Anesthesiology
1999; 91:1064–71

Quantitative and Qualitative Effects of Isoflurane on Movement Occurring after Noxious Stimulation

Joseph F. Antognini, M.D., Xiao Wei Wang, M.D.,† E. Carstens, Ph.D.‡*

Background: **Anesthetic potency is assessed by determination of the anesthetic concentration that prevents gross, purposeful movement in response to noxious stimulation. It is unclear whether anesthetics cause a progressive decrease in the number and force of limb movements evoked by noxious stimulation, or a step decrease (consistent with an all-or-none effect at the site of action). The authors hypothesized that isoflurane and halothane would progressively depress the movement response.**

Methods: **Isoflurane minimum alveolar concentration (MAC) was determined in rats (N = 14) using a clamp applied to a hind paw. Lateral head movements and flexions of the forelimbs and hindlimbs were measured with force transducers. Isoflurane was adjusted to 0.6, 0.9, 1.1, and 1.4 MAC, the noxious stimulus applied, and the force and number of limb and head movements determined. Force and movement determinations were made in seven additional halothane-anesthetized rats.**

Results: **Isoflurane MAC was 1.3 ± 0.1%. In general, if movement occurred after application of the noxious clamp, the head and all limbs were involved. At 0.6 MAC, the median number of extremity and head movements was 3.5 (10th–90th percentile, 2.0–11.4) with force generated per movement (force/movement) = 6.4 (2.0–13.2) N-s. Movement number decreased to 2.1 (0.25–4.2) at 0.9 MAC ($P < 0.05$), but force/movement was unchanged at 4.5 (0.4-15.1) N-s (Newton-second). At 1.1 MAC, movement number and force/movement decreased to 0.2 (0.0–1.5) and 0.1 (0.0–3.2) N-s, respectively ($P < 0.005$). No significant movement occurred at 1.4 MAC. The halothane-anesthetized rats had similar findings, although at 0.6 MAC they generated more movements (10.5 [5.2–19.8]) than the rats receiving isoflurane ($P < 0.05$).**

Conclusions: **The results indicate that increasing anesthetic concentration from 0.6 to 0.9 MAC had little effect on the motor system controlling the force of limb movements, and the neural system generating repeated limb movements was depressed, consistent with a differential anesthetic effect at separate sites. (Key words: Brain; pain; spinal cord.)**

THE minimum alveolar concentration (MAC) has been used for more than three decades as a standard to measure anesthetic potency.[1] Its utility is based on the presence or absence of movement occurring after application of a supramaximal noxious stimulus. The movement is considered positive if it is gross and purposeful. Thus, minimal movement such as straining, coughing, and sometimes simple withdrawal of the stimulated extremity is arbitrarily defined as absence of movement. Although the general impression is that anesthetics progressively depress movement, this has not been quantitatively determined in prior MAC studies. Whether supramaximal noxious stimulation in lightly anesthetized animals consistently produces flexion of the stimulated extremity and crossed extension of the opposite extremity in an alternating pattern has not been fully elucidated. In part, this is because the noxious stimulus is removed when gross, purposeful movement first appears, thereby making it difficult to fully describe the movement. Because differing motor patterns (flexion withdrawal *vs.* movement of all extremities) use different combinations of neural circuits, a description of how anesthetics alter these patterns would guide further investigation of specific neural circuits. Thus, before we can answer the question "how" anesthetics alter movement, we must first answer the question "what" movement is affected.

In the present study, we investigated anesthetic effects on motor patterns resulting from noxious stimulation. Our initial hypothesis was that isoflurane and halothane would result in a progressive decrease in the number and force of the movements, which would be most consistent with anesthetic action at one site. We now report that isoflurane and halothane at lesser concentrations (0.6–0.9 MAC) first decrease the number of move-

* Associate Professor.

† Visiting Research Scientist, Department of Anesthesiology.

‡ Professor, Section of Neurobiology, Physiology and Behavior.

Received from the University of California, Davis, California. Submitted for publication January 22, 1999. Accepted for publication May 19, 1999. Supported in part by the Foundation for Anesthesia Education and Research, Rochester, Minnesota, with a grant from Abbott Laboratories, Chicago, Illinois, and grant no. R01 57970 from the National Institutes of Health, Bethesda, Maryland. Presented in part at the annual meetings of the Association of University Anesthesiologists, Pittsburgh, Pennsylvania, May 13–16, 1999, and the American Society of Anesthesiologists, Dallas, Texas, October 9–13, 1999.

Address reprint requests to Dr. Antognini: TB-170, University of California–Davis, Davis, California 95616. Address electronic mail to: jfantognini@ucdavis.edu

ments, and at greater concentrations (0.9–1.1 MAC), these anesthetics decrease both movement number and force per movement.

Methods

The study was approved by the local animal care and use committee. Male rats (retired breeders weighing 429 ± 59 g; N = 14) were placed into a plexiglass box and anesthetized with isoflurane 5%. A tracheostomy was performed in each rat and a 14-gauge catheter was placed into the trachea. The rats were mechanically ventilated with a rodent ventilator and the end-tidal CO_2 was adjusted to 29 ± 5 mmHg. An internal jugular vein was cannulated and saline infused at 3 ml/h. Rectal temperature was maintained at 37.5 ± 0.5°C using a heating lamp and heating pad.

