

Evoked EEG patterns during burst suppression with propofol

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Background. During EEG suppression with isoflurane or sevoflurane anaesthesia, median nerve stimulation causes cortical responses of two kinds: an N20 wave with a latency of 20 ms and an EEG burst with a latency of 200 ms. We tested the possibility that median nerve stimulation during EEG suppression with propofol would cause an EEG response that was consistent enough to be of use for neuromonitoring.

Methods. Eight patients were anaesthetized with propofol to allow burst suppression. Electrical stimulation of the median nerve was applied during general anaesthesia and the EEG was measured.

Results. The EEG response to a painful stimulus had four successive components: (i) N20 and P22 potentials, reflecting activation of fast somatosensory pathways; (ii) a high-amplitude negative wave, possibly reflecting activation of the somatosensory cortex SII bilaterally; (iii) a burst (i.e. a negative slow wave with superimposed 10 Hz activity, probably reflecting an arousal mechanism); and (iv) a 13–15 Hz spindle, probably originating from the thalamus, similar to sleep spindles. These could be seen separately and in different combinations. Bursts and spindles during burst suppression were also seen without stimulation. In deepening propofol anaesthesia, spindles were seen in the continuous EEG before burst suppression was achieved. In deep anaesthesia, spindles were seen when bursts had ceased, and painful stimuli evoked sharp waves without subsequent bursts.

Conclusion. In addition to SSEP (somatosensory evoked potentials), three different evoked responses are noted that could be useful for clinical monitoring.

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Different anaesthetic agents cause different EEG patterns. Consequently, neither time- nor frequency-based measurements can provide a simple index of depth of anaesthesia, which is considered to be a single measure. The pattern of burst suppression, which is characteristic of deep anaesthesia, also varies depending on the anaesthetic used. Interest in burst suppression has increased because the EEG is now being used to assess the depth of anaesthesia.^{1–2}

Methods based on the bispectrum and approximate entropy can measure the hypnotic component of anaesthe-

sia. These methods are surprisingly insensitive to the agents used when obtunding agents such as propofol and volatile anaesthetics are used.^{3–4} These techniques use measurement of burst suppression during deep anaesthesia.

Somatosensory stimuli cause enhanced somatosensory evoked potentials (SSEPs) and trigger bursts during EEG suppression with isoflurane or sevoflurane.^{5–7} We could not cause bursts with painless stimuli during propofol anaesthesia. We wanted to see if somatosensory potentials, bursts or other EEG features could be caused by stimulation of the

Table 1 Latencies, amplitudes and durations of evoked bursts and spindles. Mean (SD)

Subject	Latency (ms)	Amplitude (μ V)	Duration (ms)	Number of bursts/spindles
Evoked bursts				
1	323 (187)	150 (41)	1323 (190)	6
2	459 (66)	117 (12)	1155 (197)	11
3	611 (65)	123 (27)	1228 (389)	9
4	514 (110)	130 (22)	1400 (316)	11
5	445 (99)	73 (22)	1073 (163)	11
6	509 (238)	90 (17)	1282 (240)	11
7	435 (108)	141 (24)	1130 (283)	10
8	500 (133)	293 (32)	1340 (416)	10
Evoked spindles				
1	2238 (299)	100 (24)	1560 (365)	5
2	2189 (297)	46 (13)	1067 (308)	9
3	2456 (240)	45 (12)	1111 (145)	9
4	2720 (519)	50 (6)	1150 (401)	10
5	2256 (308)	36 (8)	1067 (278)	9
6	5680 (760)	40 (8)	1210 (328)	10
7	2713 (740)	46 (9)	975 (212)	8
8	2361 (293)	67 (10)	656 (101)	9

median nerve during EEG suppression with propofol, and if these features were potentially useful in assessing information processing during deep anaesthesia and in measuring depth of anaesthesia.

Materials and methods

Patients

The study was approved by the Ethics Committee of the University of Oulu. All patients gave written informed consent. Eight ASA I patients (four male and four female) undergoing elective surgery took part. Their mean (range) age was 40 (30–53) yr, weight (range (SD)) 72.5 (7.5) kg and height 170 (7.7) cm. Patients with evidence of systemic neurological disease or taking medication known to affect the central nervous system were excluded.

