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Relationship between Normalized Adductor Pollicis Train-of-four Ratio and Manifestations of Residual Neuromuscular Block

A Study Using Acceleromyography during Near Steady–state Concentrations of Mivacurium

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ABSTRACT

Background: Baseline acceleromyographic adductor pollicis train-of-four (TOF) ratio varies significantly between individuals and is often greater than unity. Thus, normalization of acceleromyography data is necessary. The relationship between normalized acceleromyographic TOF ratio, lung volumes, and clinical signs of residual neuromuscular block was studied.

Methods: In 12 healthy volunteers, three steady–state levels of neuromuscular block were achieved with mivacurium infusions. TOF ratio was measured acceleromyographically at the adductor pollicis using a preload. Lung volume measurements and a series of clinical tests were made at each stable block and reconciled to the normalized TOF measures.

Results: None experienced airway obstruction or arterial oxygen desaturation, even at normalized TOF ratio less than 0.4. Functional residual capacity remained unchanged whereas vital capacity decreased linearly with decreasing TOF ratio. The ability to protrude the tongue was preserved at all times. The ability to clench the teeth was lost in one volunteer at normalized TOF ratio of 0.84 but retained in four at normalized TOF ratio less than 0.4. Four volunteers lost the ability both to raise the head more than 5 s and to swallow, with the most sensitive individual demonstrating these effects at normalized TOF ratio of 0.60. At mean normalized TOF ratio of 0.42, the mean handgrip strength was approximately 20% of baseline value.

Conclusion: Lung vital capacity decreased linearly with decreasing TOF ratio. Responses to clinical tests of muscle function varied to a large extent among individuals at comparable TOF ratios. None of the volunteers had significant clinical effects of neuromuscular block at normalized acceleromyographic TOF ratio greater than 0.90.

What We Already Know about This Topic

- ❖ Mechanomyography and the more recently applied acceleromyography differ in what is measured.
- ❖ The correlations between mechanomyography and functional measures of muscle strength may not apply to acceleromyography.

What This Article Tells Us That Is New

- ❖ In 12 healthy volunteers receiving low-dose infusions of mivacurium, the relationship between normalized train of four (TOF) ratio using acceleromyography and common muscle function tests was highly variable, and at TOF ratio >0.9 there was no significant residual neuromuscular block.

ACCELEROMYOGRAPHY, measurement of the isotonic acceleration of a muscle contraction, offers a simple and clinically applicable technique for the monitoring of neuromuscular block in clinical practice,[1] and commercial devices are now available to enable the anesthesia practitioner to employ it. Much of the large body of research into the effects of neuromuscular-blocking drugs is based on a different technique, mechanomyography, in which isometric muscle contractions are measured. It is clear that acceleromyo-

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graphy- and mechanomyography-based data cannot be used interchangeably.[2–4] Even at baseline, in the absence of neuromuscular-blocking drugs, acceleromyographic and mechanomyographic measurements may yield systematically different values.[3] Consequently, recommendations and practices that are based on research using mechanomyography may not be applicable for the practitioner using acceleromyography. For instance, the recommendation that the mechanomyographically measured train-of-four (TOF) ratio should be 0.9 at the end of anesthesia[5–8] may not apply to acceleromyography-derived TOF values.

The baseline value of acceleromyographic adductor pollicis (AP) TOF ratio is often greater than 1.0,[2,3,9] whereas the mechanomyography equivalent is frequently between 0.9 and 1.0.[3] It is likely that some of the difference between values of the TOF ratio yielded by the two methods would be eliminated by normalizing TOF values to the baseline recording.[3] Because the baseline value among patients is highly variable with acceleromyography,[9] normalization is also necessary if values are to be compared between individuals. At present, there is no information in the literature on the relationship among normalized acceleromyographic TOF ratio and clinical measures of neuromuscular function.