Isoflurane MAC was determined before quantitative measurement of the movement patterns. End-tidal isoflurane was measured from the tracheal catheter using a calibrated anesthetic agent analyzer (Datex, Helsinki, Finland; calibrated with Puritan-Bennett gas standard, Lenexa, KS). The end-tidal isoflurane concentration was maintained constant for at least 15 min, and a noxious mechanical stimulus was applied to a hind paw for 10 s using a clamp (Brink and Cotton 1; Warren Tool Group, Inc., Garrettsville, OH).[2] Gross, purposeful movement of the head or limbs was considered positive; straining, coughing, and withdrawal of the stimulated limb were considered negative. Depending on the response, the isoflurane was adjusted up or down 0.2%, equilibrated for 15 min (end-tidal and inspired isoflurane concentrations were within 0.1% of each other), and the clamp was re-applied. This process was continued until two isoflurane concentrations were found that just permitted and just prevented movement. The MAC was the average of these. In 10 rats, MAC was also determined using the tail as the site of stimulation. Because the tail was thicker than the hind paw, this resulted in slightly higher applied force to the tail (1.4 N/mm^2 *vs.* 1.2 N/mm^2).

Quantitative measurement of the movement pattern was determined by attaching the head and limbs of each rat to calibrated force transducers. Sutures were placed through the skin and underlying tissue of the distal portion of each limb, with inclusion of the Achilles tendon in the hind paw. Two sutures were placed through the animal's nose. The other ends of the suture were attached to force transducers (fig. 1). The force transducers were attached to Grass DC amplifiers (Grass Instruments, Braintree, MA), and the output was fed into a personal computer where the data were digitized and stored for off-line analysis using a commercially available program (PolyViewPro, Grass-AstroMed, Inc., Braintree, MA). The rats were placed on a small stage that permitted the limbs and head to lie above the stage, thereby minimizing any frictional forces that might interfere with movement. The force transducers were attached along the axis of the extended limb, thus registering increased force when the limb was flexed and pulled toward the body. The force transducers attached to the nose were positioned orthogonal to the long axis of the body to measure lateral head movements in the horizontal plane.

The isoflurane concentration was adjusted to 0.6, 0.9, 1.1, and 1.4 MAC (order alternated and counterbalanced) using each animal's individual MAC (N = 14 except 1.4 MAC, where N = 12). Each end-tidal anesthetic concentration was maintained for at least 15 min before testing. The clamp was hung from a bar so as not to impede hind-paw movement. The clamp was applied to the hind paw for 10 s, and the force of each head and limb movement, as well as the number of movements, was recorded. In a few cases, the movements occurred or persisted a few seconds after removal of the noxious stimulus; these were included in the analysis. The clamp was applied to the tail for 10 s 1–2 min after the hind-paw application.

An additional seven rats were anesthetized with halothane to determine if there were any anesthetic-specific effects. All procedures were identical to those used in the isoflurane-anesthetized rats, except that, before testing, at least 25 min elapsed when a new end-tidal halothane concentration was achieved. Rectal temperature was maintained at 37.4 ± 0.2°C, and end-tidal CO_2 was 30 ± 4 mmHg.

Statistical Analysis

Weight, temperature, and end-tidal CO_2 data are presented as mean ± SD. Force and movement data are presented as the median and 10th–90th percentile range. The force tracings were integrated to obtain the total generated force (N-s [Newton-second], or impulse). The number of movements, the total force developed for all limbs and the head combined, and the force/movement were log-transformed[3] and compared at each of the anesthetic concentrations using analysis of variance or repeated measures analysis of variance, followed by *post hoc* analysis using the Student–Newman–Keuls test. The values obtained from hind-paw stimulation were compared (analysis of variance) to those obtained from

