Duration of control stimulation does not affect onset and offset of neuromuscular blockade at the corrugator supercilii muscle measured with phonomyography or acceleromyography

[La durée de la stimulation contrôlée n'a pas d'effet sur le début et la fin du blocage neuromusculaire du muscle sourcilier mesuré par phonomyographie ou accéléromyographie]

Thomas M. Hemmerling MD DEAA,* François Donati MD PhD FRCPC,* Denis Babin MSC*, Pierre Beaulieu MD PhD,†

Purpose: Phonomyography (PMG) is a novel technique for measuring neuromuscular blockade (NMB). The effect of the duration of control stimulation on the onset and duration of blockade was investigated using PMG and acceleromyography (AMG).

Methods: After induction of anesthesia, a microphone was placed above the middle portion of the left eyebrow, and an acceleromyographic probe was placed above the middle portion of the right eyebrow. Twenty patients were randomized to receive bilateral, single-twitch, facial nerve stimulation (0.1 Hz, 20 mA) with three minutes (n = 10) or ten minutes (n = 10) of supramaximal stimulation before mivacurium 0.2 $mg \cdot kg^{-1}$ was administered. Onset, maximum effect, and offset of NMB were measured.

Results: Using PMG, lag time, onset time, maximum effect, and time to reach 75% of control twitch height (mean ± SD) were 36 ± 27 sec, 136 ± 35 sec, 89 ± 10%, and 12.1 ± 4.5 min, respectively, after three minutes of control stimulation and were 40 ± 22 sec, 122 ± 40 sec, 93 ± 3%, and 12.4 ± 4.9 min, after ten minutes. Using AMG, the values were 38 ± 23 sec, 106 ± 28 sec, 79 ± 6%, and 14.3 ± 5.9 min, respectively, after three minutes and were 34 ± 22 sec, 106 ± 28 sec, 76 ± 10%, and 14.9 ± 3.7 min, after ten minutes. Compared to PMG, AMG revealed significant bias for onset time (-30 sec), maximum effect (-16%) and time to reach 75% of control twitch height (1.5 min), with wide limits of agreement of 66 sec, 22%, and 5.6 min, respectively.

Conclusion: The duration of control stimulation did not influence the time course of blockade measured by either method. Three minutes of supramaximal stimulation is sufficient to measure pharmacodynamic parameters. AMG measures a shorter onset and longer recovery time and reduced anesthesiology the maximum effect compared to PMG.

Objectif : *La phonomyographie (PMG) est une nouvelle technique de mesure du blocage neuromusculaire (BNM). L'effet de la durée de la stimulation contrôlée sur le délai d'installation et la durée du blocage neuromusculaire a été vérifiée en utilisant la PMG et l'accéléromyographie (AMG).*

Méthode : *Après l'induction de l'anesthésie, un microphone a été placée au-dessus de la partie médiane du sourcil gauche et une sonde accéléromyographique a été placée au-dessus de la partie médiane du sourcil droit. Vingt patients ont été répartis au hasard pour recevoir une stimulation simple bilatérale du nerf facial (0,1 Hz, 20 mA) et trois minutes (n = 10) ou dix minutes (n = 10) de stimulation supramaximale avec l'administration de 0,2 $mg \cdot kg^{-1}$ de mivacurium. Le délai d'installation, l'effet maximal et la fin du BNM ont été enregistrés.*

Résultats : *Avec la PMG, la période de latence, le début, l'effet maximal et le temps nécessaire pour atteindre 75 % de la de la stimulation contrôlée (moyenne ± écart type) ont été de 36 ± 27 sec, 136 ± 35 sec, 89 ± 10 % et de 12,1 ± 4,5 min, respectivement après trois minutes de stimulation contrôlée et de 40 ± 22 sec, 122± 40 sec, 93 ± 3 % et 12,4 ± 4,9 min après dix minutes. Avec l'AMG, les valeurs ont été de 38 ± 23 sec, 106 ± 28 sec, 79 ± 6 % et de 14,3 ± 5,9 min, respectivement après trois minutes et de 34 ± 22 sec, 106 ± 28 sec, 76 ± 10 % et de 14,9 ± 3,7 min après dix minutes. Comparée à la PMG, l'AMG a révélé un biais significatif pour le moment du début (-30 sec), l'effet maximal (-16 %) et le temps d'atteindre 75 % de la stimulation contrôlée (1,5 min) avec de grandes limites de concordance de 66 sec, 22 % et 5,6 min respectivement.*

