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Improved Amplitude of Myogenic Motor Evoked Responses after Paired Transcranial Electrical Stimulation during Sufentanil/Nitrous Oxide Anesthesia

Cor J. Kalkman, M.D., Leon H. Ubags,† Henk D. Been, M.D.,‡ Astrid Swaan, M.D.,† John C. Drummond, M.D.§*

Background: **Measurement of motor evoked responses to transcranial stimulation (tc-MER) is a technique for intraoperative monitoring of motor pathways in the brain and spinal cord. However, clinical application of tc-MER monitoring is hampered because most anesthetic techniques severely depress the amplitude of motor evoked responses. Because paired electrical stimuli increase tc-MER responses in awake subjects, we examined their effects in anesthetized patients undergoing surgery.**

Methods: **Eleven patients whose neurologic condition was normal and who were undergoing spinal or aortic surgery were anesthetized with sufentanil–N_2O–ketamine. Partial neuromuscular blockade (single-twitch height 25% of baseline) was maintained with vecuronium. Single and paired electrical stimuli were delivered to the scalp, and compound action potentials were recorded from the tibialis anterior muscle. The amplitude and latency of the tc-MERs were measured as the interval between paired stimuli was varied between 0 (single stimulus) and 10 ms. All recordings were completed before spinal manipulation or aortic clamping.**

Results: **Median amplitude of the tc-MER after a single stimulus was 106 μV (10th–90th percentiles: 23–1,042 μV), and the latency to onset was 33.2 ± 1.4 ms (SD). With paired stimuli (interstimulus interval 2–3 ms), tc-MER amplitudes increased to 285 (79–1,605) μV, or 269% of the single-pulse response ($P < 0.01$). Reproducibility of individual responses increased with paired stimulation. Onset latency decreased to 31.4 ± 3.2 ms ($P < 0.05$). Maximum amplitude augmentation was observed with interstimulus intervals between 2 and 5 ms and in patients with low-amplitude responses after single-pulse stimulation.**

Conclusions: **Application of paired transcranial electrical stimuli increases amplitudes and reproducibility of tc-MERs during anesthetic-induced depression of the motor system. The effect may represent temporal summation of stimulation at cortical or spinal sites. The results of this study warrant further clinical evaluation of paired transcranial stimulation. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, opioid: sufentanil. Monitoring, spinal cord function: motor evoked response; transcranial stimulation.)**

INTRAOPERATIVE monitoring of motor evoked responses to transcranial electrical or magnetic stimulation (tc-MERs) provides a method for monitoring conduction in descending motor pathways during operations in which there is a risk of spinal cord injury. The addition of tc-MERs to intraoperative somatosensory evoked response monitoring may, at least theoretically, decrease the occurrence of false-negative results that have been reported during monitoring of somatosensory evoked responses.[1,2] A retrospective survey by the Scoliosis Research Society involving 33,000 patients undergoing spinal surgery revealed that 28% of the neurologic damage that occurred had not been detected by monitoring of somatosensory evoked potentials.[3] Responses of muscle origin, referred to as compound muscle action potentials (CMAPs), are highly specific for impulses transmitted by the motor tracts and can be recorded noninvasively from muscles in the upper or lower limbs. In awake subjects, CMAPs resulting from transcranial stimulation (TCS) are large (several millivolts) and can be recorded after the application of a single transcranial stimulus.

However, during anesthesia considerable tc-MER amplitude depression occurs with most anesthetic regimens. The myogenic response is completely abolished, even with very low concentrations of volatile anesthetic agents, which makes tc-MER recording impossible at

* Staff Anesthesiologist, Department of Anesthesiology.

† Research Associate, Department of Anesthesiology.

‡ Staff Orthopedic Surgeon, Department of Orthopedics.

§ Professor of Anesthesiology, Department of Anesthesiology, University of California at San Diego; Anesthetist-in-Chief, Department of Veterans Affairs Medical Center, San Diego, California.

