Does the Immobilizing Effect of Thiopental in Brain Exceed That of Halothane?

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Background: Recent studies suggest that anesthetics such as isoflurane act in the spinal cord to suppress movement that occurs during noxious stimulation. The authors examined the effect of halothane and thiopental on suppression of noxious-evoked movement using a model of differential anesthetic delivery. They hypothesized that halothane and thiopental, similar to isoflurane, would suppress movement primarily *via* an action in spinal cord.

Methods: Goats were anesthetized and prepared for differential anesthetic delivery. Anesthesia was maintained with halothane (n = 5) or thiopental (n = 5). Anesthetic requirements were determined (noxious clamp on a dewclaw for 1 min) during halothane or thiopental (*via* infusion) delivery to the whole body and delivery only to the head.

Results: Control (whole body) halothane requirement was 0.9 ± 0.2%; halothane requirement in the head during differential delivery was 3.4 ± 1% (*P* < 0.01). During selective halothane delivery, the electroencephalogram was greatly depressed or was isoelectric even though the animals moved during noxious stimulation. Control (whole body) plasma thiopental requirement was 20 ± 10 µg/ml. When thiopental was selectively delivered to the head, the electroencephalogram was active in all five animals, and cranial thiopental requirement was 42 ± 6 µg/ml (*P* < 0.01).

Conclusion: These data suggest that halothane and thiopental, like isoflurane, act in spinal cord to suppress movement occurring with noxious stimulation. However, halothane appears to be less potent in the brain as evidenced by the electroencephalogram data, suggesting that action in spinal cord plays a more significant role for halothane than for thiopental.

THE spinal cord has emerged as an important site of anesthetic action. One of the end points of anesthesia is immobility in response to noxious stimulation. We previously showed that this end point likely occurs as the result of action within the spinal cord.[1] In other studies, Rampil *et al.*[2,3] demonstrated that anesthetic action in the brain was not required to prevent movement arising from noxious stimulation. Isoflurane was the anesthetic in these studies.[1–3] Although it has been tacitly assumed that most, if not all, anesthetics act in a similar way, this

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has not been rigorously tested. Furthermore, additional information in the past decade has revealed that various anesthetics appear to act differently at different receptors.[4] Such differences could lead to varied clinical effects among anesthetics, including sites of action for specific end points such as immobility. Thus, it remains unclear if previously published isoflurane data[1–3] can be extrapolated to other anesthetics. We tested the hypothesis that other anesthetics would have similar effects in spinal cord to suppress movement. We examined halothane, another volatile anesthetic, and thiopental, an intravenous anesthetic with receptor actions that differ from those of isoflurane and halothane.[4]

Methods

The animal care committee at the University of California–Davis approved the study. Ten female goats were anesthetized with halothane (n = 5) or isoflurane (n = 5) by mask. The tracheas were intubated and mechanical ventilation initiated. A peripheral intravenous catheter was placed for fluid and drug administration. Bilateral neck dissections were performed to permit differential anesthetic delivery as previously described.[1,5,6] In brief, the carotid arteries and jugular veins were isolated, and the occipital arteries were ligated. This ensured that systemic arterial blood could not travel through the vertebral arterial system, across the occipital arteries, and into the carotid system. The basilar artery in goats is small and normally does not transmit systemic blood into the cranial circulation.[7] This prevents systemic blood from reaching cerebral and brainstem structures above the level of the upper cervical cord and caudal medulla during differential anesthetic delivery.[6] Neck tissues (muscle, skin, *etc.*) were ligated to minimize cranial venous blood from crossing over to the systemic circulation, and *vice versa*.[5] To permit bypass, a large cannula was placed into a carotid artery (directed toward the head), and Y cannulae were placed in the jugular veins. A small catheter placed in the carotid artery and directed toward the heart was used to measure systemic blood pressure and for blood chemistry and gas analysis (table 1). In the other carotid artery, a small catheter was placed and directed toward the head to permit measurement of cranial blood pressure during bypass. The bypass unit (Bentley B-10 Plus bubble oxygenator; Baxter, Irvine, CA; roller pump; Sarns, Ann Arbor, MI) was primed with blood (≈ 500 ml). Temperature was measured from the rectum and nasopharynx (table 2). The bifrontal electroencephalogram was monitored with a

