Comparison of Isoflurane Effects on Motor Evoked Potential and F Wave

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Background: Volatile anesthetics produce surgical immobility by suppressing the motor system. The anesthetic action site in the motor pathway is unclear. Anesthetic effects on the whole and the lower portion of motor pathway can be studied by measuring the motor evoked potentials (MEP) and the F wave. This study measured the effect of isoflurane on the MEP and the F wave.

Methods: With institutional review board approval, we studied 12 adult patients with American Society of Anesthesiologists physical status I or II. After intubation, anesthesia was maintained with nitrous oxide/oxygen and propofol infusion. MEPs were elicited by transcranial electrical stimuli (train-of-five pulse; stimuli intensity 40–160 mA) through electrodes placed in the scalp at C3/C4 positions and recorded at the anterior tibialis muscle with an Axon Sentinel-4EP monitor. F waves were elicited by an electrode fixed over the posterior tibial nerve at the medial malleolus and recorded at the abductor hallucis muscle. After end-tidal concentration of isoflurane was maintained at 0.5% for 20 min, the MEP and F wave were measured again. MEP and F-wave changes before and after isoflurane were analyzed using paired Wilcoxon test with Bonferroni correction. The difference between the changes in MEP and F wave was analyzed using Friedman's test.

Results: Motor evoked potential amplitudes (median, 205 μV; 25th–75th percentiles, 120–338 μV), F-wave amplitude (median, 100 μV; 25th–75th percentiles, 64.2–137.5 μV), and F-wave persistence (59 ± 29%) were decreased to 0 μV (0–15 μV), 49 μV (12.4–99.6 μV), and 30 ± 31%, respectively, by 0.5% isoflurane. MEP amplitude suppression was different from the changes in F-wave amplitude and persistence (P < 0.02).

Conclusions: Isoflurane 0.5% suppresses the motor pathway by decreasing both MEP and F wave. The MEP is suppressed more than the F wave. (Key words: Electrophysiology; spinal cord; volatile anesthetics.)

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Received from the Department of Anesthesiology, New York University Medical Center, New York, New York. Submitted for publication October 11, 1999. Accepted for publication January 15, 2000. Support was provided solely from institutional and/or departmental sources. Presented in part at the annual meeting of American Society of Anesthesiologists, Orlando, Florida, October 17–21, 1998.

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Anesthesiology, V 93, No 1, Jul 2000

DESPITE the widespread use of volatile anesthetics since the mid-19th century, the mechanism and the site of anesthetic action remain unknown. Recent studies suggested that surgical immobility is produced by anesthetic suppression in the spinal cord motor neurons. It is still unclear whether the spinal cord and brain are equally sensitive to inhaled agents and how anesthetics act on different parts of the motor system.

Anesthetic effect on the motor pathway can be measured by electrophysiological methods: the motor evoked potential (MEP) and the F wave. The MEP is elicited by transcranial stimulation over the motor cortex and recorded by electrodes placed in the corresponding muscle. Therefore, MEP measures the functional integrity of the entire motor pathway (fig. 1A). The F wave is evoked by a supra maximal stimulus to the peripheral nerve, generated by antidromic spinal motor neuron activation and recorded as late muscle potentials by electrodes placed in muscle (fig. 1B). Since both afferent and efferent arcs of the F wave consist of the same α motor neuron, the F wave is useful in evaluating spinal motor neuron excitability and lower motor pathway integrity.

Volatile anesthetics can suppress MEP and the F wave. This study was designed to measure isoflurane effects on the whole motor system and the lower motor pathway by comparing the changes of the MEP, the F wave, and the M wave before and after isoflurane. The anesthetic effects on the spinal motor neuron, axonal and synaptic transmission, and muscle were also analyzed.

Methods

After receiving institutional review board approval and obtaining written informed consent, 12 adult patients, American Society of Anesthesiologists physical status 1 or 2, undergoing elective surgery with general anesthesia were studied. Patients with a history of stroke, Parkinson's disease, myasthenia gravis, muscular dystrophy, myotonic dystrophy, and other motor system diseases or preoperative use of drugs that may affect MEP/F wave (e.g.,
ISOFLURANE SUPPRESSES MEP AND F WAVE

Fig. 1. (A) Illustration of the motor pathway and motor evoked potential (MEP) measurement. The stimulus at the motor cortex elicits action potentials propagating to the spinal cord, activating motor neurons and producing muscle responses. (B) The F-wave pathway. The stimulus at the peripheral nerve evokes action potentials in the motor fiber, which activate motor neurons and produce F waves.

