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No Correlation between Quantitative Electroencephalographic Measurements and Movement Response to Noxious Stimuli during Isoflurane Anesthesia in Rats

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A meaningful use of the electroencephalogram (EEG) for monitoring depth of anesthesia has proven elusive. Although changes in the EEG with changing anesthetic dose or concentration have been noted for 60 yr, it has been difficult to demonstrate reliable, quantitative correlation between the EEG and other physiologic measures of anesthetic depth. We attempted to correlate several quantitative EEG measurements in rats, including average amplitude, spectral edge frequency, and burst suppression ratio, with the movement response to supramaximal noxious stimulation. We anesthetized 21 Sprague-Dawley rats with isoflurane 1.5% and allowed them to breathe spontaneously. After equilibration, EEG was recorded for off-line analysis; then a noxious stimulation was delivered with a tail clamp and the somatic response noted. Isoflurane concentration was adjusted up and down. and the EEG and movement response to tail clamp were assessed at each level until the minimum alveolar concentration was determined in each rat. We found no EEG dose response to increasing inspired concentrations of isoflurane, except for an increasing degree of burst suppression. We found no difference in any parameter between rats that responded and those that did not respond to stimuli at a given concentration of isoflurane. Finally, we found that the presence of burst suppression did not predict lack of response. (Key words: Anesthetics, volatile: isoflurane. Electroencephalography: burst suppression. Monitoring: depth of anesthesia; electroencephalography. Potency: MAC (ED_{50}).)

A CLINICALLY RELEVANT use of the electroencephalogram (EEG) for monitoring depth of anesthesia has proven elusive.[1,2] Many investigators have reported changes in EEG activity during administration of anesthetic drugs.[3,4] Results from several studies have differed: some have suggested a clinically useful correlation between quantitative EEG and patient hemodynamic response to noxious stimuli,[5,6] whereas others have failed to demonstrate this relationship.[7,8] Levy reported a subtle but statistically significant change in the EEG power spectrum at the onset of amnesia during enflurane anesthesia.[9] Other facets of the anesthetic state, such as stress-hormone response, have yet to be correlated with the EEG.

Depth of anesthesia is a difficult state to define and quantify: the only point along the continuum of anesthetic effect for which there is an unequivocal, on-line test is the point at which a subject ceases to respond with movement to a supramaximal noxious stimulus. During inhalation anesthesia, this threshold is commonly described by the ED_{50} (MAC) concentration of anesthetic required to prevent movement. An EEG-based patient monitor that could ascertain the patient's likelihood of response (*i.e.*, movement, hypertension, awareness) before skin incision would be a useful addition to the current array of monitors. One preliminary study of 18 surgical patients receiving 1.0 MAC isoflurane anesthesia suggested no correlation between movement in response to incision and quantitative EEG analysis.[10]

To examine the potential relationship between the EEG and the movement response to stimulus, we studied the response to tail-clamp stimulus in rats during isoflurane anesthesia.

Materials and Methods

After receiving approval of our study protocol from the University of California, San Francisco, Committee on Animal Research, we studied 21 approximately 3-month-old Sprague-Dawley rats, with approximately equal gender distribution. Before study, the rats were housed individually, allowed at least 1 week to acclimatize after shipment, and given access to food and water *ad libitum*.

The study used an apparatus that allowed for the simultaneous testing of as many as four animals. After being weighed, each animal was placed in a stoppered 30.5-cm (12-inch)-long Plexiglas cylinder with an internal diameter of 6.4 cm (2.5 inches). The head-end stopper contained a gas inflow port, and the tail-end stopper contained a gas effluent port, an intravenous catheter port, and a hole for the rat's tail. Anesthesia was induced using isoflurane 2.0% in oxygen from a common source, flowing at approximately 1 l/min per cylinder. After induction, a 20-G catheter was inserted into a femoral vein, and infusion of lactated Ringer's solution was initiated at 10

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$ml \cdot kg^{-1} \cdot h^{-1}$ using a syringe pump (model 22, Harvard Apparatus, South Natick, MA). Rectal temperature was controlled to 37.5 ± 0.5° C using infrared heating lamps. After instrumentation, the isoflurane concentration in the fresh gas flow was set to 1.5%, and the animals were allowed to breathe spontaneously and equilibrate for 40 ± 7 min (mean ± SD). The rats were rotated axially in the cylinders to clear airway obstruction as needed.

