The H-reflex as a Measure of Anesthetic Potency in Man

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The effects of different concentrations of halothane with oxygen and with 70 per cent nitrous oxide on the amplitude of the H-reflex (a spinal monosynaptic reflex) were studied in 12 volunteers. In six subjects on mechanical ventilation the mean amplitude of the H-reflex was 21.5 per cent of the awake response at 0.3 per cent halothane–N_2O (MAC); 20 per cent at 0.8 per cent halothane–O_2 (MAC); 7.5 per cent at 0.8 per cent halothane–N_2O. In six subjects breathing spontaneously at a Pa_{CO_2} of 46.7 torr, the amplitude of the H-reflex was 23.5 per cent at 0.3 per cent halothane–N_2O; 27.3 per cent at 0.8 per cent halothane–O_2; 14.2 per cent at 1.5 per cent halothane–O_2; 11.6 per cent at 0.8 per cent halothane–N_2O; 4.25 per cent at 1.5 per cent halothane–N_2O. Halothane 0.3 per cent with 70 per cent N_2O and halothane 0.8 per cent with oxygen were equipotent in their effects on both the H-reflex and the response to noxious stimulation. Increase in Pa_{CO_2} depressed the H-reflex. Measurement of the H-reflex may provide a means of correlating central nervous system depression with anesthetic dose.

THE COMPARATIVE POTENCIES of general anesthetic agents are difficult to assess in man since there is no satisfactory measure of the effects of these drugs on the central nervous system. The neurologic signs and electroencephalographic patterns associated with clinical anesthesia are difficult to define and quantify. The measurement proposed by Eger *et al.*,[1, 2] the minimum alveolar concentration (MAC) of an anesthetic that prevents motor responses to noxious stimulation, provides useful information but defines equipotency for only one concentration of each drug. Moreover, the determination of MAC by the responses of patients to skin incision provides an average value of MAC for a group, but does not lend itself to the determination of MAC for a single subject.

An ideal measure of anesthetic potency should be: a) graded in relation to depth of anesthesia, or more precisely, to anesthetic concentration; b) easily and repeatedly quantifiable; and c) relatable to clinical end points. These criteria might be met by a neural response such as the spinal monosynaptic reflex, whose amplitude is known in experimental animals to decrease as anesthetic concentration increases.[3, 6]

The only quantifiable spinal monosynaptic reflex accessible in man is the H-reflex, a response elicited by electrical stimulation of the tibial nerve.[7, 8] A single stimulus applied to this nerve causes two distinct contractions of the calf muscles which can be recorded electromyographically (fig. 1). The first contraction (M-response) appears after a delay of approximately 5 msec and is due to direct excitation of the motor nerve fibers. The second contraction (H-response) appears after a delay of approximately 30 msec and is due to discharge of spinal motoneurons excited transsynaptically via the afferent limb of the reflex arc. The purpose of this study was to evaluate the usefulness of the H-reflex as a measure of anesthetic potency in man.

Methods

Twelve healthy unmedicated male volunteers between the ages of 22 and 32 years were studied. Informed consent was obtained from all subjects. Using local anesthesia a catheter was placed in the brachial artery and

