THE AUDITORY STEADY STATE RESPONSE DURING SUFENTANIL ANAESTHESIA

G. PLOURDE AND J. F. BOYLAN

SUMMARY

The auditory steady state response (ASSR) is a sinusoidal evoked potential elicited by rapidly repeated auditory stimuli. The ASSR was recorded in eight patients during high-dose sufentanil anaesthesia for cardiac surgery in order to assess its usefulness as a measure of the level of consciousness. The electroencephalogram (EEG) was recorded for comparison. The ASSR was present before induction in all patients. It was attenuated severely or possibly abolished with loss of consciousness, and reappeared at low amplitude 5–10 min later and remained attenuated until the end of surgery. The amplitude increased with early signs of awakening in the Intensive Care Unit. With few exceptions, changes in the simultaneously recorded EEG were similar to those of the ASSR. The ASSR deserves further evaluation as a tool for monitoring level of consciousness during high-dose opioid anaesthesia.

KEY WORDS

It is difficult to assess the level of consciousness during high-dose opioid anaesthesia. Concomitantly administered neuromuscular blocking agents interfere with ability to move in response to verbal command or pain. Use of beta-blockers and drugs with vasodilating properties may mask autonomic signs of light anaesthesia. Periodic reports of recall of intraoperative events with high-dose opioid anaesthesia [1] have led to the assertion that opioids do not maintain unconsciousness [2], despite their ability to produce sedation and unresponsiveness [3, 4]. Large doses of opioid produce slowing of the electroencephalogram (EEG) with predominance of delta activity [5–9]. These changes, however, do not imply unconsciousness [10, 11]. Similar changes may occur in conscious patients with minimal mental impairment [10]. Satisfactory evaluation of the level of consciousness is, therefore, not yet available.

The auditory steady state response (ASSR) is a sustained sinusoidal evoked potential elicited by repetitive auditory stimuli. It appears when the rate of stimulus delivery is sufficiently fast to produce overlapping of the responses to each stimulus [12–14]. The ASSR is most prominent with stimulus rates around 40 Hz. The ASSR amplitude reflects the level of arousal or alertness; it is reduced by approximately 50% in both physiological and sedative-induced sleep [15, 16]. Spontaneous amplitude fluctuations over approximately 1 min have been reported in normal volunteers and these may reflect concurrent changes of arousal [17]. The ASSR is abolished or attenuated markedly during nitrous oxide–isoflurane anaesthesia [18, 19].

We studied the effects of high-dose sufentanil on the ASSR in eight patients undergoing coronary artery surgery. The EEG was recorded for comparison.

PATIENTS AND METHODS

After institutional Ethics Committee approval and written informed consent, we studied eight patients (seven males), who were devoid of...

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hearing or neurological disorder. All were undergoing elective coronary artery bypass grafting. The mean age was 56 yr (range 41–68 yr).

**Anaesthetic technique**

In addition to their routine nitrate, beta-blocker and calcium channel blocker medication, the patients were premedicated with oral lorazepam 0.04 mg kg\(^{-1}\) 90 min before operation. Anaesthesia was induced with sufentanil 5 \(\mu\)g kg\(^{-1}\), injected over 3–5 min and preceded by pancuronium 0.02 mg kg\(^{-1}\). After the patient failed to open the eyes on two consecutive commands, pancuronium 0.08 mg kg\(^{-1}\) was given to facilitate tracheal intubation. The lungs were ventilated mechanically to maintain the end-tidal partial pressure of carbon dioxide at 4 kPa (SARA mass spectrometer, Allegheny International). The pulmonary artery catheter was then inserted. Further increments of sufentanil 1–2 \(\mu\)g kg\(^{-1}\) were given before skin incision, sternotomy, aortic cannulation and after cardiopulmonary bypass (CPB) to prevent or correct hypertension and tachycardia. Arterial hypertension (MAP greater than 30 % of preoperative values), and tachycardia (greater than 90 beat min\(^{-1}\)) not corrected by sufentanil, were treated with nitroglycerin or nitroprusside, and propranolol, respectively. Nasopharyngeal temperature was monitored continuously. Non-pulsatile cardiopulmonary bypass was used with a flow of 2.0 litre m\(^{-2}\) min\(^{-1}\) under moderate hypothermia (28 °C). Bubble oxygenators and arterial filters were used. No carbon dioxide or glucose was added to the perfusion. The arterial partial pressure of carbon dioxide (measured at 37 °C) was 4–5.3 kPa. Full rewarming (urinary bladder temperature greater than 34.5 °C) was achieved before discontinuation of CPB. The patients were questioned about recall of intraoperative events after 2 days, and also at 1–3 months after the operation.