The MAC of isoflurane was determined using a modified alligator clip (model 60, Mueller Electrical Co, Cleveland, OH) applied to the proximal tail for 60 s and vigorously manually rotated ±45° at approximately 1 Hz. A positive response was prospectively determined as a movement of the head or extremities, excluding exaggerated respiratory movements. Following the first stimulation and response, the inspired isoflurane concentration was adjusted in 10% decrements or increments (*i.e.*, 0.15 vol%) until each rat had demonstrated two independent crossovers between movement and no movement. The time during which the inspired concentration for these 0.15 vol% steps was constant before testing was 27 ± 2.3 min. This duration was validated as sufficient to allow close equilibration of end-tidal to inspired concentration isoflurane in a series of tracheostomized, spontaneously ventilating rats in similar experimental conditions.‡ The MAC for each rat was taken as the mean of the concentrations at the midpoint of the two movement–no-movement crossovers. Inspired isoflurane concentration was continuously monitored using an infrared analyzer (model 222, Puritan Bennett) that was checked and calibrated at appropriate intervals with a tank secondary standard.

EEG signals were obtained from a pair of subdermal platinum needle electrodes (model E-2, Grass Instrument Co., Quincy, MA) placed in a biparietal bipolar configuration, with a third needle placed suboccipitally as a signal ground. Electrode impedance was always less than 10KΩ and balanced to within 2KΩ. A single channel of the EEG was amplified, filtered (−3 db at 0.5–30 Hz), and digitized at 128 Hz (8-bit resolution) using a Neurotrac® (Moberg Medical, Conshohocken, PA). After anesthetic equilibration for each step (0.15 vol%) change in inspired concentration, at least 60 s of contiguous, artifact-free signal was recorded. The digitized data were serially transferred to a Macintosh IIfx (Apple Computer, Cupertino, CA) with which quantitative analysis was performed using custom-written software developed within the LabView 2 (National Instruments, Austin, TX) programming environment. The EEG data were divided into 15 sequential 4-s-long epochs. Each epoch was quantified[4,11] into five parameters (see Appendix) (root-mean-square voltage amplitude, zero crossing frequency, and burst suppression ratio), spectral edge frequency, and burst-compensated spectral edge frequency). These parameters are reported as the mean of the 15 epochs. All of the raw EEG waveform data and the derived quantitative data were manually overread to ensure freedom from artifact. The dose response of each quantitative EEG parameter was tested with one-way analysis of variance. At each isoflurane step for which there were responders (movers) and nonresponders (nonmovers), the mean values of the parameters for the movers and the nonmovers were compared with a two-tailed t test. A P value < 0.05 was considered significant.

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Results

The mean age of the rats was 98 ± 8 (SD) days, and their weight was 358 ± 100 g (the large variance was due to gender-related weight differences [52.4% female]). The MAC of isoflurane was determined to be 1.3 ± 0.1%. We obtained movement–no-movement crossovers at three isoflurane concentrations (1.15, 1.3, 1.5 vol%). There was no useful dose response in the frequency-based quantitative EEG data (table 1). The measurements reflecting the development of burst suppression—burst suppression ratio, burst-compensated spectral edge frequency, and root-mean-square voltage amplitude—revealed significant changes with increasing isoflurane. At each isoflurane concentration (1.15, 1.3, and 1.5 vol%) where there were both responders and non-responders to tail clamp, there were no significant differences between responding animals and nonresponding animals in any of the five quantitative EEG measurements (table 1). Pooling data from all tail clampings in which the animal moved, 27% of animals had periods of electrographic suppression totaling greater than 5% of the EEG sample, and 9% of animals had greater than 20% suppression (fig. 1). Figure 2 provides an example of burst suppression at 1.0 MAC (1.3%) in an animal in which movement in response to stimulation occurred. EEG monitoring, but not recording, was continued during tail-clamp stimulation for one animal in each run of four. Visual inspection of the EEG signals at these times revealed substantial contamination by motion artifact but only occasional visually apparent change in the degree of burst suppression phenomena.

