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Modulation of Cerebral Function by Muscle Afferent Activity, with Reference to Intravenous Succinylcholine

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Cerebral Function and Muscle Afferent Activity Following Intravenous Succinylcholine in Dogs Anesthetized with Halothane: The Effects of Pretreatment with a Defasciculating Dose of Pancuronium. By WL Lanier, PA Iaizzo, and JH Milde. ANESTHESIOLOGY 1989; 71:87–95. Reprinted with permission.

Abstract

By the mid-1980s, it was widely assumed that if the depolarizing muscle relaxant, succinylcholine, given IV, produced increases in intracranial pressure, it did so because fasciculations produced increases in intrathoracic and central venous pressures that were transferred to the brain; however, there was no direct evidence that this was true. In contrast, we explored the possibility that the succinylcholine effect on the brain was explained by the afferentation theory of cerebral arousal, which predicts that agents or maneuvers that stimulate muscle stretch receptors will tend to stimulate the brain. Our research in tracheally intubated, lightly anesthetized dogs discovered that IV succinylcholine (which does not cross the blood-brain barrier) produced a doubling of cerebral blood flow that lasted for 30 min and corresponded to activation of the electroencephalogram and increases in intracranial pressure. Later, in our Classic Paper, we were able to assess simultaneously cerebral physiology and afferent nerve traffic emanating from muscle stretch receptors (primarily muscle spindles). We affirmed that the cerebral arousal response to succinylcholine was indeed driven by muscle afferent traffic and was independent of fasciculations or increases in intrathoracic or central venous pressures. Later research in complementary models demonstrated that endogenous movement (*e.g.*, coughing, hiccups) produced a cerebral response very similar to IV succinylcholine, apparently as a result of the same muscle afferent mechanisms, independent of intrathoracic and central venous pressures. Thus, the importance of afferentation theory as a driver of the cerebral state of arousal and cerebral physiology during anesthesia was affirmed.

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I consider it a great honor to have been invited to contribute to ANESTHESIOLOGY's ongoing series Classic Papers Revisited. The invitation was initiated by my dear friend, the late David S. Warner, M.D., who was series editor at the time. He knew my research career perhaps as well as anyone. Specifically, he knew of my fascination with understanding the scientific underpinnings of commonly observed clinical phenomena and my suspicion of any "conventional wisdom" that was promulgated without empirical support. Of several long lines of research that I engaged in during my 37 yr on the Mayo Clinic (Rochester, Minnesota) faculty (fig. 1), one addressed these issues and taught me about scientific method and the emotional highs and lows of a sustained research program more than any other: *i.e.*, the modulation of cerebral function by muscle afferents. In 1994, I codified and named this effect "the afferentation theory of cerebral arousal."[1] As I have summarized previously, "Afferentation theory predicts that agents or maneuvers that produce muscle stretch or contraction of extrafusal striated muscles or that directly stimulate muscle stretch receptors (primarily the intrafusal muscle spindles) will stimulate the brain. In contrast, agents or maneuvers that lessen muscle stretch or contraction tend to stabilize brain function or encourage its quiescence."[2]

It was this line of research—published almost exclusively in ANESTHESIOLOGY, and culminating with a 1989 report that directly correlated cerebral stimulation and muscle afferent activity in an animal model[3]—that Dr. Warner and I agreed should form the foundation for my Classic Papers Revisited story. The research that my team and I performed provides a framework to understand the following phenomena of relevance to clinical anesthesiology and intensive care medicine: How does succinylcholine—the depolarizing muscle relaxant that does not cross the blood-brain barrier[4] and has no effect on the brain when injected into the carotid arteries or when given IV after spinal cord transection[5]—increase intracranial pressure (ICP)? And why does ICP increase in tracheally intubated subjects who move, hiccup, or cough, given that the tracheal tube prevents closure of the glottis and sustained increases in intrathoracic pressure?