**Auditory steady state responses (ASSR)**

An IBM-AT compatible computer with two analog-to-digital (a–d) conversion cards was used for stimulus control and signal acquisition.

**Stimuli.** Tonebursts (500 Hz, 15 ms duration, 5 ms rise/fall time, 90 dB peak sound pressure level (SPL)) were presented binaurally at a rate of 40 s\(^{-1}\) via insert earphones (Etymotic Research, model ER3A). The frequency was increased randomly (on average 10 times per minute) to 900 Hz for 75 ms to produce “target” stimuli, to which patients were required to respond by button press. (This was, of course, possible only when the patients were not paralysed.) The percentage of detected targets (i.e. button press present) was used to measure responsiveness [20].

**Recording.** The EEG was recorded with gold-plated cup electrodes attached with saline gel and collodion. Inter-electrode impedances were less than 5 kΩ (10 Hz). Three electrodes were placed according to the International 10–20 system [21] at frontal (Fz), central (Cz) and parietal (Pz) mid-sagittal scalp locations, with reference to the right mastoid (M2). A fifth channel was used to record button presses. Vertical eye movements (EOG) were recorded to allow rejection of data contaminated by eye movements. The amplification band-pass was from 0.16 to 100 Hz. The amplifiers (Grass Model P511K) followed the EEG convention that negativity at the scalp electrode, relative to the reference (mastoid), was plotted upwards.

The a–d epoch lasted 1490 ms, with a sampling frequency of 668 Hz per channel and a resolution of 12 bits. The interval between onset of successive epochs was 2000 ms signal. (The 510 ms between the end of an a–d epoch and the beginning of the next epoch was required for averaging and other computations.) Epochs contaminated by ocular movements or other artefacts were rejected. The rejection level was +87.5 μV on all channels. Successive epochs were averaged on-line in groups of 30–60, corresponding to recording periods of 90 or 180 s. (A 90-s recording consisted of 45 epochs of 2 s. On average, 33 % of these 45 epochs included “target” stimuli and could not be used for the ASSR. Thus about 30 epochs were used for ASSR, the exact number depending on the actual number of target stimuli (probability of 0.33 per epoch) and the number of epochs rejected because of artefacts.)

**Measurements.** Responses were analysed using fast Fourier transform [22] of the unfiltered averaged traces.

**Electroencephalogram**

**Recording.** The EEG was recorded for 2 s after each ASSR average waveform. The recording parameters were identical to those used for the ASSR.
Measurements. The following measures were derived from the power spectrum of the EEG: median [23] and spectral edge (95 % quantile) [24] frequencies, and relative power in the delta (0.5–3.4 Hz) frequency band. These measurements were determined after digitally filtering the EEG from 0.5 to 32 Hz, in accordance with current anaesthetic practice [25].

Design

Recordings were obtained at the following times: pre-induction (15–45 min before induction of anaesthesia); early induction (from the beginning of the sufentanil injection to loss of consciousness, judged by failure to open the eyes on command); late induction (the 90-s period immediately after loss of consciousness); post-intubation (tracheal intubation was performed 4–5 min after the beginning of induction. Recording was started 1 min after intubation and lasted 15–25 min. The pulmonary artery and urinary bladder catheters were inserted during this period); pre-CPB surgery (before, during or after aortic and atrial cannulation, the only time when electrocautery was not used); CPB (hypothermia) (28 °C); CPB (normothermia) (before discontinuation of CPB); post-CPB (from 5 to 20 min after haemodynamic stability); ICU (90–120 min after arrival in the Intensive Care Unit).