Discussion

Since 1936,[12] a pattern of intermittent cortical activity known as burst suppression has been noted to occur after administration of large doses of barbiturates or some volatile anesthetics. Burst suppression has been defined as a "pattern characterized by bursts of theta and/or delta, at times intermixed with faster waves, and intervening periods of relative quiescence."[13] This type of EEG pat-

TABLE 1. Quantitative EEG Measurements after Equilibration at Five Concentrations of Isoflurane and Immediately Before Tail Clamp Stimulation

	No Move						Move					
Dose	n	BSR	ZXF	SEF	BSEF	RMS	n	BSR	ZXF	SEF	BSEF	RMS
1.0							8	1 ± 2	9.4 ± 0.8	27.9 ± 1.1	27.5 ± 0.8	16 ± 10
1.15	6	3 ± 4	9.2 ± 0.7	27.4 ± 0.9	26.5 ± 1.8	20 ± 10	21	1 ± 4	9.5 ± 1	27.1 ± 2.1	26.7 ± 2.1	18 ± 11
1.3	15	6 ± 10	9.2 ± 0.9	27.1 ± 2.3	25.3 ± 2.2	20 ± 8	22	6 ± 9	9.4 ± 1	26.8 ± 2.5	25.2 ± 2.8	17 ± 8
1.5	32	26 ± 17*	9.3 ± 1.2	28.2 ± 2.3	20.7 ± 4.2	17 ± 8	2	45 ± 0*	9.4 ± 0.8	31.0 ± 2.1	17.1 ± 1.2*	7 ± 0.5
1.7	9	41 ± 16*	9.3 ± 1.2	29.1 ± 2.7	17.0 ± 4.2*	12 ± 6						

Values are means ± SD.

The measured electroencephalogram (EEG) parameters are burst suppression ratio (BSR), zero crossing frequency (ZXF), spectral edge frequency (SEF), burst-compensated spectral edge freuqency (BSEF), and average voltage (RMS). The reported values are grouped by whether the subjects responded to tail clamp immediately after EEG measurement.

* Different from 1.0% isoflurane.

tern has been associated with deep levels of anesthesia because the doses of barbiturates (*i.e.*, thiopental 4 $mg \cdot kg^{-1} \cdot h^{-1}$ [14]) required to reliably induce the pattern were thought to be larger than routine anesthetic induction doses and because the concentration of isoflurane or desflurane required was thought to be greater than that ensuring immobility (*i.e.*, > 1.0 MAC[15,16]). Furthermore, this pattern of pharmacologically induced suppression of cortical electrical activity has been associated with a diminution of cortical metabolic activity and demand that decreases with increasing dose until suppression is complete, at which point additional drug administration does not further alter the cortical metabolism.[17–19] Burst suppression is not a stable phenomenon: at a fixed anesthetic dose, without extrinsic changes in stimulation, the percentage of time cortical activity is suppressed varies with time.[20] Therefore the best statistical estimates of burst suppression ratio are derived from relatively long recordings (> 5 min). Surgical patients cannot be assumed to be at stable anesthetic states or stimulation, so to be a clinically useful measurement, one must compromise and reduce the analysis time. Finally, it was historically assumed that EEG suppression was *prima facie* evidence of deep anesthesia simply as a marker of a relative lack of neuronal electrical activity.

Our results indicate little apparent EEG dose response over a clinically useful range of isoflurane concentrations in rats. The frequency spectrum–based measurements (spectral edge frequency, zero crossing frequency) revealed no trend or significant change with changing isoflurane concentration. These data reconfirm our previously reported lack of sensitivity of frequency-based EEG