Laboratory Investigation Beginnings

My participation in laboratory research in animal models began in the summer of 1983. I had recently arrived at Mayo

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Fig. 1. William L. Lanier, M.D. Dr. Lanier served on the faculty of the Mayo Clinic Department of Anesthesiology and Perioperative Medicine and its Division of Neuroanesthesiology for 37 yr, retiring in September 2021. He was engaged in both clinical and laboratory research during the entirety of his career and was promoted to Professor of Anesthesiology in 1995. From 1993 to 1994, he was President of the Society for Neuroscience in Anesthesiology and Critical Care (Raleigh, North Carolina) and received its Distinguished Service Award in 2014. He was Editor-in-Chief of *Mayo Clinic Proceedings* from 1999 through mid-2017, and at the completion of his term, the journal was receiving submissions from 60 nations and had an impact factor that had increased from 2.0 to 7.2. In 2015, Dr. Lanier received the Council of Science Editors (Mullica Hill, New Jersey) Distinguished Service Award for his activities in educating editors and editorial board members. Dr. Lanier's original research has focused on neuroprotection, cerebral physiology, and clinical neuroanesthesiology. He also has published extensively on the quality of medical evidence, medical ethics, and professionalism.

Clinic to complete a 12- to 24-mo fellowship in neuroanesthesiology under the mentorship of John D. Michenfelder, M.D. The first laboratory study on which I would serve as first author began in early 1984 and evaluated the effects of the nondepolarizing muscle relaxant, atracurium—approved just months before for clinical use in the United States—on cerebral physiology.[6] Atracurium was of interest because it has a primary metabolite, laudanosine, that is a cerebral stimulant and potential convulsant. Shi *et al.* soon reported that laudanosine altered anesthesia requirements in a rabbit model.[7] Our research[6] employed the laboratory's workhorse model, the canine sagittal sinus outflow model of cerebral function, which allowed near-instantaneous measurement of cerebral blood flow, the electroencephalogram (EEG), and ICP, and intermittent measurements of cerebral metabolic oxygen consumption.

Our studies were conducted during 1.0 minimum alveolar concentration (MAC) and sub-MAC halothane concentrations. Dealing with lightly anesthetized dogs with electrodes, pressure monitors, and sagittal sinus catheters coming from the brain was a tricky business. Sometimes unparalyzed animals would move, either spontaneously or in response to some stimulus (*e.g.*, touch, loud sound), and when they moved, we feared they would harm the functionality of the endotracheal tube, arterial and venous catheters, or more. To prevent any inadvertent stimulation of the dog, we locked the doors of the laboratory (to prevent visitors from entering), disconnected the telephones, packed the dog's ears with cotton plugs, limited touching or moving the animal, and communicated with each other using hand gestures and flash cards. Thus, for literally hundreds of hours during the ensuing years, the laboratory (with as many as seven investigators and technicians working simultaneously) functioned in complete silence when running protocols. Dr. Michenfelder seemed somewhat taken aback when he first tried to visit and check on our progress, only to find the door locked and no one speaking once he was given entrance.

Despite our best efforts, in unparalyzed dogs anesthetized with 1.0 MAC halothane, we would sometimes observe spontaneous episodes of EEG activation, and the activation would often correlate with new-onset muscle twitching. If the movement progressed to hiccups, bucking, or coughing, the EEG activation would persist, and there would be a tendency toward cerebral blood flow increases (later reported by Lanier *et al.*[8]). When we observed a dog beginning to twitch before establishing control conditions, we would inject a small dose of succinylcholine IV to prevent the dog from moving further. To our surprise, cerebral blood flow would predictably increase by a considerable amount; however, our observations could not reconcile which was more responsible for the cerebral blood flow increase: spontaneous arousal, movement, or succinylcholine.

Learning about Possible Modulation of Cerebral Function by Muscle Afferents

My reading on the possible mechanisms by which muscle relaxants might affect cerebral function introduced me to research on carbon dioxide physiology, adrenergic physiology, release of drug metabolites, histamine release, and—for the first time in my life—modulation of cerebral function by muscle afferents.