Before each recording (30–60 epochs), a message informed the patient, addressed by his/her first name, that all was well and instructed him/her to count the target stimuli mentally, if possible. This message was through the insert earphones. During pre-induction, early induction and ICU the patient was asked also to keep the eyes closed and to respond to each auditory target stimulus by a button-press. Within each period (other than induction), multiple ASSR average waveforms were obtained. They were averaged digitally before measurement.

Because of time constraints during induction, the EEG was recorded only during late induction. No EEG data are available, therefore, for early induction.

Statistical analysis

The Rayleigh test for phase coherence [26, 27] was used to determine if the responses could be distinguished reliably from background noise. The differences between recording periods were analysed by one-way analysis of variance (ANOVA) for repeated measures, using the Geisser–Greenhouse adjustment of the significance levels [28, 29]. Tukey's HSD [28] test was used for post-hoc comparisons. Criteria for significance were \( P < 0.05 \) for ANOVA and \( P < 0.01 \) for the comparisons to reduce the likelihood of spurious significance.

RESULTS

Anaesthesia

The mean doses of sufentanil for all patients were 5.7 \( \mu \text{g kg}^{-1} \) at induction, 1.3 \( \mu \text{g kg}^{-1} \) before skin incision and 1.8 \( \mu \text{g kg}^{-1} \) before sternotomy. Four patients received additional sufentanil (mean dose for the four patients = 2.6 \( \mu \text{g kg}^{-1} \)) after sternotomy or during aortic dissection to treat arterial hypertension (three patients) or tachycardia (one patient). These four patients later required intraoperative vasodilator therapy or propranolol, or both. Two required enflurane briefly to produce rapid control of severe hypertension, one during aortic cannulation and the other after emergence from CPB. (The recordings obtained during administration of enflurane were not included in the analysis. Recording was resumed only when the enflurane could no longer be detected in expired gas.) Three patients received sufentanil (mean dose 1.2 \( \mu \text{g kg}^{-1} \)) after CPB. The mean duration of surgery was 228 (SD 59) min and average duration was 99 (58) min. Three patients required adrenaline or noradrenaline during termination of CPB. Inotropes were discontinued within 12 h. All patients had an uneventful recovery and tracheal extubation took place on the first morning after operation. All patients denied conscious recall of intraoperative events.

Mean (SD) nasopharyngeal temperature was 35.9 (0.4) °C during post-intubation, 35.4 (0.5) °C during pre-CPB, 29.1 (2.4) °C during CPB (hypothermia), 35.1 (1.4) °C during CPB (normothermia), 35.6 (1.0) °C during post-CPB and 36.6 (0.8) °C in the ICU.

Target stimuli detection and level of sedation

The detection rate was 66 (SD 26) % during pre-induction. There was a significant (\( P < 0.01 \), Tukey’s HSD) reduction in detection rate during early induction (12 (11) %) and ICU (11 (13) %). The number of patients who detected 5 % or more target stimuli was eight during pre-induction, five during early induction and four during ICU (fig. 1). For these three periods, the percentage of
detected target always exceeded 5% when the ASSR amplitude was 0.22 μV or more. With ASSR amplitudes less than 0.22 μV, the detection rate ranged from 0 to 95%. During the other periods, anaesthesia and muscle paralysis prevented button-pressing.

During the pre-induction period, the patients were either drowsy or intermittently asleep and the eyes were closed most of the time. All opened their eyes on request, usually on the first instance. During sleep, however, the request had to be repeated once or twice to arouse the patient. Some patients fell asleep towards the end of individual 180-s recording periods.

It was extremely difficult to assess the level of consciousness in the ICU. Five patients opened their eyes at least once. There were minute-to-minute changes in ability to detect target stimuli and open the eyes on command. The relationships between these two measures could not be assessed because the changes were too rapid.