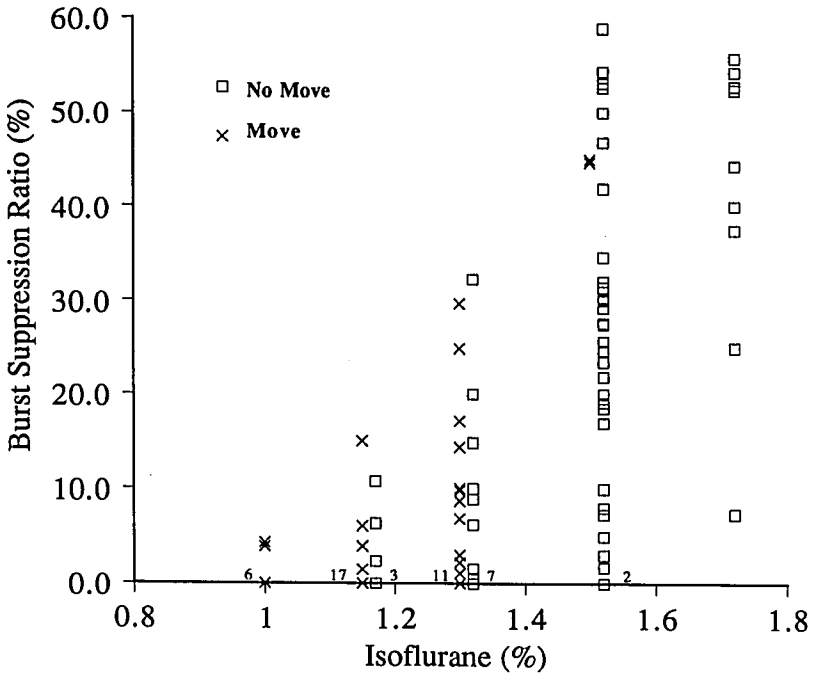

FIG. 1. Pooled burst suppression ratio (BSR) EEG data from 115 isoflurane concentration tail-clamp trials in 21 animals. The EEG data were collected immediately before application of tail-clamp stimulus. At three isoflurane concentrations, there were both responding and nonresponding animals. None of the quantitative EEG parameters examined, including BSR, discriminated between these two groups. The small numbers near the abscissa represent the number of respective data points overlaid at zero suppression.

