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Cerebral Stimulation Following Succinylcholine in Dogs

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The effects of iv succinylcholine (SCh) on the electroencephalogram (EEG), cerebral blood flow (CBF), cerebral metabolic rate (CMR_{O_2}), intracranial pressure (ICP), central venous pressure (CVP), and mean arterial pressure (MAP) were tested in halothane-anesthetized dogs. Six dogs were maintained at 0.87 ± 0.00% (mean ± SE) expired halothane (1.0 MAC) and received both SCh 1.0 mg·kg^{-1} and lactated Ringer's solution placebo 0.05 ml·kg^{-1}. Fasciculations began 24 ± 4 s after iv SCh. Fasciculations were followed by immediate EEG arousal in five of six dogs and increases in CBF in all six. Average CBF was 151 ± 14% of control for the 0–15 min measurement period and 127 ± 7% of control for the 15–30 min period. Both were significantly greater than pre-SCh control values and placebo group values. Peak CBF of 177 ± 19% of control occurred 3 min after iv SCh and was accompanied by a peak ICP of 435 ± 131% of control. ICP values were significantly different between SCh and placebo treatments only during the periods of greatest CBF (1 to 5 min after iv SCh). Average Pa_{CO_2} values after iv SCh were significantly greater than pre-SCh control values and placebo values during each 15-min measurement interval. Average Pa_{CO_2} was 116 ± 2% of control during the 0–15 min measurement period, 114 ± 2% of control during the 15–30 min period, and 109 ± 1% of control during the 30–45 min period. CVP, MAP, and CMR_{O_2} did not significantly change after iv SCh. In two dogs maintained at 1.32 ± 0.01% expired halothane (1.5 MAC), SCh 1.0 mg·kg^{-1} produced Pa_{CO_2} changes comparable with those in dogs maintained at 1.0 MAC halothane without comparable changes in CBF, ICP, or EEG. In an additional two dogs receiving pancuronium 0.2 mg·kg^{-1} and 1.0 MAC halothane, SCh had no meaningful effect on any variable measured. The authors conclude that iv SCh increased ICP in the dog secondary to increases in CBF. They hypothesize that the CBF increases are related primarily to SCh-induced increases in afferent muscle spindle activity and secondarily to increases in Pa_{CO_2}. (Key words: Brain: blood flow; electroencephalogram; intracranial pressure; metabolism; oxygen consumption. Neuromuscular relaxants: succinylcholine.)

THERE ARE MANY conflicting reports in the literature concerning the effects of the depolarizing neuromuscular relaxant succinylcholine (SCh) on intracranial pressure (ICP) in laboratory animals and humans.[1–7,§,¶,**] Despite these reports, there is theoretic evidence that suggests that iv SCh administration may be followed by increased ICP in patients with decreased cerebral compliance secondary to increased cerebral blood flow (CBF).

Succinylcholine has been reported to stimulate cerebral electroencephalogram (EEG) activity when applied topically to the cerebral cortex[8] and after iv administration.[9–11] The former effect is thought to be due to direct depolarization of neurons,[8] while the latter effect is felt to occur *via* stimulation of afferent muscle spindles.[9–11] Although EEG activation following large doses of atracurium produced no significant effect on CBF in dogs receiving sub-MAC halothane concentrations,[12] EEG activation resulting from electrical stimulation of the sciatic nerve in halothane-anesthetized dogs[13] and induction of seizures in enflurane-anesthetized dogs[14] resulted in both increases in CBF and metabolism. Kuramoto *et al.* have shown that cerebral stimulation resulting in mild EEG activation in dogs receiving 0.9% inspired halothane may cause increases in CBF that exceed increases in cerebral metabolic rate for oxygen consumption (CMR_{O_2}).[13] Thus, EEG activation by iv SCh could be accompanied by increasing CBF with or without meaningful increases in cerebral metabolism. A second mechanism by which SCh may affect the brain is induced increases in arterial carbon dioxide tension (Pa_{CO_2}).[15] Increases in Pa_{CO_2} are known to increase CBF[16,17] and cerebral blood volume (CBV)[16] and cause EEG activation.[18] Thus, ICP might significantly increase after SCh administration in susceptible individuals due to CO_2-induced increases in CBF.

The existing contradictory data regarding the cerebral stimulating effects of SCh may be explained by differences in study design and subject selection. Variations in anesthetic depth, Pa_{CO_2}, and skeletal muscle activity as well as preexisting cerebral function alterations may explain the lack of cerebral stimulation in various studies. Accordingly, the present study was designed to control these variables and to determine if iv SCh produces alterations in CBF, CMR_{O_2}, ICP, central venous pressure (CVP), mean arterial blood pressure (MAP), or the EEG in halothane-anesthetized dogs. Additional studies were performed to evaluate the alteration in these responses produced by increasing anesthetic depth and by induction of nondepolarizing neuromuscular blockade prior to SCh administration.

