Br. J. Anaesth. (1988), **60**, 372–378

EFFECT OF SURGICAL STIMULATION ON THE AUDITORY EVOKED RESPONSE

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SUMMARY

Previous studies have shown a dose-related effect of a number of general anaesthetic agents on the early cortical waves in the auditory evoked response (AER). In this study the effect of surgical stimulation on these waves was examined in 11 patients anaesthetized with thiopentone, nitrous oxide and halothane and paralysed with pancuronium. The inspired nitrous oxide concentration and end-tidal halothane concentration were held constant at 70% and 0.3%, respectively, and baseline AER recordings were made. Following surgical stimulation there was a progressive and significant increase in the amplitude of waves Nb and Pb/Pc. Unambiguous autonomic responses were seen in three patients, but these were not significantly correlated with changes in the AER. We conclude from this, and previous studies, that the amplitude of cortical waves in the AER are sensitive not only to anaesthetic concentration but also to surgical stimulation. The AER may, therefore, provide a useful index of depth of anaesthesia, that is the balance between the effects of surgical stimulation and anaesthetic depression on central nervous system activity.

At present there is no objective method of measuring "depth of anaesthesia" in routine clinical use. Approaches based on clinical signs such as changes in arterial pressure, heart rate and the size of the pupil are of limited value [1]. Consequently, anaesthetists rely on their experience to predict which dose of anaesthetic will provide the required anaesthesia. The numbers of patients reported to be awake but paralysed during anaesthesia, particularly for Caesarean section [2] reflect the shortcomings of this method.

To remedy this problem the anaesthetist should be provided with a signal which is not influenced by neuromuscular blocking drugs, shows graded responses with changing anaesthetic concentrations, behaves in the same fashion with all general anaesthetics, and reflects the activity of the central nervous system (CNS). Various electroencephalographic techniques have been used for monitoring brain function during anaesthesia [3, 4]. However, although these techniques have shown changes with increasing anaesthetic concentrations, a measurement has yet to emerge that changes in the same way with all general anaesthetics. In a series of investigations we [5–10] and others [11] have evaluated the usefulness of changes in the electroencephalogram (EEG) in response to an auditory click stimulus, as an index of depth of anaesthesia. This auditory evoked response (AER) may be subdivided into the brainstem response, which is obtained in the first 15 ms after stimulation, the early cortical response (from 15 to 80 ms) and the late cortical response (from 80 to 1000 ms). All of the anaesthetics that we have studied (halothane, enflurane, isoflurane, Althesin, etomidate and propofol) produced dose-related changes in the early cortical part of the response.

All of these data were obtained in patients anaesthetized before surgery; that is, patients who were undisturbed by extraneous stimuli other than the auditory clicks. However, the concept of "depth of anaesthesia" implies a state of the central nervous system resulting from a balance

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Accepted for Publication: September 21, 1987.

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between the depression caused by anaesthetic drugs and arousal caused by surgical or other stimuli. An important requirement for a technique measuring depth of anaesthesia is that it reflects this balance. Thus if the AER remained unchanged when the anaesthetized patient was suddenly subjected to a surgical stimulus, the AER would be interpreted as a measure of anaesthetic concentration, but not of CNS activity. This study was designed to determine if the AER—obtained in an undisturbed patient during light steady-state anaesthesia—would show arousal in association with surgical stimulation.

PATIENTS AND METHODS

Patients and anaesthesia

Eleven female patients aged between 26 and 50 yr were investigated. Each patient had given informed consent to a study, the design of which was approved by the Northwick Park Hospital Ethics Committee. The patients were admitted for the operations listed in table I. Morphine 10 mg and atropine 0.6 mg were used as preoperative medication and anaesthesia was induced with thiopentone 2–4 mg kg^{-1}. The trachea was intubated following pancuronium 0.1 mg kg^{-1} and the lungs ventilated with 70% nitrous oxide in oxygen. The ventilation was adjusted to maintain an end-tidal carbon dioxide tension in the range 4.5–5.5 kPa (Hewlett–Packard capnograph 42710A). After the induction of anaesthesia, halothane was added to the inspired mixture and adjusted to maintain a constant end-tidal concentration of 0.3% (BOC Medishield mass spectrometer). Oesophageal temperature was measured with a thermistor positioned in the oesophagus at the level of the aortic arch. Arterial pressure and heart rate were recorded automatically at 5-min intervals (Dinamap: 843XT, Critikon).

