Power spectral analysis of EEG during sufentanil infusion in humans

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The purpose of this study was to examine the relationship of continuous sufentanil infusion (0.71 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 14 min) and the response of the power spectrum of the electroencephalogram (EEG) performed during the induction of anaesthesia in 12 patients undergoing CABG surgery. Data were collected at various times including the preinduction period, every minute during the infusion period (minute 0 to 14), and 15, 20 and 25 min after the start of the infusion (1, 6 and 11 min respectively after completion of the infusion). Within three minutes of the sufentanil infusion, the total power and the relative power of delta increased to near maximum, while the 95% spectral edge and the mean frequency decreased markedly. In spite of the continued infusion of sufentanil, there were very little further changes in the EEG activity. This ceiling effect for the EEG changes appear to coincide with the failure to respond to verbal command. We conclude that the power spectrum of the EEG failed to respond to increasing doses of sufentanil during its infusion after the rapid initial changes.

Le but de cette étude était d'examiner la relation d'une perfusion continue de sufentanil (0.71 $\mu g \cdot kg^{-1} \cdot min^{-1}$ pour 14 min) et la réponse du spectre de puissance de l'électroencéphalogramme (EEG) obtenue durant l'induction de l'anesthésie chez douze patients devant subir un pontage aortocoronarien. Les données furent obtenues à des temps différents incluant la période de préinduction, chaque minute durant la perfusion (minute 0 à 14), et 15, 20 et 25 minutes après le début de la perfusion (1, 6 et 11 minutes respectivement après la cessation de la perfusion). En dedans de trois minutes de la perfusion de sufentanil, la puissance totale et la puissance relative de l'onde delta augmenta pour presqu'atteindre le maximum, alors que la crête spectrale de 95% et la fréquence moyenne ont diminué d'une façon marquée. Malgré la perfusion continue de sufentanil, il n'y avait que très peu d'altération dans l'activité de l'EEG. Cet effet de plafonnement pour les alterations de l'EEG coïncide approximativement avec la non-réponse à la commande verbale. On conclut que la spectre de puissance de l'EEG a manqué de répondre à l'augmentation de la dose de sufentanyl lors de sa perfusion après les changements rapides initiaux.

Key words

ANAESTHETICS, INTRAVENOUS: sufentanil;
BRAIN: electroencephalography;
MONITORING: electroencephalography, power spectral analysis.

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Narcotic anaesthesia with fentanyl or sufentanil has been used extensively in cardiac surgery because of the minimal side-effects of these drugs on the cardiovascular system. One of the problems with narcotic anaesthesia is that it may not provide complete amnesia.[1,2] Utilization of computerized analysis of the electroencephalogram (EEG) has been suggested to determine the depth of anaesthesia.[3,4] Bovill *et al.* investigated the effects of a bolus dose of sufentanil (15 $\mu g \cdot kg^{-1}$) on the EEG and its power spectral analysis.[5] They found that there was a rapid increase in delta activity with an increase of the total power. Similar observations were made with bolus doses of fentanyl.[6] The rapid change in the EEG activity could be merely due to a rapid increase of the plasma concentration of these agents as a result of bolus administration. With a gradual increase of the dose, the total power and the delta activity may show different patterns. In this study, sufentanil was infused at a rate of 0.71 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to investigate the effects of a gradual increase of plasma sufentanil concentration on the power spectrum of the EEG. In particular, we examined whether the changes in the power spectrum of the EEG would parallel the increasing dose of sufentanil during its infusion.

Methods

The study was approved by our Institutional Review Board. Twelve consenting patients undergoing coronary artery bypass grafting were studied. Their mean age and weight were 59.3 yr (±7.5 SD) and 73.2 kg (± 9.6)

respectively. None of the patients had serious neurological disorders. On the day of surgery, each patient received an *im* injection of 0.1 $mg \cdot kg^{-1}$ morphine and 0.4 mg scopolamine as premedication. Their regular preoperative cardiac medications were continued up to the time of the surgery. In the operating room, before induction of anaesthesia, a peripheral venous catheter, a radial artery catheter, and a Swan-Ganz catheter were inserted while the EGG and BP were monitored. A warming blanket was placed under the patient beforehand. Cardiac output and arterial blood gases were measured. A Nellcor Pulse Oximeter sensor was applied to the patient's index finger and a Stat-Temp temperature sensor was applied to the patient's forehead.