Methods

Subjects were ten unmedicated, fasting mongrel dogs weighing 12 to 17 kg. Anesthesia was induced with hal-

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othane in N_2O 67% and O_2. Dogs were intubated without the use of neuromuscular relaxants, and ventilation was controlled. After intubation, anesthesia was maintained with halothane in N_2 and O_2. Ventilation and FI_{O_2} were adjusted to maintain serial blood gases (IL® electrodes at 37° C) at Pa_{O_2} 144 ± 2 mmHg and Pa_{CO_2} 40 ± 0 mmHg (mean ± SE). 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 the level of the junction of the superior vena cava and right atrium for mean CVP measurement. Heart rate (HR) was calculated from an average rate over a 6-s interval measured from a lead II electrocardiogram. During the preparatory period, dogs were given lactated Ringer's solution (LR) 5 ml · kg^{-1}. Individual dogs were given additional infusions of LR 5–10 ml · kg^{-1} as needed to maintain MAP ⩾ 60 mmHg. Bicarbonate was given as needed to maintain a buffer base (BB^+) near 40 mEq/l.

Mild spontaneous motor activity (hiccupping, coughing, muscle twitching) is a common problem in unparalyzed dogs maintained at 0.87% expired halothane (1.0 MAC). In an attempt to attenuate the motor effects of hiccupping and coughing, the phrenic nerves were located bilaterally with a needle electrode attached to a nerve stimulator (Block-Aid™ Monitor, Burroughs Wellcome Co.), and 4.0 ml of bupivacaine 0.25% was injected at each nerve. Because this maneuver proved largely ineffective in eliminating hiccups, control measurements were taken during periods in which spontaneous motor activity mimicked the study period. Control measurements prior to SCh neuromuscular blockade were taken during periods of no visible motor activity, while muscle twitching and infrequent hiccups were permitted during the pre-placebo control periods.

After heparinization (with 300–400 units · kg^{-1} iv), the saggital sinus was exposed, isolated, and cannulated as previously described.[19] 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.[20] Blood flow was continuously recorded using a square wave electromagnetic flow meter (ET 300 API®, Carolina Medical Electronics).[21] Blood oxygen contents were calculated from measurements of oxyhemoglobin concentrations (CO-oximeter®, IL 282) and oxygen tensions (IL® electrodes).[22] CMR_{O_2} was calculated as the product of CBF and the arterial–sagittal sinus blood O_2 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 epidural fiberoptic device (LADD Research Industries, Inc.). Brain temperature was monitored by a parietal epidural thermistor and maintained at 37° C with heat lamps. Inspired and end-expired halothane and CO_2 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.

The cerebral effects of SCh *versus* LR placebo were tested in six dogs. Because the "anesthetic" and "awake" EEG patterns may be similar between dogs, while the patterns are distinctly different for a single dog, the "anesthetic" and "awake" EEG patterns were determined for each dog. After recording an "anesthetic" EEG at 0.87% expired halothane, an "awake" EEG pattern was recorded at 0.45% expired halothane.[12,23] The "awake" pattern was identified by a stable reduction in amplitude and an increase in frequency of the EEG. During the study period, the "shifting" EEG, which represents the interface between "awake" and "anesthetic" patterns, was identified by a stable equal distribution of "awake" and "anesthetic" patterns or the appearance of high-amplitude slow waves.[12,23] Examples of the various patterns are seen in figure 1. Expired halothane was maintained at 0.87 ± 0.00% 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 FI_{O_2} changed. After the control period, three dogs were given SCh 1 mg · kg^{-1} iv, and physiologic and cerebral variables were measured for 45 min. After a 30–45 min pause at which time CBF, CMR_{O_2}, and EEG had stabilized, a control period was repeated, and the above sequence was repeated with LR placebo 0.05 ml · kg^{-1}. In three other dogs, SCh and LR placebo were given as previously outlined, except the sequence was reversed.

Further studies were performed in four dogs to determine if SCh-induced alterations in CBF were prevented by increasing anesthetic depth or by prior nondepolarizing neuromuscular blockade. These four dogs were initially prepared as the previous six dogs. Two dogs received 1.32 ± 0.01% expired halothane (1.5 MAC), and two dogs were given pancuronium 0.2 mg · kg^{-1} 15 min before and halothane 0.88 ± 0.00% expired during the study period. Control measurements of cerebral and systemic variables in these four dogs were followed by the administration of SCh 1.0 mg · kg^{-1} iv as in the previous six dogs.

In three dogs maintained at 1.0 MAC halothane without pancuronium pretreatment and two dogs maintained at 1.5 MAC halothane, neuromuscular function was assessed during the preparatory period and at the completion of the study period following SCh administration by visual examination of hindlimb plantarflexion in response to stimulation of the tibial nerve with a 1 Hz supramaximal twitch using a MiniStim® (Professional Instruments Co.). In all groups, CMR_{O_2}, CBF, and ICP were determined a

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minimum of five times during each control period and averaged. After each drug intervention, cerebral responses were expressed as a per cent of control for each dog, and an average response was calculated for the time periods 0–15 min, 15–30 min, and, when applicable, 30–45 min. In the group of six dogs maintained at 1.0 MAC halothane, values following treatment with SCh or placebo were compared with their respective control periods using Bonferroni's correction of paired t tests, and values between SCh and placebo treatments were compared using paired t tests. Values were considered significantly different if they achieved a $P < 0.05$ or its Bonferroni corrected equivalent by paired t tests. In the two dogs maintained at 1.5 MAC halothane and the two dogs receiving pancuronium plus 1.0 MAC halothane, values were expressed as mean ± SE; however, they were not included in comparisons of statistical significance due to the small number of subjects.