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Address reprint requests to Dr. Kalkman: Academisch Ziekenhuis bij de Universiteit van Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

end-tidal isoflurane concentrations as low as 0.3%.[4,5] N_2O is also a powerful depressant of tc-MER,[6] as are benzodiazepines,[7,8] barbiturates and propofol.[8] Drugs that have only minor effects on tc-MERs are those known to maintain or increase muscle tone and include etomidate,[8] ketamine,[9,10] and synthetic opioids.[8] Most authors have been able to record tc-MERs using a N_2O–opioid technique,[5,6,11] although the depression of conduction in the motoneuronal system may be so severe, as to preclude effective intraoperative tc-MER monitoring in a subset of patients.

One possible strategy for overcoming anesthetic-induced depression is facilitation of the motoneuronal system responsiveness. It has been shown that voluntary contraction of the target muscle group improves the amplitude of tc-MERs.[12–14] Involuntary facilitation can also be achieved by the properly timed application of dermatomal stimulation immediately before stimulation of motor neurons.[15,16] The facilitation that is observed is presumed to be the result of some sort of "priming" of the anterior horn cell as a result of afferent input from the peripheral nervous system to the dorsal horn. It also appears that facilitation of myoneural responsiveness can be achieved by stimuli of central nervous system origin.

In nonanesthetized subjects, electrical TCS using paired stimuli with an interstimulus interval (ISI) of 2–3 ms has been shown to increase the amplitude of tc-MERs.[17] The presumption has been that this facilitation also occurs at the level of the spinal cord, although some or all of the effect could be at the level of the cerebral cortex. The current study sought to determine whether the facilitating effect of paired stimulation observed in nonanesthetized subject persists during sufentanil–N_2O anesthesia in patients undergoing surgical procedures with an inherent risk of spinal cord injury. The study compared the latency and amplitude of tc-MERs in response to single transcranial electrical stimuli with the responses to paired electrical stimuli, at various ISIs.

Materials and Methods

Nine patients undergoing spinal surgery and two patients undergoing thoracic aortic aneurysm repair gave informed consent to participate in this institutionally approved study. The neurologic status of all patients was normal. The patients received diazepam, 10 mg orally, 1 h before surgery. Anesthesia was induced with etomidate 0.3 mg/kg and sufentanil 1.5 μg/kg and was maintained with sufentanil 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and N_2O 50%. When there were clinical signs that the level of anesthesia was light, ketamine 0.3–0.5 mg/kg was administered intravenously. Muscle relaxation was monitored electromyographically at the hypothenar eminence with a Relaxograph (Datex, Finland), and the amplitude of the single-twitch response was maintained at 25% of control with vecuronium with a closed-loop infusion system. Monitoring included the electrocardiogram, hemoglobin blood O_2 saturation by pulse oximetry, central venous pressure, invasive arterial blood pressure, end-tidal CO_2 concentration, and nasopharyngeal temperature. Figure 1 shows the apparatus used to record tc-MERs to single and paired TCS. Two identical transcranial electrical stimulators (D180A, Digitimer, Welwyn Garden City, UK) were used. The stimuli from both units were delivered to the scalp by two 9-mm silver electroencephalographic disc electrodes, attached to the skin with collodion, with the anode positioned at C_z[18] and the cathode at F_z (International 10–20 system). The units were triggered either simultaneously or sequentially. The ISI could be varied between 0 (single pulse) and 10 ms. Myogenic responses were recorded from the skin over the left and right tibialis anterior muscles with adhesive gel Ag–AgCl electrodes (Cleartrace, Medtronic Andover Medical, Haverhill, MA); the active electrode was placed over the muscle belly, referenced to an electrode placed over the muscle tendon. A ground electrode was placed on the left leg, proximal to the knee. The signal was amplified 5,000–20,000 times (adjusted to obtain maximum vertical resolution), and filtered between 30 and 1,500 Hz with a biologic amplifier (3T PS-800, Twente Technology Transfer, Twente, The Netherlands). These amplifiers have an extremely high-input impedance ($>10^{12}$ Ω), and the common mode rejection ratio is greater than 95 dB. The responses were displayed and stored on a Macintosh Quadra computer (Apple Computer, Cupertino, CA) with 12-bit analog-to-digital conversion and motor evoked response (MER) acquisition software written with the LabView data acquisition development system (National Instruments, Austin, TX).