To obtain four channel recordings of the EEG, five silver/silver chloride disc electrodes were placed on the scalp according to the 10–20 international system of electrode placement. The montages used were: F_4-A_2, C_4-A_2, P_4-A_2 and T_4-A_2. A ground electrode was placed on the left ear (A_1). The impedance of the electrodes was less than 3000 ohm. A Nicolet Pathfinder I was used to record and analyze the EEG and a filter was set at 0.5–70 Hz. Sensitivity was 200 μV. Data analysis was performed by digitizing each channel of the EEG recording at 256 Hz. Artifact rejection was on and the line frequency suppression was set at 60 Hz. On-line power spectral analysis was performed with a Fast Fourier Transformation using a four-second epoch producing power spectrum with a resolution of 0.25 Hz. The resulting spectral array was displayed. The raw EEG was also recorded on magnetic tape for further analysis. Of the four channels, C_4-A_2 was used to acquire the numerical analysis in our study because other channels showed essentially similar changes in the spectral array. A set of numerical data was acquired every 20 sec, thereby providing three sets of data per minute. For each minute, however, only one set of data was kept for final analysis. The set selected for final analysis was always derived from the epoch showing the least artifacts. Spectral bands of 0.25–3.75 Hz (delta), 4–7.75 Hz (theta), 8–13 Hz (alpha) and 13.25–32 Hz (beta) were analyzed for the total power (power of the entire bands of 0.25–32 Hz), the relative power of each band (proportion of the power of each band relative to the total power), the 95% spectral edge (the frequency at 95 percentile of the total power in the range from 0.25–32 Hz) and the mean frequency.

The EEG recording and its spectral analysis were started in the operating room as preinduction data before the induction of anaesthesia while vascular access lines and other monitors were being placed. Then, 1 mg vecuronium was administered, which was followed by an infusion of sufentanil at a rate of 0.71 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 14 min (total 10 $\mu g \cdot kg^{-1}$). When the patient failed to

