origin on a logarithmic scale. The brainstem waves represented by the Roman numerals I–V are generated from sites in the brainstem.[46 47 57] The early cortical (or middle latency waves) No, Po, Na, Pa, Nb are generated from the medial geniculate and primary auditory cortex.[50 90] The late cortical waves P1, N1, P2, N2 and P3 are generated from the frontal cortex and the association areas.[55 80]

Somatosensory evoked potentials (SEP) can be recorded by stimulating almost any nerve trunk at various levels. The most frequently studied are those in response to median and ulnar nerve stimulation. Constant current stimulation of the median nerve through a pair of surface electrodes strapped to the patient's wrist gives the responses generated by the fine touch somatosensory pathway (fig. 2). N13 is thought to originate from the dorsal column nucleus cuneatus,[56] N14 from the medial lemniscus,[1] and N20 and N35 from the region of the thalamus and primary cortex.[1 25 38] Subsequent waves probably originate from the frontal cortex and association cortices.

The SEP elicited in response to cutaneous painful stimuli have a longer latency depending on the site and type of stimulus. The nociceptive signal travels via small diameter myelinated A-delta and unmyelinated C-fibres to the dorsal horn via the dorsal root ganglion. Second order neurones relay the signal to the thalamus via the spinothalamic tract. Third order neurones project from the thalamus to the primary sensory cortex where the conscious perception of pain occurs.[16]

A "vertex potential"[3] is the SER associated with the sensation of pain and it is labelled according to polarity (P = positive and N = negative) and latency. Components with latencies at 100–700 ms are thought to coincide with secondary cortical processing involved in stimulus recognition and localization and with the magnitude and characterization of painfulness. These are called *late* components (fig. 3A) to distinguish them from the *ultra late* components (fig. 3B) which have latencies of 1–2 s.[2 15 43]

C. THORNTON, PHD, R. M. SHARPE, FRCA, Academic Department of Anaesthetics, Imperial College School of Medicine, Northwick Park and St Mark's Hospitals, Harrow HA1 3UJ.

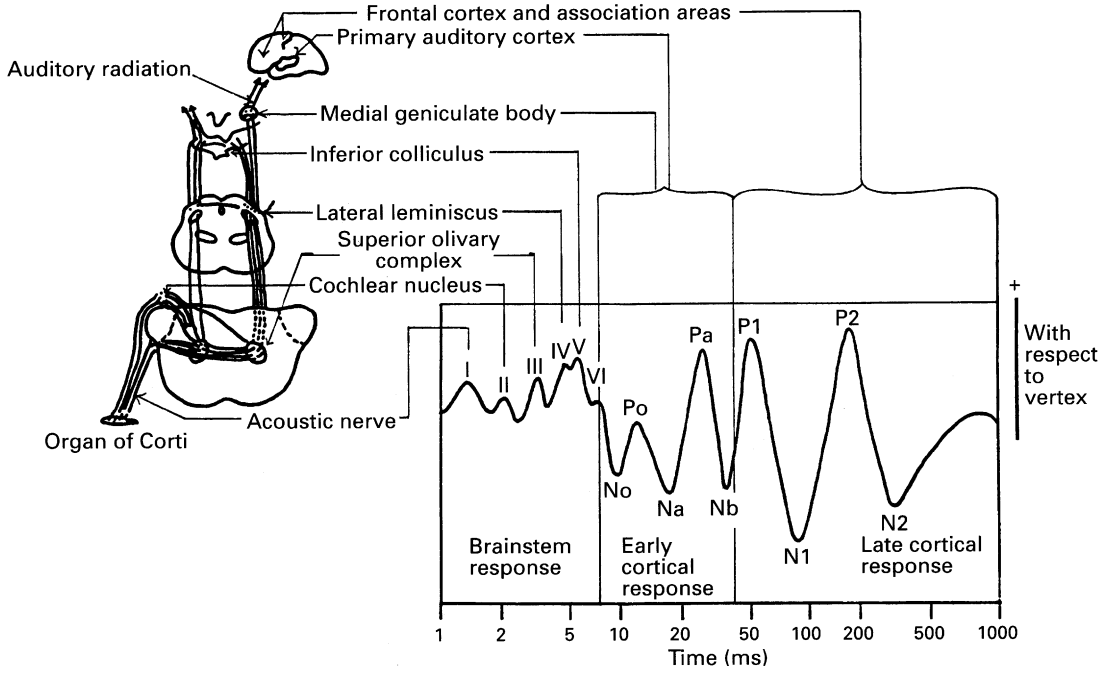

Figure 1 Auditory evoked response. This diagram describes the nomenclature of the response and shows its anatomical relationship with the auditory neuraxis. The brainstem response has a well documented anatomical relationship with the auditory neuraxis, whereas later responses have origins which are less easy to define.