In the study presented here, we explore the relationship between normalized acceleromyographic AP TOF ratio, lung volume measurements, and clinical signs of residual neuromuscular block during low-dose mivacurium infusion. We studied lung volumes because impairment of the functional residual capacity (FRC) or vital capacity (VC) of the lungs may contribute to maintenance of already existing (or the development of new) atelectases in the postoperative period.[10–12] We wished to determine whether residual effects of neuromuscular-blocking drugs may contribute to such impairment. The remaining observations were those that are frequently made for clinical assessment of neuromuscular function during recovery from anesthesia: tongue protrusion, teeth clenching, swallowing, ability to raise the head, speaking, ability to keep eyes open, maintenance of clear vision, and handgrip strength. Our investigation was conducted in awake volunteers so that we could establish stable conditions and because we wanted to study the effect of a neuromuscular-blocking drug in the absence of anesthetics or other medications that might influence the observations.[13–15]

Materials and Methods

The Institutional Review Board at the University of California, San Francisco, approved the study. Twelve healthy volunteers: 6 men (29 ± 3 yr, 75 ± 5 kg) and 6 women (27 ± 3 yr, 57 ± 4 kg) were enrolled after an in-depth interview and written consent. Subjects between 18 and 35 yr of age with a normal airway examination were included. Women who were pregnant or currently breast feeding and individuals with body mass index greater than 25, history of smoking, medications known to interfere with neuromuscular-blocking drugs, family or personal history of problems related to anesthesia, acid reflux, or current upper-airway infection, were excluded. Whenever neuromuscular-blocking drugs were administered, volunteers were in the supine or almost-supine position and were observed by two trained anesthesiologists. Blood pressure was recorded every 15 min, and heart rate, electrocardiogram, and arterial oxygen saturation were recorded continuously. The study subjects were breathing oxygen during measurements of lung volumes, otherwise just room air. An intravenous catheter was inserted into the antecubital vein in the left arm, and lactated Ringer's solution was infused. Emergency equipment and drugs (including edrophonium for reversal of mivacurium block) were readily available at all times. Thermal comfort was ensured and body temperature supported by covering volunteers with blankets on request or if intermittent hand skin temperature measurements showed values less than 32°C.

Mivacurium Administration and Recording of Neuromuscular Block

Mivacurium was infused into the intravenous catheter in the left arm using a Harvard infusion pump (Harvard Clinical Technology, Inc., Natick, MA). We chose to study mivacurium because stable, near steady–state blood concentrations can be obtained relatively rapidly[16] due to its rapid elimination.[17] In each study subject, a stable acceleromyographic AP TOF ratio within three different ranges was targeted: TOF ratio of 0.85–0.95 (block level 1), TOF ratio of 0.65–0.75 (block level 2), and TOF ratio of 0.45–0.55 (block level 3). The most profound block level that we wanted to study was chosen based on data showing that an AP TOF ratio of 0.4–0.5 is regularly encountered during recovery from clinical anesthesia after tracheal extubation.[18] The initial infusion rate was in the range 1.0–1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ targeting an AP TOF ratio in the range 0.85–0.95.[19] After a stable block was established and measurements made, we altered the mivacurium dose rate by 10–30% and waited for a new stable level of block. After the final set of measurements, the mivacurium infusion was terminated and neuromuscular function allowed to recover spontaneously. The total duration of the mivacurium infusion was recorded.

Neuromuscular block was quantified using the TOF ratio at the left AP muscle measured acceleromyographically. The commercially available TOF Watch SX (Schering-Plough Corporation, Kenilworth, NJ) was employed. The thumb was placed in a specially designed finger holder (Schering-Plough Corporation) that applies approximately 75 g of preload. It allows the thumb to move in a consistent direction with nerve stimulation and enhances the repeatability of measurements.[3]

The stimulus current was set in the range 25–35 mA (15 mA above threshold for the TOF Watch SX to detect thumb movement). Supramaximal stimulation is not required for reliable acceleromyographic AP TOF measurements because the mean TOF ratio does not change as long as the stimulating current is maintained more than 10 mA above the thresh-

old for detection of the twitch response.[20] Individual TOF ratios obtained may differ up to 10% from values obtained with supramaximal stimulation if the stimulating current is maintained 15 mA above the threshold.[21] At regular intervals, the stimulus intensity was transiently increased by 5 mA to ensure that the stimulus threshold had not altered during the experiment. We did not employ supramaximal nerve stimulation because we did not believe that the volunteers would easily tolerate that stimulus intensity for the duration of our planned observations.