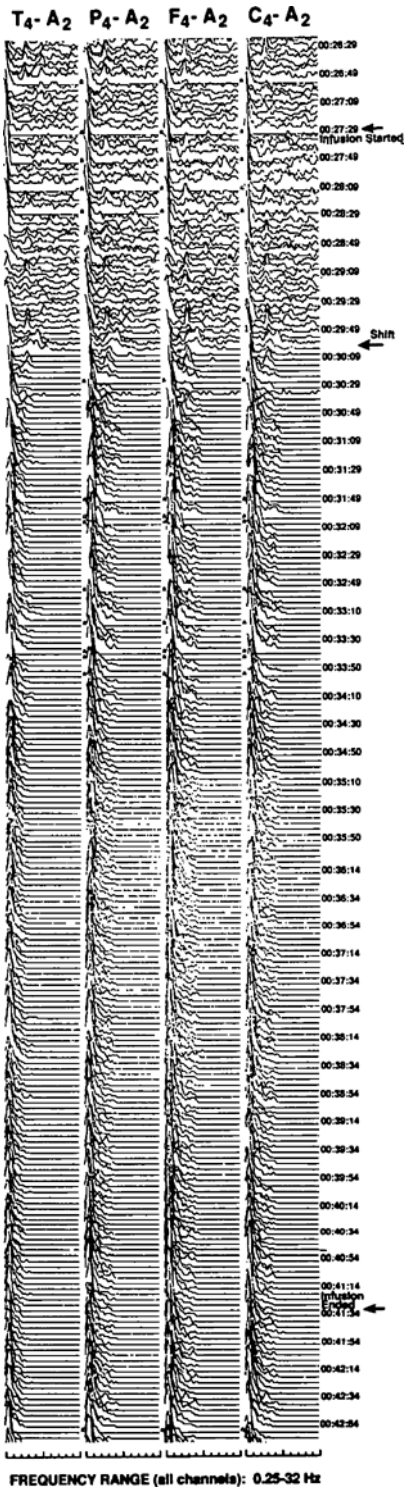

FIGURE 1 Typical spectral array with four-second epochs from a patient during sufentanil infusion at a rate of 0.71 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Frequency range (all channels) is 0.25–32 Hz. "A" represents artifact. Abrupt "shift" toward low frequency is observed at about 2.5 min of the infusion. No further changes are observed after three minutes in spite of continued infusion.

open his/her eyes on the verbal command, "Open your eyes!", which was repeated every five seconds, vecuronium 0.15 mg · kg^{-1} was administered. The lungs were ventilated by mask with 100% oxygen. End-tidal CO_2 was monitored with a Sara Cap to maintain it in the range of 35–40 mmHg. After 14 min of the sufentanil infusion, lidocaine 100 mg was administered and the patient's trachea was intubated. After 14 min of infusion, no further sufentanil was given. If needed, vasoactive medications were administered to control BP and heart rate. During the induction period and up to the time of the skin incision, the EEG recording and its spectral analysis were performed continuously. Numerical data obtained at various times including the preinduction period, every minute during the infusion (min 0 to 14), and 15, 20 and 25 min after the start of the infusion (1, 6 and 11 min after completion of the infusion) were subjected to analysis of variance with repeated measures and the Student-Newman-Keuls multiple comparison test. A P value <0.05 was considered statistically significant.

Results

A picture of the successive power spectra of four-second epochs from a typical patient is shown in Figure 1. The raw EEG from the same patient is shown in Figure 2. Within two minutes of the infusion of sufentanil, the frequency of the EEG decreased rapidly. At three minutes typical delta waves became predominant. However, with a further increase of the dose there was little change in the EEG.

Results of the computer-analysis of the EEG are shown in Figure 3. There were relatively large variations among patients resulting in big standard deviations. Changes in the total power were significant ($F = 10.12$, $P < 0.0005$). It increased rapidly from 179.9 μV^2 (± 110.3 SD) to 370.6 μV^2 (± 182.8) between zero and three minutes of the infusion of sufentanil ($P < 0.001$). It reached the peak of 436.7 μV^2 (± 113.5) at six minutes, then gradually declined. The 95% spectral edge changed significantly ($F = 19.99$, $P < 0.0005$). It decreased rapidly from 19.42 Hz (± 9.25 SD) at the beginning of the infusion to 8.71 Hz (± 3.88 SD) at three minutes ($P < 0.001$). It declined further to 6.08 Hz (± 2.32 SD) at six minutes of the infusion, then showed little change during the remainder of the study period. Changes in mean frequency were also significant ($F = 9.42$, $P < 0.0005$). After a minor initial increase, it showed a rapid decrease from 7.00 Hz (± 5.01 SD) at one minute to 3.10 Hz (± 1.54 SD) at three minutes of the infusion ($P < 0.001$). It further declined slightly to 2.08 Hz (± 0.73 SD) at six minutes, then showed little further change during the remainder of the study. The relative power of delta showed significant changes ($F = 13.86$, $P < 0.0005$). It