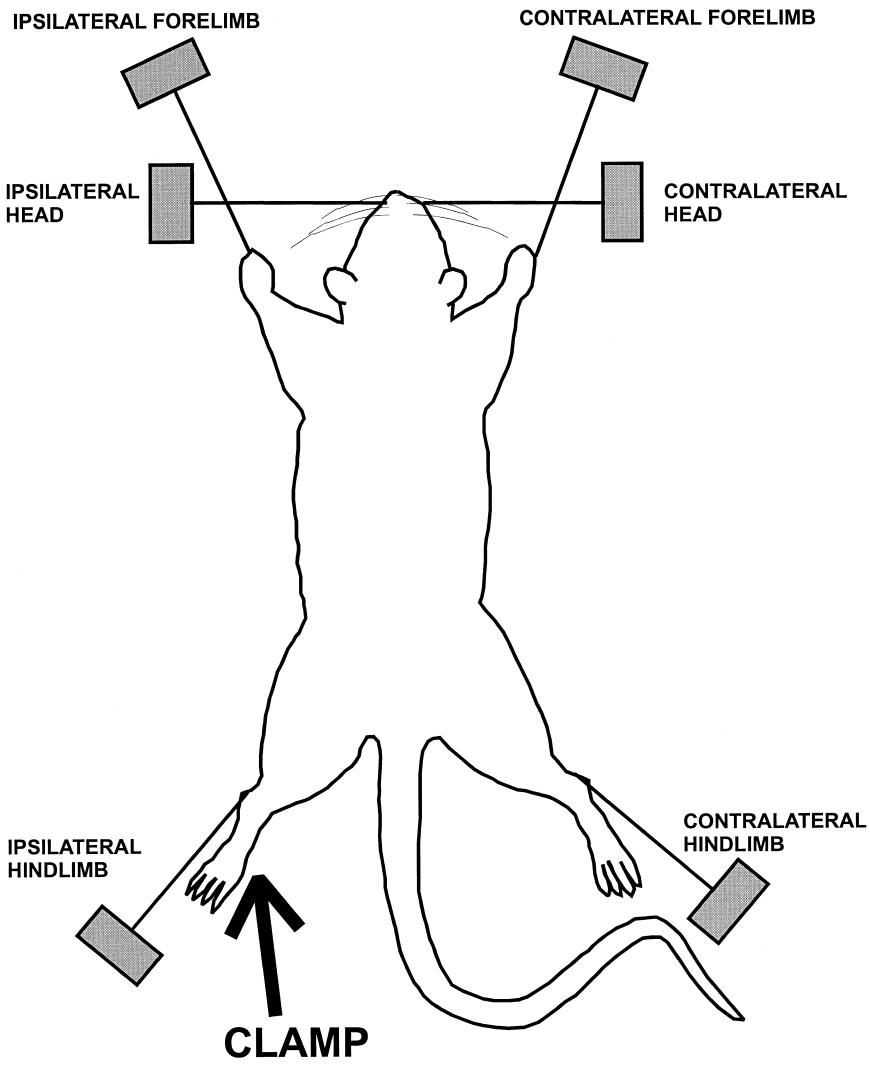

Fig. 1. Each limb was attached to a force transducer (FT) *via* a suture placed through the skin and underlying tissue; in the hind paws, the suture was placed around the Achilles tendon, whereas in the forepaw, it was placed between the ulna and radius or through the overlying connective tissue. Two sutures, placed through the nose and attached to FTs, permitted determination of head movement. When the clamp was applied, the head turned toward the stimulus, resulting in increased force measured by the contralateral head FT.

tail stimulation. A P value < 0.05 was considered significant.

Results

Isoflurane MAC for the clamp applied to the hind paw was 1.3 ± 0.1% (mean ± SD), and was 1.2 ± 0.1% when the clamp was applied to the tail (no significant difference). When the clamp was applied to the hind paw at 0.6 MAC, there was immediate vigorous movement of all limbs and the head that generally persisted until the clamp was withdrawn. The limb movements did not seem to be alternating, but, rather, were in phase with each other and occurred simultaneous with the head movement (fig. 2). In addition, in many cases there was a fast (5–7 Hz) oscillatory movement of the limb, consistent with a shaking motion, that was superimposed on the larger gross flexion movement (fig. 3). Summary data are presented in figure 4 and table 1. When the isoflurane was increased to 0.9 MAC, there was a significant decrease in the total force and number of movements over the 10-s period ($P = 0.0067$), but the force generated per movement was not significantly different from that obtained at 0.6 MAC. At 1.1 MAC, the total force, number of movements, and force/movement decreased substantially ($P < 0.005$). At 1.4 MAC, there was no movement, except for a slight withdrawal of two extremities in one animal. The force/movement did not change when the isoflurane concentration was in-

