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# The Relationship between Acceleromyographic Train-of-four Fade and Single Twitch Depression

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***Background:*** **During offset of nondepolarizing neuromuscular block, a train-of-four (TOF) fade ratio of 0.70 or greater is considered to reliably indicate the return of single twitch height (T1) to its control value. Studies using mechanomyography or electromyography confirm this observation. The authors' impressions when using the acceleromyograph as a neuromuscular monitor did not support these results. Therefore, the authors studied the relation between T1 and the TOF ratio (when measured by acceleromyography) during recovery from neuromuscular block.**

***Methods:*** **Sixteen adult patients were studied. Anesthesia was induced with intravenous opioid plus 2.0–2.5 mg/kg propofol. Laryngeal mask placement or tracheal intubation was accomplished without the use of muscle relaxants. Anesthesia was maintained with nitrous oxide, desflurane (2.0–3.0%, end-tidal), and fentanyl. The response of the thumb to ulnar nerve stimulation was recorded with the TOF-Guard® acceleromyograph (Organon Teknika BV, Boxtel, The Netherlands). TOFs were administered every 15 s. After final calibration, 0.15 mg/kg mivacurium was administered. No further relaxants were administered. T1 and the TOF ratio were then recorded until the TOF ratio had returned to its initial value (± 5%).**

***Results:*** **At a TOF ratio of 0.70 (during recovery of neuromuscular function), T1 averaged only 69 ± 8% of control. At a TOF ratio of 0.90, T1 averaged 86 ± 5% of control. To achieve 90% recovery of T1, a TOF ratio of 0.93 ± 0.08 was required.**

***Conclusion:*** **Assumptions regarding the relation between T1 and the TOF ratio derived from studies using mechanomyography and electromyography do not necessarily apply to observations obtained using acceleromyography.**

THERE is a growing consensus that optimal recovery of neuromuscular function after administration of nondepolarizing relaxants requires return of the train-of-four fade ratio (TOF) at the adductor pollicis to a value of 0.90 or greater.[1–3] Nevertheless, the original "gold standard" of a TOF ratio of 0.70 is still an important benchmark. Although significant subjective symptoms of residual weakness are to be expected at this latter level of recovery, respiratory mechanics (peak negative inspiratory pressure, vital capacity, maximum expiratory flow rate) are usually well-preserved.[4] Unfortunately, subjective estimation of the extent of TOF fade is poor at best. It is difficult to detect (by palpation or visual estimation) that any fade exists after the TOF ratio exceeds 0.40–0.50,[5] and accurate mechanomyographic or electromyographic measurement of neuromuscular recovery is rarely available in the clinical setting. Thus, for many anesthetists, the TOF fade ratio is something that he or she reads about but cannot attempt to measure.

With the introduction of portable, battery-operated, and relatively inexpensive acceleromyographic monitors in the mid 1990s, the ability to quantify the TOF ratio in daily practice became possible. However, there is considerable controversy regarding the accuracy of these devices. Harper *et al.*[6] noted that the limits of agreement between acceleromyographic and mechanomyographic values were unacceptably wide. When the mechanomyographic TOF ratio was 0.70, the corresponding acceleromyographic TOF valued varied between 0.4 and 1.0. Loan *et al.*[7] had similar findings. If these observations are correct, then a TOF ratio of 0.70 measured with acceleromyographic techniques may give the clinician a false sense of security regarding the state of neuromuscular recovery. Of equal importance, an increasing number of scientific articles are being published in which acceleromyography is the primary monitoring technique.[8–10] Thus, the meaning of the acceleromyogram-derived TOF ratio has considerable importance.