Anaesthesia

No premedication was used. After establishing EEG monitoring (see below), general anaesthesia was induced with propofol i.v., which was given until burst suppression was achieved. After induction of anaesthesia, the lungs were ventilated with oxygen 100% through a face mask. Rocuronium bromide 0.5–0.6 mg kg⁻¹ i.v. was given, the trachea was intubated, and controlled ventilation with air:oxygen 2:1 was begun. Additional doses of rocuronium were given as needed, indicated by measurements of neuromuscular transmission.

The propofol infusion was adjusted to maintain EEG burst suppression (14–29 mg kg⁻¹ h⁻¹). Lidocaine was not added to the propofol. No patient complained of pain associated with propofol administration. Blood pressure was measured non-invasively at 5-min intervals, and ECG, end

tidal carbon dioxide and oxygen saturation were monitored continuously. Ventilation was adjusted to keep FE'_{CO_2} between 4.5 and 6 kPa, using a Datex Capnomac Ultima anaesthetic agent monitor (Datex, Helsinki, Finland). Mean arterial pressure was maintained above 70 mm Hg by rapid infusion of sodium chloride 0.9% if necessary.

EEG recordings and stimulation

EEG signals were recorded continuously using a NeuroScan Synamp amplifier (Neuroscan, El Paso, TX, USA). Silver-silver chloride electrodes were applied on the nose and to the Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, CPz, CP3, CP4, T3, T4, T5, T6, Pz, P3, P4, O1 and O2 points, the cervical spine of C7, the left and right zygoma, and over the mastoids (M1, M2). The reference electrode was attached to FCz. Bandpass was 0.05–1000 Hz with a sampling rate of 5000 Hz.

The patient was not touched or stimulated in any way during the experiment. The median nerve was electrically stimulated using surface electrodes at the wrist with a Medelec ST-10 stimulator (Medelec, Old Woking, UK) using 0.1 ms 100 mA pulses triggered manually during periods of EEG suppression.

Results

During EEG burst suppression, median nerve stimulation induced responses with four distinct components. The three large-amplitude components are shown in Figures 1 and 2.

Short-latency response, 20–30 ms after stimulus

An N20 potential was recorded contralaterally to the stimulus from P3-M2 or P4-M1. The amplitude was 2–5 μ V, the latency of the peak was 22–26 ms and the

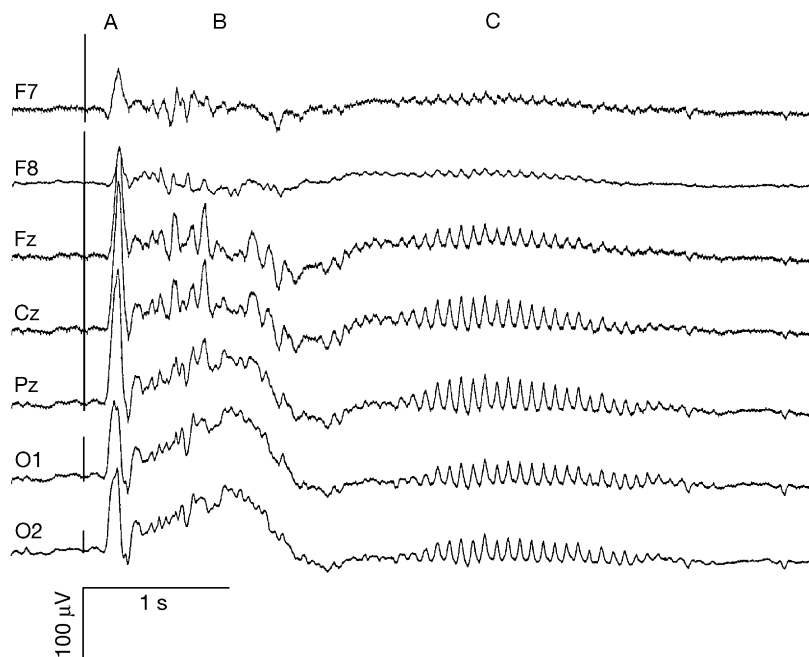


Fig 1 Response to a painful electrical stimulus during suppression. The vertical line indicates the time of the stimulus. This is followed by a large negative sharp wave (A). After this, a negative slow wave (B) with mixed-frequency activity constitutes the burst. After return to the DC level, there is a spindle-shaped rhythmic series of waves, resembling sleep spindles, with a frequency of 13 Hz (C). Reference: tip of the nose. Bandpass 0.05–427 Hz.

