Cerebral Function and Muscle Afferent Activity Following Intravenous Succinylcholine in Dogs Anesthetized with Halothane: The Effects of Pretreatment with a Defasciculating Dose of Pancuronium

William L. Lanier, M.D.,* Paul A. Iaizzo, Ph.D.,* James H. Milden†

The effects of iv succinylcholine (SCh) on cerebral blood flow (CBF), muscle afferent activity (MAA), electromyographic activity (EMG), visible fasciculations, and PaCO₂ were tested in 12 dogs anesthetized with 0.87% end-expired halothane (1 MAC). Six dogs (group I) received treatments of both SCh 1.0 mg/kg iv and saline placebo 3.0 ml iv. Fasciculations and substantial increases in EMG activity were observed in all six dogs given SCh. At the onset of fasciculations, there were parallel increases in MAA and CBF to peak values of 466% ± 77% of control (mean ± SE) and 136% ± 5% of control, respectively, at the 1-min measurement point. Thereafter, both MAA and CBF declined toward control values. An additional six dogs (group II) were prepared as above; however, they were pretreated with a defasciculating dose of pancuronium 0.01 mg/kg iv 5 min before being given SCh 1.0 mg/kg. These dogs were also given treatments of saline placebo 3.0 ml iv during another portion of the study. None of these six dogs had visible fasciculations following SCh, and only in one was slight EMG activity detected. Following iv SCh, there were parallel increases in both MAA and CBF. The peak MAA value of 255% ± 56% of control occurred at the 1-min measurement point and was followed by a gradual decline in MAA. CBF increases were greatest during the periods of greatest MAA (i.e., the 1- to 3-min measurement points). The largest increase in CBF (128% ± 9% of control) occurred at the 3-min measurement point. Following SCh in both groups I and II, there were significant increases in PaCO₂, but these increases could not account for peak CBF values in either group. The authors conclude that CBF increases following iv SCh are primarily related to SCh-induced increases in MAA and secondarily related to SCh-induced increases in PaCO₂. These data demonstrate that it is not the presence or absence of fasciculations per se that determines the cerebral response to SCh; instead, it is the effect of SCh on the muscle afferents that correlates with the peak cerebral response. (Key words: Anesthetics, volatile: halothane. Brain: blood flow; electroencephalogram; intracranial pressure; metabolism; oxygen consumption. Muscle: electromyogram: skeletal. Nerve: afferent activity. Neuromuscular relaxants: pancuronium; succinylcholine.)

IN A PREVIOUS STUDY, we evaluated the effects of the depolarizing neuromuscular relaxant succinylcholine (SCh) on intracranial pressure (ICP) in lightly anesthetized dogs and demonstrated that the increases in ICP following iv SCh occurred during periods of increased cerebral blood flow (CBF). The periods of greatest CBF coincided with the periods of EEG evidence of cerebral arousal. It is unlikely that the cerebral response to SCh was due to direct cerebral stimulation by the relaxant, for SCh does not cross the blood-brain barrier (BBB), and the drug has no effect on the EEG when injected into the carotid arteries. Instead, we hypothesized that the cerebral effects of SCh were primarily related to SCh-induced increases in muscle afferent activity (MAA) producing cerebral stimulation, and secondarily related to SCh-induced increases in PaCO₂. This hypothesis and our previous observations were consistent with other reports that SCh produced EEG evidence of arousal in cats and humans and activation of afferent muscle spindles in cats. The following study was designed to test this hypothesis by observing the effects of SCh on the EEG, CBF, cerebral metabolic rate for oxygen consumption (CMRO₂), intracranial pressure (ICP), the electromyogram (EMG), MAA, PaCO₂, and mean arterial blood pressure (MAP). Additional studies were performed to determine if pretreating dogs with defasciculating doses of the nondepolarizing relaxant pancuronium would have any effect on either the cerebral and/or muscle response to iv SCh.

