

## The Accuracy of Train-of-four Monitoring at Varying Stimulating Currents

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Train-of-four (TOF) monitoring of neuromuscular block at submaximal current stimulation has been recommended because it is less painful than monitoring at supramaximal stimulation. The measurement error, however, when using submaximal stimulation has not as yet been fully elucidated. The authors therefore quantified the measurement error of TOF monitoring at low currents near the initial threshold for stimulation (ITS) by assessing precision (the difference between duplicated TOF ratios measured at the same current) and accuracy (the difference between TOF ratios at lesser currents and the TOF ratio at 58 mA, which served as the reference standard method). A stable neuromuscular block at a TOF ratio of 0.40 and subsequently 0.70 was established in 20 patients using a continuous infusion of atracurium. The ulnar nerve was stimulated at the wrist using TOF stimulation, and the evoked twitch response of the adductor pollicis muscle was measured with a force-displacement transducer. The stimulating current was varied in 5-mA steps between ITS and 55 mA. Whereas there were no statistical significant differences between the mean TOF ratios at the different currents, the standard deviation increased with decreasing currents ( $P < 0.01$  at currents  $< 40$  mA). The precision was acceptable except at ITS, where the limits of precision (mean intracurrent difference in TOF ratio  $\pm$  two standard deviations) exceeded 0.05, which was the chosen acceptable difference. The standard deviation of the accuracy was significantly increased at currents  $\leq$  ITS + 25 mA ( $P < 0.01$ ). At currents  $<$  ITS + 25 mA, the limits of accuracy (mean intercurrent difference in TOF ratio  $\pm$  two standard deviations) exceeded the chosen acceptable difference. It is concluded that the accuracy of TOF ratio monitoring is unacceptable at currents  $<$  ITS + 25 mA. (Key words: Monitoring, neuromuscular function; neurostimulation; train-of-four.)

IN CLINICAL ANESTHESIA, train-of-four (TOF) stimulation is commonly used to evaluate nondepolarizing neuromuscular blockade. The degree of block can be assessed directly from the TOF ratio even though a preparalysis value is lacking.<sup>1</sup> Traditionally recommended has been supramaximal stimulation of the nerve, *i.e.* a stimulus exceeding what is necessary to elicit a maximal motor response.<sup>2</sup>

However, TOF stimulation at maximal current of the ulnar nerve *via* surface electrodes is associated with sig-

nificant discomfort in awake patients emerging from anesthesia.<sup>3</sup> Brull *et al.* recently evaluated whether TOF ratio monitoring can be accomplished safely at lesser currents.<sup>4</sup> In their study they demonstrated a high correlation between the mechanically recorded TOF ratios at 20, 30, and 50 mA, and they also found that there were not any statistical significant differences between the mean TOF ratios at the different currents. Without quantifying the error of measurement, they concluded that TOF ratio monitoring at 20 or 30 mA is just as reliable as TOF ratio monitoring at 50 mA.

The aim of the present study was therefore to evaluate the repeatability (the difference between replications of TOF ratio determinations at different currents) and to quantify the agreement of TOF ratio determinations at low and high currents. This was done by quantification of precision and accuracy.

### Materials and Methods

Following local Ethics Committee approval and informed consent, we studied 24 healthy patients undergoing minor surgery. None of the patients suffered from neuromuscular disease or received any drug that might interfere with neuromuscular function.

Anesthesia was induced with thiopental and was maintained with fentanyl, nitrous oxide, and midazolam or halothane. Neuromuscular blockade was induced with a bolus and maintained with a continuous infusion of atracurium. Tracheal intubation was performed in all patients and ventilation was controlled and adjusted to maintain the end-tidal carbon dioxide concentration between 4.5 and 5.5 kPa (34 and 41 mmHg) (Normocap, Datex, Finland).

A Myotest DBS<sup>®</sup> nerve stimulator (Biometer, Denmark) was used to stimulate the ulnar nerve at the wrist *via* conducting rubber surface electrodes with a circular contact area of 0.8 cm<sup>2</sup>. The stimulating pattern was TOF giving four 0.2-ms square-wave currents at 2 Hz every 12 s. The current setting of the nerve stimulator had previously been adjusted in 5-mA steps by using a digital storage oscilloscope (Hameg type HM 208, Atimco, Denmark) and a resistive load of 2.5 k $\Omega$ . The maximal output of the nerve stimulator was 58 mA. The current output was constant as long as the resistive load was less than 3.5 k $\Omega$ .

The evoked twitch responses of the thumb were recorded mechanically by a Myograph 2000<sup>®</sup> (Biometer). The TOF ratios were recorded from the digital display

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on the myograph, which calculated the ratios following analog-to-digital conversion of the twitch response. The heights of the first twitch in TOF were obtained from hand ruler measurement of the twitch responses on the recording paper, where a 25-mm deflection represented a twitch height of 100%. The resting load was set at 250–300 g.