The concept that muscle activity might affect cerebral function was introduced by Nathaniel Kleitman, Ph.D., "the father of sleep research," who observed that sleep-deprived volunteers could remain awake for days if they were encouraged to move, *i.e.*, much longer than in volunteers who remained quiescent or recumbent.[2,9] In the

ensuing decades, others would identify muscle afferents, predominantly muscle spindles, as likely responsible for movement-associated brain stimulation. Specifically, cleverly designed studies would determine that activation of muscle spindles, or electrical stimulation of nerve pathways carrying muscle afferent traffic, would stimulate the brain, and succinylcholine was a known activator of muscle spindles (reviewed elsewhere[1,2,5]).

Focused Studies to Examine the Mechanisms of Action of Succinylcholine on the Brain

Enriched by this information, I hypothesized that succinylcholine might stimulate the brain *via* muscle spindles, and this would in turn affect cerebral blood flow, cerebral blood volume, and ICP. Such a concept was antithetical to "conventional wisdom" in anesthesiology. At the time, the overwhelmingly popular (although unproven) concept of why succinylcholine might increase ICP, if it increased it at all, related to the presumed effect of succinylcholine-induced fasciculations on intrathoracic pressure. According to this line of thought, fasciculations would increase intrathoracic pressure, which in turn would increase central venous pressure (CVP). This presumably would cause passive venous congestion and increases in intracranial blood volume, which would result in increases in ICP (fig. 2). Amazingly, of the probably thousands of patients who had received IV succinylcholine while having their CVP measured in real time, I could not find peer-reviewed data from even a single patient reporting on whether fasciculations altered CVP.

Our initial formal study[8] in the canine sagittal sinus outflow model used a background of 1.0 MAC halothane and determined that IV succinylcholine produced a peak mean cerebral blood flow increase that was almost two times baseline values (fig. 3). Fasciculations began a mean of 24 s after IV succinylcholine and ceased at 37 s. Cerebral blood flow changes began within the first minute after IV succinylcholine, peaked at 3 to 4 min, and remained greater than baseline for approximately 30 min. The ICP response paralleled that of cerebral blood flow, presumably due to an increase in cerebral blood volume. CVP did not meaningfully change, nor did cerebral perfusion pressure or cerebral metabolic oxygen consumption. There was a delayed increase in $Paco_2$ after IV succinylcholine, but this was inadequate to account for the cerebral blood flow response during the first 15 min (fig. 3). Further, the EEG became activated in five of six dogs, concomitant with the greatest cerebral blood flow increase. However, in two additional dogs given a 1.5 MAC halothane anesthetic, or another two dogs given 1.0 MAC halothane and a supra-paralyzing dose of pancuronium IV, subsequent IV succinylcholine produced no meaningful cerebral response.[8]

Our succinylcholine study in a canine model was published in May 1986.[8] A parallel ICP report in humans by Minton *et al.*—who also identified that pretreatment with a paralyzing dose of a nondepolarizing relaxant would abolish the ICP response to IV succinylcholine—was published in August 1986.[10] Consistent with our observation in dogs,[8]