Table 1. Hematocrit, Glucose, and Blood Gas Values

	Control-Body Arterial	Bypass-Torso Arterial	Bypass-Oxygenator-Arterial
Hct	25 ± 5	23 ± 4	24 ± 4
Glucose (mg/dL)	121 ± 46	154 ± 58	141 ± 40
pH	7.36 ± 0.11	7.33 ± 0.07	7.36 ± 0.04
P_{O_2} (mmHg)	344 ± 182	303 ± 108	469 ± 69
P_{CO_2} (mmHg)	36 ± 12	37 ± 7	33 ± 5
BE (mEq/l)	−4 ± 4	−5 ± 4	−5 ± 3

The control values consist of data obtained pre- and postbypass. The bypass-torso values were obtained from the torso (systemic) circulation during bypass and the bypass-oxygenator values were obtained from the arterial limb of the bypass unit.

Mean ± SD.

Hct = hematocrit; P_{O_2} = partial pressure of oxygen; P_{CO_2} = partial pressure of carbon dioxide; BE = base excess.

Grass 8–10 electroencephalogram machine (AstroMed, West Warwick, RI). Electroencephalogram signals were amplified (Grass Model 8A5; AstroMed) and filtered (0.3–35 Hz). The raw electroencephalogram was digitized (250 samples/s) and downloaded to a computer in two halothane-anesthetized animals and all five thiopental-anesthetized animals.

The minimum alveolar concentration (MAC) was determined in the halothane-anesthetized animals. End-tidal halothane was measured with a calibrated Ohmeda Rascal II® agent analyzer (Ohmeda, Salt Lake City, UT). We chose this analyzer because, when using infrared techniques for measurement of halothane in animals that produce methane, falsely high halothane concentrations can be produced.[8] Based on our preliminary studies using the Rascal II® analyzer (Raman spectroscopy), we determined that methane did not interfere with Raman spectroscopic measurement of halothane. End-tidal halothane was adjusted to approximately 0.9% and maintained for 15–20 min, and a clamp was applied to a dewclaw on a hind limb and oscillated (≈ 1 Hz) for 1 min. We sought gross, purposeful movement, which usually consisted of pawing motions of the extremities or turning of the head toward the stimulus. Coughing, straining, stiffening, and simple withdrawal of the stimulated extremity were considered negative. If the animal showed purposeful movement, then the end-tidal halothane was increased 0.2%, whereas it was decreased if the animal did not move. The new halothane concentration was maintained for at least 15–20 min, and the stimulus was applied again. This process was continued until two halothane concentrations were found that permitted and prevented movement. Halothane MAC was the average of these two bracketing concentrations.

After control MAC determination, bypass was initiated by diverting cranial venous blood into the oxygenator and reinfusing it into the cranial circulation *via*

the carotid artery cannula. Bypass flows were 600–700 ml/min. Gas flow to the oxygenator was oxygen (95%) and carbon dioxide (5%). A halothane vaporizer was placed in line with the gas flow. Exhaust from the oxygenator was sampled (calibrated Datex Capnomac Ultima® agent analyzer; Datex, Helsinki, Finland) for halothane concentration in the arterial blood perfusing the brain.[1,5,6] Glucose was infused (10–20 mg/min) into the oxygenator to maintain adequate glucose concentrations in the oxygenator. To achieve complete bypass, the remaining carotid artery was temporarily ligated. Halothane delivery to the torso was discontinued. Once bypass had stabilized (venous return equaled pump flow) and the end-tidal (torso) halothane was 0.3% or less (average, 0.1–0.2%), cranial halothane requirements to suppress movement were measured. The dewclaw clamp was applied as before for 1 min. Depending on the response, the halothane concentration to the head was increased or decreased, the concentration stabilized for 20 min, and the clamp was applied again. Based on our previous experience with isoflurane,[1] larger incremental changes in halothane were made, as compared with the 0.2% changes made before bypass. This process continued until two halothane concentrations were found that just permitted and prevented movement. Cranial halothane requirement was the average of these. Halothane delivery to the torso was initiated, bypass was terminated, the carotid artery ligature was removed, and cranial venous blood was diverted to the systemic circulation, thereby reestablishing native circulation. Halothane MAC was determined after bypass at the conclusion of the experiment.