After achieving a stable anesthetic state, at least 20 min after induction of anesthesia, stimulus intensity (0–100%, $\approx$0–1,200 V) was adjusted to achieve maximal responses with single-pulse stimulation, typically 600–700 V. At least 20 min after skin incision, but before any surgical interventions that might have resulted in impaired spinal cord functioning, quadru-

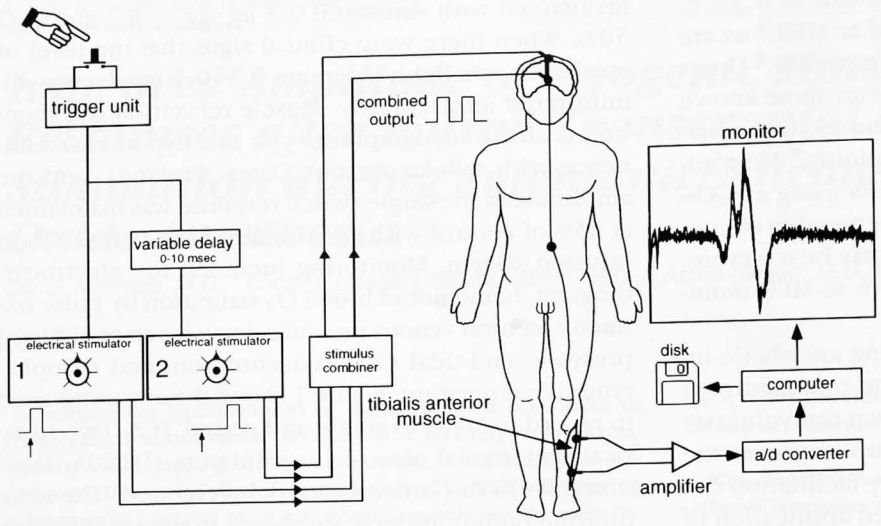

Fig. 1. Experimental apparatus for single or paired transcranial electrical stimulation and recording of compound muscle action potentials (CMAPs) from the tibialis anterior muscle. Stimulation was triggered manually. The trigger pulse to the second stimulator unit was delayed between 0 and 10 ms. Output from the two units was combined by means of diodes.

plicate CMAPs in response to single and paired TCS were recorded. Responses to paired stimulation were acquired every 2 min, while ISI was increased from 1 to 2, 3, 5, 7, and 10 ms. The effect of paired stimulation was also assessed after reducing the stimulus intensity to a level that elicited threshold responses to a single transcranial stimulus.

Peak-to-peak amplitudes and onset latency, as measured from the beginning of the first pulse, were determined from the average of the four individual responses. tc-MER latencies were normally distributed and are expressed as mean ± SD. The coefficient of variation was calculated for the amplitudes of four consecutive single-sweep tc-MERs acquired with single or paired (ISI 3 ms) stimulation. Because tc-MER amplitude data did not appear to be normally distributed, amplitudes are presented as medians, with the 10th and 90th percentiles. Differences in amplitude and latency between single and paired stimulation were compared using Wilcoxon's signed-rank test.

Results

Patient characteristics are presented in table 1. Single-pulse TCS elicited tc-MERs in all but one patient. Large interpatient amplitude variability was observed. The median amplitude of the right tibialis anterior muscle response was 106 (23–1,042) μV, and the onset latency was 33.2 ± 1.4 ms. With paired TCS (ISI 2–3 ms), median tc-MER amplitude increased to 285 (79–1,605) μV or 269% of the single-pulse response ($P <$ 0.01) (fig. 2). With single-pulse stimulation the coefficient of variation for the amplitude of four consecutive responses within an individual patient was 43%. With paired stimulation, with an ISI of 3 ms, the coefficient of variation was 17%. When ISI was increased to 5 or 7 ms, no further augmentation occurred. An ISI of 10 ms often elicited two overlapping responses of lower amplitude.