Methods

This protocol was approved by the Institutional Animal Care and Use Committee. Twelve unmedicated fasting mongrel dogs weighing 15.2 ± 0.7 kg (mean ± SE) were studied. Anesthesia was induced and maintained during the preparatory period with halothane 1.5–2.5% inspired in O₂ and N₂. Following tracheal intubation without the use of neuromuscular relaxants, ventilation was mechanically controlled. Ventilation and FiO₂ were adjusted to maintain control blood gases (Instrumentation Laboratory, Inc. electrodes at 37°C) at PaO₂ near 150 mmHg and PaCO₂ near 40 mmHg. Cannulae were inserted into a femoral artery for blood sampling and pressure measurements and a femoral and forelimb vein for fluid and drug administration. A PE90 catheter (Becton Dickinson Co.) was inserted via the right external jugular vein to

* Assistant Professor of Anesthesiology.
† Instructor in Anesthesiology.

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Address reprint requests to Dr. Lanier: Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905.
FIG. 1. The method for quantitation of muscle afferent activity data using a saturating diode circuit. The raw MAA data in group II dog consisted of a biphasic signal of approximately 16-24 μV amplitude superimposed upon a constant background noise signal of approximately 7 μV amplitude. The total signal (A) was first bisected so that only positive components of the original signal remained (B). Next, a threshold level was set to remove the remaining contamination from background electronic noise. This procedure resulted in tracings that represented only positive deflections above background noise (C). Because the amount of background noise was similar in all recordings, identical electronic processing circuit settings were used to remove background noise contamination from MAA signals in recordings from all dogs. After the raw signals had been processed, the positive signal deflections above background noise were directed to an integrating circuit for quantitation. During periods of muscle quiescence prior to SCH administration, MAA was used to estimate the background firing of MAA receptors (D1). However, following SCH, there were dramatic increases in MAA (D2). In this particular example, the processed traces represent MAA data immediately before and after administration of SCH 1.0 mg/kg. The integrated MAA signal was six times greater at point D2 than at point D1.

the level of the junction of the superior vena cava and right atrium for central venous pressure (CVP) measurement. Heart rate (HR) was determined over a 6-s interval measured from a lead II electrocardiogram. During the preparatory period, dogs were given 0.9% saline solution in 10-ml/kg increments as needed to maintain MAP ≥ 60 mmHg. Likewise, bicarbonate was given as needed to maintain a buffer base near 40 mEq/l.

MAA was measured using a modification of techniques described in cats and humans. Briefly, through a skin incision over the posterior aspect of the right hind limb, a branch of the tibial nerve passing to the gastrocnemius muscle was isolated and severed near its proximal origin. Thus, motor activity through the nerve was eliminated. Afferent electrical activity from the distal nerve branch was monitored using a shielded bipolar silver electrode. The nerve and electrode were surrounded by cotton pledgets, bathed in mineral oil, placed between muscle planes, and the skin incision was closed to maintain physiologic temperature of the nerve. MAA was amplified using a Grass Model 78B polygraph, visually displayed on an oscilloscope, and recorded using a Hewlett Packard Model 3968A FM instrumentation tape recorder. MAA was later quantitated using a saturating diode integrating circuit. The biphasic afferent muscle signal was bisected so that only positive deflections above background noise were directed to the integrating circuit (fig. 1). Using this monitoring system, the responsiveness of the transected nerve could be checked by dorsiflexion of the paw. In contrast to the increases in activity following dorsiflexion of the paw, stimulation of pain receptors of the hindlimb did not alter the level of spontaneous activity. The methodologies used to detect MAA in peripheral nerve were validated by simultaneously using an established preparation to monitor MAA in the dorsal columns of the spinal cord. In pilot studies in two dogs anesthetized with 1.0 MAC halothane and having controlled ventilation, the dorsal spinal cord was exposed following a laminectomy, and dorsal rootlets carrying muscle afferent receptor activity were selectively isolated. In these studies changes in MAA recorded from the dorsal nerve rootlets mimicked the increases in activity recorded from the tibial nerve following either mechanical stretch of the hind limb or the administration of SCH 1.0 mg/kg.

Electromyographic activity (EMG) was recorded using bipolar platinum fine wire electrodes placed in the semitendinous muscle of the right hind limb. These signals were amplified and displayed using a Grass polygraph.