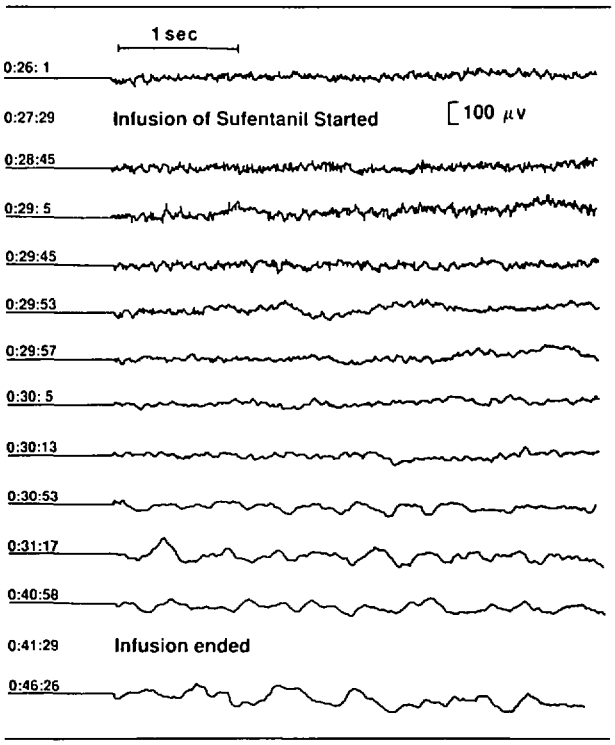

FIGURE 2 Raw EEG with four-second epochs which was obtained from the same patient shown in Figure 1. Rapid changes of the EEG from the start of the infusion up to the point indicated with 0:30:53 are noted. Further infusion of sufentanil did not considerably affect the EEG.

rapidly increased from 0.54 (± 0.29 SD) at one minute to 0.76 (± 0.20 SD) at three minutes of the infusion ($P < 0.001$), further increased to 0.88 (± 0.09) at six minutes, then showed little change. The relative power of theta ($F = 2.85$, $P < 0.0005$) rapidly increased from 0.07 (± 0.06 SD) at zero minute to 0.14 (± 0.09 SD) at three minutes of the infusion ($P < 0.025$), had a gradual decrease to 0.09 (± 0.06 SD) at six minutes, then remained relatively constant. The relative power of the alpha ($F = 8.90$, $P < 0.0005$) showed a rapid decline from 0.12 (± 0.09 SD) at zero minute to 0.05 (± 0.07 SD) at four minutes of the infusion ($P < 0.025$), then little further decline. The relative power of the beta ($F = 6.88$, $P < 0.0005$) declined rapidly from 0.19 (± 0.23 SD) at zero minute to 0.02 (± 0.03 SD) at three minutes of the infusion ($P < 0.001$), then it remained less than 1%. Overall, the variables used in our study showed the largest changes between zero and three minutes of the infusion. With continued infusion after three minutes, however, no further statistically significant changes were observed in any of the variables. Patients failed to respond to verbal command at an average of 149 sec (± 48 SD, range 85–245 sec) after the start of the sufentanil infusion. Ten out of 12 patients failed to respond within three min. At