At the conclusion of the study, the dogs were killed, and the brains were removed and weighed so that CBF and CMR_{O_2} could be expressed as a function of brain weight.

Results

Control cerebral and systemic data are listed in table 1. In the group of six dogs maintained at 1.0 MAC halothane anesthesia, there were no significant differences between control values prior to SCh or placebo treatments, nor were there significant differences in Pa_{O_2}, MAP, temperature, or expired halothane concentrations within groups during the study periods.

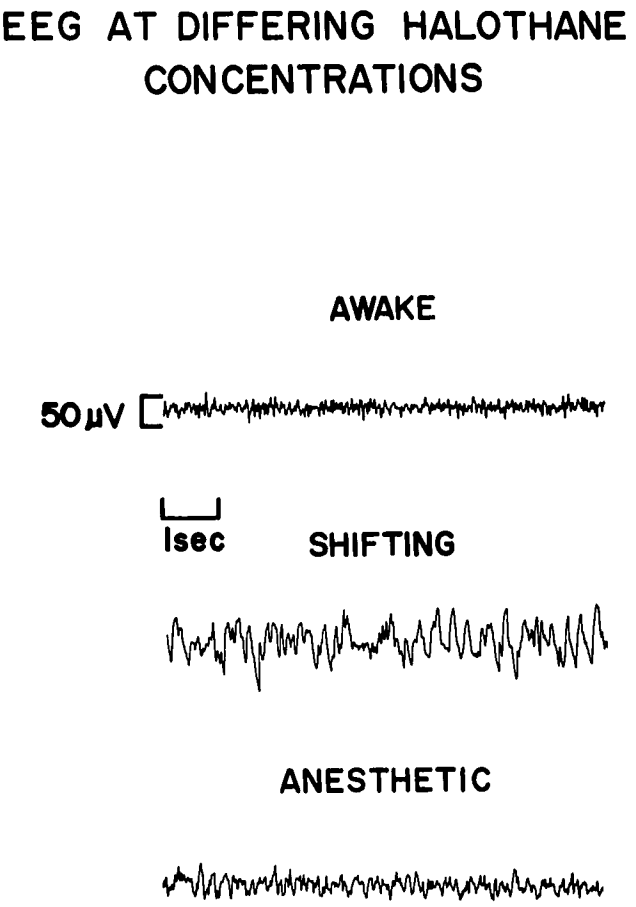

FIG. 1. Examples of various EEG patterns at differing halothane concentrations in dogs. (From Lanier WL, Milde JH, Michenfelder JD[12]).

TABLE 1. Control Systemic and Cerebral Values* Prior to Succinylcholine (SCh) or Placebo Treatments

	Treatment Groups			
	SCh 1 mg·kg^{-1} iv	Placebo iv	SCh 1 mg·kg^{-1} iv	SCh 1 mg·kg^{-1} iv
	1.0 MAC Halothane	1.0 MAC Halothane	1.5 MAC Halothane	1.0 MAC Halothane + Pancuronium
	n = 6	n = 6	n = 2	n = 2
Wt (kg)	13.2 ± 0.5	13.2 ± 0.5	13.0 ± 2.0	13.2 ± 1.8
Pa_{O_2} (mmHg)	143 ± 5	144 ± 2	151 ± 4	138 ± 1
Pa_{CO_2} (mmHg)	40 ± 0	40 ± 1	40 ± 0	41 ± 0
pH	7.33 ± 0.01	7.33 ± 0.01	7.31 ± 0.01	7.31 ± 0.02
BB+ (mEq·l^{-1})	41 ± 1	42 ± 1	41 ± 1	40 ± 1
CBF (ml·100 g^{-1}·min^{-1})	66 ± 6	68 ± 6	92 ± 27	76 ± 3
CMR_{O_2} (ml·100g^{-1}·min^{-1})	3.53 ± 0.18	3.60 ± 0.17	3.82 ± 0.48	3.37 ± 0.36
ICP (mmHg)	4 ± 1	4 ± 2	11 ± 2	5 ± 1
CVP (mmHg)	4 ± 1	3 ± 1	3 ± 3	8 ± 4
Brain temperature (°C)	37.0 ± 0.1	37.1 ± 0.1	37.1 ± 0.0	37.1 ± 0.0
MAP (mmHg)	96 ± 5	94 ± 7	85 ± 0	82 ± 15
Heart rate (beats·min^{-1})	106 ± 11	103 ± 6	124 ± 6	135 ± 45
Measured halothane (% expired)	0.87 ± 0.00	0.87 ± 0.00	1.32 ± 0.01	0.88 ± .00

* All values are expressed as mean ± SEM.
BB+ = buffer base; CBF = cerebral blood flow; CMR_{O_2} = cerebral metabolic rate of oxygen consumption; ICP = intracranial pressure; CVP = central venous pressure; MAP = mean arterial pressure.