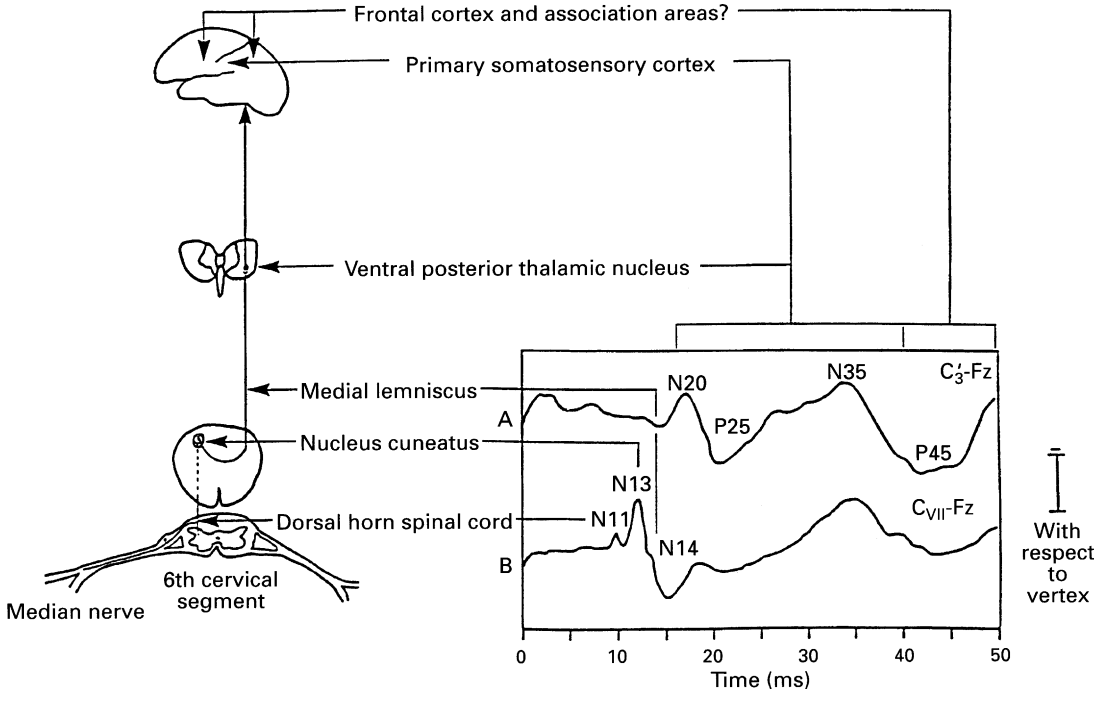

Figure 2 Somatosensory evoked response. This diagram shows waveforms obtained when the stimulating electrode is placed at the wrist above the median nerve and the recording electrodes are above (A) the somatosensory cortex and (B) the seventh vertebra. The nomenclature of the response and its anatomical relationship with the fine/touch somatosensory neuraxis is shown.

Visual evoked responses have been studied extensively by neurophysiologists, but little research exists with respect to anaesthesia.

EVOKED RESPONSE—TECHNICAL CONSIDERATIONS

Equipment for recording and analysing evoked responses

A system that can be used to record evoked responses is shown in figure 4. Developed at Northwick Park Hospital[49] specifically for use in the operating theatres, it consists of a small multichannel pre-amplifier, linked via an optical fibre cable to a personal computer (PC) fitted with a specially adapted digital signal processing board. This ultimately could fit into any multimode monitoring device. The EEG is recorded from scalp electrodes, amplified and relayed to the computer. The pre-amplifier also produces the stimulus, in the diagram an auditory stimulus, which is applied to the patient's ears via miniature earpieces. Software installed on the PC

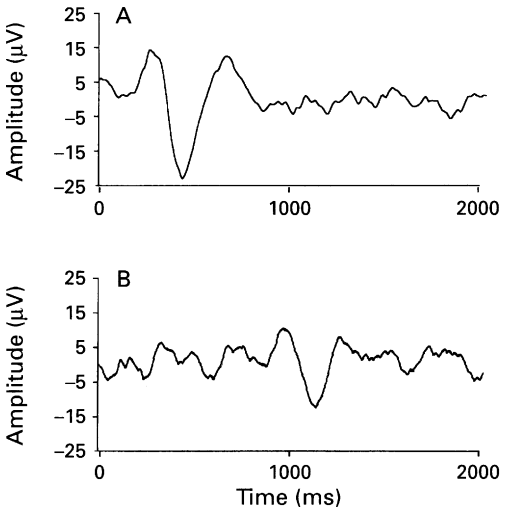

Figure 3 Argon laser-evoked vertex potentials, showing (A) the late potential, latency 430 ms and (B) a single sweep ultralate potential with a latency of 1150 ms.

analyses the EEG with respect to the stimulus to produce an averaged evoked response, which is constantly updated and displayed on the screen. There are a number of commercial evoked response systems available. Apart from the obvious features such as portability and ease of use, the equipment should be flexible in terms of filtering and analysis. For use in the operating theatres, good isolation against diathermy frequencies to prevent damage to the amplifiers and a low intrinsic noise level are required.

The following sections review briefly the technical details, such as electrode placement, stimulus type and repetition rate, how many responses should contribute to the average and what filtering should be applied? Many of the methodologies were developed previously by audiologists, neurologists and psychologists who were the first to use evoked response techniques routinely. These technical considerations and the factors affecting the evoked responses have been fully reviewed previously.[82]

Electrode placements

All evoked responses derived from the EEG described, are recorded from bipolar surface electrodes. In the case of the auditory evoked responses shown in figure 1 the electrical potential recorded from an electrode placed on the centre of the top of the head (reference or inactive electrode) is subtracted from that recorded from an electrode placed over the temporal lobe, on the mastoid process (active).

Some evoked responses can be recorded using an active electrode placed at a distance from the neural generator (farfield potentials). For example good brainstem and early cortical AER can be recorded from an active electrode placed over the inion process at the back of the head, some distance from the temporal lobe. This is useful in awake subjects as there is less interference from pre-auricular muscle tone. The late and ultra late potentials in response to nociceptive stimuli are recorded from the vertex (active) referred to linked mastoids.

Stimulus characteristics

Type of stimulus. The stimulus modality depends on the sensory pathway of interest (i.e. auditory, somatosensory, nociceptive or visual). Then the precise type of stimulus has to be chosen. Early cortical auditory evoked responses are best evoked by clicks of short duration (100–500 ms). For visual responses, a short flash of approximately 12 μs duration is often chosen.

Somatosensory stimuli (mechanical, electrical or laser) can be applied cutaneously, thus stimulating peripheral receptors of specific sensory modalities such as pain and touch. Alternatively, electrical stimuli can be applied more proximally by surface electrodes over a major nerve trunk. This stimulates all modalities (including motor and sensory) in the trunk depending on the duration and intensity of the stimulus.

