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Spinal Cord Motoneuron Excitability during Isoflurane and Nitrous Oxide Anesthesia

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Background: **Recent evidence suggests that the spinal cord is an important site of anesthesia that is necessary for surgical immobility, but the specific effect of anesthetics within the spinal cord is unclear. This study assessed the effect of isoflurane and nitrous oxide on spinal motoneuron excitability by monitoring the H-reflex and the F wave.**

Methods: **Eight adult patients, categorized as American Society of Anesthesiologists physical status 1 or 2, who were undergoing elective orthopaedic surgery were anesthetized with 0.6, 0.8, 1.0, and 1.2 times the estimated minimum alveolar concentration (MAC) of isoflurane. Nitrous oxide was added in graded concentrations of 30%, 50%, and 70%, whereas the isoflurane concentration was decreased to maintain a total MAC of 1. The H-reflex of the soleus muscle and the F wave of the abductor hallucis muscle were measured before anesthesia and 15 min after each change of anesthetic concentration. Four or more trials of the H-reflex and 18 trials of the F wave were recorded at each concentration of anesthesia. The effect of the anesthetics on the H-reflex and F wave was analyzed using Dunnett's test.**

Results: **H-reflex amplitude was decreased to 48.4 ± 18.6% of preanesthesia level at 0.6 MAC isoflurane and to 33.8 ± 19.1% when isoflurane concentration increased from 0.6 MAC to 1.2 MAC. F wave amplitude and persistence decreased to 52.2 ± 33.6% and 44.4 ± 26% of baseline at 0.6 MAC isoflurane, and to 33.8 ± 26% and 21.7 ± 22.8% at 1.2 MAC isoflurane. Isoflurane plus nitrous oxide (total 1 MAC) decreased H-reflex amplitude to 30.4–33.3% and decreased F wave persistence to 42.8–56.3% of baseline.**

Conclusions: **Both isoflurane alone and isoflurane plus nitrous oxide decrease H-reflex and F-wave amplitude and F-wave persistence. These effects suggest that isoflurane and nitrous oxide decrease motoneuronal excitability in the human spinal cord. This may play an important role in producing surgical immobility. (Key words: Anesthesia: mechanisms. Anesthetics, volatile: isoflurane. Anesthetics, gases: nitrous oxide. Electrophysiology: H-reflex; F wave. Spinal cord.)**

PREVENTING purposeful movement in response to a surgical incision or a painful electrical stimulus,[1,2] a principle characteristic of general anesthesia, has been used routinely to determine anesthetic requirements and potency.[3,4] The mechanism for surgical immobility produced by inhaled anesthetics is not adequately understood. Recently it was shown that anesthetic requirements were unaltered in rats after decerebration[5] or after hypothermic transection between brain and spinal cord,[6] suggesting that immobility is primarily produced by an anesthetic effect on the spinal cord.

Spinal cord motoneuron excitability can be measured using Hoffmann's reflex (H-reflex) and F wave. The H-reflex is a monosynaptic or oligosynaptic reflex produced by electrical stimulation of afferent fibers in the mixed peripheral nerve.[7,8] This reflex is mediated by large sensory (Ia) and motor (Aα) fibers.[7–9] Clinically, the H-reflex is used to assess the integrity of both motor and sensory fibers. In addition, the response is affected by descending influences that alter the excitability of the spinal motoneuron pool.[7] The F wave is a late muscle potential evoked by a supramaximal stimulus to the nerve. In contrast to the H-reflex, the F wave is not a reflex; the afferent and efferent arc to and from the spinal cord consists of the same alpha motor neuron. The F wave thus is generated by antidromic activation of the spinal motor neuron.[9–11] As with the H-reflex, the F wave is useful in evaluating the excitability of the motoneuronal pool.[8–10] Few studies have measured the effect of general anesthesia on the H-reflex and F wave.[12–16] One recent study[16] showed that isoflurane depressed the F wave in rats, suggesting that anesthetics

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may produce surgical immobility by depressing the excitability of α-motor neurons.