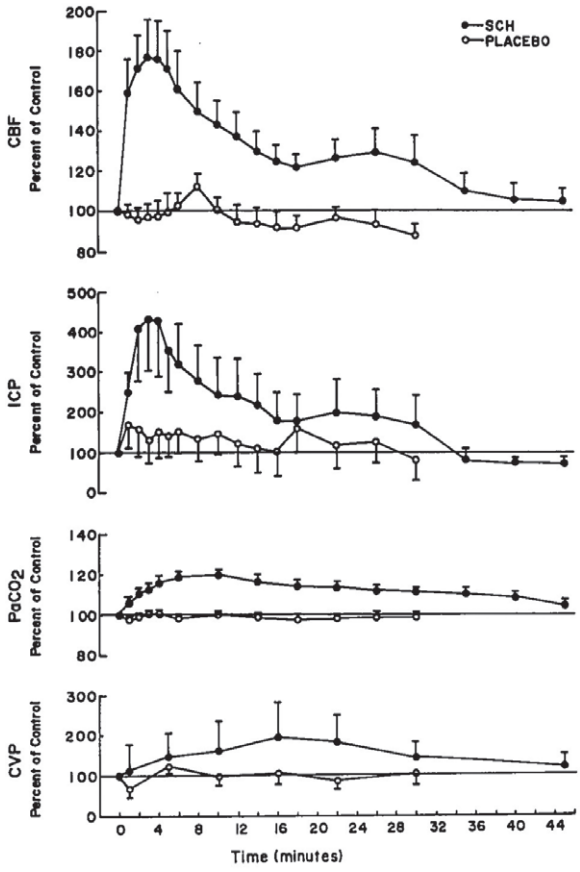

Fig. 3. Cerebral response to IV succinylcholine (SCH) in lightly anesthetized dogs. Values are presented as percent of baseline; *vertical bars* = 1.0 SE; N = 6. CBF, cerebral blood flow; CVP, central venous pressure; ICP, intracranial pressure. From Lanier *et al.*[8]

Fasciculations or Movement →
↑ Intrathoracic Pressure →
↑ Central Venous Pressure →
↑ Cerebral Venous Pressure →
↑ Cerebral Blood Volume →
↑ Intracranial Pressure

Fig. 2. Discredited explanation of intracranial pressure increases after IV succinylcholine or movement in tracheally intubated subjects.

Minton *et al.*[10] reported in five unpretreated patients that IV succinylcholine did *not* alter CVP.

Based on our cerebral blood flow and EEG data, I speculated that the effect of succinylcholine on muscle afferent activity, and the subsequent cerebral response, were akin to what one might expect from sticking the finger of an awake or lightly anesthetized human into an electrical outlet. The intense induced afferent activity (of all forms) would cause the brain to become electrically activated, and cerebral blood flow, cerebral blood volume, and ICP would respond accordingly. (We eventually discovered that cerebral blood flow was more sensitive than the EEG in signaling a cerebral arousal response to peripheral nerve traffic,[3,8] a pattern confirmed by others.[11]) In accordance with this concept, sufficiently deep anesthesia or profound cerebral dysfunction (*e.g.*, coma) would prevent the cerebral response to succinylcholine, independent of any alterations in muscle afferent activity.

Bringing Muscle Afferent Activity Measurements into the Studies

To further my research, I applied for an American Society of Anesthesiologists (Schaumburg, Illinois; later Foundation for Anesthesia Education and Research) Starter Grant to evaluate the mechanisms of succinylcholine's effect on the brain. The proposed research would directly measure muscle afferent activity traffic from peripheral nerves.

Before submitting the grant, in pilot studies, I attempted to measure muscle afferent activity traffic from a peripheral nerve that enervated a major muscle in the leg of an anesthetized dog. I naively assumed that measuring muscle afferent activity traffic would be no more difficult than measuring the EEG, but this simplistic view initially proved disastrous. Specifically, at the end of some other experiments in anesthetized dogs, James Milde, the lead laboratory technician, and I performed a cutdown on the leg of a dog, then attached wires with needle endings into the peripheral nerve of a major muscle. We amplified the response to dynamic passive muscle stretch and IV succinylcholine employing a polygraph and attempted to record the tracings on a strip recorder.

When this failed, I approached my colleague, the eminent neurologist and electroencephalographer, Frank W. Sharbrough, M.D., who thought the frequency of muscle afferent traffic might be too rapid to be recorded by pen and paper, and suggested attaching the output of the polygraph to an oscilloscope or audio speaker. Not having access to an oscilloscope, I opted for the latter. Upcoming studies still revealed no response. I informed Sharbrough of this, and he asked which amplification and filter settings I was using on the polygraph. I told him, and he replied, "Goshawmighty, Bill, with those settings, you will probably pick up radio traffic between the airplanes flying overhead." "To heck with you, Frank," I told him, as I stormed off, back to the laboratory. "I'll show him," I thought.