Conclusion : *La durée de la stimulation contrôlée n'influence pas l'évolution du blocage mesuré selon l'une ou l'autre méthode. Trois*

From the Department of Anesthesia,* Neuromuscular Research Group, Centre Hospitalier de l'Université de Montréal (CHUM) and the Department of Anesthesiology,† Université de Montréal, Montréal, Québec, Canada.

Address correspondence to: Dr. Thomas M. Hemmerling, Centre Hospitalier de l'Université de Montréal (CHUM), Hôtel-Dieu, Département d'anesthésie, 3840, rue Saint-Urbain, Montréal, Québec H2W 1T8, Canada. Phone: 514-890-8000, ext. 14570; E-mail: thomashemmerling@hotmail.com

Accepted for publication April 4, 2002.
Revision accepted August 14, 2002.

minutes de stimulation supramaximale suffisent pour mesurer les paramètres pharmacodynamiques. L'AMG, comparée à la PMG, mesure un délai d'installation plus court et un temps de récupération plus long et réduit l'effet maximal.

ONSET and duration of neuromuscular blockade (NMB) is affected by the duration of control stimulation (stabilization period) before injection of the blocking agent. When force is measured at the adductor pollicis muscle, onset is shorter and duration is longer when the stabilization period is long.[1] This dependence on duration of stimulation is not seen with acceleromyography (AMG).[2]

Phonomyography (PMG) has been introduced recently as a tool to provide a surrogate measure of NMB at the adductor pollicis muscle,[3,4] based on the fact that skeletal muscle contraction generates intrinsic low-frequency sounds.[5] The mechanical impulse of contraction creates pressure waveforms, which can be detected with a microphone and used to determine NMB after administration of muscle relaxants. Since this technique is relatively new, the effect of control stimulation on onset and offset of NMB remains unclear.

The corrugator supercilii muscle (Figure 1) has been used recently to measure NMB because its onset and offset of NMB is shorter than measurements at the orbicularis oculi and adductor pollicis muscle.[6] For rocuronium, measurements at the corrugator supercilii muscle are more reflective of NMB at the larynx than measurements at the adductor pollicis muscle.[7] AMG has been the only method used to measure neuromuscular blockade at the corrugator supercilii muscle.[6–8] One recent study comparing PMG with mechanomyography at the adductor pollicis muscle stated that the two methods cannot be used interchangeably.[3]

Because results may be affected by duration of stimulation, it is important to establish whether the period of control stimulation affects the time course of NMB when a new technique or a new site is used. We undertook this study to determine the effect of the control stimulation period on onset and offset of NMB with PMG and AMG at the corrugator supercilii muscle and to define the limits of agreement between both methods.

Methods

Twenty patients undergoing elective general surgery under general anesthesia using controlled ventilation with a laryngeal mask airway were included. We excluded pregnant women, patients with neuromuscular, hepatic or renal disease, and patients receiving medications known to interact with neuromuscular blocking drugs. Institutional Ethics approval was obtained and informed consent was given by the patients.

Anesthesia was induced with *iv* propofol 1–2.5 $mg \cdot kg^{-1}$ and *iv* remifentanil at 0.1–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. After loss of consciousness, ventilation was applied via face mask for two minutes, a laryngeal mask airway (size 4 for women, size 5 for men) was inserted, and its cuff filled with air. Anesthesia was maintained with sevoflurane 1–2 volume % end-tidal with 60% air in oxygen. Analgesia was provided with *iv* remifentanil 0.05–0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Minute ventilation was set to maintain an end-tidal pCO_2 of 30–40 mmHg.