The effect of general anesthesia on the H-reflex and F wave has not been studied systematically, particularly in humans, and some basic questions have not yet been addressed. For example, can the anesthetic effect in the spinal cord be monitored by measuring the H-reflex and F wave? Do clinically used concentrations of inhalation agents suppress the H-reflex or F wave in humans? If they do, is the effect dose dependent? Do volatile anesthetics and nitrous oxide have a similar effect on spinal motoneuron excitability? To address these questions, we studied the influence of two commonly used inhalation agents, isoflurane and nitrous oxide, on the H-reflex and F wave.

Methods

Eight patients (seven men and one woman; ages 19–36 yr, weight 83.8 ± 22.6 kg, height 173.7 ± 3.6 cm, American Society of Anesthesiologists physical status 1 or 2), undergoing elective orthopaedic surgery under 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.

Baseline maximum H-reflexes, F waves, and direct muscle response (M wave) were recorded before induction of anesthesia using a Cadwell Sierra EMG/EP (Cadwell Laboratories, Kennadwick, Washington). The H-reflex was evoked by placing the cathode (constant-current stimulator) over the posterior tibial nerve at the popliteal fossa. Surface electrodes on the soleus muscle recorded the H and M responses. Stimuli lasted 1 ms (square wave electrical pulse) and intensity was varied (electrical current 5–30 mA) to achieve maximum H-reflex amplitude. Maximal M wave amplitude was evoked with supramaximal stimulation to the posterior tibial nerve. Both H and M amplitudes were measured from positive peak to negative peak. To confirm the response as an H-reflex, the amplitude had to exceed that of the M wave. In all cases, a representative control M wave was monitored and stimulus intensity was maintained constant. However, if the leg was inadvertently manipulated during surgery, minor adjustments were made in the stimulus intensity so that the test M-wave amplitude matched the preanesthesia level. At least four trials of H-reflex were recorded at an interstimulation interval of 30 s.

F waves were recorded in the abductor hallucis muscle after posterior tibial nerve stimulation at the medial malleolus of the ankle. Series of 18 stimuli of supramaximal intensity were delivered. F-wave latency, maximal peak-to-peak amplitude, and persistence (the number of measurable F waves divided by the number of stimuli) were determined. To distinguish F waves from background noise, we accepted only appropriately timed deflections from the baseline with an amplitude of at least 40 μV. The filter setting was 10 Hz and 5 kHz.

Anesthesia was induced with intravenous fentanyl (100 μg) and propofol (2 mg/kg), and the trachea was intubated after intravenous succinylcholine (1.5 mg/kg) was administered. Muscle relaxants were not used again after intubation. Isoflurane in oxygen (1 MAC = 1.14% in oxygen)[1] was administrated to achieve a steady end-tidal concentration of 0.68% (0.6 MAC). Respiratory gases were monitored continuously with a mass spectrometer (Perkin-Elmer MGA1100, Pomona, CA). Ventilation was controlled to maintain end-tidal carbon dioxide tension between 32–38 mmHg with tidal volume of 10–12 ml/kg and rate of 8–12 breaths/min. Blood pressure and temperature were monitored continuously using an automatic blood pressure cuff (Dinamap, Johnson & Johnson Hospital Supplys, New Brunswick, NJ) and an esophageal probe, respectively. Blood pressure was maintained at no less than 75% of preanesthesia level with an intravenous infusion of Ringer's lactate solution. Temperature was maintained within 1°C of preoperative values using a warming blanket.