The TOF ratio was monitored, recorded, and later analyzed using TOFMON software (Schering-Plough Corporation). Four consecutive TOF ratios were averaged to obtain a single value. The variability at baseline and at all three levels of stable block was calculated and compared using the SD of four consecutive TOF ratio readings. A variability less than 5% was considered adequate. During the mivacurium infusion, the TOF ratio was considered to have reached a stable level if values obtained 10 min apart differed by 2% or less. The mivacurium infusion was commenced when we obtained a TOF ratio control value after 10 min of continuous nerve stimulation.

Normalized acceleromyographic AP TOF ratios were calculated at all levels of stable block by dividing each TOF ratio with that subject's baseline value. The time required to establish each stable block and to complete recovery of acceleromyographic AP TOF ratio after termination of the mivacurium infusion was also determined and recorded.

We were prepared to terminate the mivacurium infusion immediately if any of the following conditions occurred: the study subject desired to discontinue or experienced insufficient airflow for tidal breathing, signs of airway obstruction (stridor) or complete loss of ability to swallow. or arterial oxygen saturation decreased below 90%. A patent upper airway was considered if no audible stridor was observed.

Pulmonary Function Tests

Lung volumes were measured using a VMAX lung function test monitor (Cardinal Health, Dublin, OH). Before measurements were made, volunteers practiced several times with each test procedure to familiarize themselves with the equipment. We paid close attention to prevention of air leak during the observations. The patency of the nose clip was checked before each measurement, and a mouthpiece with a flange was used to facilitate breathing without leakage. If the volunteer was unable to maintain a tight seal due to the effect of mivacurium, an investigator assisted the volunteer, making sure that the lips were in close contact with the flange during measurements. Even small air leaks are detected by the VMAX, and a warning signal is displayed to notify the operator.

To verify that lung volumes would not change over time, even in the absence of mivacurium, half of the volunteers (three men, three women) participated in a control study on a separate study day. Lung volumes were tested at regular intervals for 4 h, which was the estimated maximal duration of the mivacurium infusion. Measurements were first obtained in the upright position followed by recordings when reclined with the upper body in 30-degree elevation. The volunteer was then positioned supine and measurements repeated immediately. Subsequent measurements were obtained in the supine position, after 15, 30, 90, 180, and 240 min. This recording technique would allow the observation of any change in lung volumes over time. The other six volunteers would undergo the control session only if we observed time-related changes in the first group.

During control studies and during mivacurium infusion, each measurement was conducted in a standardized fashion. Normal tidal respiration on room air was first established. Then FRC was measured using the nitrogen washout technique after abruptly changing the inspired gas to oxygen.[22] Next, room air-tidal respiration was again established, and with coaching, the volunteer performed a maximal expiration followed immediately by a maximal inspiration. VC was determined as the lung volume between maximal inspiration and maximal expiration. Closing volume (CV) was finally determined as a percentage of the VC from the nitrogen expiration curve after a single breath of oxygen.[22] The following variables were subsequently calculated based on measurements of FRC, VC, and CV: residual volume (RV) or the volume of gas in the lungs after a maximal expiration, closing capacity (CC) as determined as RV + CV, inspiratory reserve volume or the maximum volume inhaled after a normal tidal inspiration, and expiratory reserve volume or the maximum volume exhaled after a normal tidal expiration.

Pulmonary function tests were conducted in duplicate while standing, sitting, then supine before mivacurium infusion and at each level of stable block. We also made observations every 15 min after termination of the mivacurium infusion until values greater than 90% of baseline were obtained.