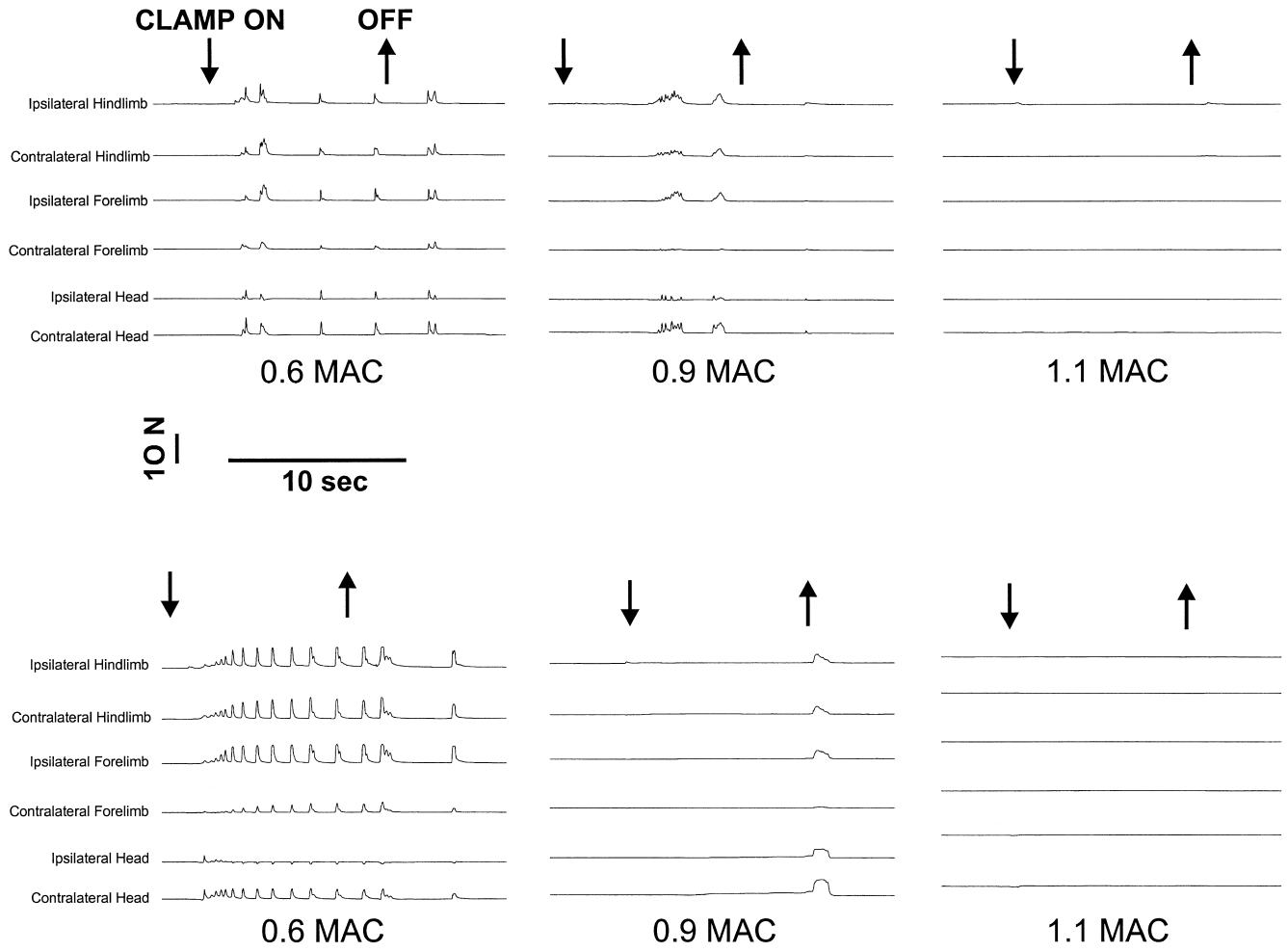

Fig. 2. Raw force tracings from two rats. Note the vigorous movement when the clamp was applied at 0.6 minimum alveolar concentration (MAC) of isoflurane (*down arrow* = clamp on; *up arrow* = clamp off). At 0.9 MAC, the movement number decreased, but the force of those movements was essentially unchanged. The extremity and head movements were synchronous, and there was no evidence of an alternating pattern. The head turned toward the stimulus, as demonstrated by the contralateral head tracing. At 1.1 MAC, no movement occurred. The tracings at 1.4 MAC were essentially the same as those for 1.1 MAC (data not shown).

creased from 0.6 to 0.9 MAC, but it decreased substantially at 1.1 MAC. Thus, the change in the total force from 0.6 to 0.9 MAC was mostly a result of decreased movement number. The forces and movement number for each limb and the head (table 1) generally reflected the overall pattern shown in figure 4. However, there were some important differences among the limbs and the head. Head movement was toward the stimulus: at 0.6 MAC, contralateral and ipsilateral head forces were 3.6 (1.0–11.1) and 1.1 (0.4–2.3) N-s, respectively ($P = 0.0001$); at 0.9 MAC, contralateral and ipsilateral head forces were 3.8 (0.1–6.3) and 0.9 (0–3.5) N-s, respectively ($P = 0.004$). At 0.6 MAC, the ipsilateral forelimb forces were greater than those of the contralateral forelimb: 6.5 (0.7–17.1) N-s and 1.7 (0.4–5.2) N-s, respectively ($P < 0.008$).

When the clamp was applied to the tail, less movement was generated compared with that obtained from clamp application to the hind paw. At 0.6 MAC, total generated force was 15.0 (5.7–26.5) N-s for the tail clamp and 35.0 (13.5–73.3) N-s for the hind-paw clamp ($P = 0.0197$), while movement number was 3.2 (1.8–5.5) and 4.7 (3.0–11.9), respectively ($P = 0.0009$). Force per movement was not different for the tail clamp compared with that for the hind-paw clamp. Total force, number of movements, and force/movement evoked by the tail clamp were affected similarly by increasing isoflurane concentration (data not shown).

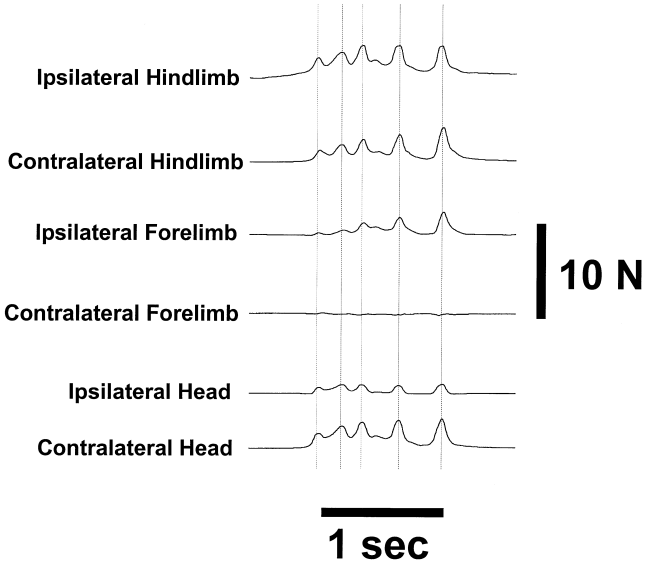

Fig. 3. Expanded raw force tracing from one rat anesthetized with isoflurane. This example shows the fast oscillation superimposed on the limb movement. The oscillations occurring in each limb and the head were synchronous, consistent with a shaking motion.