In pain studies using evoked potentials there is much discussion as to the suitability of stimuli. Ideally a stimulus should be: (1) exclusively painful (i.e. touch, pressure receptors, should not be triggered by non-painful stimuli); (2) quantifiable in terms of the intensity and duration; (3) easily applied, removed and repeated without generating tissue damage. Habituation to the response should not occur.

Electrical stimuli have been used extensively in pain research as they are easy to apply, quantify and repeat. However, the stimulus is unnatural and the strong electrical current required to produce pain

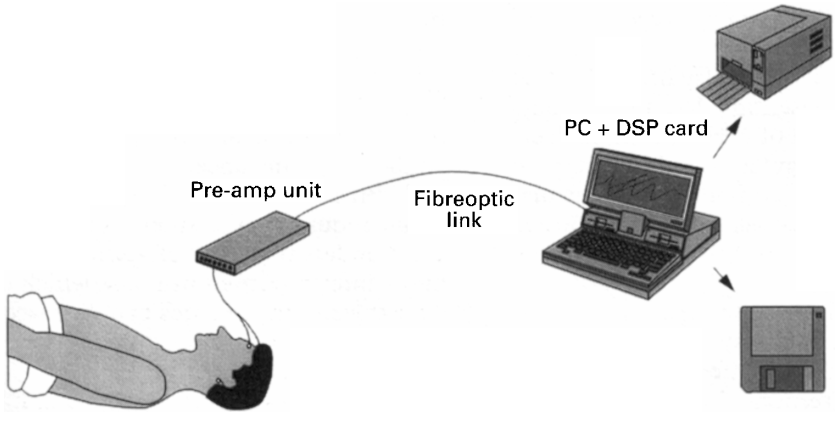

Figure 4 Recording evoked responses. The system developed at Northwick Park Hospital consists of a small multichannel pre-amplifier, linked via a fibreoptic cable to a personal computer (PC). The stimulus (in this case clicks) are generated by the pre-amplifier and presented to the patient through miniature ear-pieces.

stimulates different nerve types, including motor (A-alpha) and mixed sensory (A-beta) nerves. Thus in addition to the pain, the subject may experience twitching, tapping and tingling. Attempts have been made to modify the electrical stimulus by removing a small core of epidermis from the skin on the pulp of the finger.[14] We have used fine intradermal acupuncture needles to deliver electrical stimuli, again the stimulus is not purely nociceptive (personal observation).

Thermal stimulation elicits a sensation that is considered more "natural".[26] Many different methods have been used, but only laser emitted radiation is useful for producing pain evoked potentials. The technique produces a painful stimulus with a relatively short duration (10 ms) that is readily "time-locked" to the EEG. Additionally, the stimulus intensity is easily quantified and varied allowing the determination of "laser pain thresholds" (the least stimulus intensity at which the subject perceives pain).

Stimulus intensity. A certain level of stimulus is required to elicit a response. Between this threshold, up to a certain point, increasing the intensity of the stimulus increases the amplitude of the response and decreases latency. The stimulus intensity may be set in relation to an individual's threshold, such as is the case for the median nerve somatosensory evoked response, where the electrical stimulus is usually fixed at 1.5 times the motor twitch threshold which ensures a supramaximal sensory stimulus. Electrical and laser stimuli are easily adjusted and quantified. For the auditory and visual evoked responses the stimulus is often set at a fixed intensity above the population's average threshold.

Stimulus presentation rate. This is important clinically, as increasing the rate of stimulus presentation can reduce the time taken to carry out the test. The number of stimuli needed to produce a clear averaged response depends on the amplitude of the response in relation to the background noise. However, increasing the stimulus presentation rate above a certain value can in itself reduce response as a result of stimuli being presented within the refractory period of the previous response and as a result of response overlapping. When responses overlap, deflections of opposite polarity occur together and the amplitude of the average is reduced. Under normal circumstances a compromise has to be reached between the clarity of the response and the time taken to obtain it. Short latency waves of the auditory (early cortical) and somatosensory evoked responses can be produced by fast stimulation rates. Usually 512–1024 sweeps are averaged, representing 1–2 min of data collection at a stimulus rate of 6 Hz. Some workers find it beneficial to use irregular stimulus repetition rates to desynchronize the response from regular sources of interference such as EEG and 50-Hz mains signals.

Side of stimulation. For all three modalities, the sensory pathways cross over in the spinal cord or brain so that the side of stimulation affects the response. This lateralization of the response has been exploited to deduce the anatomical origins of the waves. After crossing over has occurred the precise location of the generators influence whether the waves are the same size or larger on the contralateral side. Stimulation from both, as opposed to one side of the body, increases wave amplitude and decreases wave latency.

Analysing the evoked response

The latencies of the peaks and troughs (in ms) along the horizontal axis and their amplitude (μV) along the vertical axis may be measured manually. This is the simplest method by which changes in evoked responses can be assessed and a valuable contribution has been made from data collected in this way.

Power spectral analysis (based on fast Fourier transformations) of the evoked response waveform has been applied by Schwender and colleagues.[72] Coherent frequency analysis may be applied to the steady state evoked response.[60] We have described an index based on the average second differential of the waveform for a time window which includes the early cortical response.[87] Doi and colleagues prefer the sum of square root of absolute difference between any two successive 0.56-ms segments of the AER waveform.[32] A novel attempt has been made by Stockmanns and colleagues[78] to derive numerical indices from evoked responses using the technique of wavelet transformation. The AER waveform is decomposed into constituent waveforms using one specific function—there are a number of known wavelet transformation functions. This approach differs from fast Fourier transformation, which is based on cosine and sine functions only. These sophisticated methods of analysis have the advantages that they are objective and can be automated but they do not necessarily provide additional or better information than the manual methods.