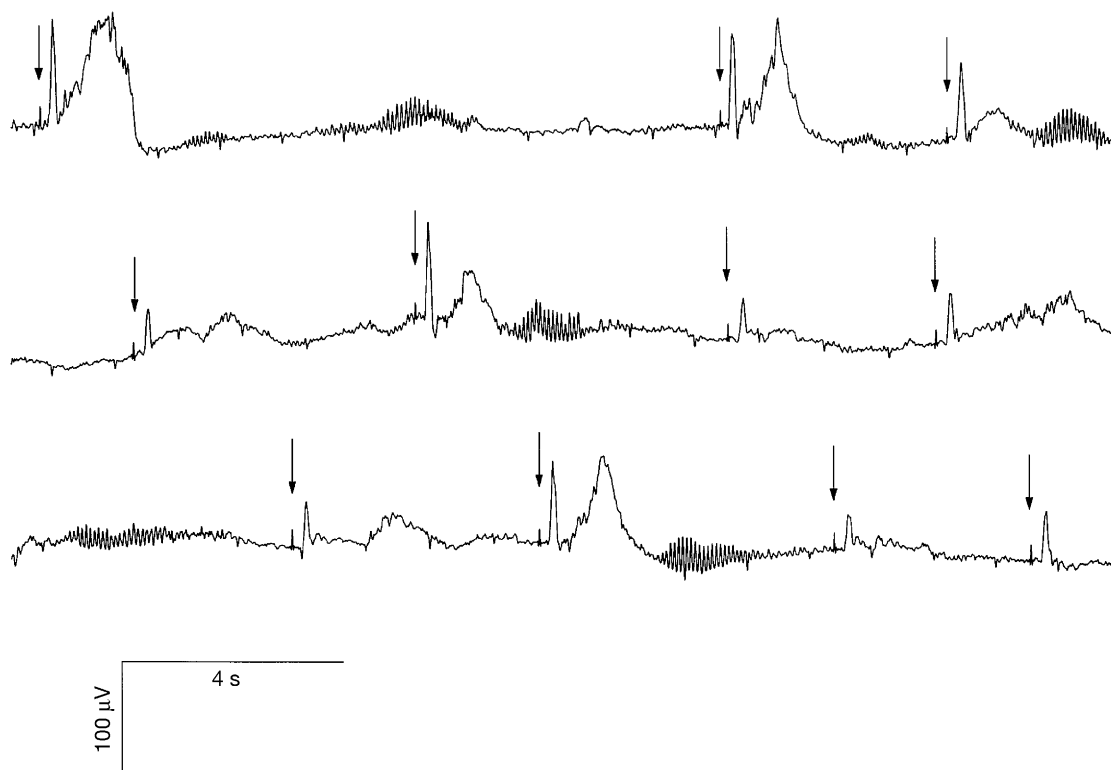


Fig 2 Median nerve stimuli, indicated by arrows, are regularly followed by a negative sharp wave (pointing upwards), and variably by a slow wave (broad wave also pointing upwards, i.e. negative) and spindle (a rhythmic run of fast waves). Three successive 20-s pieces of EEG from electrode Pz, referred to tip of nose. Bandpass 0.05–34 Hz.