Clinical Measures of Muscle Function

Eight clinical measures of muscle function were evaluated every 5 min during the infusion of mivacurium and at each level of stable block. These were: ability to protrude the tongue, teeth clenching ability, ease of swallowing, ability to head raise more than 5 s, ease of speaking, ease of eye opening, subjective clarity of vision, and objectively measured handgrip strength. Baseline evaluations were obtained before commencement of the mivacurium infusion and observation continued until complete recovery from the effects of mivacurium. All eight assessments were performed in the supine position.

Tongue Protrusion. Movement of the tongue forward and away from the pharyngeal wall is controlled by the genioglossus muscle.[23] This action secures the retroglossal volume and helps to maintain airway patency.[24,25] Examining the ability to protrude the tongue is a crude functional test of the genioglossus muscle. Volunteers were asked to stick out the tongue. Tongue protrusion was determined as either maintained or not maintained.

Ability to Clench Teeth. Closure of the jaw exerts traction on muscles that insert on the hyoid bone, which stabilizes and expands the pharyngeal airway.[26] The masseter muscle may therefore be involved in the maintenance of the patent airway when the resistance to the airflow during breathing increases.[27] This function was tested by placing a wooden tongue depressor between the volunteer's incisors and requesting the volunteer to retain it while an investigator attempted to pull it out.[19] Teeth clenching was determined as either maintained or not maintained.

Ease of Swallowing. Normal swallowing causes approximation of the vocal cords[28] and is an important protective mechanism against aspiration of gastric content. Therefore, this function is also important for the maintenance of a patent upper airway. Volunteers were asked to swallow saliva and to grade subjectively whether it was more difficult than normal. Volunteers were also continuously observed for signs of inability to swallow (*e.g.*, drooling). If a volunteer reported normal initiation of swallowing then, during stable block, we conducted a swallowing test. The volunteer was asked to sip and swallow water using a straw or, if the volunteer was unable to make a tight seal around the straw, 5 ml of water was placed behind the tongue using a syringe. Study subjects were considered unable to swallow if they reported that a saliva swallow could not be initiated or if they were unable to raise the larynx.[28] The water test was not performed if the ability to swallow was lost.

Ability to Head Raise, Speak, and Open Eyes. Head-raising ability, speech, and ease of eye opening were all determined as either maintained or not maintained.

Clarity of Vision. Volunteers were asked to focus on an object approximately 3 feet away. We determined clarity of vision as maintained or not maintained from subject response. With this technique, we were not able to differentiate clearly between blurry vision and double vision, but we could detect when subjective visual disturbances occurred.

Handgrip Strength. Measurements of handgrip strength were performed on the right hand using a calibrated hydraulic hand dynamometer with a peak force indicator needle (Jamar 5030J1; Sammons Preston, Chicago, IL). The repeatability of the device has been demonstrated.[29] During testing, the right arm was resting on an arm board by the volunteer's side while an investigator stabilized the dynamometer. A significant change in handgrip strength during mivacurium block was considered as greater than 10% reduction of the baseline value.

Adequate recovery from neuromuscular block (*i.e.*, no clinically significant effects of residual neuromuscular block) was considered only if all the following criteria were met: intact ability to protrude the tongue, clench the teeth, and swallow, and FRC and VC less than 10% lower than the baseline value.

Statistics

Statistical analyses were made using JMP version 7.0 (SAS Institute, Cary, NC), and the significance level was set at $P < 0.05$ when relevant. The relationships between acceleromyographic AP TOF ratio and the continuous variables from pulmonary function testing and handgrip strength measurements were analyzed using linear regression, accounting for repeated measures. The relationships between acceleromyographic AP TOF ratio and the remaining clinical measures of muscle function were analyzed by calculating the fraction of individuals with intact function at each level of stable neuromuscular block. Wilcoxon signed rank test was used to analyze the difference in the times needed to obtain the first and subsequent stable neuromuscular blocks.

Results

All 12 subjects completed the study without incident: signs of airway obstruction were not observed at any level of neuromuscular block, normal tidal respiration was always maintained, and the arterial oxygen saturation did not decrease during the experiment in any subject.