To confirm no residual effects of the short-acting muscle relaxant used during induction, M waves were checked from 20 to 30 min after induction. When maximal M-wave amplitudes returned to preanesthesia levels, the H-reflex and F wave were elicited again. Isoflurane end-tidal concentration was then increased in steps to 0.91% (0.8 MAC), 1.14% (1 MAC), and 1.37% (1.2 MAC) sequentially after the H-reflex and F wave were evoked at each concentration. Stimulation was adjusted to elicit the maximum H-reflex while maintaining the preoperative level of M-wave amplitude. Nitrous oxide (1 MAC = 104%) was added in graded steps (30%, 50% and 70%) and the isoflurane concentration was decreased to 0.81%, 0.59%, and 0.37%, respectively, to maintain a total of 1 MAC of anesthetic agents. Each anesthetic end-tidal concentration was maintained for at least 15 min before recording H-reflex and F wave.

Data were collected and stored in the Cadwell Sierra

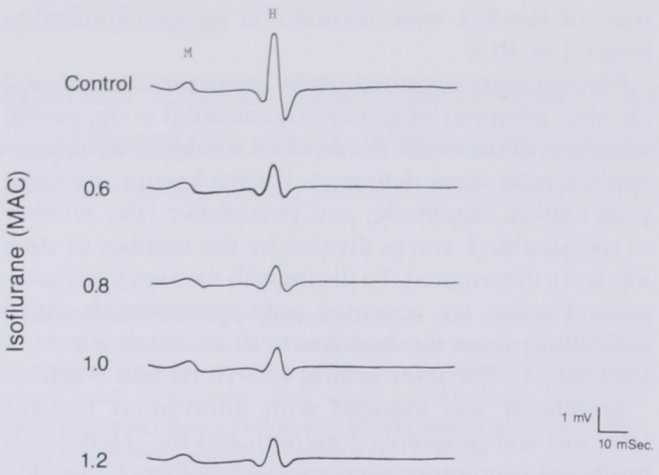

Fig. 1. Original tracings of H-reflex before and during isoflurane anesthesia (stimulus intensity, 40–60 mA). M = M wave; H = H-reflex.

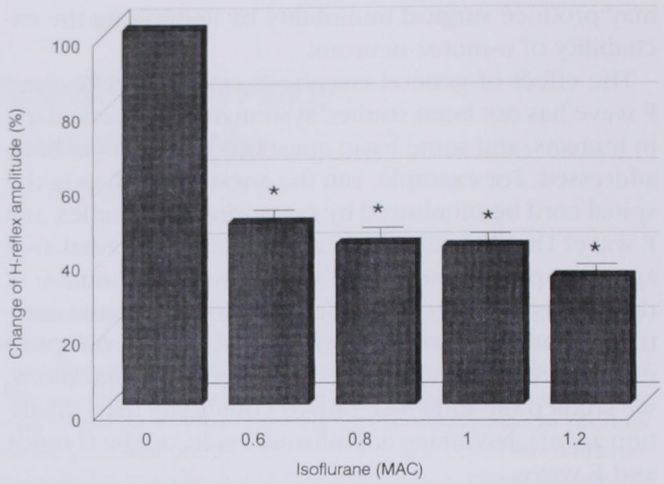

Fig. 2. Decrease of H-reflex amplitude after isoflurane anesthesia. Data are expressed as mean ± SEM. *$P < 0.05$ compared with preanesthesia levels.

EMG/EP computer for subsequent analysis. The averaged H-reflex amplitude of four traces at each level of anesthesia was calculated. Data were analyzed using a statistical program (SAS 1994; Statistical Analysis Systems, Cary, NC). All descriptive values are reported as means ± SD. Dunnett's test was used for analysis of variance in H-reflex and F wave before and after anesthesia. Probability values less than 0.05 were considered significant.

Results

Both H-reflex and F wave were recorded in a reproducible manner in all participants except one (patient 7), in whom we could not evoke the F wave. The latencies of H-reflex and F wave after general anesthesia remain unchanged from preanesthesia values. The maximal M-wave amplitude was not altered by exposure to isoflurane or nitrous oxide, suggesting that both agents do not depress neuromuscular transmission.