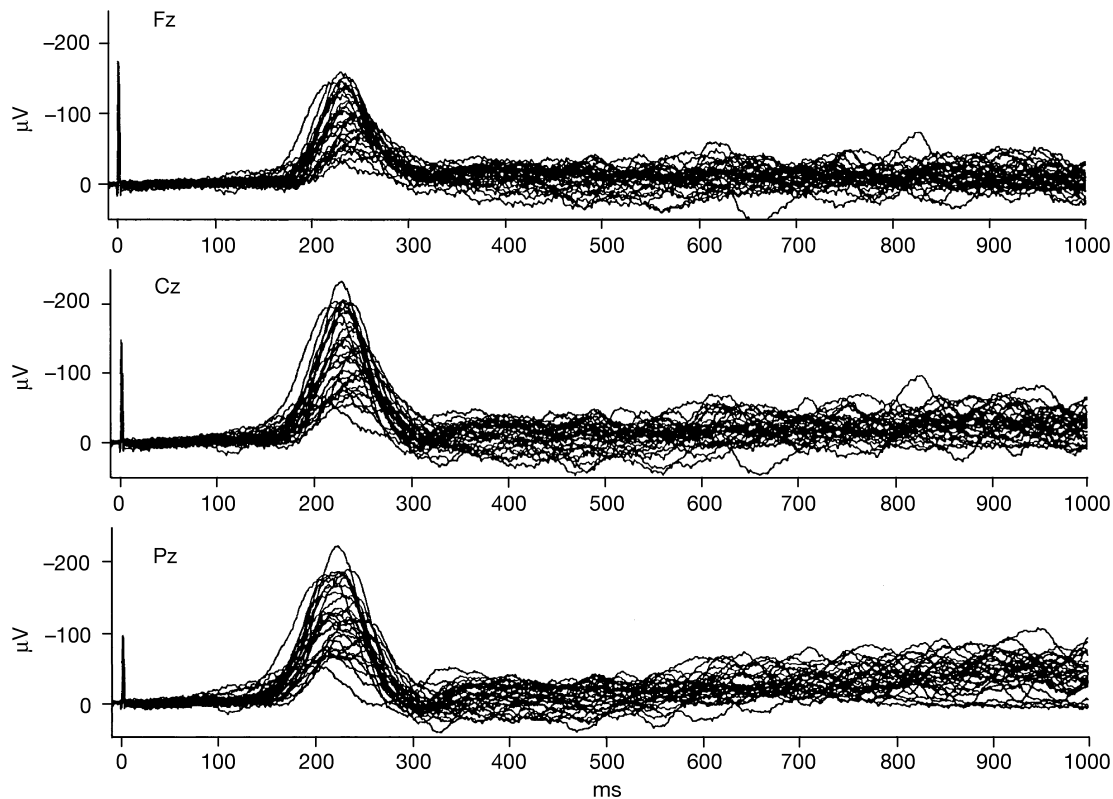


Fig 3 Sharp waves after 32 painful stimuli during EEG suppression are superimposed. Note the very constant waveform and latency of ~150 ms to onset and 220 ms to peak, while amplitude varies. With this patient, these evoked responses were not followed by a burst because the propofol anaesthesia was deep. Reference electrode on the tip of the nose, bandpass 0.05–427 Hz.

duration had a range of 4–10 ms. A P22 was recorded contralaterally to the stimulus, using a central area electrode (C3-M2 or C4-M1). The amplitude had a range of 2.5–4 μV , a peak latency from 22 to 27 ms and duration 7–12 ms. These correspond to N20 and P22 waves seen in awake subjects. There was no difference in the amplitude or latency of SSEP recordings made in awake subjects and during anaesthesia.

Negative sharp wave

A large-amplitude negative wave was recorded with an onset latency between 100 and 450 ms, peak from 180 to 1000 ms, duration 650–2000 ms and amplitude 40–330 μV . This negative sharp wave occurred in all scalp electrodes, with the greatest amplitude in central and occipital areas using a nose or ear reference (Fig. 3). The negative sharp-wave response was seen after most stimuli. This negative sharp wave was also seen when stimuli were applied during continuous EEG and during bursts, but the amplitude was less than during suppression.

Burst: a slow wave with 10 Hz superimposed activity

After the large-amplitude negative wave, a smaller negative wave of long duration was recorded. On this negative slow

wave ~10 Hz mixed activity was superimposed, with maximum amplitude on the descending part of the slow wave. This is the typical burst of propofol-induced burst suppression.⁸ This burst had a duration of 1–3 s and amplitude 50–180 μV . With the nose or C7 as reference, the greatest amplitude was seen with the occipital and parietal midline electrodes.

Spindle

The fourth distinct component was a spindle with a frequency of 13–15 Hz and a typical latency of 1 s, but latencies up to 6–7 s were recorded. The duration was between 2.2 and 5.7 s and the amplitude was 35–100 μV . It sometimes started on the slow-burst wave but often distinctly after it (Fig. 1). It was clearly different from the slow-burst wave or the rhythmic component of this burst (Fig. 1). It was asymmetrical, with negative excursions from the DC level.

