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The Cerebral and Systemic Effects of Movement in Response to a Noxious Stimulus in Lightly Anesthetized Dogs

Possible Modulation of Cerebral Function by Muscle Afferents

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Background: Afferentation theory predicts that agents or maneuvers that stimulate muscle stretch receptors (*i.e.*, muscle afferents) will produce cerebral stimulation. From this theory it follows that, regardless of the source (*e.g.*, drug effect, active muscle movement), increases in stretch receptor activity should result in a similar effect on the brain. The present study tested the hypothesis that active muscle movement in lightly anesthetized subjects would result in cerebral stimulation.

Methods: Studies were conducted in six dogs who were lightly anesthetized with halothane (0.70% end-expired). The following physiologic variables were quantified before and for 6 min after the initiation of a standardized (1-min duration) noxious stimulus to the trachea and the skin overlying the hind limb: cerebral blood flow, cerebral metabolic rate for oxygen ($CMRO_2$), cerebral perfusion pressure, cerebral vascular resistance, electroencephalogram activity, electromyogram activity, arterial carbon dioxide partial pressure ($PaCO_2$), central venous pressure, and serum epinephrine and norepinephrine concentrations. Response to stimulation was evaluated initially in unparalyzed dogs and later was evaluated in the same dogs after they were paralyzed with intravenous pancuronium (0.2 mg/kg).

Results: In unparalyzed dogs, stimulation produced episodes of coughing plus head and limb movement during the 6-min study period. Accompanying the movement was activation of the electromyogram, an increase in electroencephalogram frequency, and a reduction in electroencephalogram amplitude. There also was a 35% increase in cerebral blood flow, a 25% decrease in cerebral vascular resistance, and a 7% increase in $CMRO_2$ *versus* the baseline values for each variable. There were no significant increases in either cerebral perfusion pressure, central venous pressure, $PaCO_2$, or serum norepinephrine concentration to account for the cerebral effects; however, serum epinephrine concentrations increased by 61%. In pancuronium-paralyzed dogs, noxious stimulation resulted in a 5% increase in cerebral blood flow, a 7% decrease in cerebral vascular resistance, and an 5% increase in $CMRO_2$ *versus* baseline levels. Electroencephalogram frequency was increased, but amplitude was unchanged. Central venous pressure, electromyogram activity, and serum norepinephrine concentration were unaffected. The serum epinephrine response was similar to that observed when the dogs were not paralyzed.

Conclusions: These data support the hypothesis that active muscle movement in lightly anesthetized subjects has an effect on the brain that is mediated in part by muscle afferent receptors. This cerebral response was manifested as electroencephalogram activation, cerebral vasodilation unrelated to central venous pressure changes, and an increase in cerebral blood flow greater than that required to meet metabolic demands. Paralysis with pancuronium abolished movement induced by stimulation (and, thus, the muscle afferent response) and also attenuated the cerebral blood flow, cerebral vascular resistance, and electroencephalogram responses. (Key words: Brain: blood flow; electroencephalogram; intracranial pressure; metabolism; oxygen consumption. Muscle: afferent activity; electromyogram; skeletal. Neuromuscular relaxants: pancuronium.)

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AFFERENTATION theory predicts that agents or maneuvers that produce muscle stretch or contraction, or directly stimulate muscle stretch receptors (*i.e.*, muscle afferents), will produce cerebral stimulation.[1–5] The purpose of this investigation was to test the physiologic implications of the afferentation theory of cerebral arousal.

Increases in muscle afferent activity (MAA) can be induced by a variety of chemical and mechanical stim-

uli. The depolarizing neuromuscular relaxant succinycholine stimulates MAA,[2-6] and this effect of succinycholine has been credited with producing cerebral stimulation after its intravenous administration in lightly anesthetized subjects.[1-i] MAA also is increased during periods of spontaneous muscle movement and is coupled with activation of the electromyogram (EMG).[7,8] In accordance with afferentation theory, cerebral stimulation should result from increased MAA input into the brain regardless of the stimulus. The purpose of the present study was to test the hypothesis that, in lightly anesthetized dogs whose lungs were ventilated mechanically, tracheal and skin stimulation that resulted in sustained periods of coughing plus limb and head movement (and, thus, increases in MAA) would result in a sustained cerebral arousal response. We also tested the hypothesis that, after pancuronium-induced neuromuscular blockade in the same lightly anesthetized dogs, tracheal and skin stimulation would not result in a subsequent cerebral stimulation, because MAA increases would be prevented by the paralyzing effect of pancuronium.