With further reading of the literature, I learned that I could eliminate the *efferent* traffic through the nerve by transecting the nerve and applying the electrode to the distal component. Milde and I attempted to use this approach to record muscle afferent activity using our polygraph or speaker system. With success, the baseline muscle afferent activity traffic (reflecting the firing of individual muscle spindles) *should have* sounded like the random falling of a small number of raindrops on a tin roof. After IV succinylcholine or passive muscle stretch, the coalesced signals (from increased muscle afferent activity traffic) should have sounded like a full-blown rainstorm. However, this is not at all what we heard as I progressively adjusted the polygraph amplifiers and filters. Initially, there was nothing apparent but a background hum. Then, with a single additional polygraph adjustment (well within the range Sharbrough had told me to avoid) and out of the dog's leg, I and everyone else in the room clearly heard a melodious, "Everybody's doing a brand-new dance now. Come on baby, do the loco-motion." My meter-long wires connected to the dog had inadvertently become a radio antenna, the polygraph had become a radio wave receiver, and I had picked up traffic from the local rock-and-roll radio station and a song from the band Grand Funk Railroad.[12] I realized I was in deep trouble!

After swallowing my pride, I snooped around the institution and discovered Paul A. Iaizzo, a Ph.D. candidate, who coached me on how to measure muscle afferent activity in response to IV succinylcholine. I included the data in a proposal for an American Society of Anesthesiologists Starter Grant, which was funded and began in January 1986. The grant was for approximately $10,000, augmented by an equal amount from my home institution. Iaizzo created the saturating-diode integrating device[3] that we used to quantify muscle afferent activity traffic for our many studies. The device was made from $23 in parts that he had purchased from a local electronics parts store, saving us a budget-busting $1,000 to $2,000 on a commercially available product.

Experimentally Correlating Muscle Afferent Activity and a Cerebral Response to Succinylcholine: The Classic Paper

Armed with the aforementioned knowledge and resources, we began to quantify the cerebral response to IV succinylcholine (as in previous experiments) while simultaneously quantifying muscle afferent activity from a peripheral muscle. No one had ever attempted to do this type of experiment before, and—as we proceeded with our research—we understood why. The complexity of the experiments appeared to increase exponentially as the number of variables we added went up linearly. For example, five laboratory technicians, in addition to Paul Iaizzo and me, were required to prepare the animals, maintain the preparations in real time, and run the protocols.

With considerable effort, we were able to complete these studies and obtain beautifully clean data. Our research indeed proved that the cerebral response to IV succinylcholine correlated with prolonged increases in muscle afferent activity (fig. 4).[3] To better appreciate the response of muscle afferent activity traffic to a single dose of IV succinylcholine, I have provided an example in the appendix, along with a description of how we processed and quantified the muscle afferent activity output.

A clinically significant question that remained was, "What is the role of fasciculations in producing the muscle afferent activity and cerebral responses to IV succinylcholine?" When reading the literature, I learned that succinylcholine can activate muscle spindles either directly as an agonist of gamma efferent receptors on the spindles, or by mechanical coupling of the spindles with extrafusal muscle fibers that contract during fasciculations. That the direct effect of succinylcholine on muscle afferent activity was the more important mechanism in determining a cerebral response was supported by the observation by Minton *et al.* that visible fasciculations were an inconsistent finding after succinylcholine. In 5 of their 13 patients (Group 1) who had the greatest ICP increases, none visibly fasciculated.[10] In contrast, all patients who visibly fasciculated had only small ICP increases. Later, Stirt *et al.*,[13] from the same institution, reported that a "defasciculating dose" of the curariform relaxant metocurine prevented fasciculations and the cerebral response to succinylcholine. However, it was unclear whether metocurine might possibly alter the mechanical activation of muscle spindles associated with fasciculations, alter the direct pharmacologic activation of muscle spindles (through gamma efferent receptors), or have some other effect that would abolish the cerebral response to IV succinylcholine. This would require further study.