Mivacurium Administration and Recording of Neuromuscular Block

Mivacurium infusion rates and resultant TOF ratios are in table 1. Generally greater mivacurium infusion rates resulted

Table 1. Mivacurium Infusion Rates and Acceleromyographic Adductor Pollicis Train-of-four Ratios

	Block Level			
	Baseline	1	2	3
Mivacurium infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0	1.45 ± 0.58 (0.8–2.3)	1.80 ± 0.59 (1.0–2.7)	2.17 ± 0.65 (1.4–3.3)
Train-of-four ratio				
Uncorrected	1.12 ± 0.04 (1.06–1.18)	0.90 ± 0.07 (0.80–1.06)*	0.67 ± 0.09 (0.48–0.80)†	0.48 ± 0.07 (0.33–0.66)‡
Normalized	1.0	0.81 ± 0.05 (0.73–0.95)	0.60 ± 0.06 (0.43–0.70)	0.42 ± 0.05 (0.31–0.60)

Stable neuromuscular blocks (uncorrected and normalized to baseline value) obtained during steady–state continuous infusions with mivacurium. All data are mean ± SD (range) unless otherwise specified.

* Significantly different from baseline. † Significantly different from baseline and block level 1. ‡ Significantly different from baseline, block level 1, and block level 2.

Table 2. Pulmonary Function Data

Variable	Block Level			
	Baseline	1	2	3
FRC	2.05 ± 0.30 (1.10–2.78)	2.05 ± 0.22 (1.01–2.87)	2.04 ± 0.32 (0.98–2.85)	2.04 ± 0.19 (1.35–2.85)
VC	4.35 ± 0.48 (2.86–6.04)	4.12 ± 0.43 (2.84–5.62)*	3.80 ± 0.41 (2.66–5.10)†	3.22 ± 0.55 (2.08–4.60)‡
VC, % reduction	0	5 ± 4 (0–12)	12 ± 5 (1–22)	26 ± 7 (8–41)
RV	1.12 ± 0.30 (0.60–1.64)	1.18 ± 0.23 (0.61–1.74)*	1.23 ± 0.20 (0.58–1.83)†	1.50 ± 0.25 (0.71–2.27)‡
CC	1.51 ± 0.26 (0.88–2.22)	1.53 ± 0.22 (0.94–2.23)	1.55 ± 0.20 (0.92–2.06)	1.84 ± 0.26 (0.96–2.52)
CV	0.44 ± 0.15 (0.12–0.70)	0.38 ± 0.12 (0.20–0.64)	0.32 ± 0.11 (0.11–0.47)	0.31 ± 0.07 (0.22–0.48)
CV, % of VC	11 ± 3 (3–15)	10 ± 3 (5–13)	9 ± 3 (3–13)	10 ± 3 (7–18)

Data are obtained at baseline and three different levels of stable mivacurium block (table 1) in 12 volunteers. All data are mean ± SD liters unless otherwise specified.

* Significantly different from baseline. † Significantly different from baseline and block level 1. ‡ Significantly different from baseline, block level 1, and block level 2.

CC = closing capacity, CV = closing volume, FRC = functional residual capacity, RV = residual volume, VC = vital capacity.

in smaller TOF ratios. The times needed to stabilize the first and subsequent stable blocks were significantly different (table 1, $P < 0.001$). The within-individual variability of TOF ratio recordings varied from 1.5 to 5% irrespective of the level of block.

Pulmonary Function Tests

In the absence of mivacurium, mean ± SD FRC changed with body position: 3.03 ± 0.90, 2.70 ± 0.66, and 2.06 ± 0.57 l in the upright, semirecumbent, and supine positions, respectively ($P < 0.05$). FRC did not change with time in the supine position (2.06 liters at baseline and 240 min). VC and CC did not change with body position or time (4.79 ± 1.10 and 1.42 ± 0.51 liters in the upright, and 4.54 ± 1.05 and 1.37 ± 0.20 liters in the supine position after 240 min, respectively).