Methods

The following protocol was approved by the Institutional Animal Care and Use Committee of the Mayo Foundation. Six unmedicated, fasting dogs weighing 15.0 ± 0.5 kg (mean ± SE) were studied. Anesthesia was induced and maintained during the preparatory period with halothane (1.5–2.5%) inspired in oxygen and nitrogen. The trachea was intubated (7.0-mm ID, 30-cm long tube) without the use of neuromuscular relaxants, and ventilation of the lungs was controlled mechanically. Thereafter, the dogs were placed in a sling to produce a body position similar to that used in standing (*i.e.,* the vertebral column approximated the horizontal plane and all four paws lightly touched the supporting table). The head was secured in the neutral position in a stereotactic device that was connected to the sling. The endotracheal tube was allowed to rest untethered over a supporting bar so that, during dog movement, any tendency for secondary stimulation of the trachea would be reduced. Ventilation and inspired oxygen concentrations were adjusted to maintain control arterial blood gas partial pressures (Instrumentation Laboratory, Lexington, MA; electrodes at 37° C) for oxygen (PaO_2) near 150 mmHg and for carbon dioxide ($PaCO_2$) near 38 mmHg. Inspired and end-expired oxygen, carbon dioxide, and halothane were measured with a mass spectrometer (Perkin-Elmer, Pomona, CA; model 1100). A one-way "J-valve" (Warren E. Collins, Braintree, MA) was placed on the expiratory limb of the Harvard ventilator (Millis, MA) to prevent air entrainment with coughing during the expiratory phase of the ventilatory cycle. Cannulae were inserted into a femoral artery for blood sampling and pressure measurements, and into femoral and fore limb veins for fluid and drug administration. Heart rate was determined from a lead II electrocardiogram. EMGs were recorded from the masseter, deltoid, and intercostal muscles with fine wire electrodes inserted into the muscles with introducing needles. Neuromuscular blockade was assessed with needle electrodes and a peripheral nerve stimulator (Bard, Billerica, MA; model 750 Digital) to provide supramaximal stimulation of the hind-limb tibial nerve. The degree of blockade was quantified by visual examination for plantar flexion of the paw. To measure central venous pressure (CVP), a PE 90 catheter (Becton Dickinson, Parsippany, NJ) was inserted *via* the right external jugular vein to the level of the junction of the superior vena cava and right atrium. Intrathoracic pressure (ITP) was measured with an esophageal balloon device.[9] Body temperature was measured with a thermistor placed in the superior vena cava *via* the external jugular vein. Brain temperature was measured with a parietal epidural thermistor. Both temperatures were maintained at 37.0 ± 0.5° C with infrared lamps and heating pads. During the preparatory period, dogs were given 0.9% saline solution in 10 ml/kg increments as needed to maintain mean arterial blood pressure (MAP) > 60 mmHg. Likewise, bicarbonate was given as needed to maintain a buffer base of approximately 40 mEq/1. The ears of all dogs were plugged with cotton, and the eyes were taped shut.

Next, dogs were prepared for the measurement of cerebral blood flow (CBF) and cerebral metabolic rate for oxygen consumption ($CMRO_2$) using previously described and validated techniques.[10] An occipital craniectomy was performed over the confluence of sinuses. After the intravenous administration of heparin (300–400 U/kg), the sagittal sinus was exposed, isolated, and cannulated.[10] This allowed blood sampling and provided for the direct measurement of CBF from the anterior, superior, and lateral portions of both cerebral hemispheres, representing approximately 54% of the total brain weight.[11] Blood flow was recorded continuously with a square-wave electromagnetic flow meter (ET 300 API, Carolina Medical Electronics, King, NC).[12] Blood oxygen contents were calculated from

measurements of oxyhemoglobin concentrations and oxygen partial pressures (CO-oximeter, Instrumentation Laboratories; electrodes).[1,11] $CMRO_2$ was calculated as the product of CBF and the arterial to sagittal sinus blood oxygen content difference. To minimize the influence of intracranial pressure (ICP) changes during the study on cerebral perfusion pressure (CPP defined as MAP − ICP), the craniectomy was sealed loosely after the cannulation of the sagittal sinus. This was intended to produce a reduction in normal cerebral elastance, resulting in minimal changes in ICP in response to cerebral blood volume changes. ICP was monitored with a parietal epidural fiberoptic device (LADD Research Industries, Burlington, VT) to assure that the preparation maintained a cerebral perfusion pressure greater than 50 mmHg. The biparietal EEG was recorded from electrodes glued to the calvarium, and the temporalis muscles were retracted mildly to decrease muscle activity artifacts. The EEG and EMG signals were amplified with a Grass model 78B polygraph (Quincy, MA) and were recorded continuously and stored on a VCR-based digital recorder (Vetter model 4000A pulse code modulation unit and model 500C recorder, AR Vetter, Rebersberg, PA).