To better understand this issue, in our aforementioned study of direct muscle afferent activity and cerebral responses to IV succinylcholine, we included in our Classic Paper parallel experiments in which six additional dogs were pretreated with a defasciculating dose of the noncurariform relaxant pancuronium.[3] Under these conditions, pancuronium abolished the fasciculations observed in all six previous dogs (apparent visibly and verified by electromyography), but the defasciculating dose of pancuronium only attenuated the muscle afferent activity

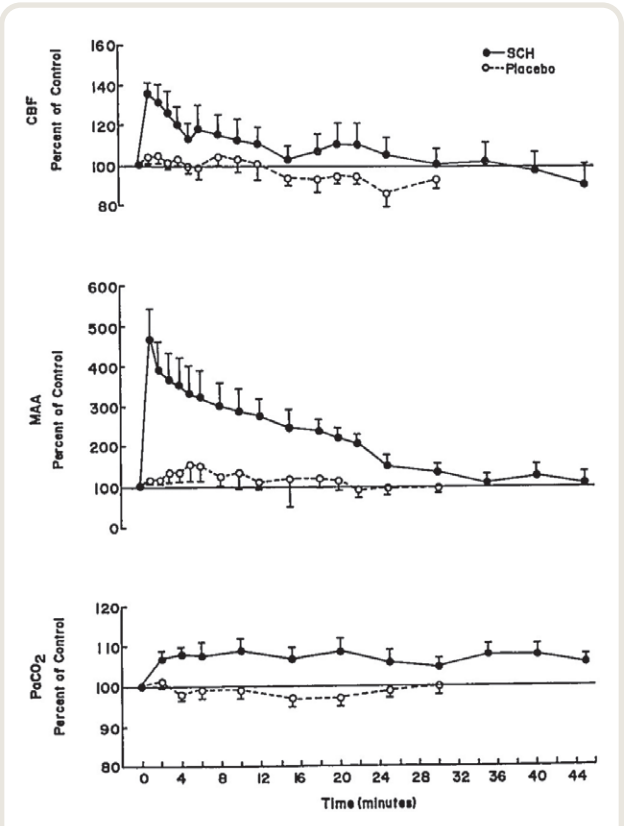

Fig. 4. Cerebral blood flow (CBF), muscle afferent activity (MAA), and $Paco_2$ responses to IV succinylcholine (SCH) in anesthetized dogs. Values are presented as percent of baseline; *vertical bars* = 1.0 SE; N = 6 for CBF and $Paco_2$, N = 5 for MAA. From Lanier *et al.*[3]

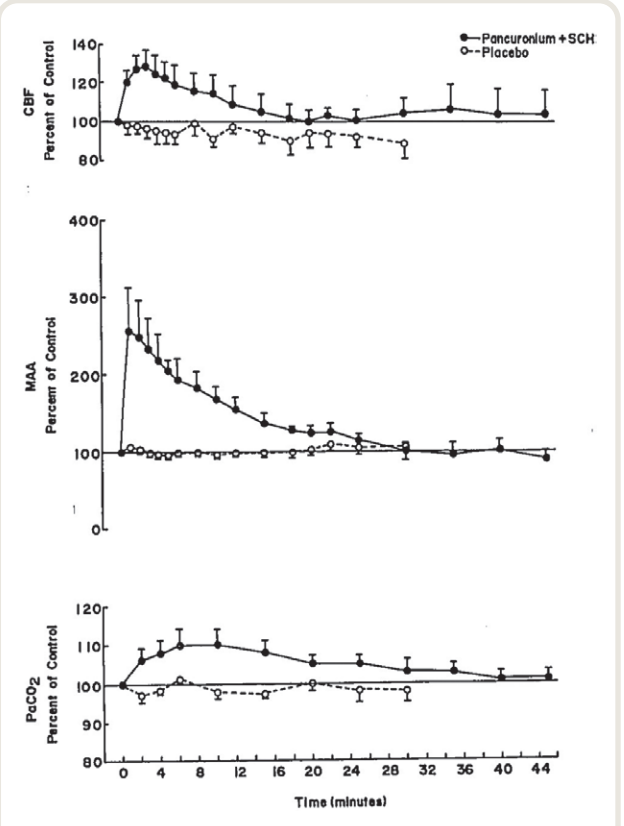

Fig. 5. Cerebral blood flow (CBF), muscle afferent activity (MAA), and $Paco_2$ responses to IV succinylcholine (SCH) in anesthetized dogs pretreated with a "defasciculating" dose of IV pancuronium. Values are presented as percent of baseline; *vertical bars* = 1.0 SE; N = 6. From Lanier *et al.*[3]