Lung volumes during mivacurium infusion are given in table 2. In all 12 volunteers VC decreased (fig. 1) and RV increased ($P < 0.001$) with decreasing normalized acceleromyographic AP TOF ratio. FRC did not change, and CV declined proportionately with VC. The largest reduction recorded in VC at block level 1 (12% in one volunteer) was observed at normalized TOF ratio of 0.88. Approximately 75% of the reduction in VC was due to loss of inspiratory reserve volume. Data suggested an increase in CC with decreasing TOF ratio ($P = 0.06$).

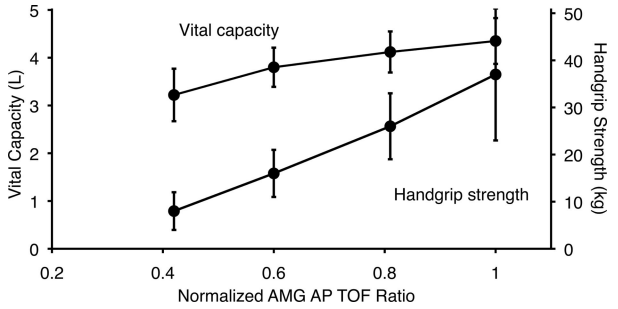

Fig. 1. The relationship between normalized acceleromyography adductor pollicis train-of-four (AMG AP TOF) ratio and vital capacity of the lungs and between normalized AMG AP TOF ratio and handgrip strength in 12 volunteers during stable mivacurium blocks. Both vital capacity and handgrip strength decreased significantly with decreasing AMG AP TOF ratio. 95% confidence interval of the slopes (upper–lower limits): vital capacity: 0.01810838–0.01093862 and handgrip strength: 1.0987737–0.6567971.

Clinical Measures of Muscle Function

Tongue protrusion, speaking, and eye opening were well preserved at all block levels in all subjects (table 3). The fraction of individuals losing the ability to clench teeth increased with reduction in normalized acceleromyographic AP TOF ratio (table 3). One subject lost this ability at normalized TOF ratio of 0.84, whereas three subjects maintained the function at normalized TOF ratio of 0.3. Swallowing became subjectively more difficult with decreasing acceleromyographic AP TOF ratio. Four subjects lost this ability completely at block level 3 (table 3); the most sensitive did so at normalized TOF ratio of 0.60, and this result corresponded with the subject's inability to raise the larynx. The same four subjects also lost the ability to raise the head more than 5 s at block level 3 (table 3).

All subjects experienced reduced clarity of vision within 15 min after starting the mivacurium infusion. This was the first sign of neuromuscular block in all volunteers and occurred in advance of changes in TOF ratio by 15–40 min. It was also the last sign to disappear as the effects of mivacurium dissipated.

In all 12 volunteers, handgrip strength decreased significantly with decreasing acceleromyographic AP TOF ratio ($P < 0.001$, table 3, fig. 1) and was on average 22% of baseline value at block level 3.

Discussion

In this study of 12 awake volunteers under partial mivacurium-induced paralysis, clinically significant effects of residual neuromuscular block were not observed if the normalized acceleromyographic AP TOF ratio was greater than 0.90. At

Table 3. Clinical Functions during Stable Neuromuscular Blocks (n = 12)

Function	Block Level			
	Baseline	1	2	3
Tongue protrusion	0	0	0	0
Teeth clenching	0	2 (0.84/0.75)	4 (0.70/0.64)	8 (0.48/0.45/0.44/0.39)
Swallowing	0	0	0	4 (0.60/0.50/0.48/0.45)
Head raise > 5 s	0	0	0	4 (0.60/0.50/0.48/0.45)
Speaking	0	0	0	0
Eye opening	0	0	0	0
Clarity of vision (mean normalized TOF at loss)	0	12 (0.81)	12	12
Handgrip strength, kg, mean ± SD (range)	37 ± 14 (14–70)	26 ± 7 (10–36)*	16 ± 5 (8–23)†	8 ± 4 (5–15)‡
Handgrip strength, % reduction	0	27 ± 15 (0–67)*	51 ± 14 (27–82)†	75 ± 10 (52–94)‡

The number of individuals with lost clinical muscle function and the handgrip strength at baseline at three different levels of stable mivacurium block were recorded. Unless otherwise specified, the numbers in parentheses are the individual normalized TOF ratio value at which function was lost.

