

Suppression of Spinal Cord Motoneuron Excitability Correlates with Surgical Immobility during Isoflurane Anesthesia

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Background: Recent evidence suggests that the spinal cord is an important site of anesthetic action that produces surgical immobility. Inhalation anesthetics depress the Hoffmann's reflex (H reflex) and F wave, indicating spinal motoneuron suppression. The aim of this study was to assess the correlation between isoflurane-induced immobility and H- and F-wave suppression.

Methods: The baseline H reflex and F wave were measured before anesthesia in 15 adult patients. After induction, 1% end-tidal isoflurane was maintained for 20 min before the H and F waves were reelicited. Using an electric stimulus applied to the forearm and grading the response as movement or no movement, the authors increased or decreased the isoflurane concentration in 0.1% steps, depending on the movement responses. The H and F waves were recorded 20 min after each change of isoflurane concentration. The correlation between H- and F-wave suppression and surgical immobility was analyzed using a paired *t* test with Bonferroni correction.

Results: H-reflex amplitude (2.74 ± 1.63 mV) and F-wave persistence ($70.69 \pm 26.19\%$) at the highest isoflurane concentration that allowed movement response to a stimulus are different ($P < 0.01$) from these (1.97 ± 1.46 mV; $43.16 \pm 22.91\%$) at the lowest isoflurane concentration that suppressed response. At 0.8% isoflurane, the H-reflex amplitude was 3.69 ± 1.83 mV with movement and 1.01 ± 1.14 mV without movement ($P < 0.01$); F-wave amplitude was 0.29 ± 0.15 mV with movement and 0.11 ± 0.06 mV without movement ($P < 0.01$); F-wave persistence was $80 \pm 22.36\%$ with movement and $34.9 \pm 25.75\%$ without movement ($P < 0.01$).

Conclusions: The degree of H- and F-wave amplitude and F-wave persistence suppression correlates with movement response, suggesting that isoflurane-suppressive action in the

spinal cord plays a significant role in producing surgical immobility. (Key words: Anesthesia mechanisms; anesthetic potency; electrophysiology; F wave; H reflex; minimum alveolar concentration.)

MINIMAL alveolar concentration (MAC), the alveolar anesthetic concentration at which purposeful movement to a painful stimulus is suppressed in 50% of patients, has been used as a guide to clinical anesthetic administration.^{1,2} However, it is still unclear how anesthetics affect the central nervous system to produce surgical immobility. Based on animal studies that show that the anesthetic requirement in rats is unaltered after decerebration³ or after hypothermic transection between the brain and spinal cord,⁴ surgical immobility is primarily produced by an anesthetic effect on the spinal cord.

Hoffmann's reflex (H reflex) and the F wave elicited by electrical stimulation of a peripheral nerve can be used to measure the effect of anesthetics in the spinal cord.⁵⁻¹² A single stimulus to the posterior tibial nerve can produce the direct muscle response (M wave; 10-15 ms delay) and the H wave (35-40 ms delay) or the F wave (55-60 ms delay), which can be recorded electromyographically.¹³⁻¹⁵ The H reflex, a monosynaptic reflex mediated by large sensory (Ia) and motor (A α) fibers,¹³ characteristically contains a centrally amplified H wave larger than the associated M wave.¹³⁻¹⁵ This response is affected by spinal motoneuron pool excitability and sensory neuron responsiveness.¹⁵ The F wave is not a reflex; the afferent and efferent arc F wave involves the same alpha motor neuron. The F wave is evoked by supramaximal stimulation of motor fibers in the nerve and generated by antidromic spinal motor neuron activation.¹⁵⁻¹⁷ The F wave therefore is useful in evaluating motoneuronal pool excitability state.^{15,16}

Inhalation anesthetics depress H-reflex and F-wave amplitude.⁵⁻⁹ In rats, F-wave suppression by isoflurane or nitrous oxide correlates well with depressed motor response to tail clamp.¹⁰ Our recent human study^{11,12}

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showed that isoflurane with or without nitrous oxide decreases H- and F-wave amplitude and F-wave persistence. In this study, we tested in humans the hypothesis that H-reflex and F-wave suppression from general anesthesia correlates with surgical immobility.