Onset latency decreased from 33.2 ± 1.4 to 31.4 ± 3.2 ms ($P < 0.05$) for paired (ISI 3 ms) *versus* single TCS respectively. When stimulus intensity was reduced to a level that elicited a threshold response with single stimulation, the amplitude-augmenting effect of paired stimulation became more pronounced. Similarly, in patients in whom maximal single-pulse stimulation elicited only low-amplitude responses, the effect of paired stimulation was more pronounced than in patients who had high-amplitude responses to single-pulse TCS (fig. 3). Although not specifically studied, paired stimulation appeared to decrease the stimulus intensity needed to elicit a detectable response. One patient had only one detectable response to four separate single stimuli. With paired stimulation and an ISI of 2–5 ms, responses of 150–350 μV could be recorded, whereas no facilitation was obtained when ISI was increased to 10 ms (fig. 4).

Discussion

The data derived in the current study indicate that application of paired transcranial stimuli, with an ISI

Table 1. Patient Data

Patient No.	Age (yr)	Gender
1	38	F
2	18	M
3	13	F
4	68	M
5	34	F
6	31	M
7	47	F
8	16	F
9	40	F
10	37	F
11	21	M

of 2–3 ms, in N_2O–sufentanil-
results in increase in tc-MER amp
patients. Our findings suggest t

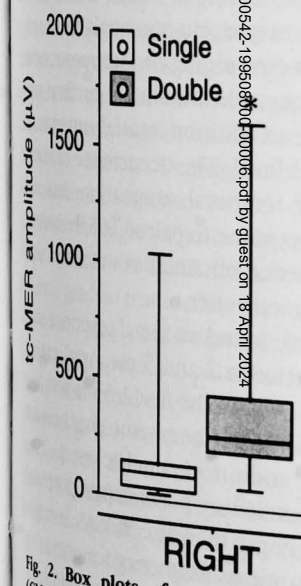

Fig. 2. Box plots of compound m (CMAPs) in the tibialis anterior mu transcranial electrical stimulation. 75th, 50th (median), 25th, and 10t bution of amplitudes of motor evoke ial stimulation (tc-MER) is skewed. single-pulse stimulation.

Table 1. Patient Data

Patient No.	Age (yr)	Gender	ASA Physical Status	Disease	Operation
1	38	F	I	Scoliosis	Transthoracic fusion and dorsal instrumentation
2	18	M	I	Scheuermann's disease, scoliosis	Transthoracic spinal fusion
3	13	F	I	Scoliosis	Cotrel-Dubousset instrumentation
4	68	M	III	Thoracic aortic aneurysm	Repair of aortic aneurysm
5	34	F	I	Scoliosis	Cotrel-Dubousset instrumentation
6	31	M	I	Scoliosis	Transthoracic fusion and dorsal instrumentation
7	47	F	I	Kyphosis	Transthoracic fusion and dorsal instrumentation
8	16	F	I	Scoliosis and kyphosis	Transthoracic fusion and dorsal instrumentation
9	40	F	I	Vertebral fracture L1	Transthoracic fusion and dorsal instrumentation
10	37	F	I	Vertebral fracture L1	Transthoracic fusion and dorsal instrumentation
11	21	M	II	Mycotic aortic aneurysm operated coarctation of aorta	Repair of aortic aneurysm

of 2–3 ms, in N_2O–sufentanil–anesthetized patients results in increase in tc-MER amplitude just as in awake patients. Our findings suggest that paired stimulation may be preferable in terms of MER amplitudes and reproducibility to the more commonly used single-pulse TCS paradigms for intraoperative monitoring.