The AER was measured using the technique previously described [5]. Click stimuli of intensity 75 dB above the average hearing threshold and 0.5 ms duration were applied at a rate of 6 s^{-1} to both ears. The EEG and click stimuli were recorded onto an FM tape recorder (Racal 4). Silver–silver chloride disc electrodes were used. The electrode sites chosen were mastoid referred to vertex and inion referred to vertex.

The EEG signals were subsequently analysed using a DATALAB DL 4000 averager. The averaged AER over the 130-ms post-stimulus interval was derived from 2048 stimulus presentations (taking 5–7 min unless there was electrical interference from the theatre equipment, in which case it could take longer). The AER was recorded continuously during a 45-min baseline period with steady-state anaesthesia before surgery. The AER was not sampled when minor procedures (e.g. bladder catheterization) were taking place. After the surgical procedure began the AER recordings were continued for a further 25 min. Particular care was taken to maintain constant end-tidal halothane concentrations. Values for the latencies of waves III and V and the amplitudes and latencies of Pa, Nb and the next positive wave, which we have labelled Pb/Pc (see Discussion), were derived from each averaged AER. In order to evaluate the autonomic response to surgery, note was made of pupillary dilatation, lachrymation, sweating, tachycardia and arterial hypertension: these were graded as shown in table II.

TABLE I. *The age and operations of the patients (all female) who took part in the study*

Patient	Age (yr)	Operation
1	41	Total abdominal hysterectomy
2	36	Bilateral stripping of varicose veins
3	38	Total abdominal hysterectomy
4	26	L. ankle triple arthrodesis
5	34	R. big toe arthrodesis
6	44	Total abdominal hysterectomy
7	36	Total abdominal hysterectomy
8	50	Total abdominal hysterectomy
9	37	Tubal surgery
10	47	Total abdominal hysterectomy
11	35	Total abdominal hysterectomy

TABLE II. *The gradation of autonomic responses of the 11 patients who took part in the study. Pupillary dilatation: + + + = sustained for longer than 1 h; + + = for longer than 10 min; + = some evidence; − = no evidence. Mean increase in arterial pressure: + + + = in excess of 20 mm Hg; + + = in excess of 10 mm Hg; + = increase 0–10 mm Hg; − = no change or a decrease. Mean increase in heart rate: + + = in excess of 10 beat min^{-1}; + = some increase; − = no change or a decrease. Sweating: + = evidence; − = no evidence. Tears: + = some evidence; − = no evidence. Anaesthetist's view: + + = unambiguous; + = equivocal autonomic response to surgery; − = no response*

Patient	Pupillary dilatation	Arterial pressure (mean inc.)	Heart rate (mean inc.)	Sweating	Tears	Overall anaesthetist's view
1	+	−	−	−	−	−
2	−	−	−	−	−	−
3	−	+ +	−	−	−	−
4	+ +	+ + +	+ +	−	−	+ +
5	−	−	−	−	−	−
6	+ + +	+ +	−	−	−	+ +
7	+	+ +	−	−	+	+
8	+	+	−	−	−	+
9	−	+ +	−	−	−	−
10	+ + +	+ +	−	−	+	+ +
11	+	−	−	−	−	−

Statistical analysis

Analysis of variance was carried out on each variable measured from the AER. Data from the 24 min before and the 24 min after the incision were used. These data (before and after incision) were each divided into two 12-min periods.

First, we compared the data before and after incision and then we compared the difference between the two periods before incision with the difference between the two periods after incision; that is, we tested for a significant surgery × period interaction. In this analysis the data before incision are used as a baseline to indicate the kind of changes that would be expected from two consecutive 12-min periods. Finally, we tested whether the effects of surgery were related to the autonomic "responder" or "non-responder" classification; that is, we tested for a significant surgery × responder interaction.

RESULTS

Description of data

Changes in the AER with surgery. The averaged early cortical responses of an anaesthetized patient before and after surgical incision are shown in figure 1. The most striking changes were in the amplitudes of Pa, Nb and Pb/Pc which were larger during surgery than before, resembling what would be expected from a lower end-tidal concentration of volatile anaesthetic—despite the end-tidal halothane concentration being maintained constant throughout. Not all patients showed these increases following incision. Pa increased following surgery in six of 11 patients, Nb increased in eight of 11 patients and Pb/Pc in nine of 11 patients. The Nb and Pb/Pc data for individual patients are plotted in figure 2.