Methods

Fifteen patients (nine men and six women) aged 20–69 yr (37.1 ± 15.1 yr, mean \pm SD), who weighed 70.2 ± 11.4 kg, measured 169 ± 10 cm, were classified as American Society of Anesthesiologists physical status I or II, and who were undergoing elective surgery during general anesthesia were studied after the protocol was approved by the institutional review board on human experimentation. Patients with a history of neuromuscular diseases such as myasthenia gravis, muscular dystrophy, myotonic dystrophy, and sciatic nerve or cauda equina injury were excluded from the study.

Before induction of anesthesia, baseline H reflexes and F waves were evoked with a single stimulus and recorded using an Axon Sentinel-4 EP machine (Axon-System Inc., Hauppauge, NY). The H reflex was evoked by placing the cathode (constant current stimulator) of a bar electrode over the posterior tibial nerve at the popliteal fossa and recorded using a surface bar electrode over the soleus muscle. Stimulus duration was 1 ms (square-wave electrical pulse). Stimulus intensity was varied (electric current, 10–30 mA) to achieve maximum H-reflex amplitude measured from positive peak to negative peak. To confirm that H reflex after a single stimulus could be reproduced, at least four trials of H reflex were recorded at an interstimulation interval of 30 s.

Using bar electrodes, the F wave was recorded from the abductor hallucis muscle after a supramaximal stimulus (electric current, 40–80 mA) over the posterior tibial nerve at the medial malleolus. To determine F-wave persistence (the number of measurable F waves divided by the number of stimuli), a series of 10 stimuli was delivered at an interstimulation interval of 2 s. To distinguish F waves from background noise, we accepted only appropriately timed (55- to 60-ms delay) deflections from baseline with an amplitude of at least $30 \mu\text{V}$. The filter setting was 100–1700 Hz to remove background noise. In all cases, a representative control M wave was monitored, and stimulus intensity was maintained at a constant level. However, if the leg was manipulated, minor adjustments were made in stimulus

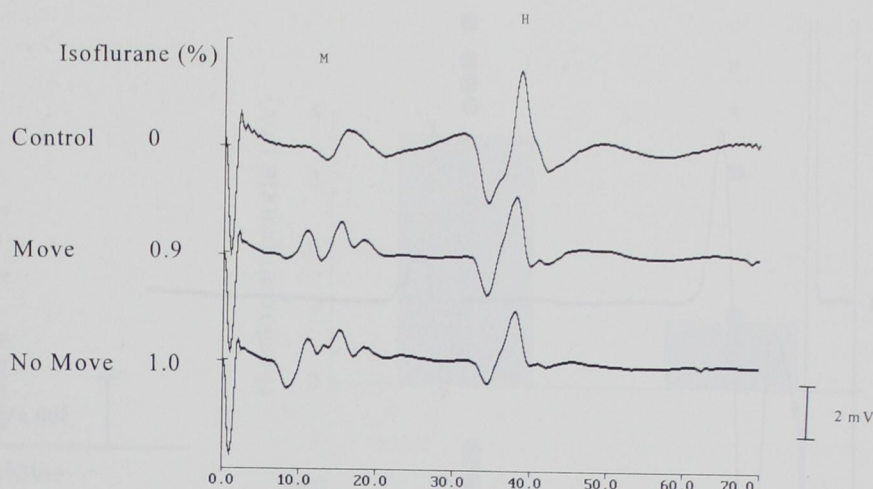
intensity so that the test M-wave amplitude would continue to match the preanesthesia response level.