In the animals anesthetized with isoflurane, once the surgical procedures were completed, thiopental (*via* intravenous infusion) was used to maintain anesthesia, and the isoflurane was discontinued. In the first animal, we determined total (whole body) thiopental requirements first before we determined cranial thiopental requirements during bypass. However, this resulted in significant residual thiopental concentrations (8 μg/ml) in the torso circulation during bypass despite waiting more than 2 h for thiopental concentrations to decrease. Therefore, in the remaining four animals, cranial thiopental requirements were determined first, followed by

Table 2. Temperature and Blood Pressure Values

	Control	Bypass-Torso	Bypass-Cranial
Temperature (°C)	38.2 ± 0.9	38.9 ± 1.1	38.7 ± 0.8
Blood pressure (mmHg)	115 ± 22	103 ± 32	71 ± 24

The torso temperature was measured from the rectum and the cranial temperature was measured from the nasopharynx.

Mean ± SD.

determination of control (whole body) thiopental requirements.

Thiopental was infused into the venous port of the bypass unit. Once bypass was stable and torso isoflurane was 0.2% or less, the noxious clamp was applied (1 min) to a dewclaw to elicit gross, purposeful movement. Depending on the response, the thiopental infusion was decreased or increased after a small bolus dose had been given (10–25 mg). After a 10–15-min stabilization period, the clamp was applied again. This process was continued until a positive and negative response was observed on trials at two different infusion rates. Five minutes before and at each pinch, blood samples were withdrawn from the cranial arterial blood port and the systemic arterial blood for later analysis of thiopental concentration. Bypass was terminated, the native circulation was reestablished, and control thiopental requirements were determined by infusing thiopental into the systemic circulation. The thiopental infusion was adjusted until a positive and negative response was observed on trials at two different infusion rates. Blood samples were obtained 5 min before and at the time of clamp application.

Thiopental was analyzed by high-pressure liquid chromatography using a method modified from Crankshaw *et al.*[9] In brief, after blood withdrawal, the samples were placed immediately on ice. Plasma and cells were separated by centrifugation, and the plasma was stored ($-70°C$) until analysis. Thiopental was extracted from plasma using a solid-phase extraction column and injected onto a Waters (Milford, MA) high-pressure liquid chromatography column. Standard curves were created (range, 0–100 μg/ml; correlation coefficients, 0.99–1.0) by injecting known quantities of thiopental in goat plasma and extracting the thiopental, as was performed for the samples. The lower limit of detection was 100 ng/ml. Regression analysis of the standard curves was used to determine actual thiopental concentrations of experimental samples.

Statistical Analysis

All data are presented as mean and SD. Prehalothane and posthalothane MAC and cranial halothane requirements were compared using repeated-measures analysis of variance. Control and cranial thiopental requirements were compared using a paired *t* test.

Results

In the halothane group, control (whole body) halothane MAC was 0.9 ± 0.2% (fig. 1). During bypass, halothane requirements increased significantly to 3.4 ± 1.0% ($P < 0.01$ compared with control). In fact, in two animals, we were unable to prevent movement using the highest available setting on the vaporizer, and despite
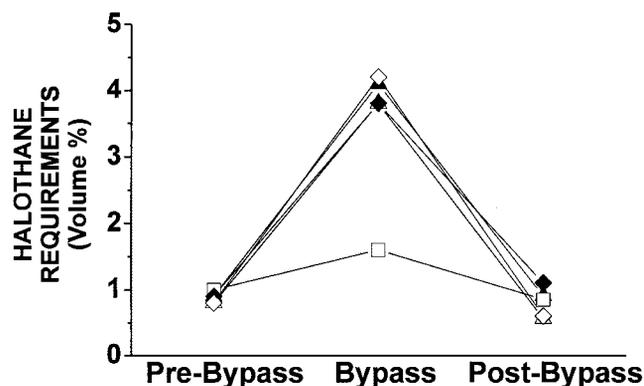
Fig. 1. Individual halothane requirements in five animals before, during, and after differential halothane delivery to the cranial circulation. In two animals, movement could not be prevented at the highest achieved cranial halothane concentration (4.0–4.2%).

achieving cranial halothane concentrations of 4–4.2%. To include the data from these two animals, we conservatively assumed that halothane requirements were the highest achieved concentration + 0.1%. Halothane requirements were 1.6% in one animal; however, at the halothane concentration at which it did not have gross, purposeful movement, vigorous reflex withdrawal occurred. Had this been counted as positive, its halothane requirement would have been 2.6%. This animal's electroencephalogram, although depressed (high amplitude, low frequency), was not isoelectric. Postbypass halothane MAC was 0.8 ± 0.2%. In all five animals, the electroencephalogram was either greatly depressed or was isoelectric, despite the fact that the animals moved with noxious stimulation.