response. The cerebral blood flow response was preserved (fig. 5). Collectively, the Lanier *et al.*,[3] Minton *et al.*,[10] and Stirt *et al.*[13] research proved that after IV succinylcholine, the presence or absence of fasciculations in an individual subject (1) is not critical for dictating a muscle afferent activity response, and (2) provides no clue as to whether or not there is a cerebral response.

Based on the findings of our study directly measuring muscle afferent activity, my colleagues and I formulated a manuscript and sent it to Anesthesiology (later published in July 1989 in the "50th Anniversary Issue" of the Journal[3]). I have to believe that the referees who reviewed the manuscript recognized the beauty of the research, as exemplified by the opening general comment of one of them: "This study represents a technical *tour de force* for which the authors are to be commended."

Looking beyond IV Succinylcholine

If afferentation theory was indeed correct, it would follow that nonpharmacologic activation of muscle afferent activity traffic should have the same effect on the brain as that after IV succinylcholine. Using our canine sagittal outflow model[1] and other complementary canine models,[14] we later determined that induced movement (initiated by tracheal and skin stimulation during sub-MAC halothane), which endogenously increased muscle afferent activity, produced the same increases in cerebral blood flow and ICP, and the same activation of the EEG (independent of CVP and intrathoracic pressure) that was observed after IV succinylcholine. The experiments were then repeated after complete paralysis with IV pancuronium. Under these conditions, pancuronium blocked the cerebral blood flow and ICP responses and attenuated the EEG response.[1,14] Collectively, this research further discredited the role of intrathoracic pressure and CVP in modulating ICP (fig. 2). Of greater importance, we now had empirical proof for a more generalized application of afferentation theory.

Conclusions

A biomedical investigator will, in the course of an entire career, typically engage in multiple lines of sustained research and other more limited investigations. Some of these, more than others, will make novel (even provocative) discoveries or help the investigator develop research skills that carry downstream benefits. Hard work is essential, and teams of talented contributors can accomplish far more than any individual. These are lessons I learned when investigating the afferentation theory of cerebral arousal.

Employing this approach and a few carefully designed experiments, our research team was able to discredit decades worth of untested conventional wisdom (fig. 2) and replaced it with an empirically supported theory.

Our research began innocently while observing the real-time cerebral response to spontaneous movement in anesthetized dogs and the subsequent effects of small doses of IV succinylcholine. The direction our research took was entirely unanticipated. From this experience, I have often considered that perhaps God sometimes drops a "crumb" of evidence off His immense table of knowledge in hopes that some soul will recognize it and use the observation to open new paths of scientific thought. This has certainly been my experience when investigating afferentation theory, and I share this experience with others who have made novel scientific discoveries based on similarly humble origins, with consequences large and small.

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Support was provided solely from institutional and/or departmental sources.

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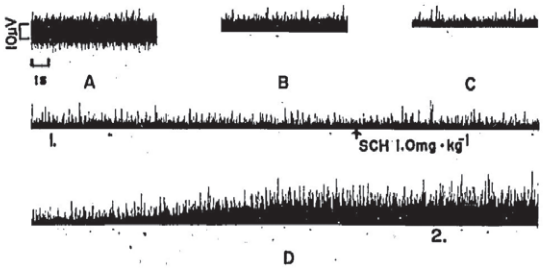
Appendix



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 (D_1); however, following iv SCh, there were dramatic increases in MAA (D_2). 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 D_2 than at point D_1.

The method for quantification of muscle afferent activity data using a saturating diode circuit. From Lanier *et al.*[3]

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