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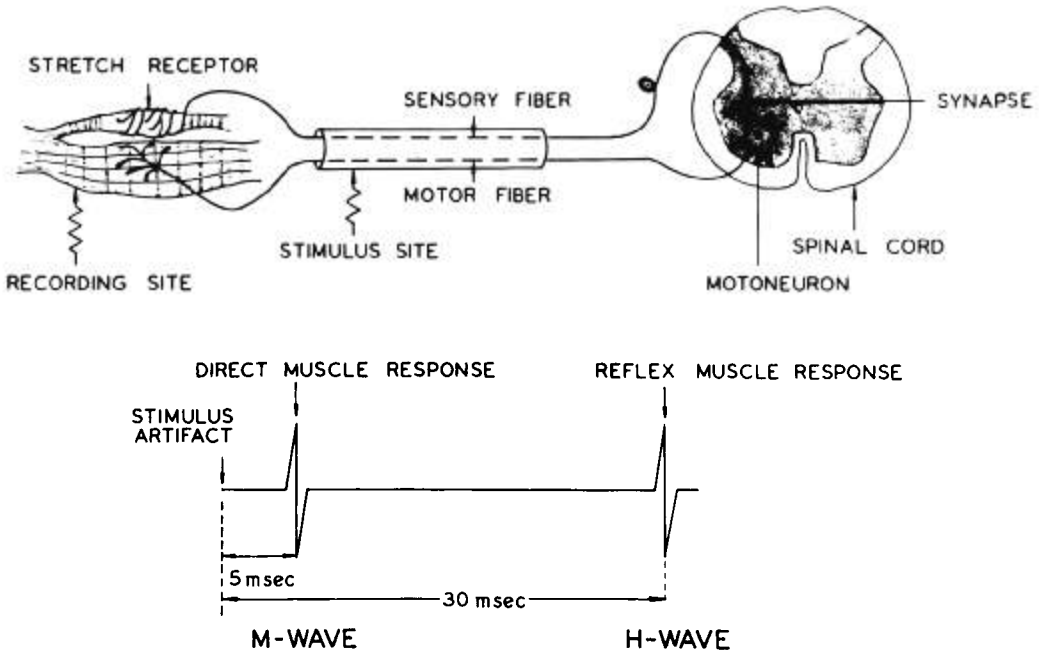

FIG. 1. Schematic representation of the neural arc involved in the H-reflex, and of the M- and H-responses observed in the oscilloscope.

connected to a strain gauge for continuous monitoring of arterial pressure. Arterial blood samples were analyzed for gas tensions and *p*H with appropriate electrodes.

Again under local anesthesia, two insulated wire electrodes were introduced 2 cm apart in the popliteal fossa until their bared tips lay close to the tibial nerve. The nerve was stimulated with rectangular electric pulses of 0.3 msec duration spaced at least 30 sec apart to allow for full recovery of reflex responses.[8, 9] The resultant action potentials of the calf muscles were recorded with silver disc electrodes, one placed on the skin over the gastrocnemius muscle and another over the Achilles tendon. The potentials were amplified, displayed on an oscilloscope and photographed.

The subjects lay supine, their lower extremities supported to prevent changes in length of the calf muscles. Control measurements of the maximum H-response to optimum stimulation, and of the M-response to supramaximal stimulation, were obtained from the awake resting subjects. Anesthesia was then induced with nitrous oxide in oxygen, followed by halothane to permit endotracheal intubation without the use of muscle relaxants. End-tidal gas, obtained from the endotracheal tube with a Rahn sampler, was analyzed continuously for carbon dioxide and nitrous oxide content with infrared analyzers and for halothane content with an ultraviolet analyzer. Esophageal temperature was maintained between 36.5 and 35.4 C.

The H-reflex was measured when the chosen end-tidal anesthetic concentration had remained constant for at least 15 minutes. Six subjects were allowed to breathe spontaneously, and measurements were made at 1.5, 0.8 and 0.3 per cent halothane with 70 per cent nitrous oxide, and at 1.5 and 0.8 per cent halothane in oxygen. In the other six subjects respiration was mechanically controlled to produce three different levels of carbon dioxide tension. In this group measurements were made only at 0.3 and 0.8 per cent halothane because of a tendency towards excessive arterial hypotension at higher concentrations of halothane.