On completion of the above preparation, halothane concentrations were decreased to 0.65–0.75% end-expired for 20 min. This halothane concentration was intended to provide analgesia and amnesia during the procedure,[13] yet provide animals that were anesthetized lightly enough to be able still to cough and move on tracheal and skin stimulation. Once the animals were quiescent, control measurements were performed, including measurement of plasma epinephrine and norepinephrine concentrations. The catecholamine concentrations were measured with high pressure liquid chromatography and electrochemical detection.[14] This methodology has a reported sensitivity of 0.01 ng/ml plasma and reported coefficients of variation of approximately 7% and 4% for epinephrine and norepinephrine, respectively. Coughing and head and limb movement then were induced in the dogs by the manual movement of the endotracheal tube back and forth along its longitudinal axis (2–3 cm) for exactly 60 s. The initiation of tracheal stimulation was defined as time = 0 min. In addition to tracheal stimulation, an electric stimulus of 3-s duration was provided to the upper medial hind limb at 30 and 45 s with a MiniStim (Professional Instruments, Houston, TX) to enhance motor activity. (In pilot studies, it was determined that electric skin stimulation enhanced the likelihood of prolonged movement following tracheal stimulation but did not affect the cerebral response to movement. That is, dogs experiencing the most movement had the most intense cerebral response, regardless of whether they received skin stimulation.) Cerebral and systemic variables were recorded at 1-min intervals for 6 min after the initiation of stimulation. (In pilot studies, it was determined that most dogs would sustain movement for this duration.) Plasma catecholamine levels were measured again at 2 and 5 min after the initiation of stimulation.

After the above sequence was completed, the halothane concentrations were increased for a minimum of 30 min to allow the dogs to return to resting state (*i.e.,* muscle quiescence). Thereafter, halothane concentrations again were decreased to approximately 0.7% end-expired for 20 min. The animals were paralyzed with pancuronium 0.2 mg/kg, and 5 min later, control variables were measured and the aforementioned study sequence was repeated.

Flow (CBF) and pressure (*e.g.,* MAP, ICP, CVP) measurements were determined from the mean response over an entire ventilatory or coughing–movement cycle. EEG recordings were computer processed to determine the mean frequency and mean amplitude with a Digital Equipment Corporation model 11-73 computer (Westminster, MA) and software developed at Mayo Clinic. Specifically, epochs of 15-s duration were analyzed at each 1-min measurement interval, and any artifacts resulting from gross animal movement were edited from the epochs before the computer-assisted analysis. After the noxious stimulus, the average cerebral and systemic responses were determined during the 6-min measurement period. These values were not weighted for time. Data from the period following the noxious stimulus were compared to data from the control periods using paired *t* tests. Similarly, paired *t* tests were used to compare values in the unparalyzed and paralyzed portions of the study. Fisher's exact test was used to compare the incidences of EMG activation. The Pearson product–moment correlation coefficient was used to assess the relationship between CBF and CPP data, and regression lines were compared using *t* tests. All data are expressed as mean ± SEM. Values were considered significantly different if they achieved a $P < 0.05$.

Results

Control cerebral and systemic variables measured in quiescent dogs before tracheal and skin stimulation are

Table 1. Cerebral and Systemic Responses to Tracheal and Skin Stimulation

	Unparalyzed		Pancuronium Paralyzed	
	Control	After Stimulation	Control	After Stimulation
CBF (ml · 100 g^{-1} · min^{-1})	66 ± 8	89 ± 14*	57 ± 6	60 ± 9†
CMR_{O_2} (ml · 100 g^{-1} · min^{-1})	3.83 ± 0.40	4.09 ± 0.46*	3.75 ± 0.41	3.92 ± 0.42*†
ITP (mmHg)	2 ± 1	4 ± 1	2 ± 1	2 ± 1
CVP (mmHg)	3 ± 1	6 ± 1	5 ± 1	4 ± 1
MAP (mmHg)	95 ± 6	98 ± 9	79 ± 4	73 ± 4*†
HR (beats/min)	118 ± 7	126 ± 5	132 ± 8	142 ± 6†
ICP (mmHg)	5 ± 1	8 ± 4	7 ± 1	6 ± 1
CPP (mmHg)	90 ± 7	90 ± 9	73 ± 4†	67 ± 4*†
CVR (mmHg · ml^{-1} · 100 g · min)	1.50 ± 0.24	1.13 ± 0.21*	1.35 ± 0.19	1.25 ± 0.21
Epinephrine (ng/ml)	2.59 ± 1.11	4.18 ± 1.45*	2.30 ± 0.79	4.38 ± 0.62
Norepinephrine (ng/ml)	1.50 ± 1.19	1.57 ± 1.08	0.58 ± 0.26	0.90 ± 0.21
EEG amplitude (μV)	141 ± 18	95 ± 7*	116 ± 16	87 ± 7
EEG frequency (Hz)	11 ± 2	15 ± 1*	10 ± 1	14 ± 1*
Pa_{O_2} (mmHg)	148 ± 2	140 ± 5*	149 ± 2	150 ± 2
Pa_{CO_2} (mmHg)	38 ± 1	38 ± 1	39 ± 1	37 ± 1*
*p*H	7.33 ± 0.01	7.32 ± 0.01	7.32 ± 0.01	7.32 ± 0.01
BB^- (mEq/l)	40 ± 1	40 ± 1	40 ± 1	40 ± 0
Brain temperature (° C)	36.9 ± 0.0	36.9 ± 0.1	37.0 ± 0.1	37.0 ± 0.0
Halothane (% end-expired)	0.70 ± 0.01	0.70 ± 0.01	0.70 ± 0.01	0.70 ± 0.01

Data are mean ± SEM. n = 6 for each measurement group.