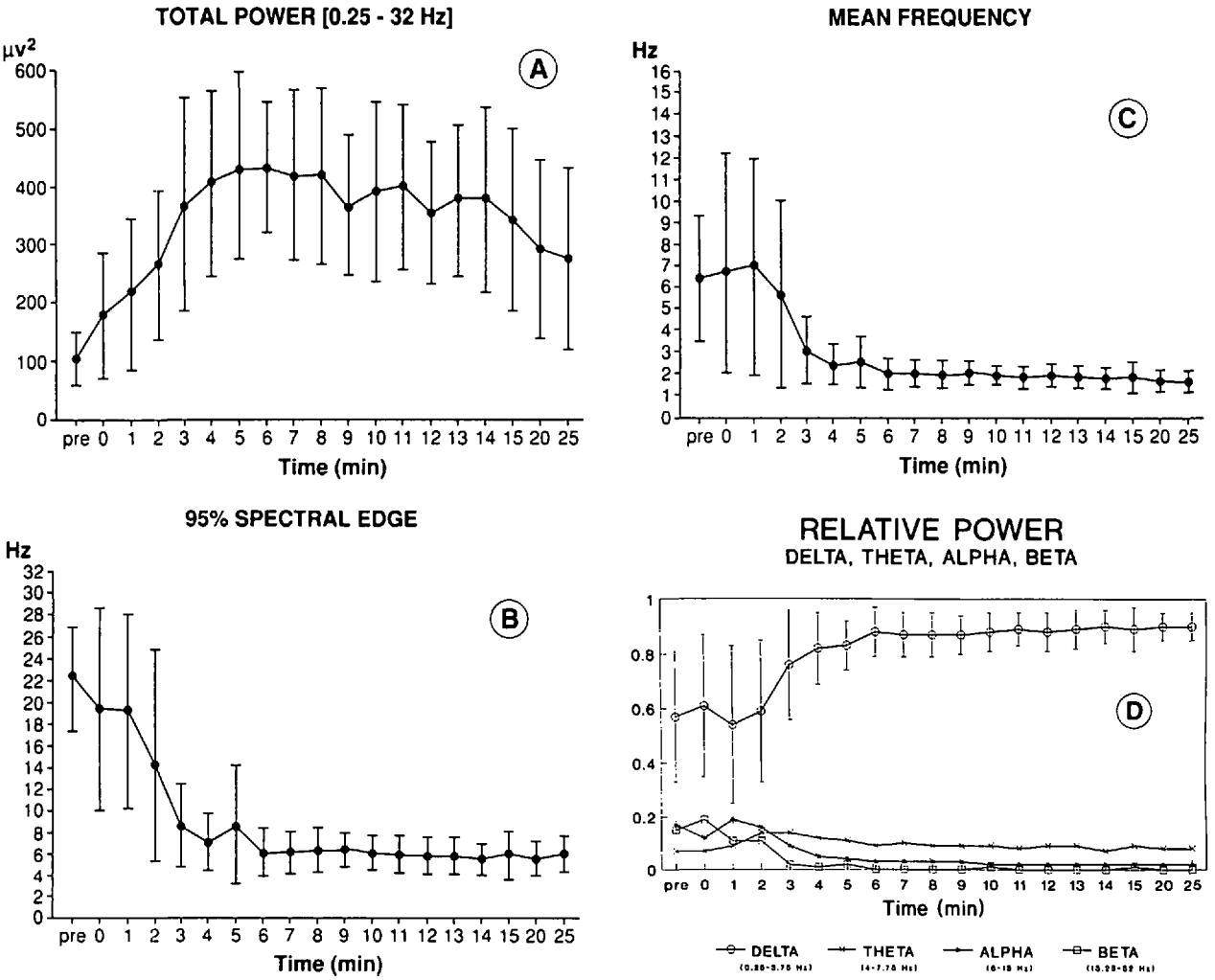

FIGURE 3 Graphic representation of the variables from the power spectral analysis with mean ± standard deviation in patients before, during, and after infusion of sufentanil at a rate of 0.71 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Numerical data show various time points including the preinduction period, every minute during the infusion (0 to 14 min), and 15, 20 and 25 min after the start of the infusion (1, 6 and 11 min after completion of the infusion). (A) Total power. (B) 95% spectral edge. (C) Mean frequency. (D) Relative powers of delta (0.25–3.75 Hz), theta (4–7.75 Hz), alpha (8–13 Hz) and beta (13.25–32 Hz).

the time of failure to respond to verbal command, the power spectral analysis of the four sec epoch showed the following: total power, 387.8 μV^2 (±170.9 SD); relative power of delta, 0.76 (±0.14 SD); 95% spectral edge, 8.58 Hz (±3.17 SD); and mean frequency, 3.04 Hz (±1.30 SD).

Tracheal intubation did not affect the EEG activity. No patient recalled any events during surgery, nor had any discomfort or complication from our study.