The halothane MAC was 1.0 ± 0.2%. In general, halothane administration resulted in similar depression of the movement response. When the rats moved, all extremities and the head were usually involved. At 0.6 MAC, the halothane rats, as compared with the isoflurane rats, had nearly twice the number of movements (figs. 4 and 5; $P = 0.0128$). Increasing the halothane concentration from 0.6 to 0.9 MAC decreased the total force generated and the number of movements (fig. 5). Although the force per movement was numerically decreased in the transition from 0.6 to 0.9 MAC, this did not reach statistical significance.

Discussion

Despite the use of MAC as a measure of anesthetic potency for more than three decades,[1] there is little information about the type of movement that occurs with supramaximal stimuli, or how that movement is affected by anesthetics. Our study suggests that at sub-MAC concentrations, isoflurane and halothane primarily decrease the number of movements evoked by a supramaximal noxious stimulus, and have less effect on the force of the movement until the isoflurane concentration approaches or surpasses 1 MAC. Our observation that the force/movement remains stable at sub-MAC concentrations suggests that the motoneuron pool that generates the movement is not depressed. However, as anesthesia was increased from 0.6 to 0.9 MAC, there was a reduction in the number of evoked head and limb movements. This might be explained by a reduction in the afferent drive onto a neural network that controls repetitive limb movements (central pattern generator [CPG]), or a direct depressant action on neurons of the CPG. Regarding the first possibility, anesthesia depresses dorsal horn

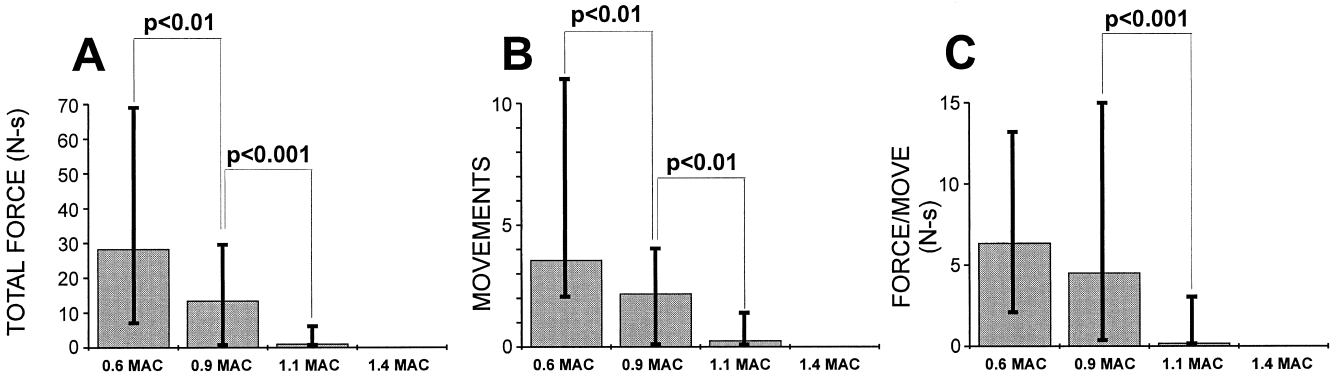

Fig. 4. Total force, movements, and force per movement for isoflurane-anesthetized rats. (*A*) The forces generated by all extremities and the head were summed for each isoflurane minimum alveolar concentration (MAC). (*B*) The movements for all extremities and the head were summed and averaged for each MAC. There was a progressive decrease in the total force and the movements. (*C*) The force per movement was summed for all extremities and the head. There was no significant difference in the force per movement between 0.6 and 0.9 MAC, suggesting that the total force decrement between 0.6 and 0.9 MAC in (*A*) was primarily a result of decreased movements. When data from the stimulated extremity were excluded, the medians and 10th–90th percentile ranges for total force (N-s), movements, and force/movement (N-s) were 20.8 (4.8–46), 3.5 (1.9–11.3), and 4.5 (1.2–11.1), respectively, at 0.6 MAC; 9.0 (0.2–23.2), 2 (0.2–4.2), and 3.3 (0.2–11.2), respectively, at 0.9 MAC; and 0.02 (0–3.5), 0.1 (0–1.4), and 0.02 (0–2.5), respectively, at 1.1 MAC.