Autonomic responders v. *non-responders*. Of the 11 patients, only three showed a clear response to

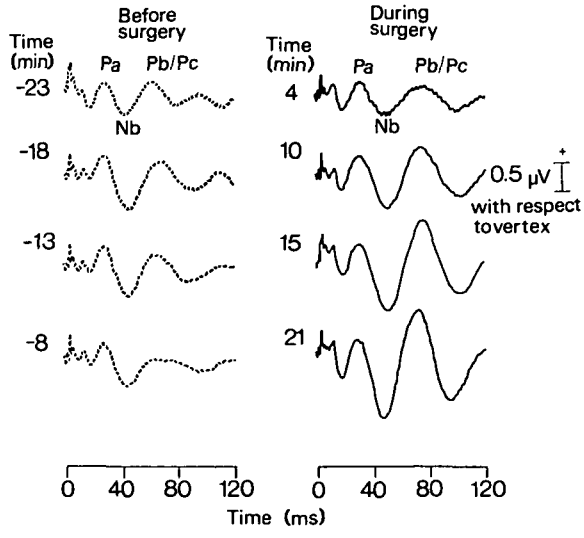

FIG. 1. The early cortical responses of one patient. In the left-hand panel are the traces before surgery and in the right-hand panel are those during surgery, starting from first incision. Each average took approximately 6 min to collect; the times given correspond to the middle of that period.

surgery as judged by autonomic signs. Data from these patients are shown on the left in figure 2. All three patients showed increases in the amplitudes of Nb and Pb/Pc. It was the possibility of a relationship between the autonomic changes and those seen in the AER that prompted us to include the "responder" and "non-responder" classification in the analysis of variance model.

Table II summarizes the changes in the autonomic responses on which this classification was

TABLE III. *Effect of surgery on the latencies and amplitudes of the brainstem and early cortical waves. Mean difference (during – before), SEM and significance of difference of data obtained before and during surgery. Mean values obtained during each 12-min period before and during surgery, together with significance of the surgery × period interaction.* $P > 0.05 = ns$

	Mean change following surgery			Means for each period				
				Before incision (min)		After incision (min)		
	Mean diff.	SEM	*P*	24–12	12–0	0–12	12–24	*P*
Latency (ms)								
I	0.01	0.019	ns	1.87	1.87	1.89	1.88	ns
III	0.02	0.017	ns	4.12	4.11	4.14	4.14	ns
V	0.07	0.016	< 0.01	6.15	6.18	6.23	6.24	ns
III–V	0.04	0.015	< 0.05	2.03	2.07	2.09	2.10	ns
Pa	0.90	0.72	ns	34.2	34.4	35.1	35.4	ns
Nb	2.1	1.60	ns	51.5	53.1	53.9	55.0	ns
Pb/Pc	3.6	2.10	ns	72.4	73.8	77.0	76.5	ns
Amplitude (μV)								
Pa	0.04	0.068	ns	0.52	0.44	0.48	0.56	ns
Nb	0.20	0.088	< 0.05	0.39	0.35	0.48	0.66	< 0.01
Pb/Pc	0.22	0.082	< 0.01	0.22	0.24	0.34	0.57	< 0.01