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TABLE 2. Cerebral and Hemodynamic Responses Following Succinylcholine (SCh) and Placebo

Parameter Measured (% control)	Time (min)	Treatment Groups: SCh 1 mg·kg⁻¹ iv, 1.0 MAC Halothane, n = 6	Placebo iv, 1.0 MAC Halothane, n = 6	SCh 1 mg·kg⁻¹ iv, 1.5 MAC Halothane, n = 2	SCh 1 mg·kg⁻¹ iv, 1.0 MAC Halothane + Pancuronium, n = 2
CBF	0–15	151 ± 14*†	99 ± 5	96 ± 2	104 ± 4
	15–30	127 ± 7*†	93 ± 6	89 ± 1	95 ± 9
	30–45	111 ± 8	—	—	—
ICP	0–15	291 ± 89	138 ± 46	114 ± 16	118 ± 39
	15–30	189 ± 70	127 ± 54	94 ± 8	98 ± 48
	30–45	97 ± 23	—	—	—
Pa_{CO_2}	0–15	116 ± 2*‡	99 ± 1	117 ± 10	101 ± 1
	15–30	114 ± 2*‡	99 ± 2	115 ± 13	103 ± 2
	30–45	109 ± 1*	—	—	—
CVP	0–15	153 ± 61	102 ± 17	56 ± 36	99 ± 0
	15–30	177 ± 64	97 ± 18	44 ± 44	108 ± 6
	30–45	135 ± 28	—	—	—
CMR_{O_2}	0–15	95 ± 2	99 ± 2	97 ± 1	99 ± 2
	15–30	96 ± 3	99 ± 2	99 ± 4	100 ± 1
	30–45	98 ± 2	—	—	—
MAP	0–15	97 ± 4	101 ± 3	99 ± 5	98 ± 6
	15–30	93 ± 5	97 ± 2	95 ± 7	95 ± 11
	30–45	93 ± 3	—		
HR	0–15	108 ± 8	113 ± 15	98 ± 2	97 ± 4
	15–30	119 ± 13	111 ± 13	107 ± 10	98 ± 5
	30–45	121 ± 13	—		

Changes are expressed as the mean per cent of control ± SEM.

CBF = cerebral blood flow; ICP = intracranial pressure; CVP = central venous pressure; CMR_{O_2} = cerebral metabolic rate for oxygen; MAP = mean arterial pressure; HR = heart rate.

* Significantly different from the pre-SCh control value (Bonferroni corrected value of $P < 0.05 \div 3 = P < 0.016$).

† Significant difference between SCh and placebo treatments in same six dogs at 1.0 MAC halothane anesthesia ($P < 0.05$).

‡ Significant difference between SCh and placebo treatments in same six dogs at 1.0 MAC halothane anesthesia ($P < 0.01$).

The magnitude of SCh-induced changes in CBF, ICP, CMR_{O_2}, CVP, Pa_{CO_2}, MAP, and HR in the group of six dogs maintained at 1.0 MAC halothane anesthesia is seen in table 2. CBF at 0–15 and 15–30 min was significantly increased over pre-SCh control CBF values and post-placebo CBF values during comparable measurement periods. CBF at 30–45 min was not significantly greater than pre-SCh control values; however, CBF did not return to—or decrease below—pre-SCh control values at any time during the 45-min measurement period. Although there were no significant SCh-induced ICP increases when comparing 15 min measurement intervals, post-SCh ICP was significantly greater than post-placebo values during the consecutive measurement periods 1, 2, 3, 4, and 5 min. Significant increases in Pa_{CO_2} occurred following SCh administration during all measurement periods. In contrast, CVP, CMR_{O_2}, MAP, and HR did not significantly change at any measurement period. During the control period, all dogs receiving SCh exhibited an "anesthetic" EEG pattern, although one dog had a few intermittent, high-amplitude slow waves. Immediately after SCh administration, there were no changes in these patterns. Fasciculation artifacts were seen in the EEG in five of six dogs, and fasciculations were visually noted in all. At the cessation of the EEG fasciculation artifact, all five dogs had a reduction in EEG amplitude and an increase in frequency consistent with an "awake" pattern. In the sixth dog without EEG fasciculation artifact, the EEG remained in the "anesthetic" EEG pattern immediately after iv SCh. The other five dogs remained in the "awake" pattern for 5 ± 1 min at which time they all returned to the "anesthetic" pattern. Placebo treatment group data were frequently contaminated with arousal EEG patterns. These interruptions in the "anesthetic" pattern persisted for 0.5 to 18 min per episode, were usually accompanied by hiccups or coughing, and were associated with a tendency to increased CBF.