* Significantly different from baseline. † Significantly different from baseline and block level 1. ‡ Significantly different from baseline, block level 1, and block level 2.

TOF = train-of-four.

this level of neuromuscular block, the VC of the lungs was close to the baseline value, and the ability to protrude the tongue, clench the teeth, and swallow was well preserved in all volunteers. Our results are consistent with existing recommendations regarding the desirable endpoint of neuromuscular reversal (mechanomyographic TOF ratio of 0.9) because a mean normalized acceleromyographic AP TOF ratio of 0.90 using preload corresponds to an uncorrected mean mechanomyography-based value of of 0.85.[3] Presently, normalization of acceleromyographic values must be performed manually when using commercially available monitoring devices, but, in future models, this recalculation may be incorporated as an optional function.

We studied a relatively small number of study subjects, a fact that reduces the reliability of our findings. We chose to perform an experiment that looked at multiple repeated measures of both the TOF ratio and clinical signs of residual neuromuscular block under steady–state conditions. Thus, each volunteer study was very time-intensive. The total number of volunteers studied was limited by available time. We are confident that the lung volume and handgrip strength measurements are representative because the variability among subjects was quite small. Also, a *post hoc* power analysis based on the VC data (maximum change from baseline 26% ± 8%, α-error 0.05) shows that only six individuals were needed to detect the mean maximum change with greater than 90% certainty. On the other hand, the responses to clinical tests of residual block varied greatly among subjects, *i.e.*, in the TOF ratio associated with each measure. These values are, therefore, imprecise, and a study with a larger numbers of individuals would be needed to improve confidence levels.

The observed effect of residual neuromuscular block on VC is consistent with results from previous investigations. In two mechanomyography-based studies, the mean reduction from baseline in VC[30] or forced VC[31] was greater than 10% at AP TOF ratio of 0.5–0.6, wherease we found a mean 12% decrease at normalized acceleromyographic TOF ratio of 0.6. Reductions in VC are associated with development of atelectases postoperatively[11,12] and may have contributed to the increased incidence of postoperative pulmonary complications found in a study by Berg *et al.*[32] in patients with pancuronium-induced mechanomyographic AP TOF ratio values less than 0.7 in the recovery room. Thus, in surgical patients, present research suggests that adequate recovery from neuromuscular blockade has not occurred unless the VC is close to the baseline level at the end of anesthesia. The data from our study indicate that this goal has been achieved in most patients if the normalized acceleromyographic AP TOF ratio is greater than 0.9.

As expected, FRC decreased as subjects went from upright to sitting or supine,[33] but it did not change during partial paralysis while the volunteer was supine. These data are consistent with results recently obtained by other investigators[34,35] using measurement techniques based on magnetic tomography or plethysmography. FRC was at all times higher than CC during our experiments, consistent with the fact that the arterial oxygen saturation did not change in any study subject. As RV increased in parallel with the decrease in VC, we expected a gradual increase in CC (RV + CV). This did not occur, probably because the absolute value of CV decreased with decreasing VC. Our data suggest, however, that CC started to increase at normalized TOF ratio of approximately 0.4 (table 2) and would likely have been larger than FRC if the block had been deepened even further. We have therefore demonstrated that residual neuromuscular block probably does not cause collapse of small airways in healthy, nonobese, young individuals, as long as the normalized acceleromyographic AP TOF ratio is greater than 0.4.

However, the FRC/CC relationship during residual neuromuscular block might be different in patients undergoing surgery because of age, underlying lung disease, or the simultaneous effect of sedative drugs.