In the thiopental group, in general, the thiopental concentrations in blood samples withdrawn at the pinch were higher than those withdrawn 5 min before the pinch. Therefore, the 5-min prepinch values and the pinch values were averaged to obtain an estimate of the effect-site concentration. Individual thiopental concentrations at each time point when each animal moved and did not move are shown in figure 2. Control thiopental requirements were 20 ± 10 μg/ml. During bypass and differential thiopental delivery, cranial thiopental requirements were 42 ± 6 μg/ml ($P < 0.01$ compared with control). In all five animals, the electroencephalogram remained active during bypass, even when movement was prevented. The average torso concentration of thiopental during differential thiopental delivery to the cranial circulation was 3 ± 3 μg/ml, and most of this was a result of the one animal in which control thiopental requirements were determined before cranial thiopental requirements. Figure 3 shows individual electroencephalogram examples during control (whole body) and differential anesthetic delivery in two halothane-anesthetized and two thiopental-anesthetized animals, demon-

Fig. 2. Individual thiopental requirements in five animals. Control (whole body) requirements indicate thiopental delivery to entire body, whereas cranial (bypass) requirements indicate delivery to the head only. The thick lines represent values when the animals moved, and the dashed lines represent values when the animals did not move. Shown are values in individual animals obtained 5 min before and at the time of clamp application to a dewclaw. There are 10 sets each (control and cranial delivery) representing the values that permitted and prevented movement in the five animals. In any individual animal, the thiopental concentration that suppressed movement was always greater than the concentration that permitted movement, and the cranial requirements always exceeded control requirements. Note that, in general, thiopental concentrations increased in the 5 min between sample withdrawals.
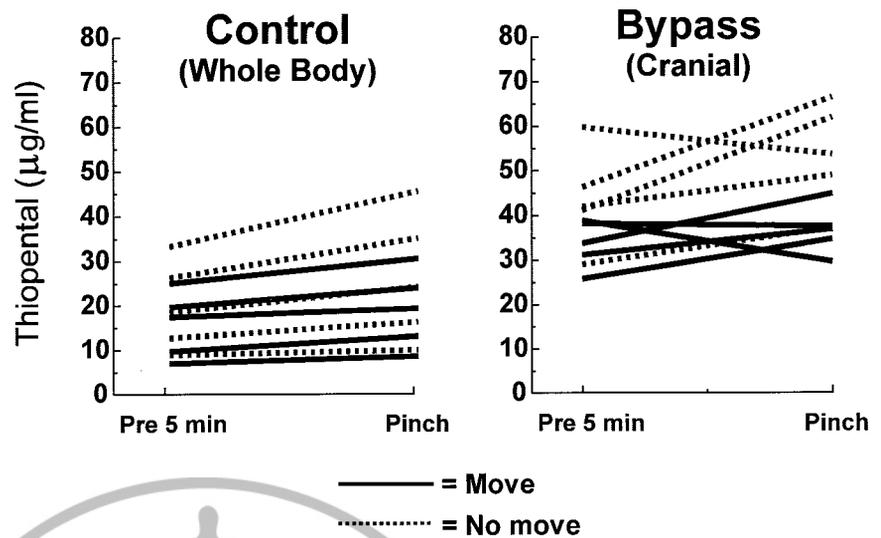
strating that, during cranial delivery, halothane greatly depressed the electroencephalogram, whereas thiopental did not, despite the latter preventing movement. Figure 4 shows individual electroencephalogram examples in three thiopental-anesthetized animals and demonstrates that the electroencephalogram remained active even when the animal did not move to noxious stimulation. During differential thiopental delivery to the head, the electroencephalograms, in general, had a lower frequency, higher amplitude pattern as compared with the electroencephalograms during whole-body thiopental delivery and was likely a result of the higher thiopental concentrations achieved during bypass. However, there was no appreciable difference between the electroencephalograms obtained during movement and those obtained during nonmovement (figs. 3 and 4).