Discussion

In this study, during slow infusion of sufentanil (0.71 $\mu g \cdot kg^{-1} \cdot min^{-1}$), the total power and the relative power of the delta band of the EEG increased to near maximum within three minutes. Other power spectra of the EEG also changed rapidly during the first three minutes of sufentanil infusion. With the continuous administration of sufentanil, the power spectrum of the EEG showed very little further change in response to increased doses of sufentanil infusion after the initial changes. This ceiling effect for the EEG changes appeared to coincide with the onset of the unconsciousness which was defined in our study as "failure to open the eyes on verbal command." Studies by Bazaral also suggested ceiling effects for the EEG changes. In their study, a fixed dose of 15 or 60 $\mu g \cdot kg^{-1}$ fentanyl produced the same patterns of deep narcotic anaesthesia (low frequency EEG activity) within 110 sec after either dose was given. Our dose of sufentanil which

produced rapid changes in the delta activity is approximately equipotent to the dose of fentanyl which produced similar changes reported by Scott *et al.*[8] Ten out of our 12 patients became unconscious within three minutes after the start of the infusion with total infused dose less than 2.1 $\mu g \cdot kg^{-1}$. Our data corresponds very well to those studies performed by Bowdle *et al.*[9] In their study, nine out of ten patients who received a bolus dose of 1.3 $\mu g \cdot kg^{-1}$ of sufentanil became unconscious after receiving the opioid alone. Flacke also showed that 47% of their patients became unresponsive after receiving less than 1.5 $\mu g \cdot kg^{-1}$ of sufentanil.[10] The dose for unconsciousness with sufentanil appeared to be about or less than 2.1 $\mu g \cdot kg^{-1}$. In our study the rapid changes of the delta band occurred during the induction of anaesthesia with loss of consciousness. In contrast with ours, Long *et al.* studied the EEG changes during emergence from anaesthesia.[11] In their studies, during emergence from fentanyl anaesthesia, an abrupt decrease in the power of the 1–4 Hz frequency band occurred within one minute of awakening. During emergence from isoflurane anaesthesia, similar changes occurred several minutes before the patients opened their eyes. Conceivably, EEG changes may occur abruptly as soon as the brain concentration of narcotics reaches the threshold for unconsciousness. Other drugs administered with subanaesthetic doses of sufentanil may affect the threshold of the brain for EEG changes. Our patients were premedicated with morphine and scopolamine. This may have raised the state of narcosis close to the threshold, the consequence of which was to show an abrupt change in EEG activity after only a short period of sufentanil infusion. If a smaller dose had been infused at a slower rate, it may have been possible to observe a dose–response relationship more clearly during the initial period of the infusion.

In our study, the 95% spectral edge also decreased rapidly until three minutes of infusion, then remained almost unchanged afterwards. A similar observation was made for the mean frequency. Schwilden and Stoeckel found that the median frequency was greater than 6 Hz in conscious patients. It decreased to less than 5 Hz during anaesthesia with isoflurane in 60% N_2O.[12] In our study, almost all the patients failed to respond to verbal command within three minutes of the sufentanil infusion which corresponded very well to the decrease of the mean frequency below 4 Hz at three minutes of the infusion.

These findings suggest that the EEG may be used to grade the depth of anaesthesia during the early induction period until consciousness is lost. To clarify this, a more objective method to examine unconsciousness should have been applied in this study. Even though patients failed to respond to verbal command, with stronger stimuli or surgical incision, they may wake up and respond. Increase in delta activity does not necessarily mean loss of consciousness as it can occur in the condition of viral encephalitis or metabolic disturbances.[13] Also, the changes of the delta power may be different at the time of loss of consciousness if a different anaesthetic agent is used. With an increasing dose of sufentanil, however, none of the variables changed further, which makes it difficult to use the EEG to grade the depth of anaesthesia after induction.

In conclusion, all the variables of EEG in our study showed rapid changes during the first three minutes of sufentanil infusion at a rate of 0.71 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Especially, there was a marked increase of delta activity during this period. These rapid changes corresponded approximately to the patients' failure to respond to verbal command. However, in spite of continuous infusion of sufentanil, there was very little additional change in the EEG activity. Therefore, the power spectrum of the EEG failed to respond to the dose increase during sufentanil infusion after the initial changes.

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