The sequence and magnitude of change in cerebral and systemic variables after SCh and placebo dogs maintained at 1.0 MAC halothane anesthesia are depicted in figure 2. After the injection of SCh, no noticeable changes occurred until the onset of fasciculations, which began

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24 ± 4 s after SCh and ceased 37 ± 4 s after SCh. EEG arousal was accompanied by immediate, concomitant increases in CBF and ICP followed thereafter by gradual increases in Pa_{CO_2}. CVP, CMR_{O_2}, MAP, and HR did not significantly change. In the three SCh-treated dogs tested for neuromuscular function, twitch had returned to normal when tested immediately after the 45-min measurement period.

In the two dogs maintained at 1.5 MAC halothane, Pa_{CO_2} increases following SCh were similar to those noted in dogs maintained at 1.0 MAC halothane. Average Pa_{CO_2} values for the 0–15 min and 15–30 min measurement period were 109% and 102% of control, respectively, for one dog and 125% and 128% of control, respectively, for the other dog. Despite these tendencies for Pa_{CO_2} increases, only minor changes in CBF, ICP, CMR_{O_2}, CVP, MAP, and HR were observed (table 2). Fasciculations occurred in both dogs but were not accompanied by an arousal EEG pattern. Neuromuscular twitch was apparently normal when tested after the 30-min measurement period in each dog. In the two dogs maintained at 1.0 MAC halothane and given pancuronium pretreatment, SCh administration had no apparent effect on CBF, ICP, Pa_{CO_2}, CVP, CMR_{O_2}, MAP, or HR (table 2). The EEG remained in a stable "anesthetic" pattern during the control period and after SCh administration.

Discussion

The use of SCh in the presence of decreased intracranial compliance remains controversial. In several animal and human studies, SCh has been reported to increase intracranial pressure[1–5,§]; however, other studies have found that SCh had no meaningful effect on ICP.[6,7,¶,**]

Our study clearly demonstrated in halothane-anesthetized dogs that increases in ICP and CBF rapidly follow SCh administration. To interpret the results of our study and understand the conflicting reports in the literature, we must first examine the most probable mechanisms for the CBF and ICP increases.

Fasciculations occurred shortly after iv SCh in the six dogs maintained at 1.0 MAC halothane. Fasciculations were preceded by an "anesthetic" EEG and immediately followed by an "awake" EEG in five of six dogs. This phenomenon is best explained by the afferent muscle spindle theory[9–11,24] which predicts that agents or maneuvers which actively or passively cause muscle stretch or contraction will stimulate the brain.[9–11] Agents that inhibit muscle stretch or contraction may decrease cerebral activity.[24,25] Induction of depolarizing neuromuscular blockade by SCh, decamethonium, and carbolonium have been shown to induce EEG arousal.[9–11] In contrast, onset of nondepolarizing neuromuscular blockade has been shown to produce electrocortical synchronization[25] and augment anesthetic depth.[24]

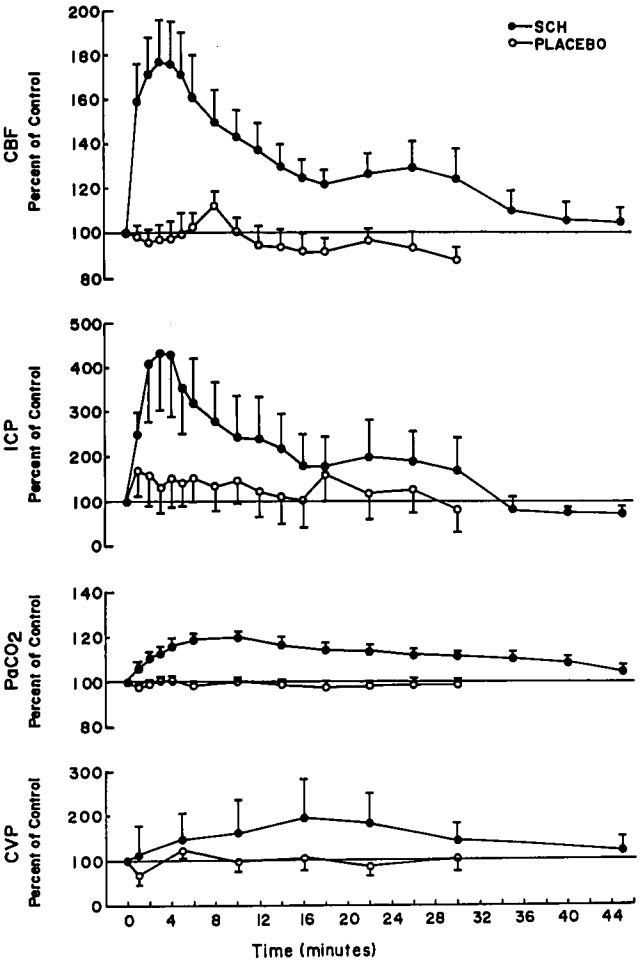

FIG. 2. The temporal relationship of changes in CBF, ICP, Pa_{CO_2}, and CVP after iv administration of SCh 1.0 $mg \cdot kg^{-1}$ or placebo in dogs maintained at 1.0 MAC halothane. All values are expressed as mean % control ± SE (n = 6).