Discussion

The measurement of MAC entails production and prevention of gross, purposeful movement in response to supramaximal noxious stimulation.[10] Our previous isoflurane study[1] and the halothane data in the current study indicate that these volatile anesthetics act largely in the spinal cord to prevent movement. Moreover, the present data suggest that not all anesthetics behave similarly. Cranial thiopental prevented movement at concentrations that still permitted an active electroencephalogram. This suggests that thiopental had a more potent effect at supraspinal sites to prevent movement compared with halothane. In contrast, the animals often moved even when the concentration of halothane delivered to the cranial circulation was sufficient to produce electrical silence in the cortical electroencephalogram. We previously reported that isoflurane significantly depressed the electroencephalogram even though movement occurred.[1] These electroencephalogram data indi-

cate that cortical depression *per se* does not contribute substantially to movement suppression.

Our thiopental data are consistent with recently published data supporting a supraspinal site of action. Gupta *et al.*[11] determined that thiopental had little effect on the F wave, which is a measure of motoneuron excitability.[11-13] Because the motoneuron is a potential site of anesthetic action, and other anesthetics, including isoflurane and halothane, depress the F wave,[12,13] it is tempting to conclude that thiopental might depress movement at supraspinal structures. Stabernack *et al.*[14] determined that intrathecal thiopental had only minor depressive effects on isoflurane MAC. These investigators suggested that thiopental probably depressed movement *via* a supraspinal action.[14] The current study suggests that thiopental has a dual effect, in that actions in both spinal cord and brain appear to contribute to movement suppression. Consistent with the action in spinal cord, we recently reported that thiopental has a direct and short-lasting depressant effect on dorsal horn neuronal responses to noxious stimulation.[15] In the latter study, however, cranial administration of thiopental had no consistent effect on nociceptive dorsal horn neurons. Conceivably, the supraspinal action of thiopental involves a descending inhibition of movement-related spinal interneuronal circuits that are interposed between the dorsal horn and motoneurons. That cranial thiopental prevented movement in the presence of an active electroencephalogram suggests that it might act preferentially at a subcortical site.