Recording of PMG

Stimulation of the motor branches of the facial nerve supplying the corrugator supercilii muscle was performed using two Ag/AgCl-electrodes (3.5 cm diameter, Safelead®, Grass Instruments, Astro-Med, West Warwick, USA) at the left temporal area. A constant current stimulator (Innervator®, Fisher and Paykel Healthcare, Auckland, New Zealand) generated single-twitch square pulses of 0.2 msec and train-of-four (TOF) twitches of 0.2 Hz with a current intensity of 20 mA on the left side. A small microphone (1.6 cm diameter, Model 1010, Grass Instruments, Astro-Med, West Warwick, USA; frequency response: 2.5 Hz to 5 kHz, signal output: 20–40 mV into 1 M) was attached using Scotch™ Tape (3M Company, London, Ontario, Canada) just medial to the left eyebrow for recording the evoked responses of the corrugator supercilii muscle (Figure 2). The microphone signal was amplified and band pass filtered between 0.5 Hz and 1000 Hz using an AC/DC amplifier (Model 7P122, Grass Instruments, Astra-Med, West Warwick, USA).

Recording of AMG

Two Ag/AgCl-electrodes were applied to the skin over motor branches of the right facial nerve supplying the corrugator supercilii muscle. They were connected to the TOF-Watch SX® (Organon Instruments, Boxlet, Netherlands) for stimulation. The AMG probe of the TOF-Watch SX® was attached to the same portion of the medial eyebrow as the microphone on the left side (Figure 2). The monitor was set at maximum sensitivity for all patients.

Protocol

After induction of anesthesia, insertion of the laryngeal mask, and application of AMG and PMG moni-

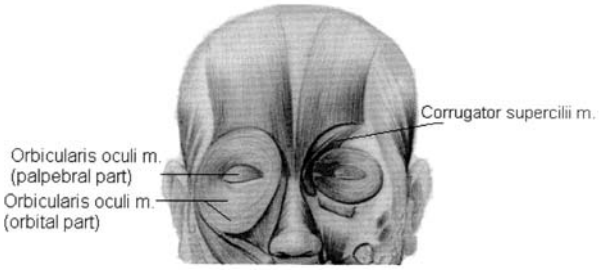

FIGURE 1 Diagram of the anatomy of the corrugator supercilii muscle.

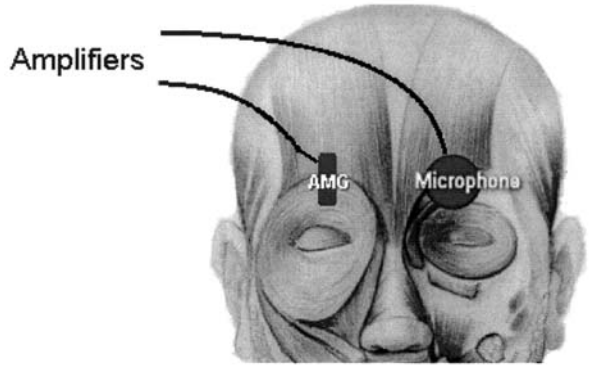

FIGURE 2 Diagram of the sites of neuromuscular monitoring with acceleromyography (AMG) and phonomyography (microphone).

tors, patients were randomized to receive supramaximal stimulation (20 mA, single-twitch, 0.2 msec, 0.1 Hz) for either three minutes (n = 10) or ten minutes (n = 10) before injection of *iv* mivacurium 0.2 $mg \cdot kg^{-1}$ into a fast-flowing infusion of Ringer's lactate. Onset and recovery of NMB were determined. Monitoring was maintained until TOF responses reached a T4/T1 ratio = 1.