**ASSR and EEG**

Recordings during CPB (hypothermia) are available for only five patients because of ambiguity in the recording instructions. These results could not therefore be included in the analysis of variance, but they will be described in the tables and figures.

The ASSR was clearly visible on the amplitude spectra relative to adjacent frequencies in all patients during pre-induction. However, it was small (0.06 and 0.08 μV) in two patients. Significant ($P < 0.01$) decreases in ASSR amplitude occurred during late induction, pre-CPB, CPB (normothermia) and post-CPB (table I). During late induction, a small 40-Hz peak could still be identified relative to adjacent frequencies in three patients. The ASSR was significantly different ($P < 0.01$, phase coherence across patients) from background noise during all periods, except late induction, CPB (hypothermia), CPB (normothermia) and post-CPB (table I) during late induction.

**TABLE I. Auditory steady state responses (mean (sd)).§**

<table>
<thead>
<tr>
<th>Period</th>
<th>Amplitude (μV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-induction</td>
<td>0.30 (0.27)**</td>
</tr>
<tr>
<td>Early induction</td>
<td>0.24 (0.18)**</td>
</tr>
<tr>
<td>Late induction</td>
<td>0.05 (0.05)††</td>
</tr>
<tr>
<td>Post-intubation</td>
<td>0.12 (0.10)**</td>
</tr>
<tr>
<td>Pre-CPB</td>
<td>0.09 (0.10)**††</td>
</tr>
<tr>
<td>CPB (hypothermia)§</td>
<td>0.05 (0.03)</td>
</tr>
<tr>
<td>CPB (normothermia)</td>
<td>0.05 (0.05)††</td>
</tr>
<tr>
<td>Post-CPB</td>
<td>0.09 (0.05)††</td>
</tr>
<tr>
<td>ICU</td>
<td>0.14 (0.09)**</td>
</tr>
<tr>
<td>ANOVA</td>
<td>$P &lt; 0.05$</td>
</tr>
</tbody>
</table>

§Based on only five patients and not included in the ANOVA. **Phase coherence present (i.e. response significantly different from residual noise) ($P < 0.01$). †† Significantly less than pre-induction ($P < 0.01$) (Tukey’s HSD).
AUDITORY STEADY STATE RESPONSE

<table>
<thead>
<tr>
<th>Period</th>
<th>Average Spectra</th>
<th>Pre-induction (2335)</th>
<th>Early induction (460)</th>
<th>Late induction (281)</th>
<th>Late induction (321)</th>
<th>Post-intub. (3240)</th>
<th>Pre-CPB (3253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPB hypoth.</td>
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<td></td>
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<tr>
<td>CPB normoth.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Post-CPB</td>
<td></td>
<td></td>
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<tr>
<td>ICU</td>
<td></td>
<td></td>
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</tbody>
</table>

**Fig. 2.** For each period, the first 500 ms of the grand-average waveform (all patients included) is depicted, with the corresponding amplitude spectrum obtained from the fast Fourier transform of the entire average waveform. The number of epochs included in the average waveform is indicated in parentheses. The ASSR peaks (i.e., the amplitude at 40 Hz) are indicated by the solid arrows. No ASSR peak could be identified during CPB. The large peak during late induction (open arrow) is 60-Hz noise (power line). CPB = Cardiopulmonary bypass.

**Thermia** and post-CPB. (During post-CPB the significance level was $P < 0.025$.)

Figure 2 shows the average waveforms for all patients and the corresponding amplitude spectra. Figure 3 shows the waveforms of one patient.

EEG results are presented in Table II. Compared with pre-induction, the median frequency was reduced significantly during all periods. The spectral edge frequency was reduced significantly during all periods except ICU. The relative delta power was increased significantly in all periods.