Filtering

To allow comparison of amplitude and latency, uniform filtering must be applied to every subject in each study (and between studies if comparisons are to be made). Some filtering of the EEG, before signal averaging and of the averaged evoked response waveform itself, can be useful. It serves to abolish frequencies which interfere with the interpretation of the waveform. Appropriate filtering can make the waveforms between runs and between subjects more reproducible but when it is too severe, it may attenuate the response of interest or even abolish it completely.[51] Digital filtering is preferable to analogue filtering as the latter can change latency and distort the signal. A compromise has to be reached, bearing in mind that both the frequency content of signal and noise may be changed by the effect or treatment studied. For instance, the dominant frequencies in children's early cortical AER are shorter than in adults requiring adjustments in filtering. The AER of children less than 2 yr of age are also more susceptible to interference from ECG, which in combination with certain filter ranges can give rise to misleading data.[63]

EVOKED RESPONSES—SUBJECT RELATED CONSIDERATIONS

Factors related to the subjects studied may influence the evoked response obtained. Consideration of these

factors is necessary when potentials are compared between different individuals and studies.

Temperature

In general, hypothermia produces an increase in latency and may also produce a reduction in amplitude, depending on the severity of the decrease in temperature.[44] Hyperthermia has the opposite effect.[12] The somatosensory evoked response is the most susceptible to changes in temperature, as a major section of the pathway is peripheral. Skin temperature influences sensory and pain thresholds elicited by laser stimulation.[4]

Skin characteristics

Skin thickness and reflectance (colour) can also influence the amount of laser energy in the vicinity of the nociceptor.[4]

Age and sex

There is much discussion on the effects of age and sex on the evoked responses, which may suggest that the effects are not large compared with the population variability and therefore can largely be discounted with respect to anaesthesia and ITU monitoring. The general trend for all responses is an increase in latency with age. Differences in amplitude may relate more to skull size than to age or sex. In some cases the elderly are less sensitive to laser stimuli, reductions in amplitude with increased latency were observed with increasing age.[37]

Natural sleep and level of arousal

The waves of the auditory evoked response before 30 ms (Pa) appear stable to changes in the level of arousal (i.e. sleep, level of alertness). Later waves change dramatically during sleep. Pb/P1 completely disappears during deep (stages 3 and 4) natural sleep.[33] It is this aspect which has been exploited to measure potential awareness during anaesthesia. In awake subjects, increased amplitudes of the late cortical responses have been shown to be associated with higher levels of alertness/attention.[65]

The effects of arousal or natural sleep on the visual or somatosensory evoked responses have not been studied extensively, probably because of the obtrusiveness of these stimuli.

Neurological disease

Many of the original applications of evoked responses were for the diagnosis of neurological diseases. Peripheral lesions affect the evoked responses and have to be considered if the evoked responses are used to monitor depth of anaesthesia or to assess pain.

The visual evoked response, for example, is affected by lens defects such as cataract[81] and conditions such as optic neuritis.[41] The auditory evoked responses are affected by conductive and sensorineural hearing disorders[34] and somatosensory evoked responses by damage to sensory nerves and nerve roots.[36] Multiple sclerosis and other demyelinating diseases can affect the response.[25 42 66] Demyelinating diseases have a selective action on A-delta fibres leaving the unmyelinated C-fibres intact. This may result in an absent late vertex potential with the emergence of an ultra late response thought to be transmitted via C-fibres.[16]

Tumours, which affect the specific nerve tracts,[57] and factors which affect the brain, such as ischaemia[67] and coma[38 45 77] can also affect evoked responses.

Monitoring awareness, depth of anaesthesia and sedation

CLINICAL REQUIREMENT

After the introduction of neuromuscular blocking drugs, many of the traditional signs of anaesthesia were rendered useless and intraoperative awareness during general anaesthesia emerged as a problem. This prompted the search for methods for detecting awareness during anaesthesia and the graded changes that occur in the CNS related to depth of anaesthesia. The anaesthetist requires a monitor of anaesthetic depth, they are then able to react to prevent awareness and tailor the dose of the drug to the patient's requirements. Prompt emergence from anaesthesia or sedation is then possible if required. Another useful application of such a monitor would be to predict if a patient was going to move in response to or during surgery in spontaneously breathing patients. A monitor of awareness could be beneficial in the ITU situation, especially in sedated patients with whom it is difficult to communicate.

The EEG has been known for some time to show graded changes with increasing concentration of inhalation anaesthetics.[28 35] Generated from within the CNS, the EEG is not affected by neuromuscular blocking agents. Attention was therefore directed towards the EEG as a possible indicator of awareness and depth of anaesthesia. However, extensive research has proved disappointing as the EEG changes seen with general anaesthetics vary for different agents.[27] The evoked responses were the next candidates for investigation. In the studies reviewed below, motor responses and psychological tests of implicit and explicit memory have been used to assess awareness and attempts have been made to correlate evoked responses with these variables.

RESEARCH EVALUATING USE OF EVOKED RESPONSES

To detect awareness during anaesthesia

Certain definitions are important for interpreting research findings. In a patient who is aware during anaesthesia, memory can be explicit or implicit. Explicit memory occurs when the patient/subject is able to recall events happening during surgery or words spoken during an experiment. Implicit memory occurs when the patient/subject's behaviour is modified by information given during "anaesthesia", but they have no direct recollection of the event.