The peak-to-peak amplitudes of the H- and M-responses were measured on the photographs and expressed as percentages of their control values. Latency of the H- and M-re-

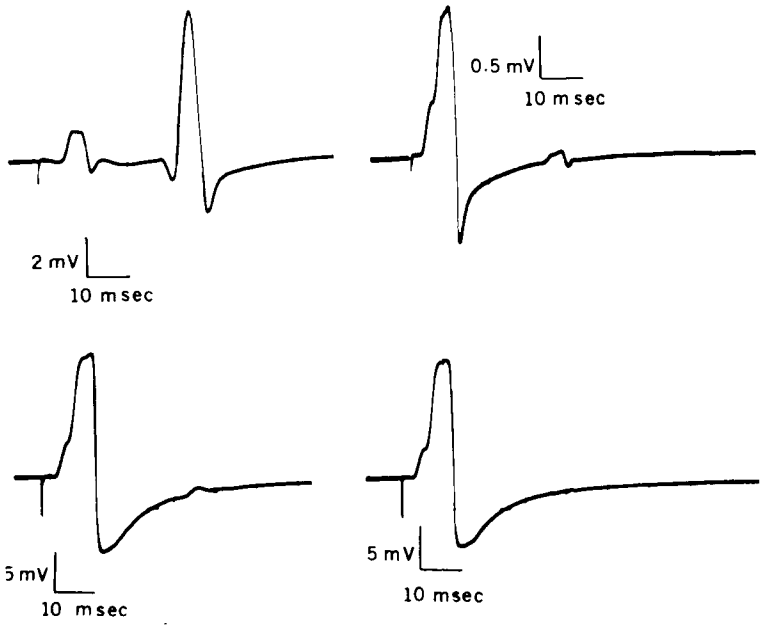

FIG. 2. Oscilloscope tracings. Records on the left side show maximum H-response (top) and maximum M-response in an awake subject. In the bottom tracing the H-response is barely visible because of its normal decrease when stimulus intensity is increased to excite all motor nerve fibers.[8] Records on the right side show these responses in the same subject during anesthesia with 1.5 per cent halothane and 70 per cent nitrous oxide. Note different scales in top records.

sponses was measured from stimulus artifact to the first corresponding deflection from baseline. To detect possible effects of anesthesia on neuromuscular transmission each measurement of the H-response was followed by one of the M-response.

Results

The first determination during anesthesia, done as soon as the subjects were unconscious and quiet, showed the H-reflex to be already smaller than when awake. As anesthesia deepened, the reflex progressively declined, but it stabilized when the end-tidal anesthetic concentration reached a constant level. Within two to three minutes of subsequent alterations in anesthetic concentration the amplitude of the reflex started changing towards a new value. This close correspondence indicates a rapid equilibration of anesthetic between arterial blood and central nervous system tissue. Figure 2 shows representative oscilloscope tracings of the responses in a subject before and during anesthesia.

The changes in amplitude of the H-reflex observed in the mechanically ventilated subjects at equilibrium with three different anesthetic concentrations and three levels of arterial carbon dioxide tension are summarized in table 1 and figure 3. The data show that the amplitude of the reflex was strongly influenced by changes in carbon dioxide tension. At all three anesthetic concentrations, the reflex was smaller at higher-than-normal, and larger at lower-than-normal, carbon dioxide tensions.

The mean values of the H-reflex in the spontaneously breathing subjects are shown in table 2. Since these observations were made at carbon dioxide tensions varying between 46.7 and 58.8 mm Hg, they presumably also reflect the effect of this gas. To dissociate the effect of carbon dioxide from that of the anesthetic agents during spontaneous respiration, we have extrapolated the amplitude of the H-reflex to an arterial carbon dioxide tension of 46.7 mm Hg. This calculation was performed using the ΔH-reflex/ΔPa_{CO_2} obtained during controlled ventilation, assuming the change in response to be linear (fig. 3). Because data were not available during controlled ventilation at 1.5 per cent halothane, correction for this concentration during spontaneous respiration was made using the slope for 0.8 per cent halothane–N_2O. The extrapolated H-reflex values are listed on the bottom line of table 2.

Halothane 0.8 per cent produced essentially the same depression of the H-reflex as 0.3 per

cent halothane with 70 per cent nitrous oxide (tables 1 and 2). The standard errors of the differences between these two anesthetic mixtures in the mechanically ventilated and the spontaneously breathing subjects were 3.86 and 3.67, respectively, both corresponding to P values greater than 0.5. Adding 70 per cent nitrous oxide to 0.8 and 1.5 per cent halothane reduced the amplitude of the H-reflex to approximately a third of that for halothane in oxygen (tables 1 and 2).