Twenty years ago, Ali *et al.*[11] demonstrated (using mechanomyography) that during offset of neuromuscular block, a TOF ratio of 0.70 or higher reliably indicated the return of single twitch height (T1) to its control value. Other investigators report similar findings. At 90% recovery of T1, McCoy *et al.*[12] reported a TOF ratio of approximately 0.60. Our clinical impression when using acceleromyography does not support these observations. In our experience, at a TOF ratio of 0.70, we have never seen full recovery of single twitch height. Therefore, we decided to study the relation between T1 and the TOF ratio (when measured by acceleromyography) during recovery from nondepolarizing neuromuscular block in a more formal manner.

We were curious about one additional matter. When acceleromyography was first described, it was emphasized that the thumb should be free to move unimpeded. However, the manufacturer of the TOF-Guard® monitor (Organon Teknika BV, Boxtel, The Netherlands) provides an arm board specifically designed to allow a small elastic preload to be added to the thumb. This device was designed to make it more likely that the thumb will return to exactly the same position after each stimulus and thus decrease baseline drift. We were therefore interested in whether an elastic preload attached to the

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**Table 1. The TOF Fade Ratio as a Function of Twitch Height (T1) and *Vice Versa***

| T1 (% Control) | TOF Ratio* |
|---|---|
| 50 | 0.41 ± 0.14 (0.17–0.68) |
| 75 | 0.77 ± 0.06 (0.65–0.88) |
| 90 | 0.93 ± 0.08 (0.85–1.14) |

| TOF Ratio | T1 (% Control)* |
|---|---|
| 0.70 | 69 ± 8 (52–83) |
| 0.90 | 86 ± 5 (77–95) |

* Mean ± SD (range), N = 16.
TOF = train-of-four.

thumb would alter the control TOF fade ratio or the relation between T1 and TOF.

## Methods

Sixteen adult patients (aged 23–52 yr) with American Society of Anesthesiologists physical status class I or II who were scheduled to undergo elective surgical procedures were included in the study. All patients were free from neuromuscular disease and had a body mass index greater than or equal to 17.5 and less than or equal to 27.5. The protocol was approved by our hospital's Human Subject Review Committee (St. Vincent's Hospital and Medical Center, New York, New York), and consent was obtained. Anesthesia was induced with 15–40 μg/kg alfentanil plus 2.0–2.5 mg/kg intravenous propofol, and laryngeal mask placement or tracheal intubation was accomplished without the use of neuromuscular blocking drugs. Anesthesia was maintained with nitrous oxide (65–70% inspired), desflurane (2.0–3.0%, end-tidal), and intermittent doses of fentanyl if required. Ventilation was controlled, and end-tidal partial pressure of carbon dioxide ($P_{CO_2}$) was maintained between 34 and 40 mmHg.

After induction of anesthesia, the evoked response of the adductor pollicis muscle to ulnar nerve stimulation at the wrist was recorded in all subjects. The monitor–stimulator used was the TOF-Guard® acceleromyograph. In half the subjects, the study arm was immobilized to the TOF-Guard® arm board, and the thumb was placed under a small preload with a single strand of an elastic rubber band (approximately 3.3 mm wide by 2 mm thick). In the remaining subjects, no preload was applied. All data were collected on a TOF-Guard® Flash RAM memory card for later transfer to a desk-top computer. Before calibration of the TOF-Guard® unit, a 5-s, 50-Hz supramaximal tetanic stimulus (250 stimuli) was administered at the ulnar nerve. Previous work from our department[13] and by others[14] has shown that the period required for baseline stabilization is shortened considerably by this procedure.

Immediately thereafter, the acceleration transducer was taped to the volar aspect of the thumb at the interpharyngeal joint, and calibration of T1 was performed. TOFs were then administered at 15-s intervals. After initial T1 calibration, an additional 5 min of TOF stimulation (every 15 s) was allowed for baseline stabilization. A second T1 calibration was performed, and 0.15 mg/kg mivacurium was administered as a rapid intravenous bolus. No further neuromuscular blocking agents were administered. Twitch height and the TOF ratio were then followed until the TOF ratio had returned to its initial value (± 5%) and had stabilized at this value for at least 3 min. In accordance with the recommendations of the Copenhagen Consensus Conference, all twitch height data recorded during recovery from neuromuscular block were "normalized" to the final T1 value.[15]

### *Statistics*

All summary data are presented as arithmetic mean ± SD. For all the parameters we studied (initial TOF ratio, TOF at T1 = 90%, and others), we compared the results in patients in whom no preload was placed on the thumb with those in whom a preload was present using an unpaired Student *t* test. Observed differences were considered significant if $P$ was less than 0.05. We also studied the relation between the TOF fade ratio and twitch height using best-fit linear and polynomial regression analysis.