Signal processing and analysis

The PMG signals were continuously sampled at 1000 Hz using the Polyview® software package (Astra-Med, Rhode Island, USA), digitized, and stored on a portable microcomputer. The single twitch PMG-signal was measured peak-to-peak (Figure 3). The AMG responses were recorded using the TOF-Watch SX® digitalized values. Peak-to-peak amplitude of PMG for

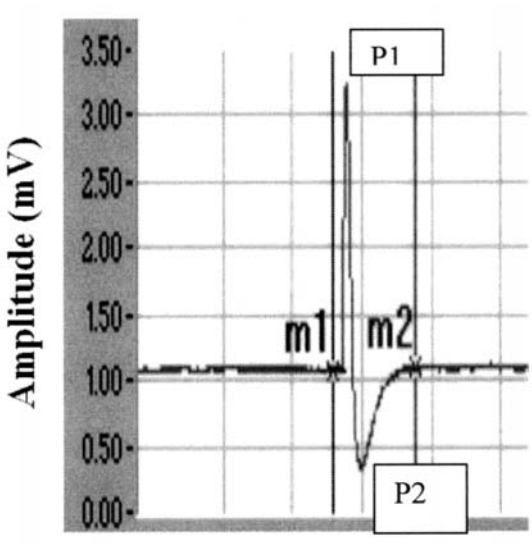

FIGURE 3 Peak (P1) to peak (P2) analysis of the phonomyography signal to determine the signal amplitude; m1 and m2 indicate the beginning and the end of the signal respectively.

each signal and AMG values were measured before administration of mivacurium, at initial detection of decrease of the control value (lag time), at 50% decrease of the control (onset 50), at maximum blockade, and at 25% and 75% recovery of the control value.

Statistical analysis

The sample size was calculated based on a power greater than 90% and an expected 20% difference in mean times between PMG and AMG.[3] Patient data and all pharmacodynamic variables were summarized as means and standard deviations (SD). The extent of agreement between the two monitoring methods were tested by the method of Bland and Altman.[10] Bias was defined as the mean difference between neuromuscular twitch responses measured by AMG and PMG and was calculated as:

$$\frac{\sum (AMG - PMG)}{n}$$

where n was the number of measurements. Precision of PMG was defined as the standard error of the mean difference, which was calculated as:

$$\div SD^2/n$$

where SD was the SD of the differences between neuromuscular twitch responses measured by AMG and PMG and n was the sample size. The upper and lower limits of agreement between the two methods was defined as the mean difference (bias) ± 2 SD.

TABLE I Pharmacodynamic data of 20 patients

Variable	*Acceleromyography (n = 10)*		*Phonomyography (n = 10)*	
	3 minutes	*10 minutes*	*3 minutes*	*10 minutes*
Lag time (sec)	38 ± 23	34 ± 22	36 ± 27	40 ± 22
Onset time (sec)	106 ± 28	106 ± 28	136 ± 35	122 ± 40
Peak effect (%)	79 ± 6	76 ± 10	89 ± 10	93 ± 3
T 75 (min)	14.3 ± 5.9	14.9 ± 3.7	12.1 ± 4.5	12.4 ± 4.9

All values are expressed as means ± SD. For each monitoring device, no statistically significant differences were seen between the three-minute and ten-minute groups.

TABLE II Bias, precision, and limits of agreement between acceleromyography and phonomyography

Variable	*Bias ± precision*	*Limits of agreement*
Lag time (sec)	-7 ± 33	-73 to +59
Onset time (sec)	-30 ± 38	-106 to +46
Peak effect (%)	-16 ± 11	-38 to +6
T 75 (min)	1.5 ± 2.8	-4.1 to +7.1

Pharmacodynamic data derived using AMG and PMG were compared between the two groups using unpaired t tests. Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using Statview® (SAA Institute, Cary, NC, USA).