**DISCUSSION**

The reduction in the ASSR during sufentanil anaesthesia was equal to or greater than that seen during stage III or IV sleep [15, 16]. Pre-induction amplitude was reduced by about 25% compared with unmedicated subjects [19], probably reflecting the sedation caused by premedication [16].

The ASSR was attenuated markedly or abolished during late induction (when responsiveness was lost) and during CPB. The very small 40-Hz peak during late induction (fig. 1) was indistinguishable from background noise (test of phase coherence across subjects). More observations are needed to determine if the ASSR is abolished or only attenuated profoundly. Nevertheless, severe attenuation of the ASSR during late induction probably indicates profound impairment of the level of arousal [19] caused by maximal plasma and brain concentrations of sufentanil [30].

The increased level of 60-Hz noise (fig. 2, open arrow) during late induction does not account for the reduction of the ASSR peak; it resulted from touching the patient for mask ventilation. This causes a transfer of energy from power lines by stray inductance [31]. Because the phase of the ASSR is locked to the stimuli, while that of the noise is not [31], contamination by 60-Hz noise...
Table II. Electroencephalogram (mean (sd)). §Because of time constraints, the EEG was not recorded during early induction. ¶Based on only five patients and not included in the ANOVA. **Significantly less than pre-induction (P < 0.01)

<table>
<thead>
<tr>
<th>Period</th>
<th>Median frequency (Hz)</th>
<th>Spectral edge frequency (Hz)</th>
<th>Relative delta (0.5–3.4 Hz) power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-induction</td>
<td>6.3 (3.8)</td>
<td>23.5 (2.0)</td>
<td>0.44 (0.19)</td>
</tr>
<tr>
<td>Late-induction§</td>
<td>1.1 (0.4)**</td>
<td>3.9 (1.3)**</td>
<td>0.94 (0.20)**</td>
</tr>
<tr>
<td>Post-intubation</td>
<td>1.3 (0.3)**</td>
<td>7.1 (2.7)**</td>
<td>0.88 (0.05)**</td>
</tr>
<tr>
<td>Pre-CPB</td>
<td>1.5 (0.8)**</td>
<td>8.1 (3.9)**</td>
<td>0.87 (0.08)**</td>
</tr>
<tr>
<td>CPB (hypothermia)‡</td>
<td>2.3 (1.3)</td>
<td>12.6 (7.8)</td>
<td>0.70 (0.16)</td>
</tr>
<tr>
<td>CPB (normothermia)</td>
<td>1.4 (0.3)**</td>
<td>9.4 (4.5)**</td>
<td>0.83 (0.06)**</td>
</tr>
<tr>
<td>Post-CPB</td>
<td>1.5 (0.4)**</td>
<td>8.7 (2.7)**</td>
<td>0.82 (0.08)**</td>
</tr>
<tr>
<td>ICU</td>
<td>2.9 (1.8)**</td>
<td>17.8 (8.7)</td>
<td>0.67 (0.17)**</td>
</tr>
<tr>
<td>ANOVA</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
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</tbody>
</table>
would not affect the ASSR unless it caused saturation of the amplifiers, which it did not. (The phase of the ASSR indicates the relative timing between the response and the stimuli. It is the steady-state equivalent of latency [31].)

The ASSR reappeared clearly during the post-intubation period and the amplitude was close to that in the ICU and similar to that seen immediately upon emergence from isoflurane anaesthesia [19]. This probably reflects lightening of anaesthesia, attributable to the rapid decrease in plasma and brain concentrations of sufentanil [30]. It might therefore be prudent routinely to administer additional sufentanil (or other anaesthetic) after tracheal intubation. Preservation of the ASSR does not definitely indicate awareness or consciousness, however. The ASSR may be recorded in comatose patients, particularly with less severe grade 1 and 2 coma [32]. Preservation of the ASSR, despite the amplitude reduction, indicates that synchronization is maintained in the neuronal circuits generating the ASSR, probably from the reticular formation (which controls arousal and sleep–wake cycles [33]), the medial geniculate and the auditory cortex [13].