## Results

The control train-of-four ratio was slightly greater in the no-load group (1.20 ± 0.11) than in the preload group (1.10 ± 0.07). This difference just reached statistical significance ($P < 0.05$). There were no other significant differences in any of the parameters measured (*e.g.*, T1 at a TOF of 0.70) when the preload group was compared with the no-load group. Therefore, we pooled the data from all the patients. The results are summarized in table 1.

Before administration of mivacurium, the control train-of-four ratio was on average 1.15 ± 0.10 (range, 0.97–1.32) and returned to a plateau value of 1.11 ± 0.09 (range, 0.94–1.26) when our observations were complete. The relation between twitch height (percentage of control) and the train-of-four fade ratio that we observed during recovery from mivacurium-induced neuromuscular block is illustrated in figures 1 and 2. When the TOF ratio returned to a value of 0.70, T1 was on average 69 ± 8% and never exceeded 85% of control. The mean TOF ratio required for 90% T1 recovery was 0.93, and a TOF



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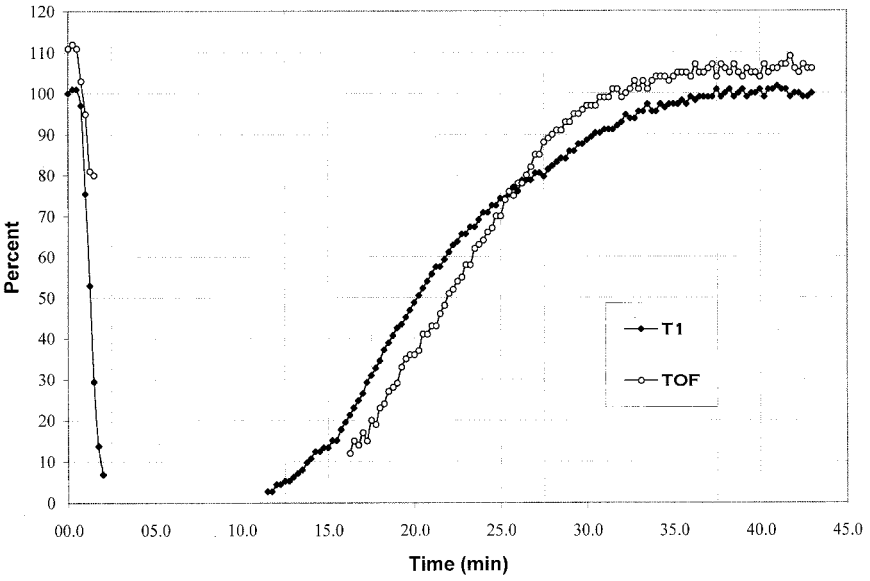


**Fig. 1. A representative individual from the preload group. Both the single twitch height (T1; expressed as a percentage of control) and the train-of-four (TOF) fade ratio (as a percentage) are plotted against time. At time 0, a bolus of 0.15 mg/kg mivacurium had been administered. The clinical duration is 16.8 min, with a $T_{25–75}$ interval of 8.8 min. When the TOF ratio has recovered to a value of 0.80, twitch height is only 79% of control.**

ratio of 1.00 was required for 95% return of twitch height.