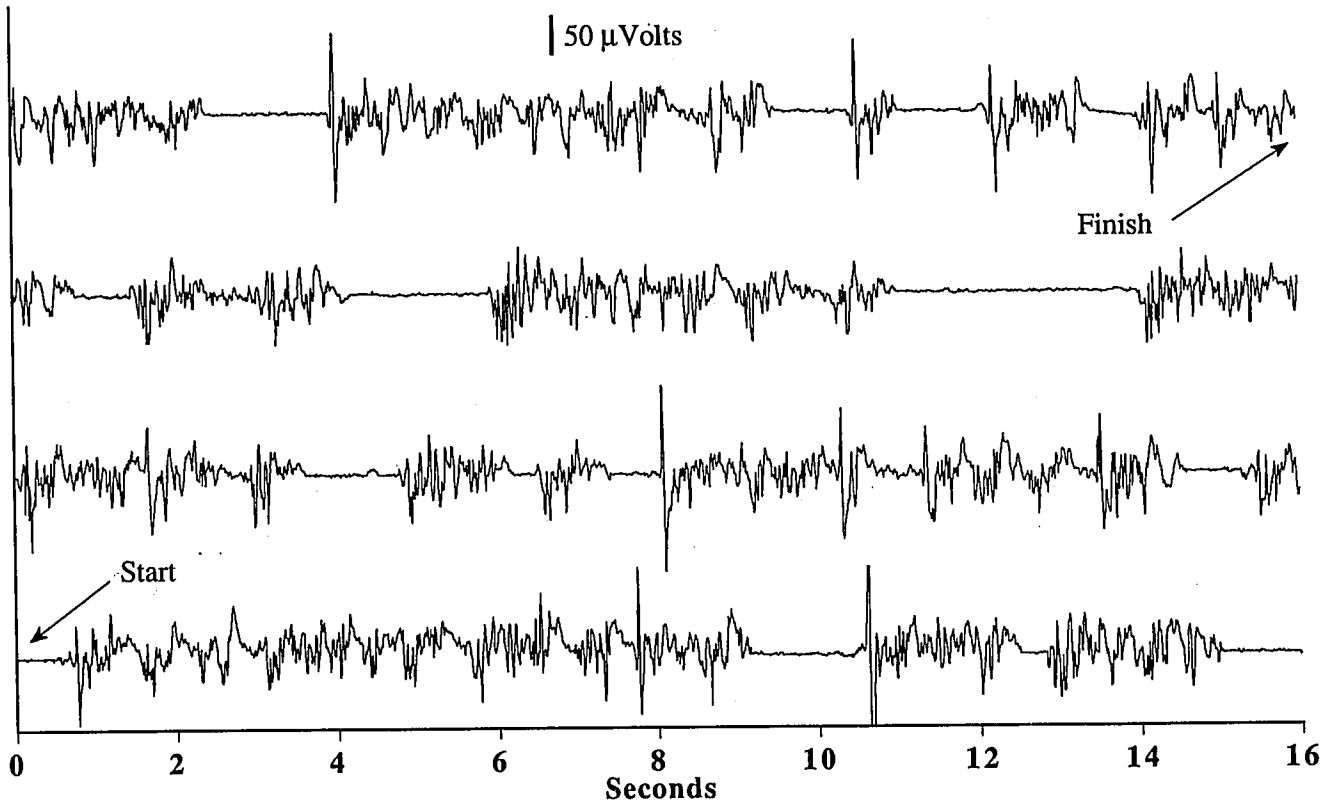

FIG. 2. Example of 64 contiguous seconds of raw EEG signal from a rat equilibrated with 1.3 vol% isoflurane. The signal demonstrates 24% suppression (zero crossing frequency = 8.6 Hz; spectral edge frequency = 27; burst-compensated spectral edge frequency = 21; average voltage = 25 μV) and the residual electrocardiographic R-wave activity apparent during cortical suppression. This animal moved in response to tail-clamp stimulus immediately after this recording. "Start" and "finish" refer to the beginning and end of the EEG recording.

measurements during burst suppression in swine[21] and in humans[16] anesthetized with isoflurane or desflurane. This lack of sensitivity has been attributed to the burst suppression pattern itself with its preservation of high-frequency activity within the burst regions. Schwilden and Stoeckel[22] reported a dose response in the 95th percentile frequency (comparable to the spectral edge frequency), and in the median power frequency (comparable to the zero crossing frequency) between 1.3 and 1.5 MAC isoflurane plus nitrous oxide. Their EEG processing technique, however, apparently removed epochs containing burst suppression patterns. However, the measurements sensitive to burst suppression phenomena (burst suppression ratio, burst-compensated spectral edge frequency, and root-mean-square voltage amplitude) did reflect increasing cortical electrical suppression with increasing inspired concentration of isoflurane.

Movement after noxious stimulation is a threshold response, in that subjects either have a purposeful movement of the head or extremities, or do not. The magnitude of the response may be graded when the subject has an anesthetic effect below the threshold. One then may reasonably ask: where is the "threshold switch" that controls this response? The question does not necessarily rule out a distributed or disseminated control, but the hypothesis that the neocortex is central to this response is rendered suspect by our data, which shows that, in many animals in this study, at least the cortical pyramidal cells that generate the scalp-derived EEG[23] appear to be electrically quiescent before stimulation at concentrations of isoflurane at which some animals move and some do not. It is possible that noxious stimulation during burst suppression alters the level of cortical activity back to continuous activity. It is likewise conceivable that response might have been better predicted by the state of the EEG at the moment of stimulation rather than by the average activity in the preceding minute.

The scope of this study was limited by motion artifact, which made accurate EEG recording during tail clamping impractical and so prevented an assessment of the effect of stimulation on the EEG. The ability of the animals to respond to noxious stimuli in the presence of isoflurane-induced "functional decortication" suggests that the movement-permissive switch is in a subcortical structure,

the functional or electrical state of which cannot therefore be detected by traditional scalp-derived EEG.

Experience with evoked potentials provide another line of evidence for a subcortical locus. Somatosensory-evoked potentials can be used to assess the afferent channel for peripheral stimuli. These potentials are quite sensitive to general anesthetics, with the cortical components of the potential being difficult to detect reliably at anesthetic concentrations greater than 0.5–1.0 MAC.[24] More recently, the efferent channel from the motor cortex to the peripheral musculature has been assessed using transcutaneous magnetically induced motor-evoked potentials. The induced motor pathway potentials are diminished in amplitude and retarded in latency by concentrations of general anesthetics even lower than those affecting the sensory pathways.[25–27] Because the function of the spinal cord and peripheral nervous system[28] appears to be relatively resistant to general anesthesia, one may speculate that the synapses in the brainstem and the thalamus, among others on the afferent and efferent limbs of the response arc, may play a dominant role in the movement-permissive switch.