H-Reflex

The mean preoperative H-reflex amplitude was 6.6 ± 2.97 mV. The maximal amplitude of M wave was 10.61 ± 3.9 mV. H-reflex amplitude decreased to 48.4 ± 18.6% of baseline at 0.6 MAC isoflurane, and to 42.8 ± 21.1%, 42 ± 20.7%, and 33.8 ± 19.1% at isoflurane concentrations of 0.8, 1.0, and 1.2 MAC, respectively (figs. 1 and 2). H-reflex amplitude suppression was significant ($P < 0.05$). Combining isoflurane and nitrous oxide to a total of 1 MAC decreased H-reflex amplitude to 32.5 ± 19.2%, 33.3 ± 20.8%, and 30.4 ± 23.5% of preanesthesia levels at 30%, 50%, and 70% nitrous oxide, respectively. The decrease was significant ($P < 0.05$) compared with preanesthesia levels but was not different compared with H-reflex amplitude at 1 MAC isoflurane ($P > 0.05$).

F Wave

The mean maximal amplitude of preoperative F wave was 0.73 ± 0.383 mV. The maximal F-wave to M-wave amplitude ratio was 6.1 ± 2.9%. The F-wave amplitude decreased to 52.2 ± 33.6%, 46.7 ± 37.8%, 42.1 ± 36.1%, and 33.8 ± 26% of preanesthesia levels at 0.6, 0.8, 1.0, and 1.2 MAC isoflurane, respectively. F-wave persistence decreased to 44.4 ± 26%, 36.8 ± 31.9%, 30 ± 27.3%, and 21.7 ± 22.8% of baseline at 0.6, 0.8, 1, and 1.2 MAC isoflurane, respectively (figs. 3 and 4). Both

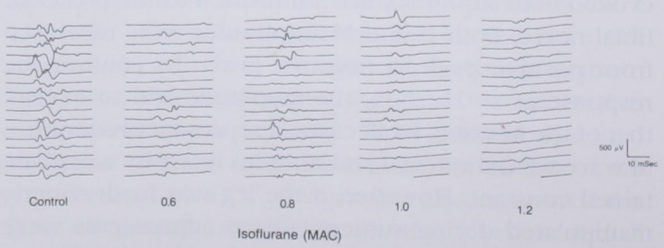

Fig. 3. Original tracings of the F wave before and during isoflurane anesthesia (stimulus intensity, 40–60 mA).

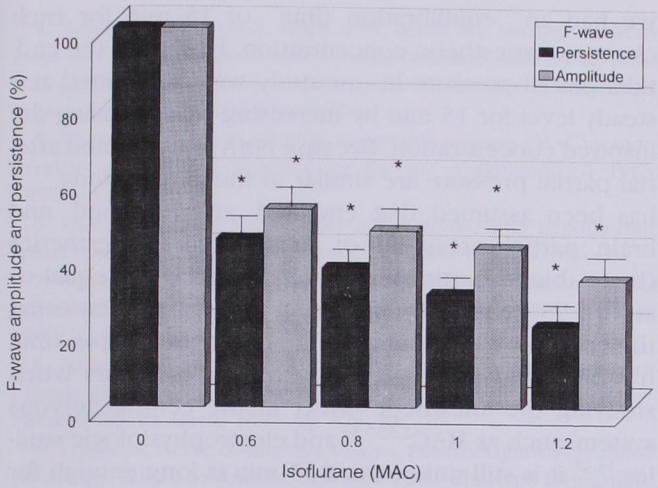

Fig. 4. Effect of isoflurane on F-wave amplitude and persistence. Data are expressed as mean ± SEM. *$P < 0.05$ compared with preanesthesia levels.