Anesthesia was induced with 50% nitrous oxide and 2% halothane in oxygen. Isoflurane, 2.5%, was substituted for halothane shortly after patients became unconscious (generally 2–3 min). The trachea was intubated without the use of a neuromuscular blocking agent. After endotracheal intubation, nitrous oxide was discontinued, and isoflurane concentration was decreased to achieve a 1% end-tidal concentration using a total gas flow of 10 l/min. Respiratory gases were continuously monitored with an infrared gas analyzer (Ohmeda 525 RGM; British Oxygen Company Health Care, Louisville, CO) in all patients. Ventilation was controlled to maintain end-tidal carbon dioxide tension between 32–38 mmHg using tidal volume set at 10–12 ml/kg at 8–12 breath/min. All patients were monitored with electrocardiograms, a finger pulse oximeter probe, automatic blood pressure cuff (Dinamap; Johnson & Johnson Hospital Supplies, New Brunswick, NJ), and an esophageal temperature probe. Mean arterial pressure was maintained at no less than 75% of preanesthesia level using intravenous Ringer's lactate solution. Temperature was maintained within 1°C of preoperative values using a warming blanket.

The H reflex and F wave were reelicited after residual halothane or nitrous oxide were $\leq 0.01\%$ and isoflurane end-tidal concentration was steady for at least 20 min. The difference between inspiratory and end-tidal isoflurane concentration was maintained at about 0.1%. Stimulation was adjusted to elicit maximum H-reflex amplitude while maintaining preoperative M-wave amplitude. To assess movement in response to pain, one pair of surface (electrocardiograph) electrodes was placed on the volar surface of the dominant forearm, 5 and 13 cm below the antecubital skin fold and 1 cm toward the ulnar side from the forearm midline. The positive electrode was placed proximally.¹⁸ A painful electric stimulus (60 mA, 50 Hz, 5 s, 0.20 ms square wave) was delivered through a peripheral nerve stimulator (model 750 digital; Dakkmed Inc., Buffalo, NY). Gross head or extremity movements within 1 min after stimulation were considered positive. However, arm movements on the stimulated side during tetanic stimulation or movement caused by reaction to the endotracheal tube (coughing or swallowing) were not considered positive responses. If a positive response was observed, end-tidal isoflurane concentration was increased in 0.1% steps until reaction to stimulus stopped. If no response was elicited, the concentration was decreased

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Fig. 1. Original tracings showed the H reflex before anesthesia, at the highest isoflurane concentration (0.9%) that allows movement response to a stimulus and at the lowest concentration (1%) that suppresses movement (H-reflex stimulus intensity, 10–20 mA). M = M wave; H = H reflex.



in 0.1% steps until stimulus reaction occurred. The individual MAC for each patient was determined using the bracketing technique (positive-negative-positive or negative-positive-negative patterns). A steady anesthetic end-tidal concentration was maintained for 20 min before the H reflex and F wave were measured. Patient movement was assessed 3–4 min after recording the H reflex or F wave. In each patient the surgical procedure began after the study recordings were completed.

Statistical Analysis

Data were collected and stored in the Axon Sentinel-4 EP computer for subsequent analysis. The averaged

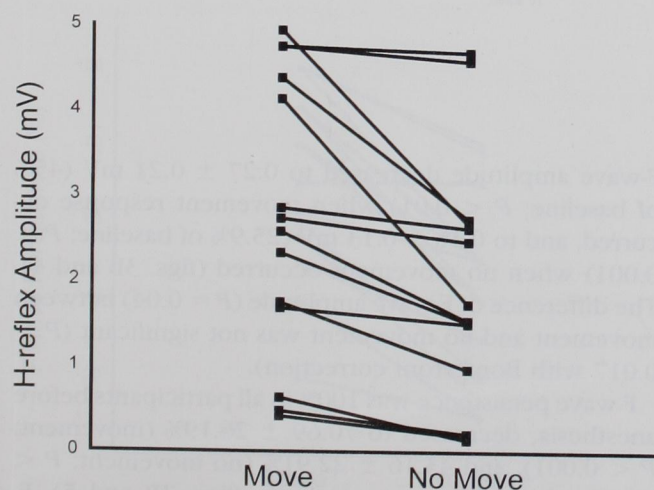


Fig. 2. Individual patient H-reflex amplitude response to stimulus during movement or no movement. The mean values of the two states are different ($P < 0.003$).