We also observed spontaneous spindles of this form, with amplitudes of 40–60 μV and durations of 1000–1150 ms. They started to appear on slow waves even before burst suppression was achieved and were also seen even when complete suppression was present and bursts had ceased.

Discussion

We found electrical stimulation of the median nerve that causes pain can generate a cortical response with four successive components during deep propofol anaesthesia. These four components may occur independently, which suggests independent mechanisms.

Propofol has been suggested as the anaesthetic of choice for monitoring SSEPs, because somatosensory potentials are better preserved during propofol anaesthesia than during anaesthesia with nitrous oxide or isoflurane.^{9 10}

Pain-evoked potentials provide an objective way to measure the sensation of pain.^{11 12} The stimulus is usually an electrical or laser stimulus, which is often to hand, but chemical, mechanical, cold and heat stimuli have also been used.^{11 12} Electrical stimuli to a peripheral nerve have been widely used, although they also stimulate other than purely nociceptive fibres.^{11 12}

In awake subjects, a painful electrical skin stimulus evokes a positive wave of the vertex 80 ms after the application of the stimulus (P80), followed by a negative wave at ~150 ms (N150), a further positive wave at 250 ms or later (P250), and occasionally a negative wave at ~330 ms.^{11 12} In magnetoencephalography (MEG) recordings with a painful stimulus from a laser, a bilateral response from the secondary somatosensory cortex (SII) has been identified with a latency of 200 ms.¹³ From the apparent relationship between the intensity of stimulation and the response amplitude, these potentials should indicate the sensory-discriminative aspects of pain. Another EEG wave, P300, could reflect the emotional and motivational features of the pain response.¹⁴ The amplitude of pain-related SSEP decreases with sleep stage¹⁵ and general anaesthesia.¹⁶

Most studies of pain with evoked potentials have analysed traces <500 ms in duration.^{11 17} These changes in cerebral potentials can only reflect the 'first pain', mediated by thin myelinated A δ fibres. Pain elicited by cutaneous C-nociceptors should only reach the brain after ~1 s.^{11 17 18}

Possible origins of the components of the response to painful stimuli during EEG burst suppression with propofol

Short-latency SSEP

The waveforms appearing contralateral to stimulation correspond to the primary cortical somatosensory responses N20 and P22. They are probably not caused by specific pain fibres but are more likely to arise from other modalities of somatosensory perception and fast-conducting fibres.^{11 12} During anaesthesia with sevoflurane, stimulation of the median nerve produces somatosensory evoked responses after every stimulus, corresponding to N20 and P22, of greater amplitude than in awake conditions. The later cortical waves are abolished.^{6 7} These adapt more rapidly than SSEPs in awake conditions. Single N20 responses were

occasionally seen during burst suppression in the present study, but they were not so large as in sevoflurane anaesthesia, where N20 values up to 10 μ V have been reported.⁶ However, they are large enough to be sometimes seen without averaging during burst suppression with propofol.

The N20 wave and, at least to some extent, also the later potentials evoked by median nerve stimulation could be generated by the posterior surface of the central sulcus, area 3b.¹⁹ The sources of P22 are less well known.²⁰ Recently, a biphasic effect of anaesthesia on N20 amplitude was reported by Vaughan and colleagues,²¹ but their method of recording may measure the sum of N20 and P22.

Negative wave: vertex wave of sleep wave or N100

This coincides temporally with the response that laser stimuli and MEG have shown to produce bilaterally in the SII area. These sources could elicit a response with the distribution of this wave.¹³ The distribution and latency of the large negative wave are like the vertex wave of physiological sleep, and are also like N100 and some components of 'cognitive potentials', such as P300.²²

During physiological sleep, a K-complex, i.e. a negative sharp vertex wave, followed by a spindle can be seen after a stimulus.^{22 23} In latency and topography, the sharp wave we observed during burst suppression resembles the K-complex,²²⁻²⁵ while in appearance it is similar to the spindle that follows it.^{22 24 25} K-complexes appear in Stage 2 sleep in response to arousing stimuli. They are maximal over the vertex.²²⁻²⁵ K-complexes may be elicited by sensory stimulation or may occur spontaneously in a stimulus-free environment.^{23 25}