It is unknown whether facilitation by paired TCS occurs predominantly at the cortical or spinal level, and

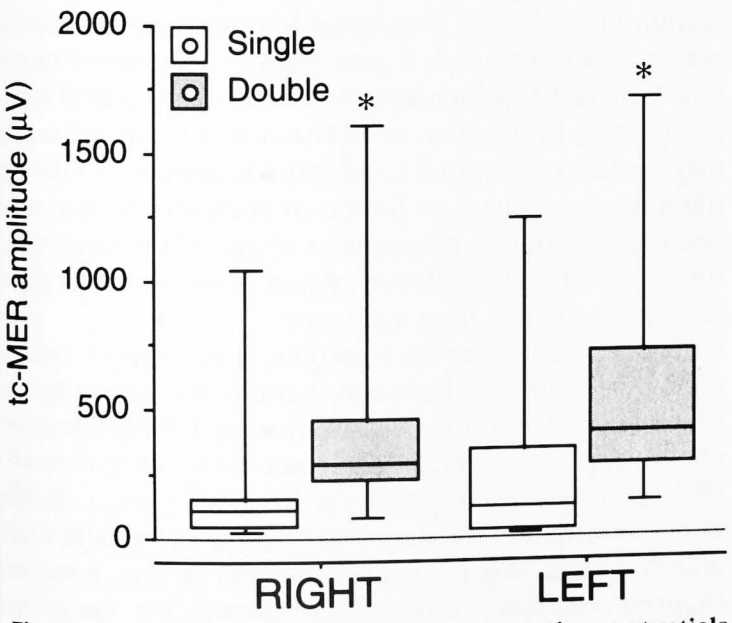

Fig. 2. Box plots of compound muscle action potentials (CMAPs) in the tibialis anterior muscle to single or paired transcranial electrical stimulation. Horizontal bars = 90th, 75th, 50th (median), 25th, and 10th percentiles. The distribution of amplitudes of motor evoked responses to transcranial stimulation (tc-MER) is skewed. *$P < 0.01$ compared with single-pulse stimulation.

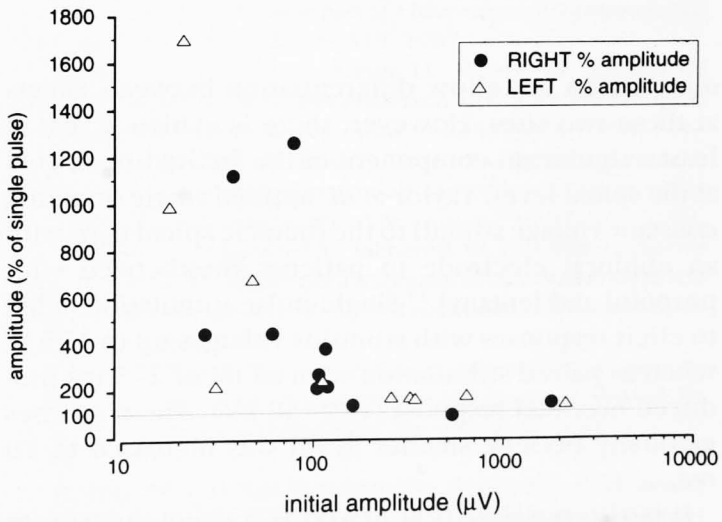

Fig. 3. Relative increase in amplitudes of motor evoked responses to transcranial stimulation (tc-MER) (expressed as a percentage of the single-pulse amplitude in the left and right tibialis anterior muscles) *versus* absolute amplitude with single-pulse TCS. Maximum augmentation occurred when single-pulse transcranial stimulation (TCS) elicited responses of less than 100 μV.