H-reflex amplitude and latency of four traces before and after anesthesia were calculated. F-wave latency, maximal peak-to-peak amplitude, and persistence were determined. H-reflex and F-wave latency was defined as the time interval from stimulus application to initial baseline deflection. Data were analyzed using a statistical program (SAS, 1994; Statistical Analysis Systems, Cary, NC). All descriptive values are reported as means \pm SD. A paired t test was used for analysis of variances in H-reflex amplitude and latency, F-wave amplitude, persistence and latency, and M-wave amplitude before and after anesthesia, and in comparisons of movement and no-movement response to a stimulus. The variances in H-reflex and F-wave amplitude and F-wave persistence with movement compared with no movement at 0.8% isoflurane were analyzed using a paired t test. Probability values < 0.05 were considered significant. To preserve the 5% significance level, the results of a paired t test were further analyzed with a Bonferroni correction.¹⁹ Only probability values < 0.017 were considered significant.

Results

The H reflex and F wave were recorded in a reproducible manner in all but one patient (patient 7) in whom we could not evoke the F wave, and one (patient 14) in whom we could not evoke the H reflex after general anesthesia. The averaged isoflurane MAC to electric stimulation in all patients was $0.79 \pm 0.19\%$ (mean \pm SD). The maximal preoperative M wave (8.8 ± 0.7 mV) remained unchanged after anesthesia (8.5 ± 0.1 mV; $P > 0.05$).

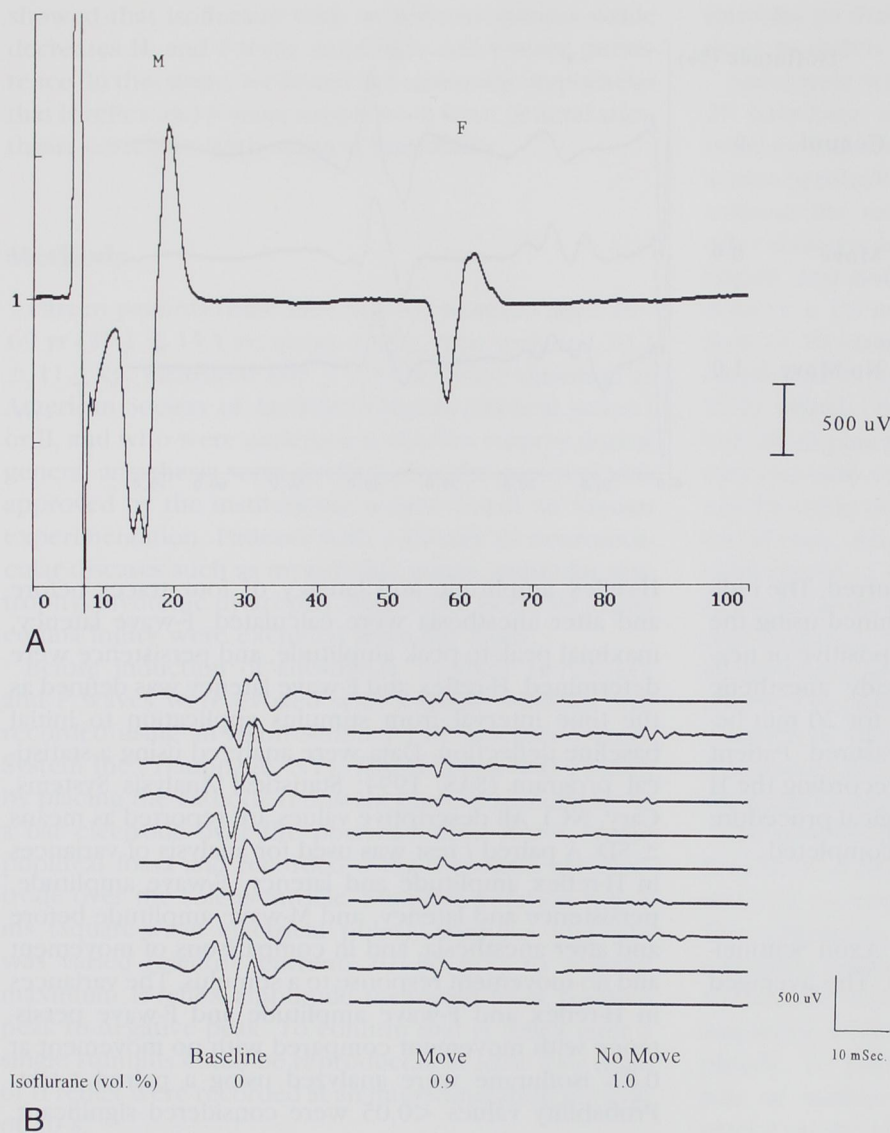


Fig. 3. (A) An original tracing of the M and F wave (M, F) before anesthesia. (B) F-wave tracings before surgery, at the highest isoflurane concentration (0.9%) that allows movement response to a stimulus and at the lowest concentration (1%) that suppresses movement (F-wave stimulus intensity, 30–40 mA).