Benzodiazepines, barbiturates, and antidepressants) were excluded from the study.

Anesthesia

Anesthesia was induced with intravenous propofol (2 mg/kg) and fentanyl (100 μg), and the trachea was intubated after succinylcholine (1.5 mg/kg) was administered. Muscle relaxants were not used after intubation. Anesthesia was maintained by using 60% nitrous oxide, propofol infusion 100 μg·kg⁻¹·min⁻¹, and supplementary fentanyl 0.5-1 μg/kg. Fentanyl was not administered 20 min before and during MEP and F-wave measurements. Ventilation was controlled to maintain endtidal carbon dioxide tension between 32 and 38 mmHg using tidal volume set at 10-12 ml/kg and a rate of 8-12 breaths/min. Respiratory gases were continuously monitored with an infrared gas analyzer (Ohmeda 5250 RGM; British Oxygen Company Health Care, Louisville, CO). Patients were monitored with electrocardiogram, finger pulse oximeter probe, automatic blood pressure cuff (Dinamap; Johnson & Johnson Hospital Supplies, New Brunswick, NJ), and an esophageal temperature probe. Blood pressure was supported to maintain mean arterial pressure values at no less than 75% of preanesthesia values using intravenous Ringer’s lactate solution. Patient’s body temperature was maintained within 1°C of preincision value (36.0-36.8°C) by warming blankets.

Motor Evoked Potential and F-wave Measurement

Baseline MEP and F waves were recorded approximately 1 h after induction using an Axon Sentinel-4 EP machine (Axon Systems Inc., Hauppauge, NY). The MEP was elicited by transcranial electrical stimuli (train-of-five square-wave pulses; time constant of 0.5 ms) through two spiral electrodes placed in the scalp at C3 and C4 positions (motor cortex areas in International 10-20 system for electrode placement). The anode and cathode were altered between C3 and C4 electrodes depending on the side of recording. Compound muscle action potentials were recorded from needle electrodes inserted in the anterior tibialis muscle. Signals were amplified 10,000 times using a PR415 SMARTAMP amplifier (Axon Systems Inc.). Stimulus intensity was varied from 40 to 160 mA to reach the maximal muscle response and maintained at the same level throughout the study. The leg with better MEP recording was chosen for study.
Using the same limb, the F wave was evoked by a constant current stimulator with a supramaximal stimulus (single square-wave pulse; time constant of 0.2 ms). The stimulation bar electrodes were placed over the posterior tibial nerve at the medial malleolus with the cathode electrode placed proximally. A supramaximal stimulation was considered to be achieved when direct muscle response (M wave) did not increase after increasing stimulus intensity (electrical current 40-80 mA). Signals were recorded by needle electrodes inserted in the abductor hallucis muscle and amplified 1,000 times using a PR415 SMARTAMP amplifier. To determine F-wave persistence, a series of 10 supramaximal stimuli was delivered at an interstimulation interval of 0.5 s. To distinguish F waves from background noise, we accepted only appropriately timed deflections from the baseline with an amplitude of at least 30 μV. In all cases, a representative control M wave was monitored. The filter setting was 100-1,000 Hz to remove background noise.

Isoflurane was introduced with a fresh gas flow of 6 l/min and adjusted to achieve a 0.5% steady end-tidal concentration. After end-tidal isoflurane was stable for 20 min and the difference between inspiratory and end-tidal concentrations was ≤ 0.1%, the MEP and F wave were measured again at the same settings.

**Fig. 2.** Comparison of the motor evoked potential (MEP) amplitude, F-wave amplitude, and F-wave persistence before and after 0.5% isoflurane. Data are expressed as mean ± SD. *P < 0.01 versus after isoflurane. **P < 0.01 compared with the changes of F-wave amplitude and persistence.

**Fig. 3.** Individual patient motor evoked potential (MEP) amplitude (A), F-wave amplitude (B), and F-wave persistence (C) before and after 0.5% isoflurane (n = 12). The mean values of the two states in A–C are different (P < 0.001).
Fig. 4. Original tracings of motor evoked potential (MEP) before (A) and after (B) 0.5% isoflurane. (Stimulus intensity, 100 mA.)

**Statistical Analysis**

Data were collected and stored for subsequent analysis in the Axon Sentinel-4 EP computer. The MEP, F-wave, and M-wave amplitudes were calculated with maximum peak-to-peak distance. MEP and F-wave latencies were determined from the time of stimulation to the first waveform deflection. F-wave persistence was calculated by the number of measurable F waves divided by 10.