To date, the early cortical auditory evoked response is the most promising of the evoked response for distinguishing a patient who is aware from one who is anaesthetized. A positive response to verbal command and in some cases recall has been

shown to be associated with an Nb latency <44.5 ms (the mean value from a discriminant function analysis).[83] This value is taken as it represents the transition between a "three-wave trace" (danger of awareness) and a "two-wave trace" (fig. 5). Using an isolated forearm technique, seven patients were studied before surgery. Anaesthesia was maintained with 70% nitrous oxide in oxygen. Every 2–3 min the patient was asked to squeeze the fingers and then let go of the investigator's hand, the AER was studied before and afte this command. If no response occurred, nitrous oxide was reduced slowly to 50% or until a clear response was seen. An unambiguous endpoint was taken when the patient gave a positive response after a period of "no response". This happened in four of seven patients and was correlated with a short (<44.5 ms) Nb latency. None of the patients had explicit memory of events. Implicit memory was not tested.[83]

In another study, volunteer anaesthetists were given sub-MAC concentrations of isoflurane (0, 0.1, 0.2 and 0.4 MAC) on 4 separate days.[62] During a period when end-expiratory isoflurane was steady, psychological tests were carried out in which the subjects were given simple or complex commands (e.g. raise your left hand) and a list of words to memorize. The AER was recorded throughout. At 0 MAC all subjects had explicit memory of the commands and remembered being asked to memorize words, at 0.4 MAC none of the subjects followed commands and had no recollection of the proceedings. (Implicit memory was not tested.) At the intermediate MAC levels there was incomplete reduction of function in some subjects. A correlation between Nb latency and response to command was demonstrated in seven of eight subjects.

In further studies, loss of verbal response to command and eyelash reflex after a bolus dose of midazolam was associated with an increase in Nb latency from 44 to 58 ms[89] and after midazolam and propofol infusion with an increase from 44.3 to 55 ms.[61] The association between Nb latency and awareness has been confirmed by other investigators who have studied the transition from consciousness to unconsciousness. Davies and colleagues[30] used a target-controlled propofol infusion to produce two clinical states which they defined as (1) "conscious" where the patient responded to verbal command and (2) "unconsciousness" where no response to verbal command occurred and the eyelash reflex was lost. Comparison of the AER was made between each state. In this study both Pa and Nb latency were able to discriminate between the two states and were statistically significant in all transitions. Several other workers found Nb latency to be the best correlate, out of a group of EEG variables, with loss of eyelash reflex[88] after propofol sedation and subsequent arousal after physiotherapy.[76]

From reports of intraoperative awareness, using a variety of anaesthetic techniques, it is often noted that the auditory input is the last sensory modality to be abolished[23 39 48] and the first to return at light levels of anaesthesia. Patients anaesthetized for cardiac surgery are often studied, as a high incidence of awareness has been reported.[40 59] For example, Schwender and colleagues studied 45 patients undergoing cardiac surgery.[71] Anaesthesia was maintained with high-dose fentanyl (1.2 mg h^{-1}), supplemented with flunitrazepam 1.2 mg h^{-1}, 0.6–1.2% isoflurane, propofol 4–8 mg kg^{-1} h^{-1} or no additional agent (control group). After sternotomy, patients were played a tape message with an implicit memory task. The AER was recorded throughout. No patient experienced explicit memory of intraoperative events, but seven patients showed implicit memory related to the tape message. A correlation with the AER, in particular Pa latency, was demonstrated. Nine patients demonstrated a shift in Pa latency of <12 ms; these included all seven patients with implicit memory. Of the remaining 23 patients, without implicit memory changes, 21 had a Pa latency shift of >12 ms.

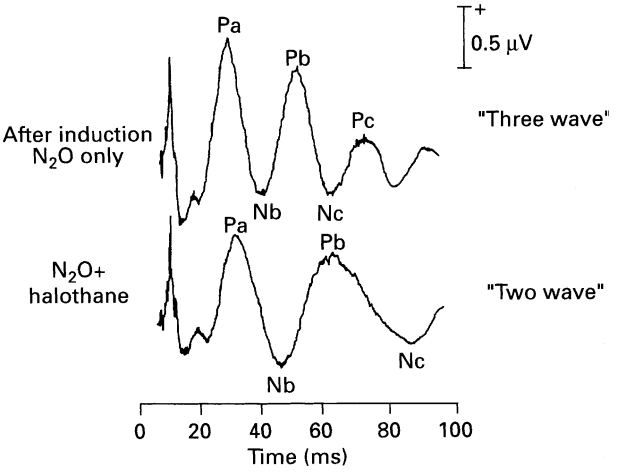

Figure 5 Early cortical response. Top: the three positive waves, Pa, Pb and Pc, with latencies of 15–100 ms, suggest light anaesthesia/potential awareness. At this time anaesthesia was maintained with 70% nitrous oxide in oxygen. Bottom: after addition of a small amount of halothane, the three waves were replaced by two positive waves, Pa and Pb, suggesting no awareness.

Generally, the amplitudes of the Pa and Nb waves are preserved during sedation with benzodiazepines.[73] As the generators of the early cortical AER are located in the primary auditory cortex and temporal lobe, this suggests that the benzodiazepines do not completely suppress cortical processing of auditory stimuli. This may have some relevance to reports of intraoperative awareness during anaesthetic techniques using benzodiazepines.[73] There is also evidence to suggest that other sensory modalities are not completely suppressed by benzodiazepines. For example there is little or no change in the amplitudes and latencies of visually evoked potentials (VEP) after administration of diazepam.[54] Changes in the SER have been demonstrated with benzodiazepines. A 60% depression of the amplitude of the cortical SSEP was demonstrated with midazolam, and small but significant reductions in latency were seen.[75]

Changes in Nb and Pa latency and derived indices which reflect these changes appear to be the best discriminators of aware and anaesthetized. An obvious application is to devise a feedback loop to control sedation at a comfortable level for the patient.[68] This could then be applied to patients in the ITU in whom it is impossible to determine adequate sedation with existing clinical tests.