What could account for the discrepant findings between some volatile anesthetics (*e.g.*, isoflurane and halothane) and thiopental? The past decade has seen a tremendous increase in knowledge regarding anesthetic effects on receptor physiology and pharmacology.[4] It is now possible to make reasonable conclusions regarding anesthetic effects on a wide variety of receptors. Volatile
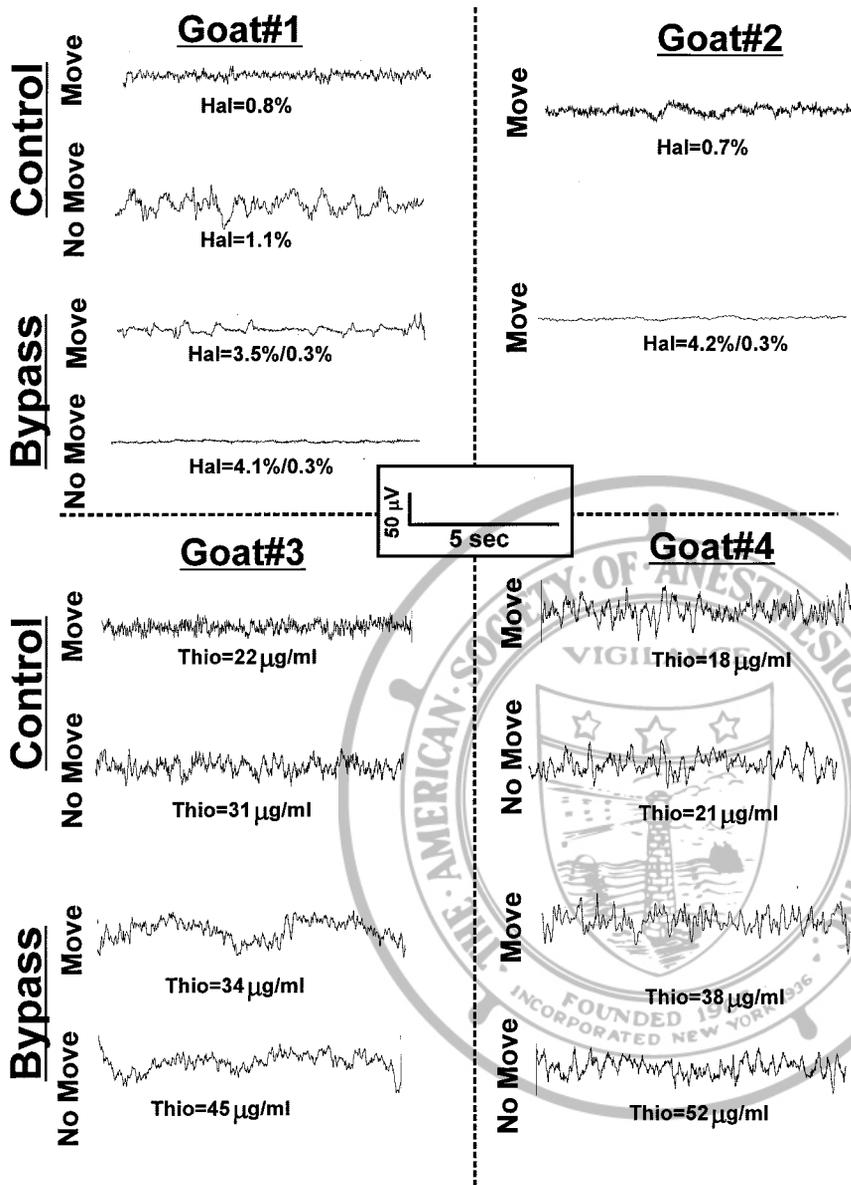
Fig. 3. Examples of electroencephalograms from two animals anesthetized with halothane and two animals anesthetized with thiopental (during movement and no movement). Control = whole-body thiopental or halothane delivery. Bypass = differential delivery of halothane or thiopental to the head. Note that the animals anesthetized with halothane had active electroencephalograms before bypass but that with differential halothane delivery to the head (low halothane concentration in torso), the electroencephalogram was significantly depressed even though the animals moved. The thiopental-anesthetized animals (see fig. 4 also) had active electroencephalograms, during both whole-body and differential cranial delivery. During differential thiopental delivery to the head, the electroencephalograms, in general, had a lower frequency, higher amplitude pattern as compared with the electroencephalograms during whole-body delivery, although the electroencephalograms obtained at movement and at no movement did not differ significantly. The halothane and thiopental concentrations are shown for each electroencephalogram, including the head–torso halothane concentrations during differential halothane delivery. Note that in goat No. 2, we did not have a permanent electroencephalogram record at the control halothane concentration at which it did not move, and during bypass we were unable to achieve sufficient cranial halothane concentrations to prevent movement. Hal = halothane; Thio = thiopental.

anesthetics in general, and halothane and isoflurane in particular, facilitate glycine receptors.[4,16–18] This presumably results in enhanced inhibition. Barbiturates, including thiopental, have little effect on glycine receptors.[16,19] Because glycine receptors are more prominent in the spinal cord than in the brainstem and brain,[20] anesthetics such as halothane and isoflurane would have predominant effects in the spinal cord as compared with the brain, at least with regard to effects on glycine receptors. Other receptor differences are possible. Halothane and isoflurane facilitate, whereas barbiturates inhibit, kainate-sensitive glutamate receptors.[4,21] Serotonergic receptors modulate nociception and motoneuronal responses.[22,23] 5-Hydroxytryptamine agonists are antinociceptive *via* action in rostroventromedulla and spinal cord.[22] Thus, a facilitatory action on 5-hydroxytryptamine receptors in spinal cord would produce antinociception.

Because halothane and isoflurane, but not barbiturates, facilitate 5-hydroxytryptamine receptors,[24] these effects on the serotonergic system might explain our findings. However, Rampil *et al.*[25] have demonstrated that 5-hydroxytryptamine 3 receptor antagonism does not alter isoflurane MAC, therefore the role of 5-hydroxytryptamine 3 receptors in anesthetic mechanisms remains unclear.