* $P < 0.05$ *versus* control.

† $P < 0.05$ between unparalyzed *versus* paralyzed states.

CBF = cerebral blood flow; CMR_{O_2} = cerebral metabolic rate; ITP = intrathoracic pressure; CVP = central venous pressure; MAP = mean arterial blood pressure; HR = heart rate; ICP = intracranial pressure; CPP = cerebral perfusion pressure; CVR = cerebral vascular resistance; EEG = electroencephalogram; Pa_{O_2} = arterial blood oxygen partial pressure; Pa_{CO_2} = arterial blood carbon dioxide partial pressure; BB^- = buffer base.

listed in table 1. There were no significant differences in any control variable measured when the unparalyzed *versus* paralyzed states were compared, with one exception: CPP was greater in unparalyzed dogs (90 ± 7) than in paralyzed dogs (73 ± 4).

In all unparalyzed dogs, the noxious stimulus produced continuous muscle activation throughout the 6-min study period. Muscle movement at any instant involved different regions or combinations of regions of the body. There were intermittent diaphragmatic activity (as documented by CVP fluctuations) and intermittent movements of the fore limbs, hind limbs, neck, and facial muscles. As expected, visible muscle activity was readily identified by EMG activation in all monitored muscles. Examples of the EMG recordings are presented in figure 1.

Although both positive and negative deflections in ITP and CVP were observed during coughing and movement, when averaged over an entire coughing–movement cycle, there were no significant changes from baseline values (table 1). In contrast, during triggered movement, there was a sustained 35% increase in CBF (fig. 2 and table 1) that was accompanied by a 25% decrease in CVR and a 7% increase in $CMRO_2$ ($P < 0.025$ *versus* baseline for all). There also was a statistically significant 36% increase in EEG frequency and a significant 33% reduction in EEG amplitude. There were no changes in MAP, CPP, $PaCO_2$, or serum norepinephrine concentration to account for the cerebral effects; however, serum epinephrine concentration increased by 61% ($P < 0.01$). As expected, at each measurement period, ICP was always within 4 mmHg of the baseline value and thus had no meaningful independent effect on CPP. The relationship between CBF and CPP was defined by the regression line:

$$CBF = 0.9\ CPP + 1$$

(n = 7 data pairs; $R = 0.47$; $R^2 = 0.22$; $P = 0.29$).

When dogs were paralyzed, there was no EMG activation (fig. 1C) or evidence of gross spontaneous movement after the noxious stimulus. During the study period, there were no statistically significant changes in CBF (5% greater than baseline; $P = 0.69$) or CVR