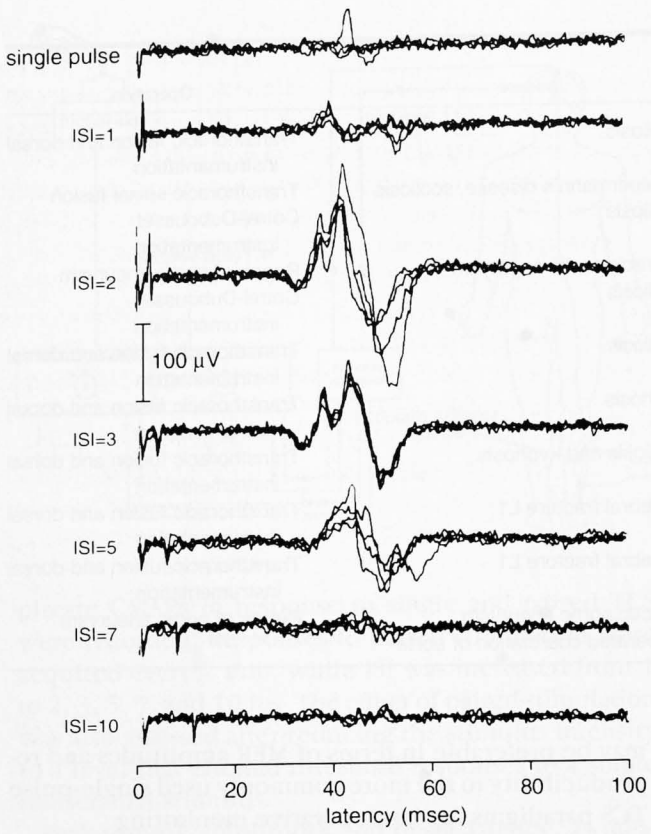

Fig. 4. Influence of interstimulus interval on amplitude of motor evoked responses to transcranial stimulation (tc-MERs) with paired transcranial stimuli. Maximum amplitude augmentation occurred with interstimulus intervals between 2 and 5 ms.

our data do not allow differentiation between effects at these two sites. However, there is evidence that at least a significant component of the facilitation occurs at the spinal level. Taylor *et al.* applied single or paired constant-voltage stimuli to the thoracic spinal cord with an epidural electrode in patients anesthetized with propofol and fentanyl.[19] Single-pulse stimulation failed to elicit responses with stimulus voltages up to 125 V, whereas paired stimulation with an ISI of 2–5 ms produced maximal responses (20–30 μV). The responses gradually became smaller as ISI was increased to 10 ms.

It is also possible that paired TCS alters the pattern of efferent activity in the descending motor pathways. That pattern is, in general, characterized by an initial direct wave followed by a series of indirect waves. Multiple indirect waves can occur as the result of repetitive transsynaptic activation in the motor cortex[20] and, accordingly, it is possible that paired stimulation increases the number of indirect waves. Epidural recordings have shown that at least one anesthetic, isoflurane, decreases the number of indirect waves after a single transcranial electrical stimulus, whereas the initial direct wave is unaffected.[21] Paired stimulation may either increase the number of cortical motor neurons firing, increase the number of indirect waves travelling down the spinal cord, or both. Therefore, it is at least possible that paired stimulation produces facilitation at both the cortical and the spinal level.

A more likely explanation for the facilitation of tc-MERs by paired TCS is that the first stimulus lowers the excitation threshold of the cortical and spinal motor neurons, thereby facilitating the initiation of neuronal discharge by the second stimulus. This phenomenon is known as temporal summation. Each time a neuronal terminal depolarizes, sodium channels open for a period of 1–2 ms. After closure of the channels, the resulting excitatory postsynaptic potential decreases over the next 10–15 ms. A second opening of the same channels within this period will result in an augmentation (temporal summation) of the excitatory postsynaptic potential.[22] The more rapid the rate of repetitive depolarization, the greater the postsynaptic potential that develops. The counterpart of temporal summation is spatial summation, which is the summation of excitatory postsynaptic potentials from several synaptic terminals converging on one motor neuron. If paired TCS increases the number of cortical motor neurons firing then, in addition, spatial summation may occur at the spinal level. The occurrence of these phenomena, spatial or temporal summation, has not been demonstrated in response to paired TCS, however, there is sufficient evidence obtained in other circumstances to suspect its occurrence.

In the current study we found maximal response augmentation with ISIs between 2 and 5 ms. Application of the second stimulus within the first 1.5 ms was less effective, perhaps because the membrane channels are still open. Because the sodium channels close 1–2 ms after stimulus and the excitatory postsynaptic potential generated by a single synapse thereafter decays, it might be predicted that the optimal frequency for obtaining facilitation would occur with an ISI in the vicinity of 2 ms.[16,17,19] Our findings were consistent with that prediction.