## Discussion

It has been 30 yr since Ali *et al.*[16,17] first described the relation between single twitch height and the train-of-four fade ratio. Their assertion that during recovery, a TOF fade ratio of 0.70 indicates full T1 recovery has been generally accepted. In the subsequent three decades, adequacy of neuromuscular recovery has commonly been estimated by measuring the TOF ratio rather than the extent of single twitch recovery. The TOF ratio has become acknowledged as a sensitive and more easily determined measure of residual block than single twitch depression because no period of baseline stabilization or calibration is required, each train-of-four acting as its own control.

Because the observations of Ali *et al.*[16,17] on the correlation between twitch height and the TOF fade ratio have been so universally agreed on, few investigators have reexamined this relation. The information available generally supports the work of Ali *et al.* McCoy *et al.*[12] (using mechanomyography) found that during recovery from nondepolarizing neuromuscular block (atracurium, mivacurium, vecuronium, rocuronium), at a TOF ratio of 0.60 or greater, single twitch had returned to 90% of control. Carroll *et al.*[18] reported essentially identical results also using mechanomyography. Pearce *et al.*,[19] again using mechanomyography, found that after the TOF returned to a value approximating 0.35, T1 was at 75% of control. Savarese *et al.*[20] noted that during recovery from mivacurium-induced neuromuscular block, 95% twitch recovery always preceded return of the TOF ratio to a value of 0.75–0.80 by 2 or 3 min. Finally, Graham *et al.*[21] reported that during spontaneous recovery from

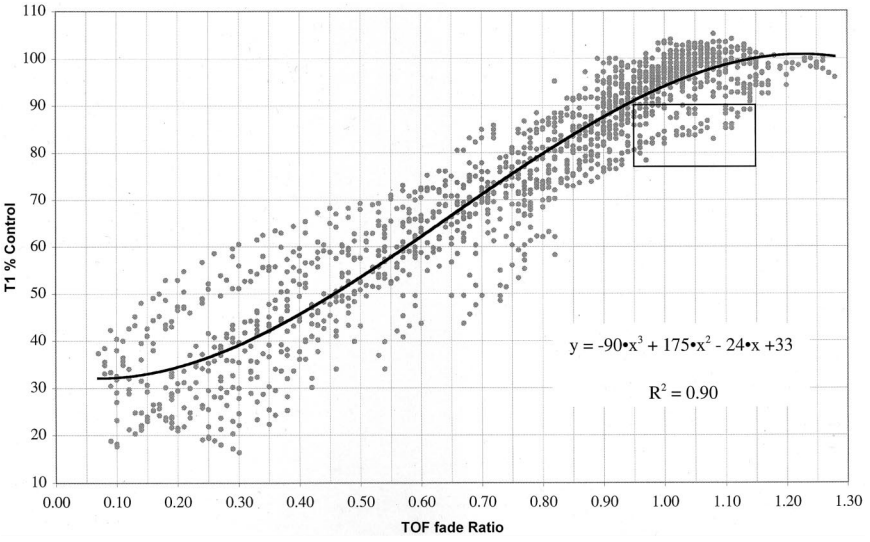


**Fig. 2. Single twitch height (T1) as a function of the train-of-four (TOF) fade ratio. The relation between T1 and the TOF ratio may be expressed more simply using linear regression analysis ($y = 73.9 \cdot x + 19$), but the coefficient of determination ($R^2$) is slightly lower (0.89). The calculated estimate of T1 for any TOF value between 0.20 and 1.10 does not differ by more than 3% of control, regardless of the equation used. The rectangle in the upper right-hand quarter of the graph encloses those data points where the TOF ratio was greater than 0.95 and T1 was still less than 90% of control.**



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pancuronium-induced block, the TOF ratio at complete T1 recovery was 0.75 ± 0.16.