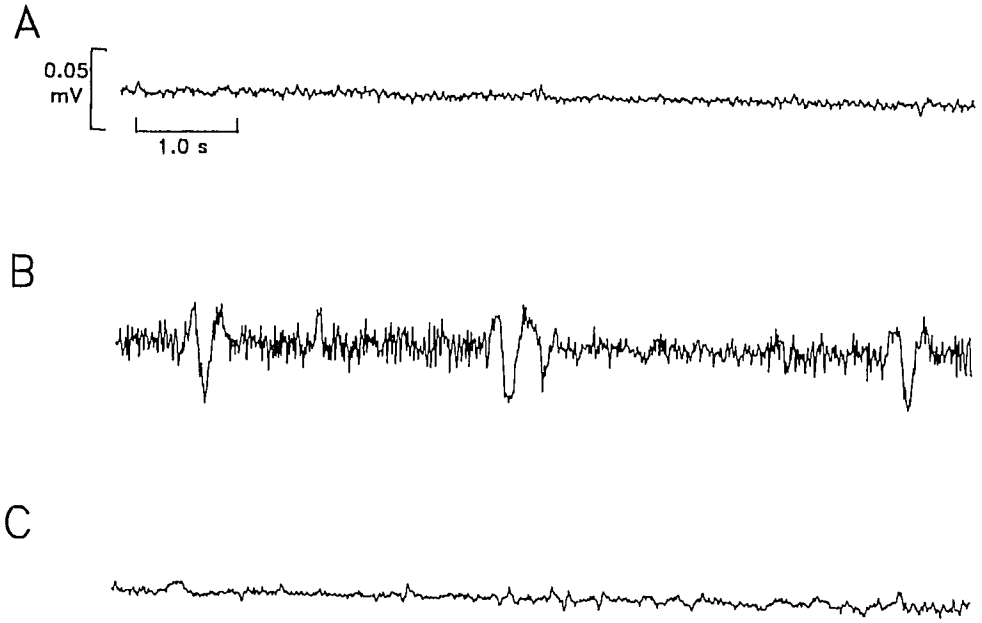

Fig. 1. Representative electromyogram (EMG) traces. Before tracheal and skin stimulation, the EMG was quiescent *(A)*. In contrast, after stimulation in unparalyzed dogs, the EMG demonstrated paroxysms of activity that coincided with visible muscle movement *(B)*. Activity was characterized by the biphasic electrical deflections of muscle depolarization, interrupted by movement artifacts from adjacent muscles. During periods of generalized movement, there was vast heterogeneity of EMG activation and muscle activity within the various muscle groups, such that, among the various recordings, there was tremendous variability in the proportions of direct EMG activity, movement artifact, and electrical attenuation or quiescence. EMG recordings after stimulation in pancuronium-paralyzed dogs showed a persistence of electrical quiescence, typical of that in the unstimulated state *(C)*. All examples were obtained from the masseter muscle of a single dog.

(7% less than baseline; $P = 0.19$); however, there was a significant 5% increase in $CMRO_2$ ($P < 0.05$ *versus* baseline). There were no significant changes in ITP, CVP, ICP, or serum norepinephrine. There was a 90% increase in serum epinephrine concentration that—although numerically greater than the 61% increase in unparalyzed dogs—did not significantly differ from baseline ($P = 0.07$), largely because of a decrease in concentration in one dog. EEG frequency significantly increased by 40%, but amplitude—which was 25% less than baseline—did not significantly change. There were unimportant, but statistically significant decreases in MAP and $PaCO_2$ (fig. 2 and table 1). At each measurement period, ICP was always within 2 mmHg of the baseline value in paralyzed dogs. The relationship between CBF and CPP was expressed by the regression line:

$$CBF = 0.3\ CPP + 38$$

($n = 7$ pairs; $R = 0.34$; $R^2 = 0.12$; $P = 0.45$).

When compared to the pancuronium-paralyzed state, noxious stimulus in the unparalyzed state resulted in significantly greater CBF, $CMRO_2$, MAP, and CPP, and significantly slower heart rates. The attainment of statistical significance within the MAP and CPP data appeared to be more of a reflection of differences during the control periods ($P = 0.06$ and 0.04, respectively) than a reflection of changes that occurred with stimulation in either paralyzed or unparalyzed conditions (fig. 1 and table 1). As expected, there was a significantly greater incidence of EMG activation recorded in the unparalyzed state. There were no significant differences in other critical variables such as ITP, CVP, ICP, serum epinephrine and norepinephrine concentrations, and $PaCO_2$. EEG changes did not differ significantly between the paralyzed and unparalyzed states, nor did the CBF/CPP regression lines.

Discussion

Data from the present study support the hypothesis that during episodes of coughing and limb and head movement, endogenously induced increases in muscle afferent activity will contribute to a sustained cerebral