To measure "depth of anaesthesia"

The early cortical AER also been investigated systematically at the deeper levels of anaesthesia.[69 74 86] It shows graded changes with the general anaesthetics halothane, enflurane, isoflurane, desflurane, sevoflurane, propofol, etomidate and Althesin and these are partially reversed by surgical stimulation, as would be expected of the changes which were monitoring "depth of anaesthesia" as opposed to concentration.

Figure 6 shows the effect of desflurane on the early cortical AER. Pa and Nb amplitudes flatten and their latencies lengthen, from a high amplitude wave at 1.5% to virtually a flat line at 6.0% end-tidal desflurane.

The brainstem waves, although showing graded changes with inhalation anaesthetics, were not affected by i.v. agents over the clinical concentration range[86] and therefore have been discounted. Late cortical waves are too sensitive and are completely abolished by sedative doses of these agents.

The effect of surgical stimuli such as first incision[85] and tracheal intubation[17] have been examined on these graded changes in the AER and shown to partially reverse them. For example, applying a stimulus when the patient is maintained with a constant anaesthetic concentration causes the AER to change to one that is associated with a lower concentration of anaesthetic (or lightening of anaesthetic depth). The effect of tracheal intubation on the AER is shown in figure 7. After intubation the latencies of Pa and Nb shorten and the amplitudes increase.

The later waves of the somatosensory evoked responses, P35/N45, show similar changes with anaesthesia to the AER. However, the electrical pulse is not as acceptable to patients as a click and the recording electrodes have to be attached to the hairy parts of the scalp at precisely measured points. This makes the system less viable as a routine clinical monitor. Good early cortical AER recordings can be made in anaesthetized patients from ECG adhesive electrodes attached at the mastoid and forehead. Another problem with the SER is that the amplitudes of the waves are very variable between patients and therefore changes in the response caused by anaesthetics would have to be compared against a "non-anaesthetized" baseline. This does not appear to be necessary for the AER. Nevertheless, the SER has proved useful as a research tool. When the SER has been studied over a range of concentrations of various anaesthetic agents, the amplitudes of the later waves (P35 and N35) behaved similarly to Pa and Nb of the AER, in that they are not particularly sensitive to analgesics such as nitrous oxide but are profoundly affected by agents such as isoflurane. These changes are reversed to some extent by tracheal intubation.[29]

The visual evoked response has received little attention as a measure of depth of anaesthesia. It merits further investigation, possibly using goggles to give flash stimuli through closed eyelids.

To predict movement to surgical stimulation

The effect shown by both early cortical auditory and somatosensory responses after tracheal intubation and surgical stimulation suggest that these responses reflect the balance in the CNS between the depressant effects of anaesthesia and sensory stimulation and are not simply monitors of anaesthetic concentration. However, the evoked responses have not emerged as reliable predictors of whether an individual patient will move during anaesthesia. For instance, a recent study by Schwender and colleagues investigated patients undergoing elective gynaecological laparotomy under midazolam "anaesthesia" with analgesia provided by continuous epidural.[70] During the study, a total of 25 movements were observed (10 spontaneously and 15 in response to verbal stimuli—"open your eyes"). After induction the only significant change in the AER was prolongation of Nb latency. There was no significant change in the AER before and during intraoperative movements compared with AER recordings when no movement occurred. There was no predictive value of the early cortical AER for whether or not the patient would move during anaesthesia.

The same conclusion was reached in a multicentre European study where 82 patients were investigated to determine if the response in the AER to a tetanic stimulus could predict if the patient would move to surgical incision.[52] None of the AER measurements made before incision predicted whether or not patients subsequently moved.

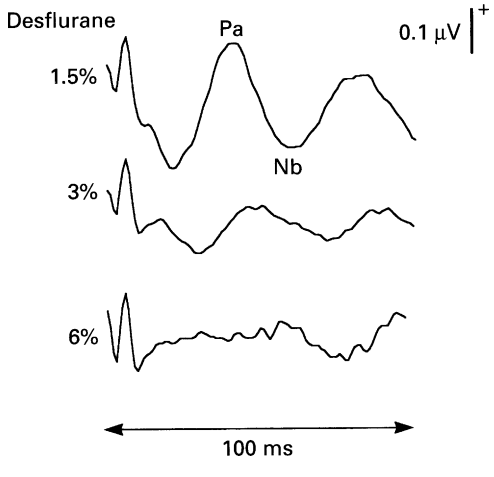

Figure 6 Early cortical auditory evoked responses in a patient receiving desflurane and 67% nitrous oxide in oxygen. Latency increases and amplitude decreases with increasing concentration.

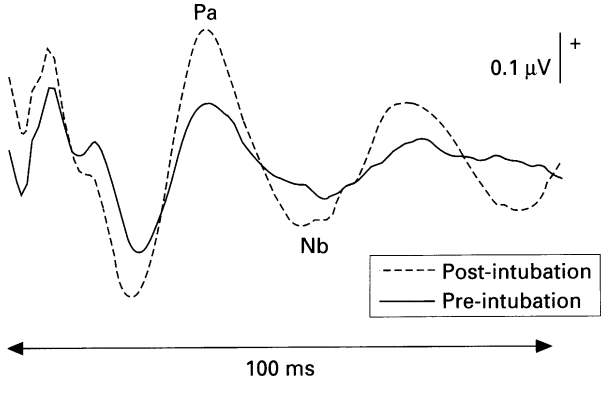

Figure 7 Early cortical auditory evoked response before and after intubation. Pa and Nb amplitudes increase and amplitudes shorten after this strong sensory stimulus, even though the anaesthetic concentrations were constant throughout.

Assessment of pain

CLINICAL REQUIREMENT

Most human pain research using evoked responses has been carried out in awake subjects. The late and ultra late potentials evoked by laser stimulation are the most promising for pain assessment.