After administration of heparin 300-400 units/kg iv, the sagittal sinus was exposed, isolated, and cannulated as previously described. This allowed blood sampling and provided direct measurement of CBF from the anterior, superior, and lateral portions of both cerebral hemispheres representing approximately 54% of the total brain weight.

Blood flow was continuously recorded using a square wave electromagnetic flow meter (ET 300 API, Carolina Medical Electronics). Blood oxygen contents were calculated from measurements of oxyhemoglobin concentrations (CO-oximeter, Instrumentation Laboratories, Inc., model 282) and oxygen tensions (Instrumentation Laboratories, Inc. electrodes). CMRO2 was calculated as the product of CBF and the arterial–sagittal sinus blood O2 content difference. A six-lead, three-channel bipolar EEG was recorded from electrodes glued to the calvarium, and a bifrontal, biparietal, and bioccipital configuration was used. ICP was monitored by an occipital epidural fiberoptic device (LADD Research Industries, Inc.). Brain temperature was monitored with an epidural thermistor and maintained near 37°C using heat lamps. Inspired and end-expired halothane and CO2 concentrations were measured with a mass spectrometer (Perkin Elmer Model 1100). The ears of all dogs were plugged with cotton and the eyes were taped shut.

Because mild spontaneous motor activity (hiccups, coughing, muscle twitching) is a common problem in paralyzed dogs maintained at 0.87% expired halothane (1.0 MAC), control measurements were taken during periods in which spontaneous motor activity mimicked
the study period. Thus, control measurements prior to Sch neuromuscular blockade were taken during periods of no visible motor activity, while mild muscle twitching and infrequent hiccups were tolerated during the preplacebo control periods.

The cerebral and muscle afferent effects of Sch versus placebo were tested in six dogs (group I). Expired halothane was maintained at 0.87% expired (1.0 MAC) for 20 min before control measurements were taken. During the 20-min stabilization period, no additional iv fluids were given, nor was ventilation or FIO2 changed. After the control period, three dogs were given Sch 1 mg/kg iv, and all experimental variables were measured for a subsequent 45 min. After this experimental period, a 30–45 min pause was provided during which the CBF, CMRO2, and EEG stabilized. Next, a control period was repeated, and the experimental period was repeated using a saline placebo 0.05 ml/kg. In three other dogs Sch and saline placebo were given as above, except that their sequence was reversed.

In an additional six dogs (group II), additional studies were performed to determine if Sch-induced alterations in CBF and MAA were prevented by prior administration of “defasciculating” doses of pancuronium. These dogs were prepared and anesthetized as the previous six dogs. These dogs differed from the previous six dogs only in the administration of pancuronium 0.01 mg/kg iv 5 min before administration of Sch 1 mg/kg iv.

At the completion of the studies, all 12 dogs were killed with iv KCl during anesthesia. The brains were removed and weighed so that CBF and CMRO2 could be expressed as a function of brain weight.

Following each drug application, the average cerebral and systemic response was calculated for each dog for the time periods 0–15 min, 15–30 min, and when applicable, 30–45 min. Data following treatments with Sch from these time periods were compared with data following placebo treatments within each group using paired t tests. When comparing the response to Sch or placebo in group I versus group II, unpaired t tests were used. All comparisons were made on raw data. In addition to the above analysis, data from each individual dog were expressed as a percent of that dog’s control value. This provided for easier recognition of the temporal relationship between cerebral and systemic changes. Statistical analyses were not performed on percent of control data. The two-tailed Fischer’s exact test was used to compare the frequency of fasciculations in group I versus group II. The Spearman rank correlation coefficient (r) was used to assess the correlation between CBF and ICP. Values were considered significantly different if they achieved a P < 0.05. All data are expressed as mean ± SE.

### Results

Control systemic and cerebral variables measured before the administration of relaxant or placebo treatments are listed in table 1. The groups were well matched for both cerebral and systemic data.