We remain puzzled by an obvious question. There is no apparent reason why the relation between T1 twitch height and the TOF fade ratio should be different when measured by mechanomyography as opposed to acceleromyography. Why the lack of correspondence between our results and the observations of such early investigators as Ali *et al.*[11]? Much of the original work on T1 *versus* TOF recovery was done using traditional long-acting blocking agents such as d-tubocurarine and pancuronium. No attempt was made to follow the TOF fade ratio until it returned to its original value. Observations were completed when T1 had returned to its "control" value. However, it is entirely possible that further recovery in twitch height may still have occurred. We now recognize that in the absence of a sufficient period of baseline stabilization, twitch height may "recover" to values far in excess of 100% of control.[13] Adequate time for stabilization may take as long as 30 min, depending on the mode of stimulation. In studies in which the relation between the TOF fade ratio and single twitch height (T1) is in question, we believe that it is important at the end of surgery to allow the TOF fade ratio to return to values greater than 0.90. After the TOF ratio has stabilized at this level, further changes in T1 are unlikely. Nevertheless, we do not believe that this explanation is sufficient to explain the disparity between our findings using acceleromyography and the observations of most investigators who rely on mechanomyographic recordings.

There is less information available about the relation between T1 and the TOF fade ratio obtained electromyographically, but there does seem to be a close correlation between electromyogram- and mechanomyogram-determined train-of-four values.[22] The limited data available supports the position that the TOF ratio lags considerably behind twitch height recovery. At a TOF ratio of 0.25, T1 is reported to be as high as 75% of control.[23] A random review of old electromyographic records from our files supports the clinical impression that after the TOF ratio exceeds 0.70, single twitch height has reliably returned to 90% or more of its control value.

When the acceleromyograph was introduced as a neuromuscular monitor, it was assumed that the relation between T1 and the TOF fade ratio documented with mechanomyography and electromyography would not differ to any appreciable extent with this new technology. However, the original reports describing this monitoring technique raised questions at the outset which have never been adequately resolved. Viby-Mogensen *et al.*[24] noted when using acceleromyography that the average control TOF fade ratio was 1.16 ± 0.12, compared with a value of 0.98 ± 0.04 with mechanomyography. The 1.16 value of Viby-Mogensen *et al.*[24] is essentially identical to the value we report (1.15 ± 0.10). If the "control" TOF ratio is 1.15, how does one interpret a recorded value of 0.70 during recovery? Is this latter value to be taken literally or is it only 61% of control (0.70/1.15 = 0.61)? The current investigation strongly suggests that a TOF ratio of 0.70 or even 0.80 measured using acceleromyography should not be equated with full recovery of twitch height. During recovery, when the acceleromyographic TOF fade ratio is 0.70, T1 is on average less than 75% of control. When the TOF ratio has turned to a 0.90, T1 is still likely to be less than 90% of control. If we accept the premise that single twitch height must exceed a value of 90–95% for neuromuscular recovery to be considered acceptable, it is clear that an acceleromyographic TOF ratio of less than 0.90 represents incomplete return of neuromuscular function.

These observations have important implications. Acceleromyographic monitors are not only being used in day-to-day clinical care but are being increasingly used as research instruments.[25] Recently, we were asked to participate in a multisite study of the comparative onset times and durations of action of two nondepolarizing relaxants. The protocol mandated the use of the TOF-Guard® neuromuscular monitor. A key recovery parameter we were required to measure was the time interval from the initial drug administration to spontaneous return of the TOF ratio to a value of 0.80. Additional data were not collected beyond this point because it was assumed, at a TOF ratio of 0.80, that no further recovery of T1 would occur. We now believe this supposition was in error, and the recovery intervals we reported were probably shorter than those that would have been recorded using mechanomyography or electromyography.

The TOF fade ratio is not a direct measure of muscle strength, ventilatory reserve, or the ability to maintain a patent airway. Nevertheless, over the past three decades, it has served as a useful surrogate end point in situations in which we cannot measure true outcomes.[26] The advent of small, battery-operated acceleromyographic monitors that can measure this parameter is therefore a welcome development. However, our observations suggest that the information these devices provide must be interpreted with caution. We recommend that TOF ratios less than 0.90 measured with these devices should be interpreted as potentially representing incomplete neuromuscular recovery.

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