Amzica and Steriade^{24 25} found a relationship between the slow (<1 Hz) oscillation and sleep K-complexes. They suggest that K-complexes are generated by a synchronized cortical network that periodically excites or inhibits cortical neurons, and that spontaneous K-complexes indicate slow oscillation. Their presence through the stages of sleep is related to the increasing synchrony within cortical networks with the deepening of sleep and sensory deafferentation. Hence, either responses from the secondary cortex or a more extensive activation of the cortex, such as a K-complex, might cause this pain-induced negative sharp wave.

Burst similarity with isoflurane-induced burst activity

A burst can be described as event-related synchronization, although it probably also reflects activation of cortical cells, which are silent during EEG suppression.²⁶

The evoked potential is followed by a burst with a latency of ~200 ms, but this does not occur after every stimulus. During anaesthesia with isoflurane, spontaneous bursts and bursts induced by vibration have distinctly different waveforms.²⁷ Photic, auditory and somatosensory stimuli cause bursts with clearly different onset waveforms and with mean latencies of 290–440 ms, sometimes up to 510 ms, from stimuli specific to the modality of stimulation.⁵

The burst suppression pattern seen in propofol anaesthesia is not the same as that seen during isoflurane or sevoflurane anaesthesia. The bursts are very slow negative waves with smooth onset and superimposed alpha-frequency waves. In isoflurane and sevoflurane anaesthesia, the bursts start and end with an abrupt DC shift,^{5,6} whereas with propofol the burst onset and end are smooth. Bursts during anaesthesia with volatile agents start with a stimulus-specific onset waveform,⁵⁻⁷ which may correspond to the negative sharp wave we noted before burst onset. In isoflurane and sevoflurane anaesthesia, the negative wave preceding the burst seems to merge with the burst and to occur synchronously with the burst onset,⁵⁻⁷ while in propofol anaesthesia they are temporally separate events. In isoflurane anaesthesia, a burst can be evoked by very minor novel stimuli.⁵ We hypothesize that this could reflect the arousal mechanism.

In our preliminary experiments with propofol anaesthesia, we could not induce bursts with minor somatosensory, photic or auditory stimuli. We now report that electrical stimuli during propofol-induced burst suppression can cause bursts and SSEP.

Spindle

The spindle is similar to the sleep spindles often seen during stage 2 sleep in response to an external stimulus, preceded by a vertex negative sharp wave. Spindles are defined as a 'group of rhythmic waves characterized by progressively increasing, then gradually decreasing amplitude'.²² In propofol anaesthesia, they appear before the onset of burst suppression, then continue to occur, sometimes during bursts, but most typically after bursts. Spindles are seen both during bursts and separately during suppression. They resemble focal epileptic discharges, which may start during a burst and continue during suppression.²⁸ In deeper anaesthesia, they persist during continuous suppression. They are probably generated by the thalamus, and during physiological sleep they are related to the blocking of sensory information flow from the thalamus to the cortex. We have not seen spindles in isoflurane or sevoflurane burst suppression.^{2,5-8} The pain-evoked responses during propofol burst suppression resemble K-complexes and spindles during physiological sleep. Some features of physiological sleep seem to be better preserved during propofol anaesthesia than in anaesthesia with other agents.

Conclusions

Painful stimulation of a peripheral nerve during propofol anaesthesia induces cortical responses with four separate components, each probably representing a different and at least partly independent cerebral mechanism. Of these responses, only the somatosensory evoked potential needs averaging. The other three responses are seen in the raw EEG without further processing, such as averaging. More studies are needed to find out whether any of these

components correspond to particular pain modalities, such as fast or slow conducting pathways. We found phenomena characteristic of propofol. For instance, the long-latency evoked potential, i.e. the sharp wave, and the burst are separated and can occur independently in propofol burst suppression. In contrast, in isoflurane or sevoflurane burst suppression the evoked waves continue as a burst, i.e. they are temporally merged. Evoked potentials are important phenomena that could be used to study sedated patients in the intensive care unit. They probably represent preconscious information processing. Systematic differences between different anaesthetic agents can be distinguished in these evoked responses.

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