In group I (no pancuronium pretreatment), fasciculations were observed visually and recorded by the EMG in six of six dogs following the iv administration of Sch 1.0 mg/kg (P < 0.05 vs. placebo). EMG evidence of fasciculations began at 22 ± 6 s following Sch and persisted for 58 ± 31 s (range 6–195 s). During violent fasciculations in one dog, the MAA recording electrode became dislodged, preventing further recording of MAA. In the remaining five dogs, a small increase in MAA began shortly before the onset of visible fasciculations. With the onset of fasciculations, there was a dramatic increase in MAA

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### Table 1. Control Systemic and Cerebral Variables prior to Sch or Placebo Treatments

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>No Pretreatment</th>
<th>Pancuronium 0.01 mg/kg Pretreatment</th>
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<tbody>
<tr>
<td></td>
<td>Sch 1 mg/kg iv</td>
<td>Placebo iv</td>
</tr>
<tr>
<td></td>
<td>(n = 6)</td>
<td>(n = 6)</td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>154 ± 4</td>
<td>159 ± 2</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>39 ± 0</td>
<td>39 ± 1</td>
</tr>
<tr>
<td>pH</td>
<td>7.32 ± 0.02</td>
<td>7.33 ± 0.02</td>
</tr>
<tr>
<td>BBF (ml·100 g⁻¹·min⁻¹)</td>
<td>41 ± 1</td>
<td>41 ± 1</td>
</tr>
<tr>
<td>CBF (ml·100 g⁻¹·min⁻¹)</td>
<td>74 ± 6</td>
<td>69 ± 10</td>
</tr>
<tr>
<td>CMRO2 (ml·100 g⁻¹·min⁻¹)</td>
<td>4.73 ± 0.48</td>
<td>4.27 ± 0.38</td>
</tr>
<tr>
<td>ICP (mmHg)</td>
<td>6 ± 4</td>
<td>6 ± 4</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>1 ± 0</td>
<td>1 ± 1</td>
</tr>
<tr>
<td>Brain temperature (°C)</td>
<td>36.9 ± 0.1</td>
<td>36.9 ± 0.1</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>92 ± 7</td>
<td>96 ± 4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>103 ± 7</td>
<td>110 ± 7</td>
</tr>
<tr>
<td>Measured halothane (% expired)</td>
<td>0.87 ± 0.00</td>
<td>0.87 ± 0.00</td>
</tr>
</tbody>
</table>

All data are presented as mean ± SE. There were no significant differences between groups.
in five of five dogs and an increase in CBF in six of six
dogs. The control EEG pattern consisted of a mixture of
slow waves with a frequency of 2–5 Hz and an amplitude
of 40–100 μV, and faster activity with a frequency of 8–
12 Hz and an amplitude of 50–120 μV. This pattern was
consistent with our previous reports of the EEG at 1.0
MAC halothane in dogs (i.e., the “anesthetic” EEG).14
The administration of 4% SCh had no effect on the EEG
in two of the six group I dogs. In the other four dogs,
SCh produced a reduction in amplitude and an increase
in frequency consistent with a cerebral arousal
response.1,14 In these four dogs, the EEG activation began
29 ± 2 s after iv SCh (i.e., at the time of visible fasci-
culations) and persisted for 2.8 ± 0.8 min. Following placebo
treatment, no fasciculations were observed, and the EEG
remained at the placebo control pattern with two ex-
ceptions: one dog had a 2-min period of hiccuping and
EEG activation beginning 3 min after placebo treatment,
and another had a 7-min period of spontaneous movement
accompanied by EEG activation beginning 8 min after
placebo treatment.

In group I SCh produced significant changes in CBF,
MAA, and PaCO₂ when comparing 15-min measurement
periods (table 2). CBF, MAA, and PaCO₂ following SCh
were all significantly greater than postplacebo values at
the 0–15 and 15–30 min measurement periods. In con-
trast, CVP, ICP, CMRO₂, MAP, and HR did not signifi-
cantly change during any of the 15-min measurement
periods.