Mean arterial blood pressures varied between 80 and 60 mm Hg. In each of two subjects a transient fall in blood pressure to 45 mm Hg did not affect the amplitude of the H-reflex. The lowest arterial oxygen tension was 140 mm Hg. The base excess, determined by use of an *in vivo* slope equal to a third of that in blood, varied between +2 and −5 mM/l. The amplitude of the M-response remained above 92 per cent of the awake value, an indication that neuromuscular transmission for single nerve impulses was essentially unchanged. The latency of the M-response never changed; that of the H-response was increased minimally (up to 3 per cent) in nine of the 174 records. Serial determinations of the H-reflex at the end of anesthesia in nine subjects showed that just before the subjects moved or coughed the reflex had recovered to a mean of 72 per cent (range 33–100) of control value.

Discussion

Halothane 0.8 per cent with oxygen and halothane 0.3 per cent with nitrous oxide depressed the H-reflex to the same extent (tables 1 and 2). These two anesthetic mixtures are thus equipotent in their effects on both the H-reflex and the response to noxious stimulation.[10, 11] Comparison at other points of the spectrum of surgical anesthesia is not possible because MAC provides no information beyond its end point, lack of movement. One criterion of anesthetic depth is the degree of relaxation of the abdominal wall. The progressive changes of the H-reflex observed in this study are of the same order of magnitude as those found by de Jong *et al.*[12] to be associated in man with abdominal relaxation ranging from fair to profound. This would indicate that changes of the H-reflex can measure a wide range of anesthetic depression.

TABLE 1. Effects of Changes in Anesthetic Concentrations and Carbon Dioxide Tensions on the H-Reflex*

	0.3 Per Cent Halothane, 70 Per Cent N_2O			0.8 Per Cent Halothane			0.8 Per Cent Halothane, 70 Per Cent N_2O		
Arterial P_{CO_2} (mm Hg)	24 ± 5.4	45.2 ± 6	63.2 ± 8.7	23.2 ± 4.5	42.6 ± 3.4	69.3 ± 11	25.5 ± 6	44.2 ± 5.6	69.2 ± 13
H-reflex amplitude	25.7 ± 12	21.5 ± 11	10.8 ± 5.3	24 ± 18	20.0 ± 17	11.4 ± 6.5	9.85 ± 6.3	7.5 ± 4.4	4.1 ± 2

* Date from six subjects ventilated mechanically. Amplitude of the H-reflex is expressed as a percentage of the awake value. Means ± SD.

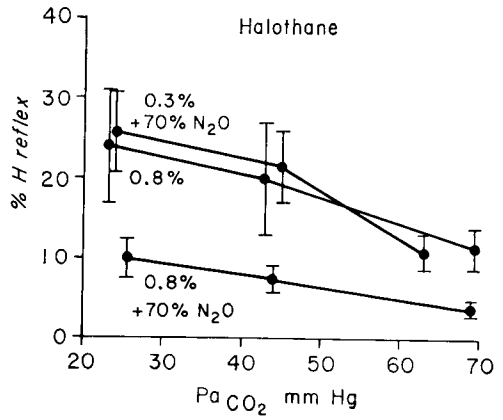

FIG. 3. Effects of changes in arterial carbon dioxide tension on the amplitude of the H-reflex expressed as the percentage of the awake value. Vertical bars represent means ± SD. Data from six subjects ventilated mechanically.