In dogs receiving SCh maintained at 1.0 MAC halothane anesthesia, CBF and ICP increases began immediately after EEG arousal; however, there was no change in CMR_{O_2}. Using a model similar to that used in our study, Kuramoto *et al.*[13] produced cerebral stimulation by electrically shocking the sciatic nerve of dogs. They demonstrated that cerebral stimulation resulting in EEG arousal in dogs receiving 0.9% inspired halothane produced CBF increases that were proportionally larger than CMR_{O_2} increases. Although we were unable to demonstrate CMR_{O_2} changes at the time of EEG changes, our methods do not allow us to exclude the possibility of regional CMR_{O_2} changes. The data of Kuramoto *et al.*[13] also suggest that CBF may be a more sensitive and persistent indicator of cerebral stimulation than EEG or CMR_{O_2}. This may explain why one dog receiving 1.0 MAC halothane in our study exhibited immediate CBF increases with iv SCh without concomitant EEG arousal. Interestingly, this

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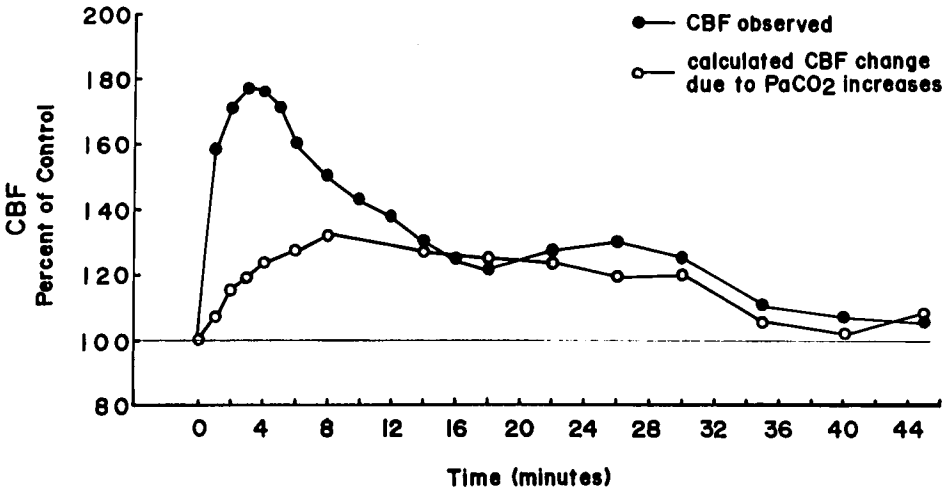

FIG. 3. The observed CBF and the calculated contributions of Pa_{CO_2} to CBF increases after iv SCh 1.0 mg·kg^{-1} in dogs maintained at 1.0 MAC halothane. A 4% increase in CBF per mmHg increase in Pa_{CO_2} was assumed.[17] All points represent a mean response for six dogs. Increases in Pa_{CO_2} can account for late—but not early—CBF increases. Initial peak increases in CBF were accompanied by an EEG arousal response in five of six dogs and are assumed to be related to SCh-induced increases in afferent muscle spindle activity.

dog had the greatest degree of EEG synchronization during the control period of any dog maintained at 1.0 MAC halothane. This may indicate a relatively deeper level of anesthesia during the control period.

CBF increases with EEG activation can explain the early increases in CBF after SCh; however, this does not explain why CBF increases persisted long after the EEG returned to control patterns. SCh has been reported to cause increases in Pa_{CO_2} comparable with those noted in our study by increasing muscle CO_2 production.[15] Pa_{CO_2} increases are known to cause EEG arousal[17,18] and increases in CBF[16,17] and cerebral blood volume.[16] Despite this evidence, we feel that afferent muscle spindle stimulation and not Pa_{CO_2} increases were responsible for the maximum period of cerebral stimulation for the following reasons: Maximum EEG arousal and CBF increases occurred shortly after SCh administration. Pa_{CO_2} increased more gradually after SCh iv and did not achieve its peak value until EEG arousal had subsided and CBF had begun declining. The Pa_{CO_2} increases in our study were probably of insufficient magnitude to produce the early EEG and CBF changes we observed. EEG arousal has been reported by increasing Pa_{CO_2} from 27 to 56 mmHg in cats[18]; however, in our study Pa_{CO_2} had increased by only 2 mmHg at the onset of maximum EEG arousal. CBF is reported to increase by 2–4% for each mmHg increase in Pa_{CO_2}.[16,17,26] The maximum increases in Pa_{CO_2} that we observed were an average 6 mmHg increase during the 0–15-min measurement period (table 2) and a peak increase of 8 mmHg at the 10-min measurement period (fig. 2). These increases could account for an average CBF increase of 24% and a peak CBF of 32%. Both predicted increases due to Pa_{CO_2} are much less than the average CBF increase of 51% during the 0–15-min measurement period and the peak CBF increase of 78% at the 3-min measurement period. However, Pa_{CO_2} increases are sufficient to account for CBF increases during the 15–30 and 30–45 min measurement periods.