The temporal relationship between SCh-induced
changes in CBF, MAA, and PaCO₂ in group I are presented
in figure 2. After the injection of SCh, no noticeable
changes occurred until the onset of MAA increases, fas-
ciculation, and EMG activation. With the onset of these
changes in muscle activity, there was desynchronization
of the EEG in four dogs, and there were increases in CBF
in all six dogs. The greatest CBF and MAA occurred at
the 1-min measurement point and was followed by a
gradual but progressive decrease in both variables with
time. PaCO₂ increased after iv SCh, achieving values of
105–109% of control (a 2–4 mmHg increase) throughout
the 45-min study period. Using paired comparisons be-
tween individual data points, ICP values following SCh
were significantly greater than values following placebo
only at the 1-, 2-, and 3-min measurement points, achiev-
ing values of 391% ± 139%, 353% ± 193%, and 355% ±
193% of control, respectively. This was an increase in
mean ICP of 5 mmHg from the control values. There
was a significant correlation between ICP and CBF follow-

| Variable Measured | Time (min) | Group I
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<tr>
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<tbody>
<tr>
<td></td>
<td>SCh 1 mg/kg iv</td>
<td>Placebo iv</td>
</tr>
<tr>
<td>CBF (ml · 100 g⁻¹ · min⁻¹)</td>
<td>Control</td>
<td>74 ± 6</td>
</tr>
<tr>
<td></td>
<td>0–15</td>
<td>87 ± 10***</td>
</tr>
<tr>
<td></td>
<td>15–30</td>
<td>80 ± 11***</td>
</tr>
<tr>
<td></td>
<td>30–45</td>
<td>75 ± 12</td>
</tr>
<tr>
<td>MAA (% control)</td>
<td>Control</td>
<td>100 ± 10</td>
</tr>
<tr>
<td></td>
<td>0–15</td>
<td>312 ± 55**</td>
</tr>
<tr>
<td></td>
<td>15–30</td>
<td>193 ± 22***</td>
</tr>
<tr>
<td></td>
<td>30–45</td>
<td>110 ± 24</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>Control</td>
<td>39 ± 9</td>
</tr>
<tr>
<td></td>
<td>0–15</td>
<td>42 ± 1***</td>
</tr>
<tr>
<td></td>
<td>15–30</td>
<td>42 ± 1***</td>
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<tr>
<td></td>
<td>30–45</td>
<td>42 ± 1</td>
</tr>
</tbody>
</table>

All data are presented as mean ± SE; n = 6 for all variables except for MAA data in group I where n = 5.

*** Significantly different between SCh and placebo treatments in the same six dogs at 1.0 MAC halothane anesthesia (†P < 0.05; ††P < 0.02; †††P < 0.01).

* Significantly different between SCh treatments in groups I and II (*P < 0.05; **P < .01).
min of iv SCh administration in four of six dogs. In these dogs EEG activation began at 31 ± 2 s after iv SCh and persisted for 3.2 ± 0.9 min. EEG activation was not observed in any placebo-treated group II dog.

In group II SCh produced significant increases in CBF, MAA, and PaCO₂ when comparing 15-min measurement periods (table 2). CBF and PaCO₂ following SCh were both significantly greater than postplacebo values at the 0–15 and 15–30 min measurement periods. MAA following SCh significantly differed from MAA following placebo only at the 0–15 min measurement period. In contrast, CVP, ICP, CMRO₂, MAP, and HR did not significantly change at any 15-min measurement period.

The temporal relationship between SCh-induced changes in CBF, MAA, and PaCO₂ in group II are presented in figure 3. Although there were no visible fasciculations following SCh in this group, there was desynchronization of the EEG in four dogs, and there were parallel increases in MAA and CBF in all six dogs. All of these changes occurred prior to the 1-min measurement point. Using paired comparisons with data following placebo treatment, there were significant increases in CBF following SCh at the 1-, 2-, and 3-min measurement points. These increases in CBF coincided with the instances of greatest MAA and were followed by gradual correlated decreases in both MAA and CBF. There were prolonged increases in PaCO₂ following iv SCh. Using paired comparisons, ICP values following SCh were significantly greater than values following placebo only at the 1–8 min measurement points. The greatest ICP values of 181% ± 44%, 185% ± 44%, and 188% ± 55% of control occurred at the 2-, 3-, and 4-min measurement points, respectively. This represented mean increases in ICP of either 3 or 4 mmHg greater than the pre-SCh control value. There was a significant correlation between ICP and CBF following SCh (rₐ = 0.98; P < 0.001) but not following placebo (rₐ = 0.26; P > 0.2).