Results

The two groups did not differ significantly in age (three-minute group, 49 ± 15 yr *vs* ten-minute group, 54 ± 18 yr) or weight (three-minute group, 75 ± 14 kg *vs* ten-minute group, 76 ± 14 kg). During recovery, a T4/T1 ratio of ≥1 was measured in all patients with both methods; however, in eight of 20 patients, time to reach 25% of control twitch height could not be determined using AMG, because the maximum effect was lower than 75%. The duration of supramaximal stimulation did not change the onset, offset, or maximum effect of NMB significantly (Table I). There was lack of agreement between the two methods (Table II). The bias ± precision of the lag time, onset time, maximum effect, and T 75% are -7 ± 33 sec, -30 ± 38 sec, -16 ± 11%, and 1.5 ± 2.8 min respectively.

Discussion

The present study shows that the duration of the stabilization period (three or ten minutes) does not affect the onset, offset, or peak effect of NMB after mivacurium at the corrugator supercilii muscle when assessed by either PMG or AMG. AMG records faster onset, less pronounced effect of NMB, and longer duration than PMG; the significant bias and wide limits of agreement indicate that these methods cannot be used interchangeably at the corrugator supercilii in clinical practice.

Differences in pharmacodynamic results seen in studies using identical methods, drugs, and dosages have been attributed not only to intergroup differences, but also to possible effects of the control stimulation period. The effect of the stabilization period on onset and offset of NMB has been evaluated for mechanomyography[1] and AMG[2] at the adductor pollicis muscle. The findings are inconsistent even when the same method is investigated. McCoy *et al.*[1] in an intergroup comparison, showed that increasing periods of control stimulation are associated with decreasing onset time for atracurium, vecuronium, and mivacurium at the adductor pollicis muscle when measured using mechanomyography. Girling *et al.* did not find any significant difference in the onset of NMB after vecuronium or atracurium after stimulation periods of three or 20 min when AMG (TOF-Guard®, Biometer International, Odense, Denmark) was used to assess NMB.[2] All these studies evaluated the effect of control stabilization period at the adductor pollicis muscle. Since the onset time depends on cardiac output, circulation time to the muscle, muscle blood flow, organ affinity, and specific pharmacokinetics of the muscle relaxant itself, these factors will differ for each muscle.[10] Therefore, even the effect of the control stimulation period might not be the same for all muscles.

Our interest in the corrugator supercilii muscle stems from a recent study showing that onset and offset of NMB at this muscle might reflect well the onset and offset of NMB at the larynx.[7] For practical purposes, we investigated two periods of control stimulation: three minutes, which is the minimum period of control stimulation,[11] and ten minutes. Since there was no difference between the two periods, we do not believe that longer stabilization periods would yield any differences. Strict criteria for good clinical research have been published for the assessment of NMB at the hand.[11] These include a stable response time for ten minutes (with variation of < 2% for at least three minutes before the administration of relaxant), the ability to record the supramaximal stimulus and demonstrate stable supramaximal response at the end of the experiment, the ability to record the complete profile of onset, duration of action, and recovery of NMB, and documentation of stability by adequate (80%–120%) return of T1 after recovery. All these criteria are met by PMG.

PMG is an easy-to-use, quantitative and sensitive monitor of NMB of the corrugator supercilii muscle.

The low frequency signals, which are generated from resonant vibrations of the muscle fibrils, should reflect the characteristics of a specific muscle. Technical specifications such as the type of microphone used (frequency range, frequency response over time, amplification system) and the muscle environment (tissue density, distance to the recording device, even contact between skin and microphone) influence the signal quality. In comparison to larger air-coupled microphones previously used to monitor NMB at the adductor pollicis muscle, the microphone used in the current study is a small condenser microphone. This microphone can be easily taped to the skin surface and provides even surface contact without an air chamber. Close and even contact between the condenser microphone and the skin surface is important and needs to be maintained throughout the monitoring period.