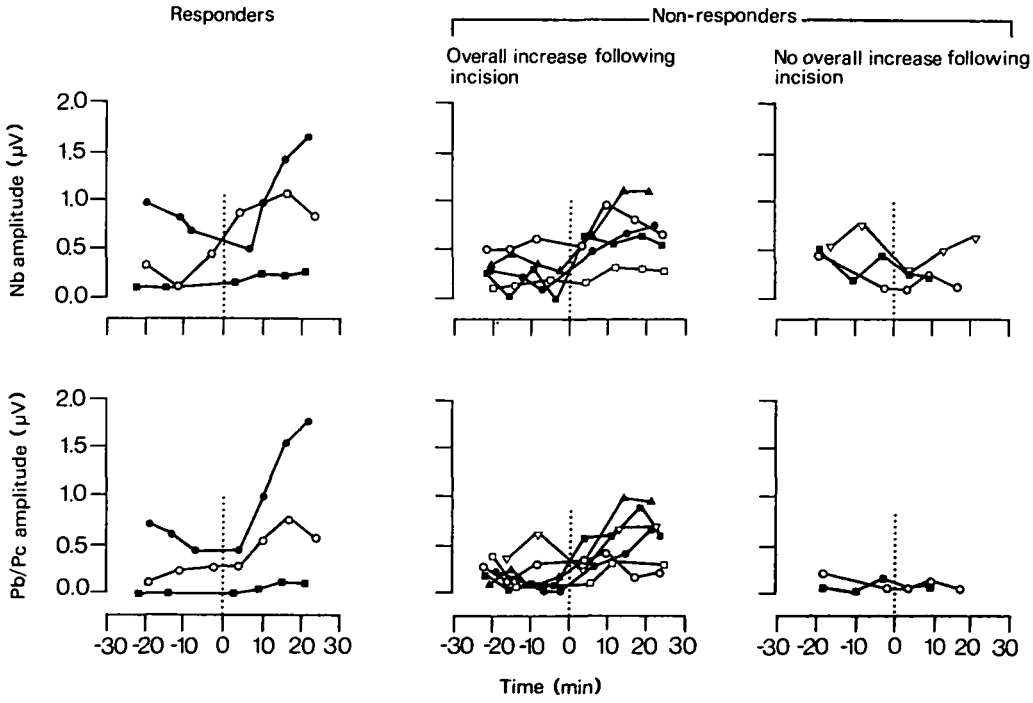

FIG. 2. Nb and Pb/Pc amplitudes against time (min) for individual patients. Incision is indicated by a vertical dotted line.

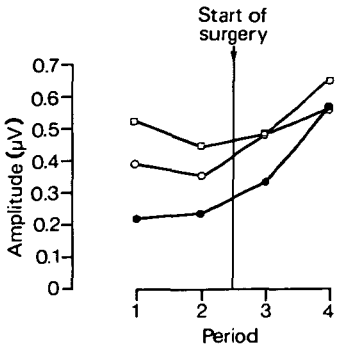

FIG. 3. The means for the 11 subjects of Pa (□), Nb (○) and Pb/Pc (●) amplitude for the periods 1 (24–12 min) and 2 (12–0 min) before incision, and periods 3 (0–12 min) and 4 (12–24 min) after incision.

based, along with the anaesthetist's overall impression at the time. The three patients who were classed as unambiguous responders had high scores for pupillary dilatation and for the mean increase in arterial pressure. None of the patients showed sufficient change in autonomic function to prompt the anaesthetist to administer more general anaesthetic agent and no patient reported awareness of the surgical procedure, hearing voices or unusual dreams.

Statistical analyses

Effect of surgery. There were significant increases in the amplitudes of waves Nb and Pb/Pc and increases in the latency of wave V and the III–V interval following surgical incision. The mean changes following incision are given in table III. The mean values for each period are also presented in table III and are plotted for Pa, Nb and Pb/Pc amplitudes in figure 3. Only the amplitudes of Nb and Pb/Pc showed significant surgery × period interactions. During surgery these values were increased during the second period compared with the first, whereas before surgery there was essentially no difference between the two periods.

Relationship to "responder" status. None of the variables tested showed a significant surgery × responder interaction; that is, responders and non-responders were not different with respect to the effect of surgery on the AER.

DISCUSSION

Before the start of surgery, at a constant end-tidal concentration of anaesthetic, the appearance of the AER was similar to previously published data with the same anaesthetic (compare the left-hand panel of figure 1 with figure 4).

Surgical stimulation partially reversed the changes in the early cortical waves brought about by halothane anaesthesia in that, before surgery (fig. 1) the AER was, in appearance, midway between the 0.12% and 0.66% end-tidal halothane traces seen in figure 4, whereas during surgery it was more similar to the 0.12% halothane trace. Increases in amplitude of waves Nb and Pb/Pc acounted for the changes in appearance. Most, although not all, patients showed these changes. This variability in response is perhaps not surprising in view of the variability in the sensitivity of individual patients to anaesthetics and surgical stimulation.

Our labelling of the positive peak following Pa possibly warrants explanation. The characteristic features of the middle latency components of the AER following induction of anaesthesia breathing 70% nitrous oxide in oxygen are *three* positive waves, Pa, Pb and Pc. With the addition of

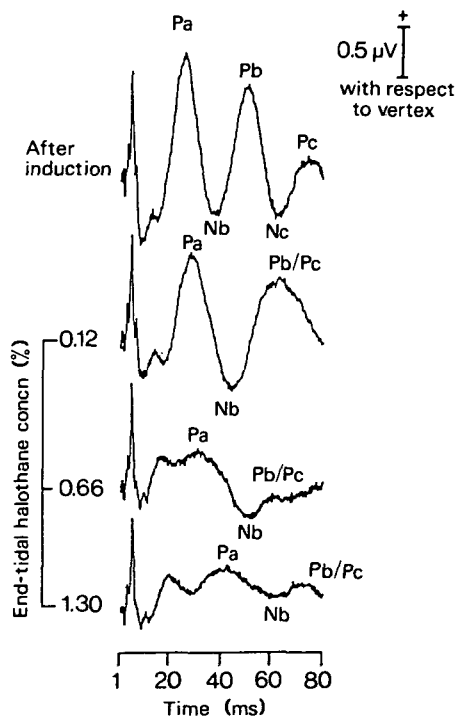

FIG. 4. The changes in the early cortical response with halothane anaesthesia; the averaged AER for one patient following the induction of anaesthesia and at the halothane concentrations given. (Reproduced after Thornton and colleagues [6], with permission.)

halothane sufficient to give an end-tidal concentration of 0.12%, only two positive waves are normally seen. There is no certainty whether Pb and Pc have combined or whether one or the other has disappeared. Because of this uncertainty, the positive wave following Pa has been labelled Pb/Pc.