Carbon dioxide[58] and argon lasers[11] have been used in the study of pain. The use of infra-red carbon dioxide laser causes a rapid increase in skin temperature[20] resulting in superficial skin lesions,[10] making this stimulus less suitable for repetitive stimulation. The local inflammation that it produces also modifies the nociceptive pathway. The visible argon laser stimulus does not produce these effects and can be applied via quartz fibre for cutaneous stimulation.[4]

The exact mechanism of pain generation by laser stimulation is unknown, but it is generally assumed that the laser heat stimulates warmth and polymodal nociceptors located intradermally.[13] As the intensity of the laser stimulus is increased, various sensations are produced (personal observation). Ranging from: (1) no sensation; (2) a slight tingling feeling (not painful) sometimes labelled "pre-pain"; (3) a definite pinprick (first pain); and (4) a delayed burning pain (second pain) usually preceded by a pinprick.

An effective method of assessing pain with evoked potentials should show graded change with pain intensity and the response to the pain stimulus should be obtunded by analgesic medication. The next section reviews the literature with these requirements in mind.

RESEARCH EVALUATING USE OF EVOKED RESPONSES

Are there graded changes with stimulus intensity?

The majority of pain studies using evoked responses have studied the late component of the vertex potential, thought to be mediated via A-delta fibres. A linear relationship between the amplitude of the vertex SEP and pain perception has been demonstrated with electrical[18 22] and laser stimulation.[11 19 79]

Is the response to pain stimulus obtunded by analgesic medication?

Opioids. Several studies[7 18 21] have shown that the amplitude of pain-evoked vertex potentials was reduced by opioids. For example, i.m. alfentanil reduced the amplitude of the laser evoked response and increased pain thresholds by 116% while sensory thresholds (warmth) were unchanged.[7] These effects were reversed by naloxone 400 μg. Sensory thresholds were not significantly affected by alfentanil, suggesting a pure analgesic effect. In this study there was no significant effect on the latency of the evoked response, despite an increase in the reaction time of the subjects (who pressed a button when they experienced the pinprick). The differences were attributed to the complex central depressant actions of opioids on arousal/attention rather than a direct nociceptive effect. This led to the criticism that central opioid action on arousal is responsible in part for the effect on the evoked response—this is discussed later.

Local anaesthetics. Studies on topical, perineural and epidural local anaesthetics support the vertex potential as a measure of pain sensation. For example, changes in the amplitude and latency of the laser evoked cortical responses reflected changes in perception of pain when the local anaesthetic EMLA cream was applied.[5 79]

The amplitude of the vertex potential elicited by argon laser stimulation was reduced by 42% after administration of the local anaesthetic bupivacaine into the epidural space at L2–3.[8] A differential effect was seen at the outer dermatomal limits of the epidural. In the caudal segments, different effects on warmth (sensory) and pain (pinprick) thresholds were seen. This could be attributed to the differential effect of low concentrations of local anaesthetic on the A-delta and C-fibres. Administration of epidural morphine produces similar reductions in amplitudes together with increased pain thresholds for up to 7 h. The changes were antagonized by naloxone. No change in the latency of the evoked response was seen.[9]

Oral analgesics and non-steroidal anti-inflammatory drugs. Studies have demonstrated a 20–35% reduction in the amplitude of the evoked response to electrical and laser nociceptive dental stimuli after administration of aspirin.[24 31] Reductions in the amplitude of the SEP produced by paracetamol and paracetamol–codeine combinations were also demonstrated in a placebo-controlled crossover study. For both drugs, the pinprick threshold was increased maximally at 2 h. Similarly, the evoked response was reduced maximally at 2 h for paracetamol alone but at 1 h for paracetamol–codeine. The evoked response did not mirror completely the changes in pain threshold.[6]

So far the ultra late vertex potential has only been elicited to acute painful electrical[43] as well as carbon dioxide[15] and argon laser[2] stimuli. It may find a place in chronic pain research as a neurophysiological correlate of C-fibre activity.[26] (Evoked responses have not yet found a role in the study of chronic pain which is thought to be modulated by C-fibres.) The ultra late potential can be elicited if a pressure block can be applied over the afferent nerve pathway which blocks the A-delta and leaves the unmyelinated C-fibres intact. In this situation the burning sensation predominates. It has been postulated that this reflects cortical processing from afferent C-fibre input because the timing of the ultra late potential (latency 1–2 s) correlates with the delayed burning sensation (so called second pain). Additionally, the difference in latency between the late and ultra late evoked potentials correlates with the different conduction velocities of the A-delta and C-fibres.

Nociception during anaesthesia

CLINICAL REQUIREMENT

Clinically we know that analgesic drugs such as opioids, nitrous oxide and NSAID obtund the pain response to surgery and reduce anaesthetic requirements. The extent to which they obtund the autonomic responses to surgery can be used as a measure of their analgesic efficacy. There have been several studies observing the changes in evoked responses to tracheal intubation and surgical stimulation and attenuation of these responses by opioids and nitrous oxide.[17 84 85] The results of these studies have led to

claims that certain aspects of evoked responses, specifically the pontine thalamic components of the somatosensory evoked response can measure the analgesic component of balanced anaesthesia.

RESEARCH EVALUATING USEFULNESS OF EVOKED RESPONSES

In studies where patients were given either nitrous oxide or isoflurane the pontine–thalamic wave (P15–N20) was profoundly depressed with nitrous oxide (fig. 8). The cortical SER waves (P35–N45) and AER waves (Pa and Nb) were more depressed by isoflurane than nitrous oxide.[53 84]

Dose-related attenuation of the pontine–thalamic wave amplitude in response to intubation with remifentanil has been demonstrated.[29] As the pons–thalamus is the likely site of opioid receptors it was speculated that these waves reflect the analgesic aspects of anaesthesia. Attenuation of the Pa amplitude response to intubation with alfentanil[17] and a direct effect on Pa amplitude of both alfentanil[17] and remifentanil[29] have been demonstrated. The position with respect to the AER waves Pa and Nb and opioids is more controversial as there are no known opioid receptors in the auditory nerve pathway.