Fig. 5. Original tracings of F-wave before (A) and after (B) 0.5% isoflurane. (Stimulus intensity, 80 mA.)
(number of stimuli). Data were analyzed using the Statistical Package for Social Science (SPSS, Chicago, IL). All descriptive values were reported as mean ± SD, and some neurophysiologic data were also reported as median and 25th–75th percentiles because of their asymmetrical distribution. The paired Wilcoxon test was used to analyze the difference between MEP before and after isoflurane (amplitude and latency), F wave (amplitude, latency, and persistence), and M wave (amplitude). The difference between MEP and F-wave changes were analyzed using Friedman’s randomized block rank test. P values < 0.05 were considered significant. To preserve the 5% significance level, the results of paired Wilcoxon test and Friedman’s test were further analyzed with a Bonferroni correction.\(^\text{16}\)

**Results**

Twelve patients (eight men, four women), aged 27–83 yr (47.6 ± 15.8 yr), weight 72.2 ± 15.7 kg, height 166.8 ± 11 cm, were studied. The MEP and F-wave responses were reproducibly measured in each patient and were stable until isoflurane was added. Baseline maximal M-wave amplitude (9.0 ± 1.0 mV) remained unchanged after isoflurane (8.8 ± 0.8 mV; \(P > 0.05\)).

Baseline MEP amplitude was 251 ± 161.7 \(\mu\)V (median, 205 \(\mu\)V; range, 119.8–338 \(\mu\)V). After 0.5% isoflurane, MEP amplitude was reduced by 91–100% to 22.5 ± 37.4 \(\mu\)V (median, 0 \(\mu\)V; range, 0–15 \(\mu\)V; \(P < 0.003\); figs. 2–4). In eight patients (66.7%), MEP amplitude was completely abolished (fig. 4). Among them, five patients had relatively small baseline MEP amplitudes (< 200 \(\mu\)V), but in one (patient no. 6), high baseline amplitude (600 \(\mu\)V) was also abolished. In another four patients, MEP was not abolished by isoflurane. Three of these four patients had baseline MEP amplitude greater than 250 \(\mu\)V. After isoflurane, MEP latency (35.2 ± 3.9 ms; median, 35.9 ms; range, 31.4–40 ms) was prolonged to 39.7 ± 4.3 ms (median, 40.9 ms; range, 37–42.3 ms; \(P < 0.02\)) with an average delay of 4.5–5 ms (range, 12.8–13.9%).

After isoflurane, mean F-wave amplitude (166.3 ± 198.4 \(\mu\)V; median, 100 \(\mu\)V; range, 64.2–137.5 \(\mu\)V) was reduced to 106.1 ± 185.3 \(\mu\)V (median, 49 \(\mu\)V; range, 12.4–99.6 \(\mu\)V; \(P < 0.003\)) with an average decrease of 36.3–51% (figs. 2, 3, and 5). F-wave persistence (59.2 ± 29.1%; median, 45%; range, 25–85%) decreased by 48.6–77.8% after isoflurane and became 30.4 ± 31.8% (median, 10%; range, 10–55%; \(P < 0.004\); figs. 2 and 3). F-wave latency (49.6 ± 8.8 ms; median, 49.3 ms; range, 45–58.5 ms) was not changed (49.9 ± 8.3 ms; median, 50 ms; range, 45.8–57.3 ms; \(P > 0.05\)) by isoflurane.

Using Friedman’s test with a Bonferroni correction, the difference between the changes in MEP amplitude, F-wave amplitude, and F-wave persistence was significant \((P < 0.01)\). Isoflurane-induced MEP suppression was different from the decreases of F-wave amplitude and persistence \((P < 0.02)\), whereas the changes between F-wave amplitude and F-wave persistence were insignificant \((P > 0.05)\).

**Discussion**

Our study demonstrates that isoflurane 0.5% decreases MEP amplitude, F-wave amplitude, and F-wave persistence and prolongs MEP latency. The same concentration of isoflurane suppresses MEP more than the F wave. Anesthetics can affect each part of the motor pathway, including cortical motor neurons (pyramidal cells), the corticospinal tract, the synapses between pyramidal fibers and spinal neurons, the interneuron, the anterior horn-motor neurons, the peripheral nerves, the neuromuscular junctions, and the muscles (fig. 1A). F-wave pathway is within the lower portion of the motor pathway. In the present study, F wave was evoked by stimulation at posterior tibial nerve near the medial malleolus, transmitted to lumbar spinal cord, and recorded at abductor hallucis muscle (fig. 1B). Depending on the body–lower extremity ratio in each individual, the total distance of F-wave neurotransmission is probably longer than the MEP pathway because F-wave latency (49.6 ms) is longer than MEP latency (35.2 ms).