The cerebral and systemic responses to iv SCh were similar in groups I and II. When comparing either the average data for 15-min measurement intervals or comparing individual data points, there were no significant

![Figure 2](image_url)

**Fig. 2.** The temporal relationship of changes in CBF, MAA, and PaCO₂ after iv administration of SCh 1.0 mg/kg or placebo in group I dogs anesthetized with 1.0 MAC halothane. All values are expressed as mean percent control ± SE (n = 6 for CBF and PaCO₂, n = 5 for MAA).

![Figure 3](image_url)

**Fig. 3.** The temporal relationship of changes in CBF, MAA, and PaCO₂ after iv administration of pancuronium 0.01 mg/kg plus SCh 1.0 mg/kg in group II dogs maintained at 1.0 MAC halothane. All values are expressed as mean percent control ± SE (n = 6).
Discussion

The observations of the present study (i.e., parallel increases in MAA and CBF) are usually accompanied by EEG activation) support our previous hypothesis that SCh-induced cerebral stimulation is due to an increase in MAA.1

As in our previous study,1 SCh produced delayed increases in PacO₂, presumably due to increases in muscle O₂ consumption.15 These PacO₂ increases may have contributed to the duration of the CBF increase; however, if we assume that CBF increases 2–4% for each millimeter increase in PacO₂,16–18 the PacO₂ increases could not account for the peak increases in CBF during the 5 min following iv SCh (figs. 4 and 5). In addition, the small PacO₂ increases could not account for the brief periods of EEG activation in most dogs.

Of the 12 dogs studied in groups I and II, all had CBF increases following SCh, and CBF increases were accompanied by EEG patterns indicative of cerebral stimulation in eight. There were no increases in CMRO₂. The occurrence of CBF increases as the most sensitive and consistent marker of cerebral stimulation in the present study is similar to previous experience with this model in which afferent input into the brain of anesthetized dogs was produced by electrical stimulation of the sciatic nerves.19 The pattern of transient CBF and EEG changes without CMRO₂ changes is distinctly different from the cerebral stimulation we reported following administration of the nondepolarizing neuromuscular relaxant, atracurium.14 Cerebral stimulation by atracurium is presumably related to a mechanism other than increased afferent input into the brain.

The receptors assumed to be primarily responsible for SCh-induced increases in muscle afferent activity are the muscle spindles.5,4 Each muscle spindle is composed of several small intrafusal skeletal muscle fibers the central regions of which are noncontractile and contain few or no actin and myosin filaments.20 In this central region are sensory receptors that detect dynamic changes (primary endings) and static changes (primary and secondary endings) in the muscle length. Our methodology did not attempt to distinguish between the two types of receptors. The intrafusal muscle spindles reside within a bundle of extrafusal, contractile skeletal muscle fibers.20 The sensory endings may become activated by passive stimulation from changes in the state of either the extrafusal contractile skeletal muscle elements to which they are coupled or intrafusal fibers may be directly excited by drugs or neurotransmitters. In contrast to the alpha efferent innervation of contractile extrafusal fibers, intrafusal fibers have gamma efferent innervation.20 Activation of the gamma efferents can also induce an increased afferent response. Thus, stimulation of muscle spindles following SCh might be due to two or more mechanisms. First, SCh-

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**FIG. 4.** The observed CBF and the calculated contributions of Paco₂ to CBF increases after iv SCh 1.0 mg/kg in dogs anesthetized with 1.0 MAC halothane. A 4% increase in CBF per mmHg increase in Paco₂ was assumed.16 Increases in Paco₂ can account for late, but not early, CBF increases. Initial peak increases in CBF occurred during the period of greatest increases in MAA and are assumed to be due to MAA increases.