The instrumentation available for the current investigation provided the capacity for the delivery of only

two successive stimuli. It is conc
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We chose to evaluate latency to o
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two successive stimuli. It is conceivable that stimulation with more than two successive pulses would further increase tc-MER amplitudes. Nadstawek *et al.,* using conventional constant current stimulators reported that at least three successive pulses of 60 mA with an ISI of 2 ms were required to obtain recordable responses (40–60 μV) during propofol–alfentanil total intravenous anesthesia.[23] Manufacturers of electrical and magnetic transcranial stimulators are currently developing stimulators that will include the option of performing multiple pulse stimulation. When these stimulators become available it will become possible to determine optimal multiple pulse stimulation paradigms. It should kept in mind, however, that multiple pulse stimulation increases the total energy delivered. Single and dual stimulation appear to be well tolerated, and dual stimulation need not necessarily result in a doubling of the net charge delivered if responses can be obtained at lower stimulus intensities. However, with multiple stimulus paradigms, both total energy delivered and duration of stimulus will increase. These protocols should be explored carefully with respect for the possibility of the epileptogenesis or direct neuronal injury that have not thus far been observed with single or dual stimuli.

We chose to evaluate latency to onset rather than latency to specific peaks because CMAPs do not have consistent, characteristic morphologic features and may exhibit significant variation both within and between patients. Onset latency appeared to decrease slightly with the application of paired stimuli in our investigation. However, we feel that there were significant limitations in our capacity to determine latency. Determination of onset latency for low-amplitude responses (which constituted many of the responses to single stimuli) was sometimes difficult. The slope of the initial CMAP deflection was occasionally sufficiently gradual that identification of the precise moment of "onset" may have been unreliable. The greater amplitudes of responses to paired stimuli, with the concomitantly more rapid deviation from baseline, may have introduced a bias toward shorter apparent latencies. A mathematical definition of onset latency (*e.g.,* a greater than 2-SD deflection from the average baseline noise level) would aid in uniform determination of CMAP onset and facilitate comparison among published results.

Our data suggest that the relative amplitude increase associated with paired stimulation is dependent on the initial amplitude of the response to single stimulation. The smaller the initial response to a single transcranial stimulus, the greater the effect of paired stimulation. This is in agreement with the results of Inghilleri *et al.,*[17] who observed that the increase of the abductor pollicis brevis MER after paired TCS in awake subjects was inversely correlated with the amplitude of the control response. In our study, paired TCS had only a minor effect in patients who had high-amplitude (>300 μV) tc-MERs in response to single-pulse TCS. Motoneuronal firing is a quantal response, and therefore tc-MER amplitudes are directly proportional to the number of motor neurons firing. If single-pulse TCS resulted in firing of all tibialis anterior muscle motor units in some of our patients, further augmentation with the application of a second stimulus would not be expected.

In conclusion, we have demonstrated that application of paired transcranial electrical stimuli significantly increases amplitudes of intraoperative MERs during anesthetic-induced depression of the motor system. The results of this study justify further clinical evaluation of the efficacy and safety of double-pulse TCS as an adjunct to monitoring during surgical procedures that place motor pathways at risk.

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Pharmacokinetic
encapsulated Fen

Orlando R. Hung, M.D.,* Sara C. Why
Michael Mezei, Ph.D.‖

Background: **Pulmonary administra**
can provide satisfactory but brief p
Liposomes are microscopic phospho
trap drug molecules. Liposomal deli
potential to control the uptake of fe
thus provide sustained drug release.
halation of a mixture of free and lip
tanyl can provide a rapid increase a
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Methods: **After obtaining institut**
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and liposome-encapsulated fentanyl
sions. Frequent venous blood samples
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* Associate Professor, Departments of
ogy, Dalhousie University, Halifax, Nova

† Research Associate, Departments of
ogy, Dalhousie University, Halifax, Nova

‡ Staff Anesthesiologist, Department
Community Health Center, Lincoln, Neb

§ Associate Professor, Department of An
School of Medicine; Staff Anesthesiolog
ministration Medical Center, Palo Alto,

‖ Professor Emeritus, College of Pharm
Halifax, Nova Scotia, Canada.

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Address correspondence to Dr. Hung:
Victoria General Hospital, 1278 Tower
B3H 2Y9 Canada.