Previous studies showed that low concentration isoflurane or enfurane abolished MEP.\(^\text{3,14}\) In contrast, volatile agents at high concentration (1.6 minimum alveolar concentration) do not abolish F wave in rats.\(^\text{5,6}\) Similarly, in humans, 0.68% (0.6 minimum alveolar concentration) isoflurane reduced F-wave amplitude and persistence by 48% and 56%, respectively. Increase of isoflurane concentration to 1.37% (1.2 minimum alveolar concentration) further decreased F-wave amplitude and persistence 18% and 22%, respectively, but did not abolish F-wave.\(^\text{4}\) In the present study, we compared isoflurane effects on MEP and F wave at the same time and found that the MEP was suppressed (91–100%) more than F-wave amplitude (36–51%) and persistence (48–77.8%). This suggests that the effect of volatile on the motor system is not mainly dependent on the distance of neurotransmission, but the intrinsic sensitivity of each part of the motor pathway.

Anesthesiology, V 93, No 1, Jul 2000
Previous studies demonstrated that clinical concentration of volatile agents suppresses synaptic transmission and decreases motor neuron excitability by inhibiting multiple voltage-gated calcium currents and hyperpolarizing neurons. However, volatile agents have minimal effect on axonal conduction in nerve fibers. In our study, F-wave latency and maximal M waves remain unaltered after 0.5% isoflurane, suggesting that isoflurane has no effect on nerve conduction in the peripheral nerve, neuromuscular transmission, or muscle contractility. The suppression of F-wave amplitude and persistence suggests that isoflurane decreases spinal motor neuron excitability. Isoflurane prolongs MEP latency but not F-wave latency, suggesting suppression of synaptic transmission in the polysynaptic motor pathway. It is still unclear whether the suppression of MEP amplitude is mainly due to isoflurane effect on the polysynaptic transmission, spinal/cortical motor neuron excitability, or both.

The electroencephalogram and middle latency auditory evoked response have been proposed for assessment of the depth of anesthesia. However, these measures fail to predict motor response to surgical stimuli. Recent evidence shows that anesthetic effect in the spinal cord is important for suppressing somatic response to noxious stimuli. The degree of spinal motoneuron (F-wave) suppression correlates well with surgical immobility. In our study, the F waves still exist, although the MEPs are almost abolished by low concentration (0.5%) of isoflurane, suggesting that spinal motor neuron excitability is not relied on the input from upper motor neurons. Much higher concentrations of isoflurane are needed to suppress the F wave and produce surgical immobility.

In our study, baseline MEP and F waves were measured during nitrous oxide/propofol anesthesia since awake patients cannot tolerate the pain and discomfort generated by transcranial electrical stimulation. Although both nitrous oxide and propofol may reduce MEP amplitude, this combination has much less suppressant effect than volatile agents and is the most common general anesthesia combination used during intraoperative MEP monitoring. We adjusted both nitrous oxide concentration and propofol infusion rate at steady levels. Similar waveform of the MEP and the F wave were reproducibly recorded in all patients until isoflurane was added. This indicates that the change of MEP and F wave in this study is produced by isoflurane. Another limitation of this study is that we could not measure isoflurane effect on cortical motor neuron excitability and the synaptic transmission in the spinal cord. Therefore, it is unclear as to which part of the motor pathway plays the most important role in MEP suppression.

In summary, this study shows that isoflurane 0.5% suppresses MEP amplitude, F-wave amplitude, and F-wave persistence and prolongs MEP latency. The same concentration of isoflurane suppresses the MEP significantly more than the F wave. Further studies are needed to elucidate the site and the mechanism of anesthetic action in the motor system.

References

1. Rampil IJ, Mason P, Singh H: Anesthetic potency (MAC) is independent of forebrain structures in the rat. Anesthesiology 1993; 78: 707-12
2. Rampil IJ: Anesthetic potency is not altered after hypothermic spinal cord transection in rats. Anesthesiology 1994; 80:606-10
16. Godfrey K: Comparing the means of several groups, Medical

Anesthesiology, V 93, No 1, Jul 2000

18. el-Beheiry H, Paul E: Anaesthetic depression of excitatory synaptic transmission in neocortex. Exp Brain Res 1989; 77:87-93


20. Fomitcheva I, Kosk-Kosicka D: Volatile anesthetics selectively inhibit the Ca^{2+}-transporting ATPase in neuronal and erythrocyte plasma membranes. Anesthesiology 1996; 84:1189-95