Table 1. Isoflurane Concentration, Integrated Force (Newton-seconds), and Movements

	Isoflurane Concentration											
	0.6 MAC						0.9 MAC					
	Head		Forelimb		Hind Limb		Head		Forelimb		Hind Limb	
	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi
Total force	3.6 1.0–11.1	1.1 0.4–2.3	1.7† 0.4–5.2	6.5‡ 0.7–17.1	5.5‡ 0.8–12.6	6.4‡ 2.7–22.6	3.8# 0.1–6.3	0.9‖ 0–3.5	0.6§ 0–1.9	0.8‖ 0–5.7	1.7‖ 0.1–5.0	1.6‖ 0.2–8.7
Movement number	3.5† 2–11.7	3.5‡ 2.0–10.4	3.5† 1.3–11.7	3.5† 2.0–11.7	3.5† 2.0–11.7	3.5‡ 2.3–11.7	2.5# 0.3–3.7	1.0‖ 0–3.7	1.5§ 0.3–4.4	1.5# 0.3–5.1	2.0‖ 0.3–4.0	2.5‖ 0.3–4.0
Force per movement	0.8 0.4–1.4	0.5 0.1–1.6	0.8 0.2–4.8	0.8* 0.2–4.8	1.2 0.3–3.5	1.5 0.8–3.2	1.0# 0.1–3.6	0.3‖ 0–1.5	0.4§ 0–0.9	0.3‖ 0–2.3	1.0‖ 0–2.4	1.2‖ 0.1–2.1
	1.1 MAC						1.4 MAC					
	Head		Forelimb		Hind Limb		Head		Forelimb		Hind Limb	
	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi
Total force	0‡‡ 0–0.9	0‡‡ 0–0.1	0‡‡ 0–0.8	0‡‡ 0–0.5	0‡‡ 0–1.0	0.1‡‡ 0–1.8	0 0–0	0 0–0	0 0–0	0 0–0	0 0–0	0 0–0
Movement number	0‡‡ 0–1.0	0‡‡ 0–1.0	0‡‡ 0–2.0	0‡‡ 0–1.7	0.5‡‡ 0–1.7	0.5‡‡ 0–1.7	0 0–0	0 0–0	0 0–0	0 0–0	0 0–0	0 0–0
Force per movement	0†† 0–0.8	0 0–0.1	0†† 0–0.5	0‡‡ 0–0.2	0‡‡ 0–0.6	0.1‡‡ 0.1–0.5	0 0–0	0 0–0	0 0–0	0 0–0	0 0–0	0 0–0

Data expressed as median and the 10th–90th percentile range.

MAC = minimum alveolar concentration; Contra = contralateral; Ipsi = ipsilateral.

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ for 0.6 *vs.* 0.9 MAC.

§ $P < 0.05$, ‖ $P < 0.01$, # $P < 0.001$ for 0.9 *vs.* 1.1 MAC.

†† $P < 0.01$, ‡‡ $P < 0.001$ for 0.6 *vs.* 1.1 MAC. One animal had very slight movement of two extremities at 1.4 MAC.

cell responses to cutaneous stimuli[4], and at concentrations between 0.6 and 0.9 MAC, there might be a significant depression of the dorsal horn cells that triggers the CPG controlling the limb movements so that overall fewer movements occur. We recently observed that isoflurane at concentrations between 0.9 and 1.1 MAC causes minimal depression of dorsal horn activity, but we did not examine the 0.6–0.9-MAC range.[5] Another possibility is that the movement is generated as part of a complex, nocifensive reflex that depends on CPGs that initiate many of the complex movements that are needed for the animal to perform normal functions, including walking, grooming, and running.[6,7] Specific brain and spinal cord sites are thought to interact with these CPGs, including the ventrolateral spinal cord and the mesencephalic locomotor region.[6,7] These receive afferent input from the spinal cord and brain and serve to initiate or terminate the complex movements. There is limited information regarding the effect of anesthesia on CPGs. Yamamura *et al.* found that ketamine depressed fictive locomotion in the lamprey.[8]

At the transition from 0.9 to 1.1 MAC, movement decreased substantially, both in force per movement and number of movements. These data suggest that not only is the number of input signals (or the intrinsic activity of the CPG) decreased, but also the output from the motoneuron pool. The decreased force per movement is consistent with decreased motoneuron excitability, which can be measured indirectly using F-wave analysis.[9] Recent work by several investigators indicates that anesthetics depress the F-wave, suggesting an effect on motoneuron excitability.[9,10] In isoflurane-anesthetized rats, King and Rampil found that the ratio of the F-wave to the M-wave decreased 50% with the transition from 0.8 to 1.2 MAC, but no depression occurred when the isoflurane concentration was increased from 0.5 to 0.8 MAC.[9] Thus, motoneuron excitability did not seem to