Areas of controversy

AWARENESS, DEPTH OF ANAESTHESIA, SEDATION AND THE AER

The early cortical AER would be a suitable basis as a method which detects intraoperative "awareness" as indicated by the patient's ability to register sound. If intra-operative awareness has to include subsequent memory (implicit or explicit) and some anaesthetists insist that it does, then the situation becomes more complicated because of the amnesic drugs used during general anaesthesia. A brain signal recorded at one point in time will not necessarily predict future behaviour accurately if events or treatments which occur in the period in between the two time points can influence behaviour. Precise definitions are necessary for understanding the research findings but these may not be as relevant to everyday clinical practice as clinical practitioners do not need to operate in borderline areas where small changes in anaesthetic depth could result in the difference between implicit or explicit memory.

Predicting movement after incision from pre-incision data has similar problems in predicting awareness. Also movements are affected by classes of drugs such as opioids, neuromuscular blocking agents, etc., which do not affect cortical activity directly. Any relationship between a spinal reflex, such as movement to surgical incision, and the cortical AER is likely to be very indirect, which may explain why the AER has such low prediction value.

PAIN ASSESSMENT AND THE SER

In general there is a relationship between the amplitude of the evoked response and the pain threshold (fig. 9).[3] Although there are occasions when dissociation occurs.[6]

It can be argued that the amplitude of laser induced vertex potentials are affected by the sedative actions of opioid analgesics and this accounts for the discrepancy between changes in the amplitudes and pain ratings. To try and separate sedative and analgesic actions, the effects of sub-anaesthetic doses of propofol and analgesic doses of alfentanil were studied on noxious stimuli.[64] Both propofol and alfentanil induced similar reductions in the amplitudes of the evoked potentials elicited by nociceptive and non-nociceptive (auditory) stimuli, but only alfentanil reduced perceived pain, indicating that the reduction in amplitude of the vertex potential by propofol was not caused by an analgesic effect.

Conclusion

Evoked responses are extracted from the background electrical and electrophysiological noise of the EEG. The early cortical AER waves Pa and Nb, which occur between 20 and 80 ms reflect the activity in the temporal lobe/primary cortex, the site of sound registration. Changes in the latency of these waves are highly correlated with a transition from awake to loss of consciousness and subsequent decreases and increases in the amplitude of these waves reflect the interplay of general anaesthetics, surgical stimulation and obtunding of the latter by analgesics. The early cortical AER

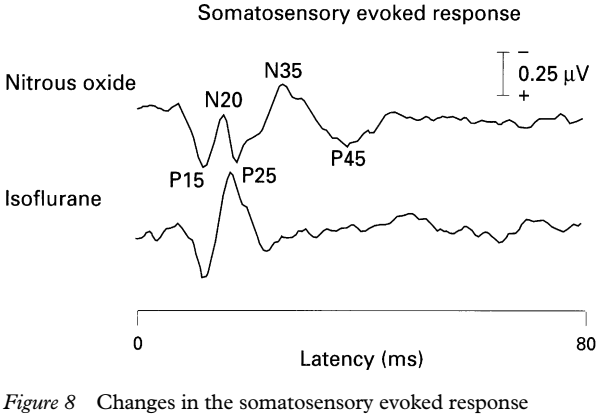

Figure 8 Changes in the somatosensory evoked response recorded from scalp electrodes and produced by stimulating the median nerve. The patient was given nitrous oxide or isoflurane. During the isoflurane period, P15–N20 and N20–P25 increased, and P25–N35 and N35–P45 were reduced compared with the nitrous oxide period.

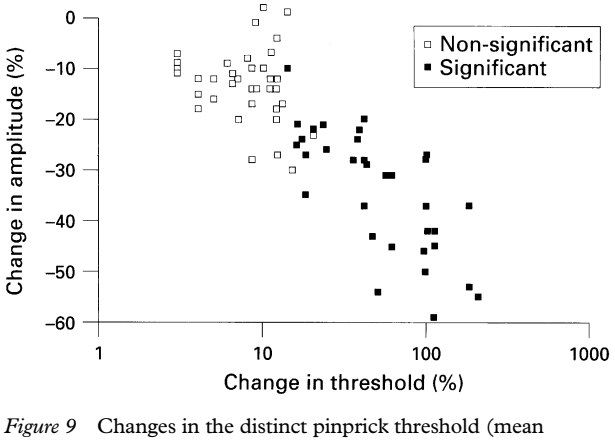

Figure 9 Changes in the distinct pinprick threshold (mean percentage change compared with baseline) compared with the corresponding change in amplitude (mean percentage change compared with baseline) of the argon laser-evoked vertex potential. Reproduced with permission from L. Arendt-Nielsen, *Acta Anaesthesiologica Scandinavica*, 1994.[3]

has real value in distinguishing between the aware and anaesthetized state and subsequent CNS depression. This would be useful in ensuring paralysed anaesthetized patients are unconscious or to control sedation during ITU or endoscopic procedures.

The laser pain evoked response shows great promise as an objective measure of pain. So far only the late vertex potential or A-delta fibre response can be detected reliably. There is much scope for further research using the ultra late vertex potential as a possible correlate of C-fibre activation. This could have enormous clinical application in chronic pain states.

Accepting some technical and subject related limitations outlined in the first part of this review, these two areas of evoked response monitoring have promising applications in the areas of general anaesthesia, intensive care and pain assessment.

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