The amplitudes of Nb and Pb/Pc were significantly increased during surgery compared with before surgery. To counter the argument that these were progressive time-related changes and not the result of surgery *per se*, we examined the surgery × period interaction. In this analysis we compared the trend before surgery with the trend following surgery. These trends were derived from the difference between two consecutive 12-min periods, this duration being chosen to include two data points from each patient. Following surgery there was a statistically significant change in the trend. The increase during surgery in the amplitude of Nb an Pb/Pc could not, therefore, be explained by a time trend occurring throughout the study and has to be attributed specifically to surgical stimulation. Further, this effect was more pronounced in the 12–24 min following incision than in the preceding 12 min. Possibly, following incision, the degree of stimulation increased as surgery progressed.

In contrast to the effect on wave amplitude, surgical stimulation did not reverse the effect of halothane on wave latencies (halothane increases the latencies). Following incision there were small increases in latency for all waves compared with pre-incision values, but only the changes in V latency and III–V interpeak interval were significant and none showed a significant surgery × period interaction. As these changes were progressive throughout the study they cannot be attributed to surgical stimulation and were possibly the result of gradually increasing anaesthetic concentration in the brain in spite of constant end-tidal halothane. The latency of the brainstem [3] and early cortical waves [12] have been shown to depend on temperature, but there were no changes in temperature in our patients which could account for these changes in amplitude or latency.

The amplitudes of the early cortical response, but not the latencies, show promise as measures of depth of anaesthesia. This fits with the results of a previous study [10] in which, in contrast to changes in amplitude, the changes in latency brought about by three inhalation agents (halothane, enflurane and isoflurane) did not correspond to their anaesthetic potency as determined by MAC.

The effects of surgery on the AER in the three patients that were classified "responders" were not significantly different from those occurring in the eight that were considered "non- or equivocal responders". However, there is little statistical power for this comparison. A lack of association between the broad classification responder–non-responder and an overall change in the AER with surgery does not preclude an association between transient cardiovascular and AER changes. There is scope for further examination of the relationship between autonomic and AER variables when it is possible to obtain reliable data for shorter periods of time.

Reversal of the depressant effect of anaesthetics on the evoked response has been reported previously. Angel and colleagues [13] showed that the amplitude of the cortical parts of the somatosensory response in rats decreased with increasing anaesthetic concentration. These changes were reversed when ambient pressure was increased. Increasing the ambient pressure also increased the dose of anaesthetic required to prevent reflex response to tail stimulation. Other workers have shown that various stimuli may reverse the effects of anaesthesia on the EEG. For example, surgical stimulation of patients anaesthetized with halothane produced an arousal pattern in the EEG; that is, a reduction in amplitude and an increase in frequency [14]. Therefore, it seems reasonable to suppose that increases in the amplitudes of the early cortical AER with surgery, which we report here, also represent arousal of the CNS. Erwin and Buchwald [15] found that the cortical waves in the AER (latencies 55–80 ms) decreased in amplitude during slow wave sleep and recovered to the pattern seen in wakefulness during rapid eye movement sleep, suggesting that waves at these latencies provide a unique probe of tonic brain activity. Picton and Hillyard [16] demonstrated an increase in amplitude of the early cortical wave (N1) (83-ms latency) in conscious man when attention was aroused by specific, transient changes in auditory signal.

In conclusion, the amplitudes of the early cortical waves show graded changes with anaesthetic drug concentrations and the changes are similar for at least six general anaesthetic drugs [5–10]. We have demonstrated in this study that

these changes are not dependent upon anaesthetic concentration alone since, at a constant anaesthetic concentration, they may be partially reversed by surgical stimulation. The amplitudes of the early cortical response, in particular of the waves Nb and Pb/Pc, seem worthy of further investigation as they reflect the balance between the depression of the CNS by general anaesthetics and its stimulation by surgery, that is the "depth of anaesthesia"

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