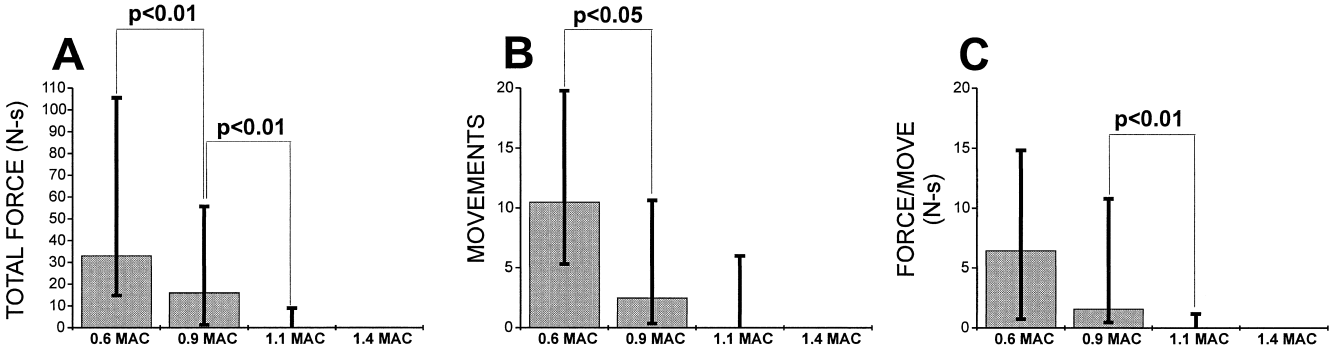

Fig. 5. Total force, movements, and force per movement for halothane-anesthetized rats. (*A*) The forces generated by all extremities and the head were summed for each halothane minimum alveolar concentration (MAC). (*B*) The movements for all extremities and the head were summed and averaged for each MAC. Movements decreased substantially between 0.6 and 0.9 MAC. (*C*) The force per movement was summed for all extremities and the head. The numerical difference in the force per movement between 0.6 and 0.9 MAC was not significant. When data from the stimulated extremity were excluded, the medians and 10th–90th percentile ranges for total force (N-s), movements, and force/movement (N-s) were 22.8 (9.1–76.1), 10.6 (5.2–19.7), and 5.5 (0.5–9.5), respectively, at 0.6 MAC; 9.4 (0.2–35.6), 2.6 (0.5–10.4), and 1.0 (0.1–7.2), respectively, at 0.9 MAC; and 0 (0–7), 0 (0–5.4), and 0 (0–1.5), respectively, at 1.1 MAC.

change at the lesser concentrations, consistent with the present results. It is possible that isoflurane might depress movement by two mechanisms: at sub-MAC concentrations, the motoneuron pool involved in the response is triggered less often, whereas at the transition from 0.9 to 1.1 MAC, there is less total output, perhaps because of diminished excitability. Anesthetics hyperpolarize motoneurons and also decrease membrane excitability.[11,12] Further study is required to investigate these possible scenarios.

In the present study we observed complex reflexes. How are these reflexes organized? Nociceptive afferents from the hind paw or tail terminate in superficial layers of the dorsal horn at lumbosacral and sacral-coccygeal segmental levels, respectively, with motoneurons controlling limb or tail movements being located in the ventral horn. Interneuronal pathways connecting dorsal horn neurons to motoneurons have not been well described. A "modular" organization of nociceptive withdrawal reflexes has been proposed for individual hindlimb muscles, with each muscle possessing a defined cutaneous receptive field within which noxious stimuli elicit contraction of the muscle.[13,14] Deep dorsal horn neurons with similar "musculotopic" receptive field organization were suggested to serve as last-order interneurons in the reflex pathway.[15] The pathway connecting somatotopically organized nociceptive afferents in the superficial dorsal horn with these putative interneurons has not yet been described, primarily because of methodologic limitations in identifying functional multisynaptic connections.[16]

Animals exhibit escape reactions ("fight or flight") when subjected to extremely stressful or harmful stimuli. Thus, we expected that the rats would have had alternating movements of their extremities, consistent with attempts to "run away" from the noxious stimulus. However, multiple synchronous limb movements occurred, possibly reflecting an effort by the rat to escape the noxious stimulus in the form of a bilateral forward propulsion (jump or gallop).[6] The observed motor behavior is also consistent with the startle reflex, which occurs with a particularly strong stimulus.[17] The rats also turned their heads toward the stimulus, an action that is dependent on neck muscles innervated by the spinal accessory nerve and upper cervical nerves.[18] Head turning can occur in brain-dead humans, especially in response to noxious stimulation.[19] Thus, it is entirely possible that the head turning we observed was spinally mediated. This is consistent with the recent finding that isoflurane acts in the spinal cord to depress movement that results from noxious stimulation.[20–22]

It is interesting to note that noxious stimulation of the tail resulted in less movement than that occurring after hind-paw stimulation. One explanation is that the tail is less sensitive to noxious stimuli as compared with the hind paw. However, this is unlikely on two counts: both tail flick and hindlimb withdrawals elicited by noxious heat occur at the same threshold temperature,[23,24] and the force applied by the clamp in the present experiment was, in fact, greater at the tail than at the paw, thereby minimizing any sensitivity differences. Alternatively, the reflexes generated by tail stimulation, compared with those arising from paw stimulation, might be slightly more sensitive to isoflurane, such that the

amount of movement is diminished, but the MAC is unchanged. One limitation of our data is the short 1–2-min period between paw and tail clamping. The paw clamping might have altered motoneuron excitability, thereby affecting the tail clamp data. The 10-s period used in the present study is similar to that used for noxious heat stimulation but is much less than that used for most MAC studies.[25] Nonetheless, using the noxious mechanical stimulus for 10 s on the hind paw, we obtained MAC values similar to those determined by other investigators,[20,26] and thus our stimulus was likely supramaximal. We do not know if and how the movement would have changed had we applied the noxious stimulus for a longer period. Finally, it is unclear how these data can be extrapolated to humans, who might not generate similar movement patterns in response to noxious stimulation.

By definition, when using each animal's individual MAC value, there should have been no movement at 1.1 MAC, yet some animals had gross, purposeful movement. This is because we first determined MAC and then used that value when determining the movement and forces. Because MAC varies slightly over time,[1] in a few rats, movement did not occur at 0.9 MAC, whereas others moved at 1.1 MAC.