Mean preoperative H-reflex amplitude (5.76 ± 2.22 mV) decreased after isoflurane anesthesia. H-reflex amplitude was 2.74 ± 1.63 mV (46.6% of baseline; $P < 0.001$) at the highest isoflurane concentration that allowed movement response to a stimulus. At the lowest isoflurane concentration that suppressed response, H-reflex amplitude was 1.97 ± 1.46 mV (34% of baseline; $P < 0.001$; fig. 1). H-reflex amplitude was significantly lower with no movement than that with movement ($P < 0.003$; fig. 2).

The maximal preoperative F-wave amplitude was 0.61 ± 0.4 mV (fig. 3A). The maximal F-wave to M-wave amplitude ratio was 6.9%. After isoflurane anesthesia,

F-wave amplitude decreased to 0.27 ± 0.21 mV (45% of baseline; $P < 0.01$) when movement response occurred, and to 0.16 ± 0.13 mV (25.9% of baseline; $P < 0.001$) when no movement occurred (figs. 3B and 4). The difference of F-wave amplitude ($P = 0.04$) between movement and no movement was not significant ($P > 0.017$ with Bonferroni correction).

F-wave persistence was 100% in all participants before anesthesia, decreased to $70.69 \pm 26.19\%$ (movement; $P < 0.001$), and $43.16 \pm 22.91\%$ (no movement; $P < 0.001$) after isoflurane anesthesia (figs. 3B and 5). F-wave persistence was significantly less at no movement than that at movement ($P < 0.001$; fig. 5).

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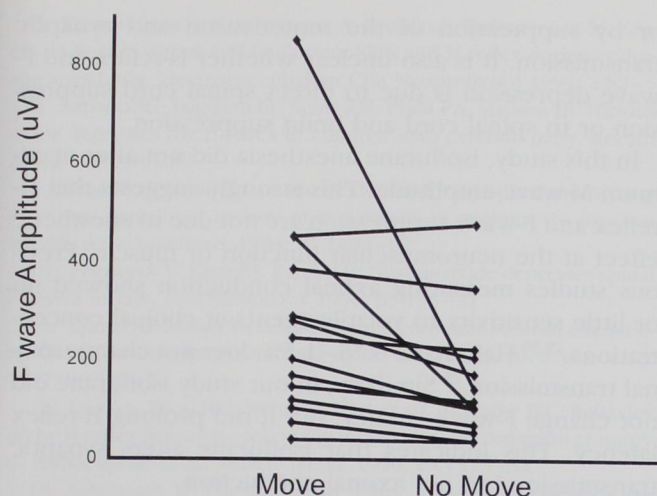


Fig. 4. F-wave amplitude comparison between responding (movement) and nonresponding (no movement) to stimuli for individual patients.

At 0.8% end-tidal isoflurane, seven patients moved in response to stimulation, whereas eight patients had no response to stimulus. The H-reflex amplitude (3.69 ± 1.83 mV), F-wave amplitude (0.29 ± 0.15 mV), and F-wave persistence ($80 \pm 22.36\%$) in patients with movement were significantly ($P < 0.01$) higher than these without movement (fig. 6; H-reflex amplitude 1.01 ± 1.14 mV; F-wave amplitude 0.11 ± 0.06 mV; F-wave persistence $34.9 \pm 25.75\%$).