AMG is the only method which has been used to measure NMB of the corrugator supercilii muscle. Several studies, however, have shown that AMG results at the adductor pollicis muscle cannot be used interchangeably with other methods such as electromyography[12] and mechanomyography.[13] AMG represents an indirect method to measure the force of contraction. As such, it cannot be regarded as a gold standard nor regarded as superior to electromyography or PMG. Originally, AMG probes were designed for use at the adductor pollicis muscle. The acceleration created by the contraction of the corrugator supercilii muscle is obviously much smaller than that of the adductor pollicis muscle, with only minimal displacement of the acceleromyographic probe. The TOF-Watch SX® provides a greater range of sensitivity than the TOF-Guard® to suit different muscles. Maximum sensitivity was set for all patients to ensure the detection of small values of acceleration. However, a maximum effect greater than 90% was not detected using the TOF-Watch SX® in any patient. In seven of 15 patients, where the peak effect was less than 75%, time to reach 25% of control twitch height could not be detected via AMG. The technical differences between the TOF-Guard® and the TOF-Watch SX® might explain the different results found in two previous studies[6,8] where onset and offset of NMB after mivacurium 0.2 $mg \cdot kg^{-1}$ was longer and the maximum effect more pronounced using the TOF-Guard®.

In summary, the duration of control stimulation did not affect PMG nor AMG when used to measure mivacurium NMB at the corrugator supercilii muscle. These two methods cannot be used interchangeably, as AMG measures a faster onset, a less pronounced peak effect, and a longer recovery at the corrugator supercilii muscle.

References

1 *McCoy EP, Mirakhur RK, Connolly FM, Loan PB.* The influence of the duration of control stimulation on the onset and recovery of neuromuscular block. Anesth Analg 1995; 80: 364–7.

2 *Girling KJ, Mahajan RP.* The effect of stabilization on the onset of neuromuscular block when assessed using accelerometry. Anesth Analg 1996; 82: 1257–60.

3 *Bellemare F, Couture J, Donati F, Plaud B.* Temporal relation between acoustic and force responses at the adductor pollicis during nondepolarizing neuromuscular block. Anesthesiology 2000; 93: 646–52.

4 *Dascalu A, Geller E, Moalem Y, Manoah M, Enav S, Rudick Z.* Acoustic monitoring of intraoperative neuromuscular block. Br J Anaesth 1999; 83: 405–9.

5 *Barry DT.* Muscle sounds from evoked twitches in the hand. Arch Phys Med Rehabil 1991; 72: 573–5.

6 *Hemmerling TM, Schmidt J, Hanusa C, Wolf T, Schmitt H.* Simultaneous determination of neuromuscular block at the larynx, diaphragm, adductor pollicis, orbicularis oculi and corrugator supercilii muscles. Br J Anaesth 2000; 85: 856–60.

7 *Plaud B, Debaene B, Donati F.* The corrugator supercilii, not the orbicularis oculi, reflects rocuronium neuromuscular blockade at the laryngeal adductor muscles. Anesthesiology 2001; 95: 96–101.

8 *Hemmerling TM, Schmidt J, Wolf T, Hanusa C, Siebzehnruebl E, Schmitt H.* Intramuscular versus surface electromyography of the diaphragm for determining neuromuscular blockade. Anesth Analg 2001; 92: 106–11.

9 *Bland JM, Altman DG.* Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1: 307–10.

10 *Donati F.* Onset of action of relaxants. Can J Anaesth 1988; 35: S52–8.

11 *Viby-Mogensen J, Engbaek J, Eriksson LI, et al.* Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. Acta Anaesthesiol Scand 1996; 40: 59–74.

12 *Nakata Y, Goto T, Saito H, et al.* Comparison of acceleromyography and electromyography in vecuronium- induced neuromuscular blockade with xenon or sevoflurane anesthesia. J Clin Anesth 1998; 10: 200–3.

13 *McCluskey A, Meakin G, Hopkinson JM, Baker RD.* A comparison of acceleromyography and mechanomyography for determination of the dose-response curve of rocuronium in children. Anaesthesia 1997; 52: 345–9.