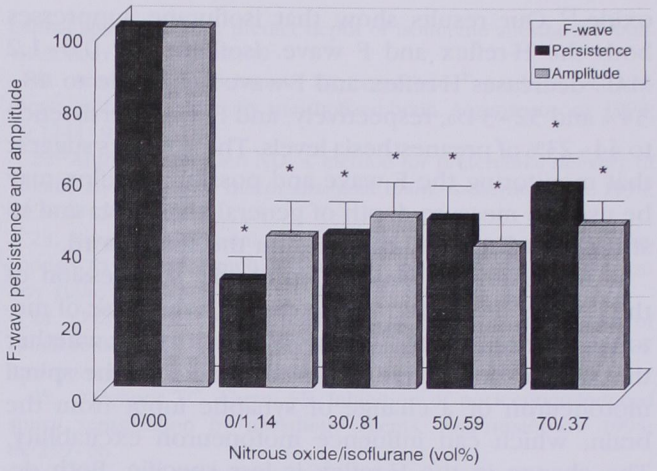

Fig. 6. Effect of combining isoflurane and nitrous oxide anesthesia on F-wave amplitude and persistence. Data are expressed as mean ± SEM. *$P < 0.05$ compared with preanesthesia levels.

decreases in F-wave amplitude and persistence were significant ($P < 0.05$).

When the mixture of isoflurane and nitrous oxide at 1 MAC was added, F-wave persistence values were 42.8 ± 31.3%, 47.3 ± 40.6%, and 56.3 ± 41.6%; F-wave amplitude values were 47.7 ± 38%, 39.7 ± 30.5%, and 45.6 ± 33.6% of preanesthesia levels at 30%, 50%, and 70% nitrous oxide, respectively (figs. 5 and 6). These changes were significant ($P < 0.05$) compared with preanesthesia levels but were not significant ($P > 0.05$) compared with those with isoflurane alone (1 MAC).

Discussion

This study provides evidence that inhalation anesthetics influence motoneuron excitability and possibly synaptic transmission in the human spinal cord.

The mechanism underlying anesthesia-induced-immobility has not been addressed. Although the level of brain suppression is thought to reflect depth of general anesthesia,[17,18] recent evidence suggests that the spinal cord is an important site of anesthetic action to suppress somatic responses to noxious stimuli. There is poor correlation between electroencephalographic change and MAC or surgical immobility during general anesthesia.[19,20] In rats, decerebration or hypothermic transection of the brain and spinal cord does not alter MAC.[5,6] In contrast, isoflurane MAC increases in the goat when the brain is selectively anesthetized *via* carotid artery bypass connected to a perfusion pump,[21–23] implying that anesthetizing the spinal cord is important in producing surgical immobility. In rats, inhalation anesthetics suppress the dorsal horn neuron response to noxious stimulation produced by subcutaneous injection of dilute formalin.[24–26]

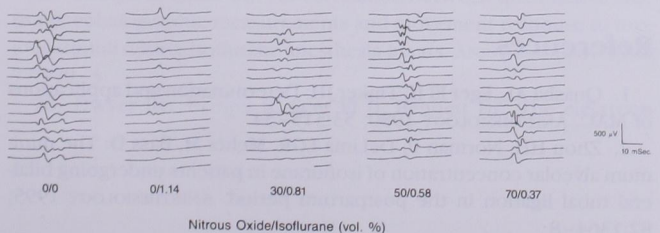

Fig. 5. Original tracings of the F wave before and when isoflurane and nitrous oxide anesthesia were combined (stimulus intensity, 40–60 mA).

Depressed synaptic transmission and decreased motoneuron excitability may explain the effect of inhaled agents on the spinal cord. Animal studies show that inhalational anesthetics depress neurosynaptic transmission[27,28] and decrease motoneuron excitability in the spinal cord.[16,29] The depression of motor neuron excitability has been shown by decreased F-wave amplitude in rats.[16]

Intraoperative measurement of the effect of anesthetics on human spinal cord neurons has rarely been reported. It has been shown that H-reflex amplitude decreased about 60% after 70% nitrous oxide[12] and 70–90% after 0.8 MAC halothane or halothane plus nitrous

oxide.[13] Our results show that isoflurane suppresses both the H-reflex and F wave. Isoflurane at 0.6–1.2 MAC decreases H-reflex and F-wave amplitude to 48–34% and 52–34%, respectively, and F-wave persistence to 44–23% of preanesthesia levels. These results suggest that monitoring the F wave and possibly H-reflex may be used to measure depth of general anesthesia and to study the effect of anesthetics on the spinal cord.