Isoflurane and halothane seem to have two effects on the movement that occurs after noxious stimulation. At the transition from 0.6 to 0.9 MAC, these anesthetics substantially decrease the number of times the animal moves, but the force of those movements is affected less. During the transition from 0.9 to 1.1 MAC, both the number of movements and the force are depressed.

References

1. Eger EI II, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: A standard of anesthetic potency. ANESTHESIOLOGY 1965; 26:756–63

2. Antognini JF, Carstens E: A simple, quantifiable, and accurate method for applying a noxious mechanical stimulus. Anesth Analg 1998; 87:1446–9

3. Zar JH: Biostatistical Analysis, 4th Edition. Upper Saddle River, NJ, Prentice Hall, 1999, pp 273–81

4. de Jong RH, Wagman IH: Block of afferent impulses in the dorsal horn of monkey: A possible mechanism of anesthesia. Exp Neurol 1968; 20:352–58

5. Antognini JF, Carstens E: Increasing isoflurane from 0.9 to 1.1 minimum alveolar concentration minimally affects dorsal horn cell responses to noxious stimulation. ANESTHESIOLOGY 1999; 90:208–14

6. Gordon J: Spinal mechanisms of motor coordination, Principles of Neural Science, 3rd Edition. Edited by Kandel ER, Schwartz JH, Jessell TM. Norwalk, CT, Appleton and Lange, 1991, pp 581–95

7. Cazalets JR, Borde M, Clarac F: Localization and organization of the central pattern generator for hindlimb locomotion in newborn rat. J Neurosci 1995; 15:4943–51

8. Yamamura T, Harada K, Okamura A, Kemmotsu O: Is the site of action of ketamine anesthesia the N-methyl-D-aspartate receptor? ANESTHESIOLOGY 1990; 72:704–10

9. King BS, Rampil IJ: Anesthetic depression of spinal motor neurons may contribute to lack of movement in response to noxious stimuli. ANESTHESIOLOGY 1994; 81:1484–92

10. Zhou HH, Jin TT, Qin B, Turndorf H: Suppression of spinal cord motoneuron excitability correlates with surgical immobility during isoflurane anesthesia. ANESTHESIOLOGY 1998; 88:955–61

11. Nicoll RA, Madison DV: General anesthetics hyperpolarize neurons in the vertebrate central nervous system. Science 1982; 217: 1055–57

12. Sirois JE, Pancrazio JJ, Lynch C III, Bayliss DA: Multiple ionic mechanisms mediate inhibition of rat motoneurons by inhalation anaesthetics. J Physiol 1998; 512:851–62

13. Schouenborg J, Kalliomäki J: Functional organization of the nociceptive withdrawal reflexes: I. Activation of hindlimb muscles in the rat. Exp Brain Res 1990; 83:67–78

14. Schouenborg J, Weng H-R, Holmberg H: Modular organization of spinal nociceptive reflexes: A new hypothesis. News Physiol Sci 1994; 9:261–65

15. Schouenborg J, Weng H-R, Kalliomäki J, Holmberg H: A survery of spinal dorsal horn neurones encoding the spatial organization of withdrawal reflexes in the rat. Exp Brain Res 1995; 106:19–27

16. Jasmin L, Carstens E, Basbaum AI: Interneurons presynaptic to rat tail flick motoneurons as mapped by transneuronal transport of pseudorabies virus: Few have long ascending collaterals. Neuroscience 1997; 76:859–76

17. Davis M: The mammalian startle response, Neural Mechanisms of Startle Behavior. Edited by Eaton RC. New York, Plenum Press, 1984, pp 287–351

18. Chiasson RB: Laboratory Anatomy of the White Rat. Dubuque, IA Brown Publishers, 1988, pp 96

19. Christie JM, O'Lenic TD, Cane RD: Head turning in brain death. J Clin Anesth 1996; 8:141–3

20. Rampil IJ, Mason P, Singh H: Anesthetic potency (MAC) is independent of forebrain structures in the rat. ANESTHESIOLOGY 1993; 78:707–12

21. Antognini JF, Schwartz K: Exaggerated anesthetic requirements in the preferentially anesthetized brain. ANESTHESIOLOGY 1993; 79:1244–49

22. Rampil IJ: Anesthetic potency is not altered after hypothermic spinal cord transection in rats. ANESTHESIOLOGY 1994; 80:606–10

23. Carstens E, Wilson CG: Rat tail flick reflex: Magnitude measurement of stimulus-response function, suppression by morphine, and habituation. J Neurophysiol 1993; 70:630–39

24. Carstens E, Ansley D: Hindlimb flexion withdrawal evoked by noxious heat in conscious rats: magnitude measurement of stimulus-response function, suppression by morphine, and habituation. J Neurophysiol 1993; 70:621–29

25. Quasha AL, Eger EI, Tinker JH: Determination and applications of MAC. ANESTHESIOLOGY 1980; 53:315–34

26. Todd MM, Weeks JB, Warner DS: A focal cryogenic brain lesion does not reduce the minimum alveolar concentration for halothane in rats. ANESTHESIOLOGY 1993; 79:139–43