In a recent case-control study, investigators[36] immediately recorded neuromuscular function whenever critical respiratory events occurred in the postanesthesia care unit. In a group of 37 patients with severe hypoxemia or airway obstruction, a mean uncorrected acceleromyographic AP TOF ratio of 0.62 ± 0.2 was observed with matched controls demonstrating TOF ratio of 0.98 ± 0.07. This result is in contrast to our findings that none of the study subjects experienced arterial oxygen desaturation or airway obstruction, even at normalized TOF ratio of 0.3. Two factors may explain this discrepancy. First, in that clinical study, the acceleromyographic recordings were not normalized. Second, the study was performed in postoperative patients simultaneously exposed to the residual effects of anesthetics and opioids, drugs known to increase the collapsibility of the upper airway.[37,38] Therefore, the residual effects of sedative drugs may have unmasked the impeding influence of neuromuscular-blocking drugs on the function of the genioglossus muscle,[34,35] an effect that was not observed in our experiment because mivacurium was used as the sole drug.

The most sensitive subject in our study lost the ability to swallow saliva completely at normalized acceleromyographic TOF ratio of 0.60 (table 3). This result is in contrast to previous investigations showing that an mechanomyography-based AP TOF ratio of greater than 0.9 is needed for full recovery of the coordination of pharyngeal muscles.[39,40] This discrepancy may only be apparent because an intact ability to swallow does not necessarily mean that the process of swallowing is normal. The propelling force and speed of swallowing may be impaired but not completely lost during residual neuromuscular block in nonanesthetized subjects.[41] That would be consistent with our observation that all volunteers reported changes in the effort required to initiate swallowing well before the function was lost entirely.

Most clinicians still do not use objective and quantified neuromuscular monitoring perioperatively[42] and instead rely on clinical observations to identify significant residual neuromuscular block. A simple test that reliably predicts a normalized acceleromyographic AP TOF ratio greater than 0.90, the TOF ratio value at which our criteria for adequate recovery from neuromuscular block were met in all 12 volunteers, would therefore be very useful. The ability to focus visually would fulfill this criterion, but is very sensitive to the effect of neuromuscular-blocking drugs and normalizes long after full recovery of all other muscular functions; in effect, it would be too conservative. Handgrip strength decreased in parallel with TOF ratio reduction, but is highly dependent on a patient's ability to cooperate; it is unlikely to be suitable in the clinical setting. The other tests that we evaluated were too insensitive, with the majority of the volunteers testing normally even at normalized TOF ratio of 0.4–0.5. Even the ability to clench teeth, a test proposed by Kopman *et al.*[19] as a potentially useful predictor of adequate recovery from neuromuscular block, was retained in our study subjects at a wide range of TOF ratios. Our data are therefore consistent with previous observations, *i.e.*, that the responses to the effect of neuromuscular-blocking drugs vary to a large extent among individuals and that a reliable clinical test for detection of significant residual neuromuscular block (*i.e.*, a test that is passed only if the normalized acceleromyographic AP TOF ratio is greater than 0.90) will probably remain elusive.[43]

Despite favorable pharmacokinetics of mivacurium, the mean time needed to establish the first stable neuromuscular block was more than 80 min, as compared with approximately 30 min for attained blocks 2 and 3. This phenomenon of delayed onset of effect may be related to the margin of safety that exists at the neuromuscular junction, *i.e.*, that more than 70% of the postjunctional acetylcholine receptors must be blocked before any change in neuromuscular function may be observed.[44,45] Also, we speculate that the third and least active isomer of mivacurium (cis-cis), which has a much longer elimination half-life (53 min) and a larger distribution volume (0.35 liter/kg),[17] may induce small changes in the TOF ratios after long-term mivacurium infusions.

In summary, we studied 12 healthy volunteers during mivacurium-induced neuromuscular block, quantified using normalized acceleromyographically measured AP TOF ratio with preload. VC, but not FRC, gradually declined with decreasing TOF ratio. The relationships between the TOF ratio and common clinical tests were highly variable among individuals. At normalized acceleromyographic AP TOF ratio greater than 0.90, no significant clinical effects of residual neuromuscular block were detected.

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