Our hypothesis of the origin of CBF increases after SCh during 1.0 MAC halothane anesthesia is best understood by examining figure 3. EEG activation by SCh began with the onset of fasciculations in five of six dogs and persisted for approximately 5 min. This brief period of EEG arousal was accompanied by an abrupt increase in CBF. As CBF increased above control values, so did Pa_{CO_2}, so that by 14 min, the increases in Pa_{CO_2} were sufficient to account for CBF increases. The period of increased CBF between the end of EEG arousal and 14-min post-SCh probably represents either the normal deterioration of CBF increases after arousal or small degrees of ongoing SCh-induced cerebral stimulation that were undetectable by the EEG.

In two dogs maintained at 1.5 MAC halothane, increases in post-SCh Pa_{CO_2} were comparable with those in dogs at 1.0 MAC halothane; however, EEG and CBF responses did not reflect cerebral arousal. The lack of stimulation of CBF and EEG after SCh was probably related to anesthetic depth. This agrees with the findings of Kuramoto *et al.*,[13] Prince and Shanzer,[27] and Lanier *et al.*,[12] who have demonstrated that small increases in anesthetic depth may greatly attenuate the EEG, CBF, and CMR_{O_2} response to arousal agents.

In the two dogs receiving pancuronium pretreatment and 1.0 MAC halothane, we assume that pancuronium pretreatment prevented depolarization of muscle tissue by SCh. Stimulation of afferent muscle spindles—and thus the EEG—would be prevented as would increased CO_2 production by the depolarizing muscle tissue. This hypothesis is supported by the observation of Mori *et al.*[9] that prior administration of the nondepolarizing neuro-

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muscular relaxants gallamine and alcuronium prevented EEG activation by SCh. Furthermore, Muldoon and Theye[15] noted an attenuation of SCh-induced muscle CO_2 production by *d*-tubocurarine pretreatment.

The absence of cerebral stimulation in dogs previously paralyzed with pancuronium supports the theory that cerebral stimulation by SCh is dependent on muscle activity and independent of direct cerebral effects of SCh. However, mechanisms not involving muscle activity must be considered. Riker and Okamoto[28] have demonstrated that SCh can induce both prodromic and antidromic stimulation of nerve tissue. Thus, it is theoretically possible that SCh stimulation of neurons may enter the CNS in both an antegrade and retrograde fashion. However, according to existing neurotransmission theory, only prodromic impulses should be transmitted to the brain. Antidromic impulses would not be able to pass retrograde through the first synapse they might encounter, and the wave of depolarization would cease.

It is unlikely that SCh can cross the blood–brain barrier in an amount sufficient to produce cerebral arousal. Motokizawa and Fujimori[11] found that while iv SCh produced EEG arousal in cats, SCh injected into the carotid arteries had no effect on the EEG. Cortically applied SCh is known to produce intense EEG stimulation and seizures.[8] However, the pharmacodynamics of cortically applied SCh do not resemble our observations. In five dogs maintained at 1.0 MAC halothane, maximum EEG stimulation in our study occurred 37 ± 4 s after iv SCh and lasted a mere 5 ± 1 min. In contrast, SCh applied topically to the cerebral cortex does not produce maximum EEG stimulation for 2 min. The maximum stimulatory effects of topically applied SCh lasts for 20 min after removal of SCh-impregnated pads, presumably due to the absence of pseudocholinesterase within the brain.

Increases in CVP secondary to muscle fasciculations have been proposed as the origin of SCh-induced increases in ICP[5]; however, recent studies have shown that increasing CVP may be ineffective in increasing ICP.[29] We were unable to demonstrate any temporal relationship between maximal increases in CVP and ICP and the occurrence of fasciculations. These findings are consistent with those of Marsh *et al.*§ and Cottrell *et al.*,[3] who were unable to find any correlation between the presence of visible fasciculations and the magnitude of ICP increases after SCh.

Although we and others have demonstrated increases in ICP with SCh, there are other studies to the contrary. Several of these studies used barbiturate anesthesia. Barbiturates are known to decrease CBF[30] and ICP.[31] Moderate doses of barbiturates will diminish EEG activity and large doses may abolish EEG activity.[30] Thus, barbiturates may interfere with the ability of afferent stimuli to reach and excite the brain, or they may result in vascular changes which prevent increases in CBF. Furthermore, the use of short-acting barbiturates (*e.g.*, thiopental) may allow large fluctuations in anesthetic depth during the measurement period, thus augmenting or attenuating the effects of SCh, depending on the doses, sequence, and timing of barbiturate and SCh administration. The ICP effects of sequential induction doses of thiopental and succinylcholine have been demonstrated in humans by Marsh *et al.*,§ who showed that ICP decreases with thiopental and returns to control levels with subsequent iv SCh. McLeskey *et al.* reported that ICP during laryngoscopy did not change from awake values following a sequence of thiopental and pancuronium, while four patients receiving thiopental and SCh had ICP values during laryngoscopy that were twice their awake values (19.7 ± 10.0 *vs.* 9.5 ± 3.2 mmHg).[1] Halldin and Wahlin reported that SCh produced a mean lumbar subarachnoid pressure increase of 7.4 mmHg (range 0.4 to 23.5 mmHg) in humans receiving surgical anesthetic doses of barbiturate.[4] These studies imply that while surgical anesthetic doses of barbiturate do not abolish the ICP increases following SCh in humans, the magnitude of ICP increases is diminished and may not be meaningfully increased from awake values.