In the setting of general anesthesia, suppression of the F wave almost certainly indicates a decrease of motoneuron excitability.[10] However, it is not clear whether this suppression is due to a direct effect on the spinal motoneuron or a change of synaptic input from the brain, which can influence motoneuron excitability. The change in the H-reflex is less specific. Both decreases in spinal motoneuron excitability or in neurotransmission of the oligosynaptic circuit may suppress the H-reflex. Whether isoflurane suppresses one or both of them is still not known.

Nitrous oxide may possess an excitatory effect in the central nervous system. For example, nitrous oxide reverses electroencephalographic burst suppression produced by isoflurane and desflurane.[30–32] The inhibition of nociception-induced spinal sensitization is reversed when nitrous oxide is added to a volatile agent.[24–26] However, a recent study shows that nitrous oxide with or without isoflurane produces a dose-dependent suppression of the F wave in rats.[33] In our study, combining nitrous oxide and isoflurane depressed H-reflex and F-wave amplitude. The degree of the depression produced by this combination is not different from that produced by isoflurane alone. It is unknown whether the effect of nitrous oxide in spinal cord motoneurons may present as excitatory or inhibitory at the different conditions.

Species differences in F-wave amplitude have been reported.[16] The ratio of F- and M-wave amplitudes in rats (25% at 0.5 MAC isoflurane)[16] is much higher than that in humans (6.1% before anesthesia in the present study). This may suggests less motoneuron excitability in humans. Our data show that both F-wave persistence and amplitude change under general anesthesia, suggesting that analysis of both F-wave persistence and amplitude is important when measuring or studying an anesthetic effect on α-motoneuron excitability in humans.

An earlier study[34] showed that both end-tidal and arterial partial pressure of isoflurane reaches about 60% of inspired partial pressure after patients breathe a constant concentration for 15 min. In the present study, we had an "equilibration time" of 15 min for each change of anesthetic concentration. However, the end-tidal partial pressure in our study was maintained at a steady level for 15 min by increasing or decreasing the inspired concentration. Because both end-tidal and arterial partial pressure are similar in the earlier study,[34] it has been assumed that end-tidal, arterial blood, and brain partial pressures of most inhaled anesthetics (brain–blood partition coefficient < 2.5) are equal or at least 95% equilibrated after a 15-min interval by using this method.[1,3] Although the 15-min equilibration time has been widely adopted by many investigators when studying the anesthetic effect in the central nervous system, such as MAC[2,3,35,36] and electrophysiologic studies,[13,37] it is still unknown if 15 min is long enough for equilibration. Another limitation of the study is surgical stimulation during H-reflex and F-wave measurement. In our study, surgical procedures included shoulder and knee arthroscopy and were begun after the end-tidal isoflurane concentration was stabilized at 1 MAC. Whether surgical stimulation under general anesthesia changes neuronal activity in the spinal cord is unknown. After surgery began, however, we observed no patient movement or significant hemodynamic change, and H-reflex amplitude, F-wave persistence, and F-wave amplitude also did not change.

In conclusion, this study shows that isoflurane with or without nitrous oxide decreases H-reflex and F-wave amplitude and F-wave persistence. Although the mechanism underlying anesthesia-induced immobility is still unclear, these results suggest that the suppressive effect of inhaled anesthetics on motoneuronal excitability may play an important role in producing surgical immobility. Additional studies are needed to determine if the action of anesthetics on the spinal cord can be assessed during operation by monitoring H-reflex and F wave.

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