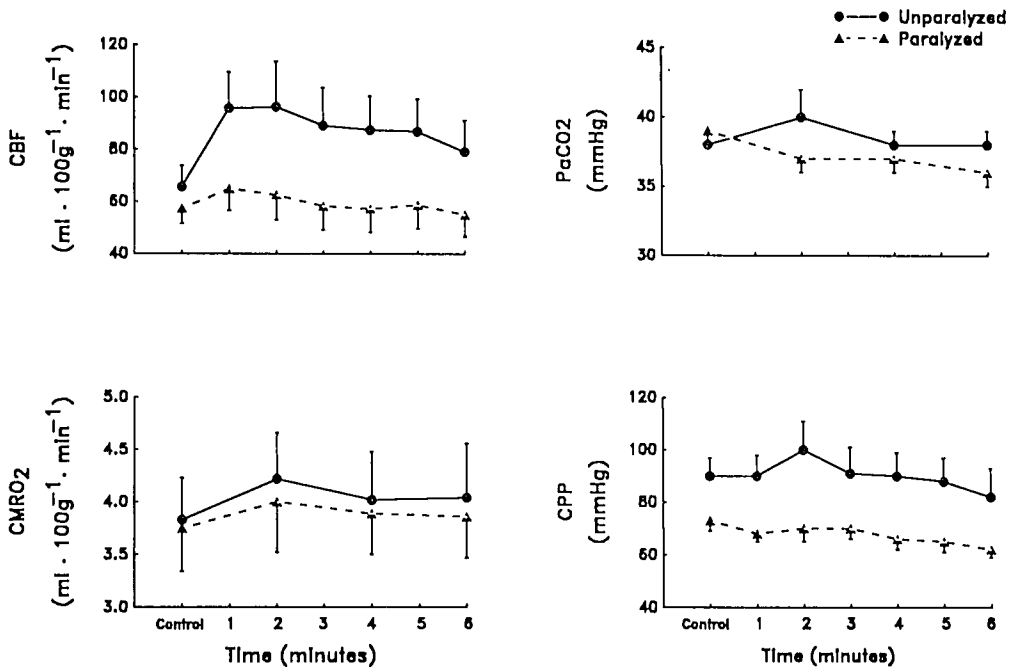

Fig. 2. Cerebral blood flow (CBF), cerebral metabolic rate for oxygen ($CMRO_2$), arterial carbon dioxide partial pressure ($PaCO_2$), and cerebral perfusion pressure (CPP) after tracheal and skin stimulation in unparalyzed and pancuronium-paralyzed dogs. Stimulation of 60-s duration was initiated immediately after control measurements (C) and continued until the 1-min measurement point. Stimulation produced movement in all unparalyzed dogs; however, movement was not detected in any dog after pancuronium treatment. Increases in CBF during movement were accompanied by an activation of the electroencephalogram (EEG) and significant increases in $CMRO_2$ and decreases in cerebral vascular resistance (CVR), but not by statistically significant changes in CPP or $PaCO_2$. In paralyzed dogs, the cerebral response to the noxious stimulus, as quantified by the combination of CBF, $CMRO_2$, CVR, and EEG measurements, was attenuated when compared to the unparalyzed state. In paralyzed dogs, there was a significant decrease in CPP and $PaCO_2$. Each dot represents the mean response for six dogs. Each vertical bar represents one SEM.

stimulation. During coughing and muscle activation (as monitored electromyographically), there was a sustained 35% increase in CBF, an increase in EEG frequency, and a reduction in EEG amplitude. These were accompanied by a 7% increase in $CMRO_2$ and a 25% decrease in CVR. In contrast, when the same dogs were paralyzed, the same noxious stimulus resulted in an attenuated cerebral response. These differences in cerebral function following the noxious stimulus could not be explained by independent alterations in $PaCO_2$, CPP, CVP, or circulating epinephrine or norepinephrine. Presumably the differences occurred because, in the paralyzed state, there was no EMG activation and, hence, no increase in MAA to modulate cerebral function. When paralyzed, the dogs had a 5% increase in CBF (not significant), a 5% increase in $CMRO_2$ ($P < 0.05$), and a 7% decrease in CVR (not significant). They experienced EEG changes; however, the EEG changes were less prominent than in the unparalyzed state. This presence of a tepid cerebral response during paralysis possibly was related to activation of pain receptors[3] or tracheal mechanoreceptors. It is unlikely that the observed differences between paralyzed and unparalyzed dogs were due to a direct influence of pancuronium on the brain. Pancuronium is neither an analgesic nor an anesthetic,[15] and it presumably does not cross the blood–brain barrier.[16] When given to quiescent subjects, it has no direct effect on CBF, $CMRO_2$, or the EEG.[16]

The findings of the present study are consistent with the afferentation theory of cerebral arousal. Afferentation theory predicts that agents or maneuvers that produce muscle stimulation and increases in MAA will produce cerebral stimulation. Supporting this theory are many clinical and laboratory observations. As reviewed by Kleitman,[17] sleep deprived subjects who were encouraged to increase motor activity, and thus increase their MAA, were less likely to fall asleep than

were subjects in whom muscle quiescence was encouraged. Giaquinto *et al.*[5] observed in cats that electric stimulation of MAA-carrying peripheral nerves produced EEG activation. Subsequent studies have demonstrated that the depolarizing neuromuscular relaxant succinycholine, a potent activator of MAA,[2,6] produces EEG activation and increases in CBF and ICP.[1-4,18] These effects are reportedly due to MAA modulation of cerebral function and not to a direct effect of succinycholine on the brain, because succinycholine does not cross the blood–brain barrier,[19] and it has no effect on the brain when injected into the carotid arteries[4] or when given intravenously after spinal cord transection.[4]

The receptor presumably most responsible for the generation of MAA after succinycholine administration and during spontaneous movement is the muscle spindle.[20] Each muscle spindle contains several intrafusal skeletal muscle fibers whose central regions 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. The intrafusal fibers and the sensory receptors are surrounded by the spindle capsule, and all these elements of the spindle reside within a bundle of extrafusal contractile skeletal muscle fibers.[20] The sensory endings of the spindles may become activated by passive stimulation from changes in the length of the extrafusal contractile skeletal muscle element to which they are coupled (*e.g.,* as occurs during passive muscle stretch or during muscle contraction induced by exercise), or they may be excited directly by drugs or neurotransmitters (*e.g.,* as occurs after the intravenous administration of succinycholine). Either mechanism results in similar activation of the muscle spindles and will produce similar increases in MAA.