The preanesthesia H-reflex latency (30.8 ± 3.3 ms) was prolonged to 31.2 ± 3.2 ms ($P < 0.01$) at move-

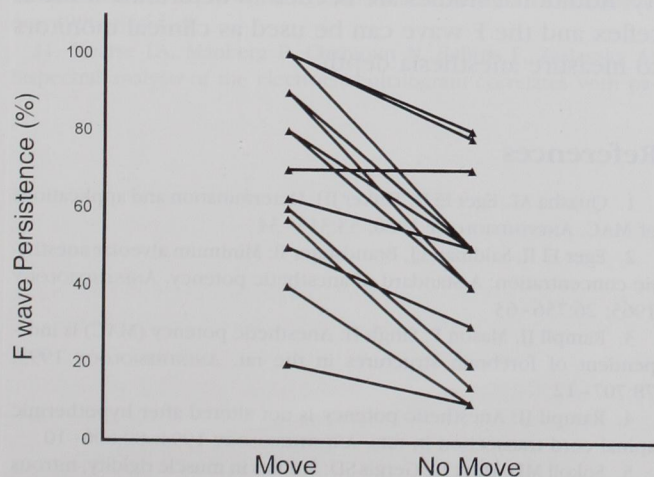
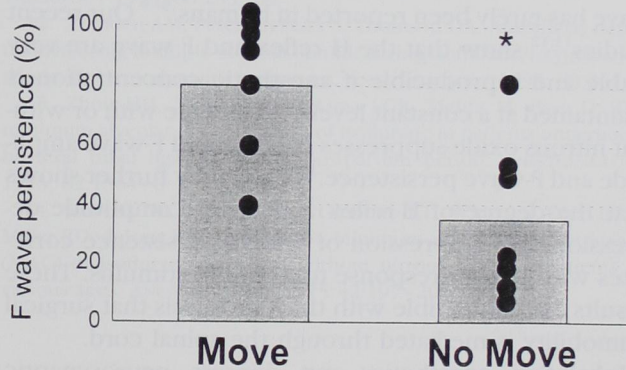
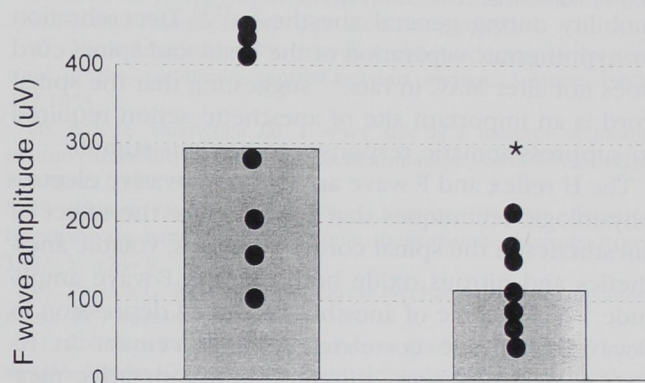
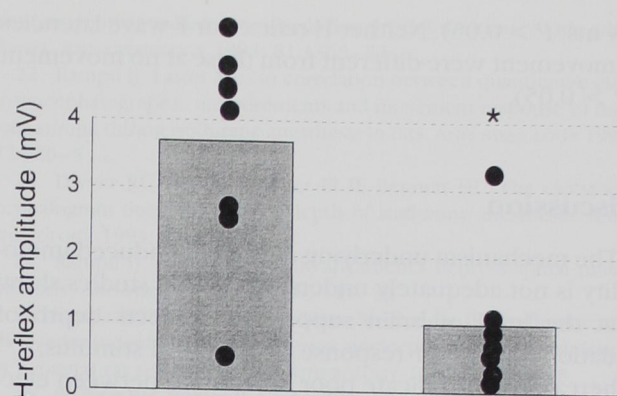


Fig. 5. Individual F-wave persistence between responding (movement) and not responding (no movement) to stimuli. The mean values of the two states are different ($P < 0.001$).



At 0.8% isoflurane

Fig. 6. H-reflex and F-wave amplitude and F-wave persistence at 0.8% end-tidal isoflurane. Responding (movement) and not responding (no movement) to stimuli were compared and analyzed with paired *t* tests and Bonferroni correction. Each dot indicated the data for each patient. * $P < 0.01$ compared with the movement state.

ment and 31.4 ± 3.3 ms ($P < 0.05$) at no movement after isoflurane. F-wave latency after anesthesia at movement (51 ± 4.8 ms) and at no movement (51.6 ± 4.5 ms) was unchanged from preanesthesia values ($51.1 \pm$

6.4 ms; $P > 0.05$). Neither H-reflex nor F-wave latencies at movement were different from these at no movement ($P > 0.05$).