We demonstrated in two dogs that prior administration of large doses of nondepolarizing neuromuscular relaxant abolished SCh-induced cerebral stimulation. This observation agrees with the human studies of Mori *et al.*[9] They found that SCh-induced EEG arousal was prevented by pretreatment with alcuronium 0.5 $mg \cdot kg^{-1}$ or gallamine 3 $mg \cdot kg^{-1}$. These doses of nondepolarizing relaxants should have produced profound levels of neuromuscular blockade similar to those achieved by pancuronium 0.2 $mg \cdot kg^{-1}$ in our study. In contrast, relaxant administration resulting in incomplete nondepolarizing neuromuscular blockade at the time of SCh administration cannot be relied on to prevent cerebral stimulation by SCh. Motokizawa and Fujimori[11] demonstrated in cats that after the EEG synchronizing effects of gallamine 2–4 $mg \cdot kg^{-1}$ had subsided (60–90 min after iv gallamine), SCh 40–200 $\mu g \cdot kg^{-1}$ iv produced EEG arousal lasting 3–10 min. Cottrell *et al.*[3] gave pancuronium 0.15 $mg \cdot kg^{-1}$ to facilitate tracheal intubation in cats in whom ICP studies were performed. Two hours after pancuronium administration, neuromuscular function had returned, and SCh 1.5 $mg \cdot kg^{-1}$ produced increases in ICP. McLeskey *et al.*[1] also attributed ICP increases during anesthesia induction to SCh in patients given *d*-tubocurarine 3 mg iv. In light of these studies, we feel that massive doses of nondepolarizing relaxants will abolish the cerebral effects of SCh. However, defasciculating doses of nondepolarizing relaxants apparently cannot be relied on to prevent the cerebral stimulatory effects of SCh.

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Still others investigating the ICP effects of SCh may have failed to control Pa_{CO_2}.[1,4,§] Alterations in Pa_{CO_2} are known to cause changes in CBF, CBV, and ICP.[16,17] Furthermore, Pa_{CO_2} may also affect EEG evidence of anesthetic depth, which in turn may alter the cerebral response to arousal.[18]

White *et al.*,[6] in a prospective, randomized human study, evaluated the effects of SCh, thiopental, fentanyl, lidocaine, or saline placebo pretreatment on the ICP response to tracheal suctioning. Interestingly, ICP values were lower after SCh pretreatment than after pretreatment with the cerebral vasoconstrictors thiopental, fentanyl, or lidocaine. Those results cannot be explained by pretreatment with nondepolarizing neuromuscular relaxants, previous administration of anesthetic or analgesic drugs, or the failure to control for Pa_{CO_2}. All of the patients in that study were comatose. As such, they would have been expected to have cerebral function alterations that may have prevented immediate cerebral stimulation with SCh. Depending on the origin of the coma, these patients may also have had altered cerebral hemodynamics[26] that precluded significant increases in CBF and ICP by an indirect arousal agent.

Naturally occurring and synthetic catecholamines and catecholamine-releasing drugs have been reported to induce EEG arousal and increase CBF.[32] Although we did not measure catecholamines, we doubt catecholamine release had a significant effect on our results, as HR and blood pressure did not significantly change with SCh.

In summary, we have demonstrated that SCh is followed by EEG arousal and CBF-induced increases in ICP. EEG arousal and CBF increases are thought to be due to SCh-induced afferent muscle spindle stimulation causing immediate cerebral stimulation, though small increases in Pa_{CO_2} probably contributed to the delayed response of CBF. Increases in CVP had little or no effect on ICP. ICP and CBF increases after SCh were blocked by either increasing anesthetic depth or by prior initiation of nondepolarizing neuromuscular blockade. CMR_{O_2} did not change with SCh in any study.

Assuming our findings are applicable to humans, we conclude that SCh may produce deleterious increases in ICP in lightly anesthetized subjects with diminished cerebral compliance. SCh-induced CBF and ICP increases may be attenuated or eliminated by increasing anesthetic depth or by administering paralyzing doses of nondepolarizing neuromuscular relaxants; however, "defasciculating" doses of nondepolarizing neuromuscular relaxants may not prevent ICP increases. Additional human studies must be performed to confirm these speculations. The lack of an effect of SCh on ICP as described in many previous reports can presumably be explained by variations in either the selection of subjects and/or study design.

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