The action potentials generated by the muscle afferents are transmitted by peripheral nerves to the dorsal spinal cord and eventually to the brain. This MAA information then is directed to higher central nervous system centers *via* several different neuronal pathways,[21,22] and these pathways converge on the cerebellum, the motor cortex (area 4), and the somatosensory cortex (area 3a).[23-25] Thus, increases in MAA have the potential to influence the functional activity within large areas of brain. In accordance with afferentation theory, increases in MAA in lightly anesthetized subjects can produce a generalized cerebral arousal. Though muscle spindles may be activated, and MAA therefore increased, by a variety of mechanisms (*i.e.,* both pharmacologic and nonpharmacologic), all MAA increases should be accompanied by activation of the same MAA pathways and should result in a similar cerebral response, *i.e.,* cerebral stimulation. The present study supports this hypothesis: Cerebral function alterations following movement were similar to those observed after intravenous succinycholine administration.

In the present study, spontaneous movement produced EEG activation and increases in CBF in excess of that required to meet cerebral metabolic demands. (This observation is qualitatively similar—and perhaps mechanistically related—to the observation that electric stimulation of the fastigial nucleus of the cerebellum results in a global increase in CBF in excess of cerebral metabolic demand.[26]) It is tempting to speculate that such a mechanism developed teleologically to arouse the brain instantaneously and provide luxury perfusion to the brain during periods of "fight and flight" using a mechanism that was independent of circulating chemical transmitters. Regardless of its origins, MAA input into the brain has important clinical implications. Hobbs *et al.*[27] reported that when children anesthetized with nitrous oxide were paralyzed with repeated boluses of the depolarizing muscle relaxant succinylcholine, the incidence of perioperative dreaming (24%) was higher than it was in children who received a nondepolarizing relaxant (9%; $P < 0.05$). This phenomenon was due presumably to the production of electric activation of the brain by succinylcholine *via* an MAA-mediated mechanism. In another study, Perlman *et al.*[28] observed that unparalyzed, mechanically ventilated preterm neonates had fluctuations in CBF velocity associated with spontaneous movement. (The present study suggests these CBF-velocity fluctuations were modulated at least in part by MAA increases.) Unparalyzed infants with CBF-velocity fluctuations experienced a 100% incidence of intraventricular hemorrhage, presumably because the immature, friable cerebral vessels were unable to tolerate the fluxes in blood flow and pressure. In other infants who experienced CBF velocity fluctuations previously, paralysis with pancuronium prevented the fluctuations in CBF velocity and significantly reduced the incidence of intraventricular hemorrhage to 36%. Finally, it long has been known that tracheally intubated patients who cough experience increases in ICP.[29] Though an increases in ITP and CVP resulting in increases in cerebral

‖ Lanier WL: Unpublished data. 1990.

venous blood pressure and volume commonly are assumed to cause such ICP increases, the present study and recent studies from our laboratory‖[29] have demonstrated in tracheally intubated dogs that there are no increases in mean CVP with coughing. The latter unpublished study additionally demonstrated that, despite no increases in CVP, there was a significant increase in ICP associated with activation of the EMG. This suggests that ICP increases were the result of an increase in cerebral blood volume accompanying cerebral stimulation modulated by increases in MAA. In support of this concept are CVR data from the present study that demonstrate a movement-associated cerebral vasodilation independent of CVP changes. Taken together, these studies suggest that if a clinical situation demands rigid control of cerebral function, the management of MAA input into the brain in neurologically impaired patients is an important consideration, much as we currently manage pain receptor input into the brain.

The present study and related studies[2,28] suggest that pancuronium, by virtue of its ability to prevent movement and increases in MAA in response to a noxious stimulus, can attenuate or prevent the cerebral stimulation that follows the noxious stimulus. As such, pancuronium produces a cerebral effect (*i.e.*, stability of cerebral function in response to a noxious stimulus) that commonly is associated with increased anesthetic depth. This does not mean that pancuronium paralysis will eliminate all afferent-mediated cerebral stimulation (*e.g.*, stimulation from pain receptors) or even all MAA-mediated cerebral stimulation. Both passive muscle stretch[2] and electric stimulation of peripheral nerves containing MAA-carrying neurons[5] will result in an increase in MAA traffic toward the brain, regardless of whether the subject is pharmacologically paralyzed. Both passive muscle stretch and electric stimulation of nerves have the potential to produce a cerebral arousal response similar to that which follows movement. Thus, although pancuronium appears to prevent some cerebral responses attributed to MAA increases, that effect is selective. However, it should be emphasized that the cerebral function-stabilizing properties of pancuronium should never be relied on as a substitute for adequate anesthesia.