The ASSR was absent during CPB with hypothermia or normothermia. In common with the 60-Hz contamination from power lines, cyclical artefacts from the roller-pumps cannot account for disappearance of the ASSR and increased residual noise does not provide a satisfactory explanation as it could mask only a very small response. The absence of the ASSR is probably attributable to depression of the brain by hypothermia or by physiological disturbances associated with rewarming [34].

The mean ASSR amplitude in the ICU was larger than in any other period except pre-induction and early induction. Detailed analysis of any relationship between the ASSR and the level of consciousness in the ICU could not be performed. The level of consciousness was difficult to assess and seemed to change rapidly. However, the following observations are offered. In general, consciousness in the ICU was impaired more than that during pre-induction (in contrast to pre-induction, the patients were often not rousable), although the patients did not have adequate surgical anaesthesia. Their level of consciousness was therefore between that of sedation and that of surgical anaesthesia. The ASSR amplitude in the ICU was also between that of pre-induction and that of surgical anaesthesia.

The attenuation of the ASSR by sufentanil contrasts with the absence of an effect of high-dose fentanyl on the transient middle latency response (MLR) [35]. The ASSR results from the superimposition of individual MLR. The amplitude of the ASSR can be predicted when the MLR is known, if one assumes that the neural generators behave linearly [31]. It would be interesting to compare the ASSR with the MLR during sufentanil anaesthesia. If sufentanil alters the MLR, the changes could perhaps explain the attenuation of the ASSR. If, on the other hand, the MLR is not modified by sufentanil, one would have to invoke non-linearities of the neural generators to account for the ASSR attenuation [31].

The ASSR may possibly be useful to predict responsiveness during paralysis with neuromuscular blockers. Responsiveness, defined as the ability of any one patient to detect at least 5% of target stimuli within a single period (pre-induction, early induction and ICU), was always present when the ASSR amplitude exceeded 0.22 µV (fig. 1). An ASSR amplitude less than 0.22 µV, however, did not imply unresponsiveness. This confirms that arousal (measured by the ASSR) and responsiveness can be dissociated [36]: neuro-vegetative patients may be unresponsive despite near normal arousal [36], and simple signal detection tasks can be performed during Stage II sleep, a state of low arousal [37]. The ability of the EEG to predict responsiveness to target stimuli could not be evaluated because we did not record the EEG during early induction. The EEG is probably not better than the ASSR, however, as the pronounced slowing of the EEG by opioids precedes loss of consciousness [38]. The relationship between the ASSR and responsiveness appears to be as follows: loss or very severe attenuation of the ASSR probably implies unresponsiveness (e.g. late induction); an ASSR greater than 0.22 µV probably implies responsiveness; intermediate ASSR amplitudes allow no prediction.

In general, the changes in EEG paralleled those of the ASSR. However, there persisted a significant difference between pre-induction and recovery for the median EEG frequency and the relative delta power. This difference was not significant for the ASSR or for the EEG spectral edge frequency. Nevertheless, the ASSR may
have provided more information than the EEG. Its marked attenuation during late induction and its disappearance during CPB are probably a more reliable indicator of unconsciousness than is the EEG. Widespread delta activity (in contrast to burst-suppression or isoelectricity) is not always associated with unconsciousness [10]. Another advantage of the ASSR is that the ASSR is influenced less by muscle artefacts than are univariate EEG descriptors [19]. Fortunately, there is no need to choose between the ASSR and the EEG. The recording procedure could be modified to record and display the ASSR and the EEG concurrently.

ACKNOWLEDGEMENTS
This study was supported by a Fellowship from the Fonds de la Recherche en Santé du Québec to G. Plourde, and by grants to G. Plourde from The Royal Victoria Hospital Foundation, the Sheridan Fund of the Canadian Anaesthetists’ Society, and the Fondation d’anesthesiologie-réanimation du Québec. A. Kellett and Dick Mowrey provided essential technical and programming support, respectively. M. Trahan performed the analysis of the EEG data. The study was facilitated by an equipment loan from T. W. Picton.

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