The role of glycine and γ-aminobutyric acid receptors in the production of anesthesia, specifically prevention of movement, is not entirely clear. Zhang *et al.*[26,27] found that picrotoxin, a γ-aminobutyric acid type A antagonist, and strychnine, a glycine antagonist, increased isoflurane MAC 40% when applied intrathecally, but this represented a ceiling effect, as no further increase was obtained with greater doses. They suggested that neither glycine nor γ-aminobutyric acid mediated the total effect of isoflurane. They discussed the inter-

Fig. 4. Examples of electroencephalograms from three animals anesthetized with thiopental (during movement and no movement). Control = whole body thiopental delivery. Bypass = differential delivery of thiopental to the head. During differential thiopental delivery to the head, the electroencephalograms, in general, had a lower frequency, higher amplitude pattern as compared with the electroencephalograms during whole-body delivery, although the electroencephalograms obtained at movement and at no movement did not differ significantly. Thio = thiopental.

esting hypothesis that thiopental, with its predominant γ-aminobutyric acid effects, might have a significant supraspinal effect.

At what spinal cord site could halothane and thiopental exert action? In addition to the previously mentioned effect of halothane on the motoneuron,[13] halothane and thiopental depress nociceptive dorsal horn neuronal responses, which could account for some of their spinal cord action.[28] We have assumed that peripheral actions of halothane, isoflurane, and thiopental do not contribute substantially to the spinal cord effect. These anesthetics either have no depressant effect on peripheral nerve conduction or peripheral nociceptors, or, in the case of halothane and isoflurane, may excite or sensitize peripheral nociceptors,[29,30] an effect inconsistent with our findings. Finally, peripheral effects of isoflurane, if any, do not alter isoflurane MAC.[31]

In four of five thiopental-anesthetized animals, we first determined thiopental requirements during differential delivery. It is possible that our control (whole body) values for thiopental, obtained after bypass, may have underestimated the true value because of deterioration caused by the bypass. If so, then the data would suggest a more significant role for the brain as a site of the immobilizing effect of thiopental (and a lesser role for the spinal cord). However, in the current study and two previous studies,[1,32] we did not find significant changes in halothane or isoflurane MAC after differential anesthetic delivery. Thus, we do not believe that obtaining thiopental control (whole body) requirements after bypass significantly affected interpretation of our data.

Our study has several limitations. The alveolar concentration of halothane and blood concentration of thiopental are not necessarily the same as the concentrations at the effect sites (presumably the brain and spinal cord). However, several studies have documented the utility of using these parameters as measures of effect-site concentration at pseudo–steady state conditions. Halothane alveolar concentrations, if stable for 10–15 min, reflect brain concentrations based on brain–blood solubility coefficient and blood flow considerations.[33] Thiopental equilibrates quickly as well, with the electroencephalogram changing with a half-life of 80 s after a change in thiopental plasma concentrations.[34] Because we usually found an increasing thiopental concentration in the 5 min between sampling, we sought to minimize any error by averaging the values. The difference between the control (whole body) and cranial thiopental values was so large that any errors associated with nonequilibrium

concentrations at the effect site were not likely to have affected data interpretation. We cannot exclude the possibility that the sites at which halothane and thiopental affect the electroencephalogram might have differing sensitivities compared with the sites at which movement is affected. In other species, halothane and thiopental prevent movement despite the presence of an active, albeit depressed, electroencephalogram.[35,36] However, thiopental further suppresses the electroencephalogram when its concentration is increased 25–50% above that needed to prevent movement,[35] whereas in halothane-anesthetized animals the electroencephalogram can remain active at concentrations greater than 3 MAC.[36] Thus, the electroencephalogram effects of halothane and thiopental do differ. Last, we recorded only the frontal electroencephalogram. In a previous study in goats, we found that isoflurane produced global electroencephalogram changes with no apparent regional differences.[37] We cannot exclude the possibility that we might have missed regional electroencephalogram effects produced by halothane and thiopental. For example, halothane and thiopental induce a posterior-to-anterior shift in electroencephalogram dominance, but this occurs at concentrations ($\approx$ 0.4 MAC) below the concentration range we investigated.[38]

We found that halothane appears to suppress movement predominantly *via* a spinal action. However, thiopental appeared to have relatively more potent supraspinal effects. What neurotransmitter systems are responsible for this difference remain to be elucidated.

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