In interpreting our data, three methodologic issues must be considered: (1) the study sequence, (2) the effect of time on the preparation, and (3) the possibility of self-reinforcement of tracheal stimulation in unparalyzed dogs. In our protocol, dogs always were studied initially in the unparalyzed state, then during pancuronium-induced paralysis. This study design was employed for several reasons. Such a design eliminated the confounding effect of additional drugs to reverse muscle paralysis. It is known that muscle-afferent receptors and the contractile, extrafusal elements of striated muscle have differing responses to the effects of muscle relaxants.[2,6,30] Although it is possible to readily measure the effect of muscle relaxants on extrafusal fibers innervated by alpha motor neurons (*e.g.*, by using an evoked twitch response),[30] it is difficult to measure the subtle effects of muscle relaxants on the intrafusal fibers of the muscle spindles, innervated by gamma motor neurons.[2,6,20] Thus, our study design eliminated the need to monitor the residual effects of pancuronium, or the confounding effect of reversal drugs, on muscle-afferent receptors or the cerebral response to those receptors. Therefore, dogs always were studied last in the paralyzed state. It is unlikely that study sequence, *per se,* affected our results, because, while conducting previous studies in lightly anesthetized subjects[1,2,16,29] and pilot studies to evaluate the cerebral effects of tracheal stimulation, we have observed that during spontaneous movement, a dog will exhibit a similar cerebral response on numerous repetitive bouts of movement. That is, the cerebral response to transient, repetitive movement episodes does not appear to fatigue. Such an effect is consistent with a mechanism dependent on muscle afferent-induced cerebral stimulation. Previous studies have demonstrated that repeated boluses of depolarizing muscle relaxants known to increase MAA,[4,31] as well as repeated electric stimulation of MAA-carrying nerves,[5] also will result in repetitive bouts of cerebral stimulation. Furthermore, when a randomized study sequence was employed previously to study the effects of succinycholine *versus* placebo in the canine sagittal sinus outflow preparation[1,2] (*i.e.*, the preparation used in the present study), the order of treatments did not appear to influence the cerebral response.[1,2]

It previously has been reported that, in the sagittal sinus outflow preparation that we used, cerebral blood flow tends to decrease at a rate of approximately 15% per h.[1,2] Additionally, in previous studies, we have observed either no changes[1,2] or a small reduction in MAP with time.[1,2] In contrast, $CMRO_2$ does not change meaningfully with time.[1] Consistent with these observations, between the unparalyzed and paralyzed control periods, we observed a 14% decrease in CBF (not significant), a 17% decrease in MAP ($P = 0.06$), and a 2% decrease in $CMRO_2$ (not significant). CPP was de-

creased by 26% ($P = 0.04$). It is unlikely that any of these observations affected the study results, because MAP (and cerebral perfusion pressure) were always within the normal autoregulatory range,[3,2] and CBF and $CMRO_2$ values were always within the normal range for this preparation.[1,2,16] Furthermore, within this range, regression analysis determined that the cerebral responses we observed were not influenced greatly by changes in CPP. Specifically, coefficient of determination data suggested that alterations in CPP could account for less than one fourth of the CBF response in unparalyzed dogs and less than one eighth the CBF response in paralyzed dogs.

During both portions of our study, dogs were exposed to a 1-min period of tracheal stimulation. When unparalyzed, dogs exhibited movement in response to this stimulus; when paralyzed they did not. It is likely that the induced movement, and not persistent tracheal stimulation in moving dogs, resulted in a cerebral response for the following reasons: Despite similar, vigorous tracheal stimulation that ceased on the 1-min measurement period in both portions of the study, paralyzed dogs never exhibited a cerebral response (even during stimulation) similar to that of unparalyzed dogs. Furthermore, the dogs were prepared in a fashion in which the head was secured and the endotracheal tube was suspended freely over a supporting bar. Thus, any secondary tracheal stimulation that resulted from dog-initiated movement should have been trivial in proportion to the investigator-induced stimulus. It should be noted, however, that direct tracheal stimulation and skin stimulation probably had some effect on the brain (perhaps mediated by pain receptors),[3] as evidenced by an EEG response to stimulation that was qualitatively similar, though varying in degree, in both the unparalyzed and paralyzed portions of the study.

In conclusion, the present study demonstrated that, in unparalyzed dogs subjected to tracheal and skin stimulation, the resulting coughing and head and limb movements were accompanied by EEG activation and an increase in CBF greater than that required to meet metabolic demands. These changes were not related to changes in CPP, $PaCO_2$, or serum epinephrine or norepinephrine concentrations. We interpret these data as evidence that MAA increases accompanying movement were largely responsible for the sustained modulation of cerebral function, a mechanism that is similar to the cerebral function alterations that follow the intravenous administration of succinycholine. In contrast, when dogs were paralyzed, tracheal and skin stimulation resulted in neither movement nor an intense cerebral response, presumably because there was not an increase in MAA in this setting.

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