**FIG. 5.** The observed CBF and the calculated contributions of Paco₂ to CBF increases after iv SCh 1.0 mg/kg in dogs pretreated with iv pancuronium 0.01 mg/kg and anesthetized with 1.0 MAC halothane. A 4% increase in CBF per mmHg increase in Paco₂ was assumed.16 Increases in Paco₂ can account for late, but not early, CBF increases. Initial peak increases in CBF occurred during the period of greatest increases in MAA and are assumed to be due to MAA increases.
induced paralysis of extrafusal muscle fibers usually begins with fascinations and contractions. This increase in extrafusal muscle activity will be detected by intrafusal elements that are mechanically coupled to the extrafusal fibers. Second, SCH will directly stimulate intrafusal fibers. Our findings support this idea. Following IV SCH, we detected an increase in the spontaneous electrical activity recorded from isolated dorsal rootlets, which also responded to muscle stretch (pilot studies). Likewise, the electrical activity recorded from cut peripheral nerves responded to similar stimuli. (The sustained increases in MAA in our preparation may have also been influenced to a small degree by increased activity from Golgi tendon organs and B organs. SCH has been reported to also excite muscle receptors other than muscle spindles; however, the amount of afferent activity from these receptors is probably small when compared with the muscle afferent activity generated by muscle spindles.) In the present study and in previous studies, the prolonged period of cerebral stimulation and MAA increases following SCH—in contrast to the brief duration of EMG activation and fascinations from extrafusal muscle fibers—may be related to the observation that SCH has differing affinities for extrafusal and intrafusal fibers. This differing effect is possibly due to a difference in the receptors being stimulated (i.e., alpha motor receptors in extrafusal fibers vs. gamma motor receptors in intrafusal fibers). The MAA increases following SCH are hypothesized to stimulate the brain in the following fashion. Increased MAA is carried by peripheral nerves to the dorsal spinal cord where it is transmitted to the brain. The cerebral cortex receives muscle afferent information via several different neuronal pathways. This information is thought to converge in the motor cortex (area 4) through intrinsic intragrey and extrinsic white matter intracortical connections. Furthermore, there is evidence that muscle afferent information has direct input into both the motor cortex and the somatosensory cortex (area 3a). Hence, it is not surprising that a direct stimulation of MAA by SCH could influence cerebral function.

Assuming that the effect of SCH on cerebral function is primarily related to activation of MAA, as we hypothesize, it would follow that the cerebral response to SCH could be modified by pretreatment with nondepolarizing neuromuscular relaxants. This modification could occur by two mechanisms. First, nondepolarizing relaxant pretreatment could modify the effects of SCH on extrafusal elements (e.g., abolish fascinations) and in turn modify the coupled activity of the intrafusal elements. Second, nondepolarizing relaxant pretreatment could modify the direct effect of SCH on the intrafusal elements.

Two recent studies examined the effect of pretreatment with paralyzing doses of nondepolarizing relaxants before giving IV SCH. In a dog study from our laboratory in which EEG activation and CBF and ICP increases were demonstrated following SCH pretreatment with paralyzing doses of pancuronium 0.2 mg/kg in two dogs abolished the cerebral response to SCH. In a similar study in lightly anesthetized humans, Minton et al. demonstrated that the ICP increases following SCH were prevented by pretreatment with paralyzing doses of vecuronium 0.14 mg/kg. Based on these studies, we concluded that pretreatment with paralyzing doses of nondepolarizing relaxants abolished the ability of SCH to produce depolarization of muscle fibers (both extrafusal and intrafusal) and thus prevented the cerebral response. This hypothesis was supported by recent pilot studies in our laboratory in two dogs receiving 1.0 MAC halothane anesthesia and pancuronium 0.2 mg/kg followed 15 min later by SCH (as in our previous report). In this setting SCH produced activation of neither the EMG nor MAA.