Quantitative EEG analysis using root mean square amplitude, zero crossing frequency, spectral edge frequency, burst-compensated spectral edge frequency, or burst suppression ratio do not appear to useful in predicting movement in response to painful stimulation during general anesthesia in rats. The observation that animals may still respond despite substantial cortical electrical suppression suggests that subcortical pathways may dominate this anesthetic-mediated response.

Appendix

This appendix contains a detailed technical description of the EEG parameters used in this study. The amplified EEG waveforms are digitized at 128 Hz into discrete digital samples batched into sequential sets of 512 samples each yielding epochs of 4.096 s:

$$\{\chi_0, \chi_1, \chi_2, \cdots \chi_{511}\} \quad (1)$$

Three quantitative parameters were obtained from this "time domain" voltage data:

Root mean square voltage, an estimate of the average voltage,

$$= \sqrt{\frac{\sum_{i=0}^{511} \chi_i^2}{512}} 400 \quad (2)$$

Zero crossing frequency is an estimate of the average frequency, based on the number of times the voltage crosses the zero axis during the 4.096-s epoch. Each zero crossing event marks a half-wave, so the result is divided by two. There is a hysteresis test (there must be a difference of at least 1.0 μV between zero crossing samples) to reduce false counting of small amplitude noise.

Zero crossing frequency

$$= \frac{\sum_{i=1}^{511} \begin{cases} 0 = \text{false} \\ 1 = \text{true} \end{cases} \Big| (\text{sgn}(\chi_i) \neq \text{sgn}(\chi_{i-1})) \wedge (|\chi_i - \chi_{i-1}| > 1\ \mu v) \Big\} \Big/ 2}{4.096} \quad (3)$$

Burst suppression ratio is the ratio of the ratio of time the EEG was suppressed (quiescent) *versus* the epoch time, providing a measure of the degree of suppression in each epoch. Numerically, this parameter is calculated in terms of the number of samples meeting the criteria for suppression *versus* the total number of samples in the epoch. The criteria for judging burst suppression is based on empiric observation and has been reported previously.[16,21] Burst suppression ratio is reported, by convention, as percent suppression.

Burst suppression ratio = 100

$$\times \frac{\sum_{i=0}^{511} \left\{ \begin{cases} 0 = \text{false} \\ 1 = \text{true} \end{cases} \Big| (|\chi_i| < 8.0\ \mu\text{V}) \wedge (\chi_i \in \text{SuppressRun}) \right\}}{512} \quad (4)$$

where

$$\text{SuppressRun} \equiv \text{a contiguous subset of EEG of} \geq 0.5 \text{ s in duration in which the absolute value of all samples is} \leq 8.0\ \mu\text{V} \quad (5)$$

After time domain analysis, the epochs are windowed with a Hanning cosine window and an estimate of the power spectrum obtained using a fast Fourier transform:

$$\text{PS[f]} = \text{power at frequency f} \quad (6)$$

where f ranges from 0 to 32 Hz in 0.244 Hz. Spectral edge frequency is an estimate of the "highest" significant frequency in an EEG epoch using pattern-match testing for the highest contiguous band at least 2 Hz wide that meets the stated power profiles where the total band power exceeds a threshold and at least one frequency bin PS[f] exceeds another threshold:

$$\left(\text{PS[f]} + \text{PS[f} - 0.25] + \cdots + \text{PS[f} - 1.75] \geq \frac{\text{Total Power}}{256}\right) \wedge \quad (7)$$

$$\left(\text{Max(PS[f], PS[f} - 0.25], \ldots, \text{PS[f} - 1.75]) \geq \frac{\text{Total Power}}{64}\right) \quad (8)$$

where

$$\text{Total Power} = \sum_{f=0}^{32} \text{PS[f]} \quad (9)$$

Then burst-compensated spectral edge frequency is a parameter that proportionally reduces the spectral edge frequency in the presence of burst suppression.

Burst-compensated spectral edge frequency

$$= \text{SEF}\left(1 - \frac{\text{BSR}}{100}\right) \quad (10)$$

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