Discussion

The mechanism underlying anesthesia-induced immobility is not adequately understood. Some studies show that the level of brain suppression reflects depth of sedation and motor response to a surgical stimulus,^{20,21} whereas others indicate poor correlation between electroencephalographic changes and MAC or surgical immobility during general anesthesia.^{22,23} Decerebration or hypothermic separation of the brain and spinal cord does not alter MAC in rats,^{3,4} suggesting that the spinal cord is an important site of anesthetic action required to suppress somatic responses to noxious stimuli.

The H reflex and F wave are two noninvasive electrophysiologic techniques that can measure the effect of anesthetics in the spinal cord.¹³⁻¹⁶ In rats, volatile anesthetics and nitrous oxide both depress F-wave amplitude.²⁴ The degree of anesthetic-induced depression in F-wave amplitude correlates with movement in response to a tail-clamp stimulus.¹⁰ Intraoperative measurement of anesthetic effects on the H reflex and F wave has rarely been reported in humans.⁵⁻⁹ Our recent studies^{11,12} show that the H reflex and F wave are very stable and reproducible if anesthetic concentration is maintained at a constant level.¹² Isoflurane with or without nitrous oxide suppresses H-reflex and F-wave amplitude and F-wave persistence.¹¹ This study further shows that the degree of H-reflex and F-wave amplitude depression and suppression of F-wave persistence correlates with patient response to a painful stimulus. These results are compatible with the hypothesis that surgical immobility is mediated through the spinal cord.

Inhalation anesthetics can depress neurosynaptic transmission^{25,26} and motoneuron excitability in the spinal cord.^{9,27} General anesthesia may suppress the H reflex by decreasing spinal motoneuron excitability, sensory neuron responsiveness, or neurosynaptic transmission.^{13,14} F-wave amplitude is related to the size and the number of activated motor units,¹⁵ and to motoneuron excitability,²⁸ whereas F-wave persistence indicates the antidromic excitability of a motoneuron pool.^{15,16} Thus suppression of F-wave amplitude and persistence suggest decreased motoneuron excitability.^{15,16} It is not clear whether isoflurane-induced immobility is produced by suppression of motoneuron excitability alone

or by suppression of the motoneuron and synaptic transmission. It is also unclear whether H-reflex and F-wave depression is due to direct spinal cord suppression or to spinal cord and brain suppression.

In this study, isoflurane anesthesia did not alter maximum M-wave amplitude. This strongly suggests that H-reflex and F-wave suppression are not due to anesthetic effect at the neuromuscular junction or muscle. Previous studies measuring axonal conduction showed no or little sensitivity to volatile agents at clinical concentrations.^{29,30} Halothane 0.75–1.5% does not change axonal transmission.²⁹ Similarly, in our study isoflurane did not change F-wave latency, but it did prolong H-reflex latency. This indicates that isoflurane alters synaptic transmission but not axonal conduction.

Tetanic stimulation is a noninvasive technique that can determine MAC in humans.^{18,31-33} This method has the advantage of measuring response to repeated stimulation using the bracketing technique and determining MAC in individual patients. With this method, isoflurane MAC was less than MAC to skin incision in our report and in previous studies.^{31,33} This discrepancy is probably attributable to differences in stimulus intensity.³¹ The lower MAC value in our study also may be due to the wide age range of patients, because isoflurane MAC decreases by about 25% from ages 26 to 64 yr.³⁴

In conclusion, we found that isoflurane-induced immobility correlates with suppression of H-reflex and F-wave amplitude and F-wave persistence in humans. These results suggest that the suppressive effect of inhalation anesthetics on spinal motoneuron excitability plays an important role in producing surgical immobility. Additional studies are needed to determine if the H reflex and the F wave can be used as clinical monitors to measure anesthesia depth.

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