The results obtained at 0.3 per cent halothane with 70 per cent nitrous oxide and at 0.8 per cent halothane in oxygen suggest that 70 per cent nitrous oxide is equivalent in anesthetic potency to 0.5 per cent halothane (tables 1 and 2). If the effect of nitrous oxide were simply additive to that of halothane, adding 70 per cent nitrous oxide to 0.8 per cent halothane should produce the same depression of the H-reflex as 1.3 per cent halothane, but in fact the observed depression was somewhat greater than that observed in response to 1.5 per cent halothane (table 1). However, the difference was not significant and the data are too limited to answer the question whether the interaction between halothane and nitrous oxide becomes more than additive as halothane concentration increases.

Our data show that an increase in the arterial carbon dioxide tension markedly depressed the amplitude of the H-reflex. The question arises whether the additional depression of synaptic transmission caused by carbon dioxide measured a narcotic effect of this gas. Against this interpretation is the observation by Eisele *et al.* that varying the arterial carbon dioxide tension between 15 and 95 mm Hg did not alter the MAC for halothane in dogs.[13] Yet, apart from the species difference, it is possible that the H-reflex and the MAC tests are different measures of central nervous system depression.

It has been well documented that the H-reflex is a monosynaptic response and that its amplitude reflects the excitability of the motoneuron pool.[7, 8, 14] This excitability is modified by complex excitatory and inhibitory influences from higher levels of the central nervous system. As anesthetics reach all areas of the central nervous system, the H-reflex changes effected by anesthesia in all probability represent the integrated spinal and supraspinal effects of the drug. Regardless of the central sites of anesthetic action, the amplitude of the H-reflex corresponds to drug concentration in the end-tidal gas, and by inference in the central nervous system, and thus may provide a clinically useful measure of anesthetic potency.

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TABLE 2. Effects of Various Anesthetic Gas Mixtures on the Amplitude of the H-Reflex*

	0.3 Per Cent Halothane, 70 Per Cent N_2O	0.8 Per Cent Halothane	1.5 Per Cent Halothane	0.8 Per Cent Halothane, 70 Per Cent N_2O	1.5 Per Cent Halothane 70 Per Cent N_2O
H-reflex amplitude	23.5 ± 12.2	26.0 ± 13	11.7 ± 6.3	9.0 ± 3.0	3.1 ± 1.1
Arterial P_{CO_2} (mm Hg)	46.7 ± 2.6	48.2 ± 3.0	53.4 ± 6.3	55.3 ± 10	58.6 ± 6.7
H-reflex amplitude adjusted to arterial P_{CO_2} of 46.7 mm Hg (see text)	23.5	27.3	14.2	11.6	4.25

* Data from six subjects breathing spontaneously. Amplitude of the H-reflex is expressed as a percentage of the awake value. Means ± SD.

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Muscle

MYASTHENIC SYNDROME In a series of 40 patients with the clinical and electromyographic features of the myasthenic syndrome, studied over the past 18 years, 70 per cent had malignant neoplasms at the time of their first examinations or subsequently. The myasthenic syndrome associated with bronchogenic carcinoma is rare. A possible cause for the syndrome was not evident among 12 patients (30 per cent) in whom no tumor was found. In patients with the myasthenic syndrome, resting muscle shows a pronounced depression of the response to a single supramaximal stimulus applied to the motor nerve. At low rates of stimulation there may be a further transient decrease of the response but, with repetitive stimulation at rates above 10 sec, there is a marked increase in the response. These patients differ from patients with myasthenia gravis, in whom there are usually only small depressions of the response of the rested muscle to a single stimulus. During repetitive stimulation, there is usually a decrease in the response at high rates as well as at low rates of stimulation. The electromyographic characteristics of the defect of neuromuscular transmission seen in the myasthenic syndrome suggest that the pathophysiology is different from that seen in myasthenia gravis and similar to that of the neuromuscular blockade produced by magnesium ion, botulinum toxin, and neomycin, all substances known to decrease the number of ACh packages released per nerve impulse. (*Elmqvist, D., and Lambert, E. H.: Detailed Analysis of Neuromuscular Transmission in a Patient with the Myasthenic Syndrome Sometimes Associated with Bronchogenic Carcinoma, Mayo Clin. Proc. 43: 689 (Oct.) 1968.*)