Further studies by Stirt et al. and the present study addressed the clinically relevant issue of the effect that pretreatment with nonparalyzing, “defasciculating” doses of nondepolarizing relaxant would have on the response to SCH. In the Stirt et al. study, humans were pretreated with metocurine 0.03 mg/kg IV, followed by a bolus of SCH 1.0 mg/kg. In contrast to the effects of SCH alone, there were no fascinations or significant increases in ICP following SCH in metocurine-treated humans. However, because of a low frequency of fascinations in the humans receiving no metocurine, the frequency of fascinations following SCH was not significantly different between metocurine-treated subjects and those not receiving metocurine. In the present study, 0.01 mg/kg pancuronium prevented visible fascinations in dogs (and significantly reduced the frequency of both visible and EMG evidence of fascinations) without preventing SCH-induced increases in MAA or affecting SCH-induced increases in CBF or ICP, or the incidence of EEG activation. When these results are considered along with the previously described studies, we conclude that the ability of a nondepolarizing relaxant pretreatment to prevent SCH-induced ICP increases is independent of its ability to prevent fascinations. The ability of “defasciculating” doses of metocurine to prevent SCH-induced increases in lightly anesthetized patients having brain tumors—in contrast to the inability of “defasciculating” doses of pancuronium to abolish the cerebral effects of SCH in dogs—may be related to the ability of metocurine to prevent SCH-induced increases in MAA. Alternatively, metocurine may directly alter cerebral function in a manner that prevents a response to SCH. This latter effect may be influenced by the ability of metocurine and its metabolites to cross the blood-brain barrier, a characteristic it presumably does not share with pancuronium.

Should our hypothesis prove correct (i.e., SCH alters cerebral function secondary to MAA increases producing...
cerebral stimulation, the clinical implications are that MAA of any origin may produce alterations in the EEG, CBF, and ICP in lightly anesthetized subjects. It would not matter whether the MAA increases were produced pharmacologically, by exogenous muscle stretch, or by endogenous muscle contraction. There is some experimental and anecdotal evidence to support such a hypothesis. Hobbs et al. recently reported that in N₂O-anesthetized children neuromuscular relaxation provided by repeated boluses of SCh was associated with a 24% incidence of perioperative dreaming compared with a 9% incidence of children given the nondepolarizing relaxant atracurium (P < 0.05). Regarding the cerebral effects of endogenous muscle contraction, we have repeatedly observed in the laboratory that spontaneous muscle contraction during hiccuping and "bucking on the endotracheal tube" in lightly anesthetized dogs will produce increases in MAA. We have also reported that this spontaneous movement in dogs is accompanied by EEG activation and increases in CBF and ICP similar to the cerebral changes following iv SCh. The most dramatic ex-

ample of this phenomenon we have observed occurred in a normocapnic dog anesthetized with 1.0 MAC halothane (fig. 6). Changes in PaCO₂, MAP, or CVP were insufficient to account for the EEG activation or increases in CBF or ICP. Similar to our observations in dogs, Perlman et al. observed fluctuations in CBF velocity during spontaneous movement in mechanically ventilated preterm neonates. Paralyzing the neonates with pancuronium prevented the CBF velocity fluctuations, presumably because the infants were unable to move and thus endogenously increase MAA. Finally, in the surgical suite, we have observed EEG desynchronization upon retraction of the neck muscles during light planes of anesthesia late in the surgical period in patients having carotid endarterectomy. The EEG changes did not appear to be related to an increased level of painful stimulation, and once the changes began, they could not be ablated by modest increases in isoflurane concentration. In these instances the EEG reverted to a pattern consistent with a surgical plane of anesthesia only after surgical retraction of the neck musculature ceased. In the laboratory in dogs we have observed that surgical retraction of muscle will produce MAA increases similar to those following SCh, and MAA returns to baseline values shortly after releasing the muscle stretch (MAA). We believe that all of the above observations suggest that MAA increase from a variety of different types of muscle stimuli may result in a pattern of cerebral stimulation in awake or lightly anesthetized subjects similar to that observed in the present study following SCh. A corollary to this hypothesis is that afferent neuronal input to the brain from receptors other than pain receptors may be responsible in determining the cerebral state of arousal, CBF, and ICP.

In summary, we conclude that the cerebral stimulation following iv SCh in lightly anesthetized subjects in previous studies1,4,6 and the EEG activation and increases in CBF and ICP seen in the present study are primarily related to SCh-induced increases in muscle afferent activity. Studies in pancuronium-pretreated dogs demonstrated that neither the cerebral nor the MAA response to SCh is solely dependent on the initiation of SCh-induced fasciculations. These studies, in agreement with human studies, suggest that the presence or absence of visible fasciculations is not a reliable indicator of the presence or absence, respectively, of a cerebral response to SCh. Furthermore, these studies suggest that afferent neuronal input to the brain from sources other than pain receptors are important in determining the cerebral state of arousal, CBF, and intracranial pressure.

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