The ulnar nerve was stimulated with 58 mA, and the atracurium infusion rate was adjusted to obtain and maintain a stable neuromuscular block at a TOF ratio of 0.40 and subsequently 0.70. The current output was then reduced in decrements of 5 mA until disappearance of the evoked twitch response, after which the current again was increased in increments of 5 mA. Two TOF stimulations were applied before changing the current output. The resulting four TOF ratio determinations at each 5-mA step were designated TOFa, TOFb, TOFc, and TOFd (fig. 1). The block was considered unstable if the TOF ratio at 58 mA changed more than 0.04 during the period of measurements:

$$\left| \frac{\text{TOFa}_{58} + \text{TOFb}_{58}}{2} - \frac{\text{TOFc}_{58} + \text{TOFd}_{58}}{2} \right| > 0.04$$

The patients were withdrawn from the study if stable neuromuscular blockade was not obtained in three attempts. We defined the initial threshold for stimulation (ITS) as the lowest current at which the height of the first twitch in TOFa was equal to or greater than 4% of that at 58 mA. The 4% limit was chosen because it represents the first clearly visible and well-defined twitch above background noise. Temperatures were measured using a electric thermometer (Ellab type TR 9, Ellab, Copenhagen, Denmark). The core temperature was measured by a probe introduced into the upper esophagus (Ellab type XOSG), and peripheral temperature was measured by a 1-cm diameter surface probe attached to the skin overlying the ipsilateral thenar muscles (Ellab type X-H7). Mean arterial blood pressures were also recorded.

Evaluation of repeatability and agreement between the TOF ratio determinations at the different stimulating currents were performed by assessing precision and accuracy using the method advocated by Bland and Altman<sup>5,6</sup> and LaMantia *et al.*<sup>7</sup>

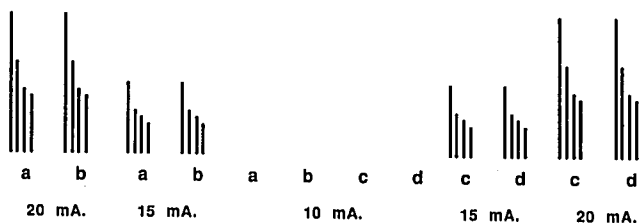


FIG. 1. Part of a mechanical twitch recording (redrawn), with the a, b, c and d nomenclature used in the calculations and the stimulation currents indicated.

Precision is an index of the repeatability of a measurement, and it quantifies the random error associated with multiple determinations performed under identical conditions. Precision was assessed by calculation of the mean and standard deviation of the differences between the duplicated TOF ratio determinations at each 5-mA step:  $\text{TOFa}_{\text{curr}} - \text{TOFb}_{\text{curr}}$  or  $\text{TOFc}_{\text{curr}} - \text{TOFd}_{\text{curr}}$ . The means  $\pm$  two standard deviations represent the limits of precision including approximately 95% of the differences.

Accuracy is an index of the difference between two methods. In the present study it quantifies the amount of systematic error of TOF ratio determinations at each of the currents less than 58 mA, with TOF ratio determination at 58 mA regarded as the reference standard method. Accuracy was assessed by calculating the mean and standard deviation of the differences between the mean TOF ratio at currents lower than 58 mA:

$$\overline{\text{TOF}}_{\text{curr}} = \frac{\text{TOFa}_{\text{curr}} + \text{TOFb}_{\text{curr}} + \text{TOFc}_{\text{curr}} + \text{TOFd}_{\text{curr}}}{4}$$

and the mean TOF ratio at 58 mA:

$$\overline{\text{TOF}}_{58} = \frac{\text{TOFa}_{58} + \text{TOFb}_{58} + \text{TOFc}_{58} + \text{TOFd}_{58}}{4}$$

The means  $\pm$  two standard deviations represent the limits of accuracy including approximately 95% of the differences. TOF ratio determinations at a given stimulating current were considered acceptable, if the absolute limits of precision and accuracy did not exceed 0.05, which was the chosen acceptable difference between the TOF ratios.

ITS was identified for each patient in order to quantify precision and accuracy at each of the different currents greater than ITS. The TOF ratios were therefore also listed according to the current greater than ITS. The TOF ratios were therefore also listed according to the current greater than ITS, *i.e.*, using ITS for each patient as the elevated zero point. If, for example, ITS was 10 mA, then a TOF ratio measured at 25 mA would be listed as obtained at ITS + 15 mA.

The standard deviations of the mean TOF ratios and the standard deviations of precision and accuracy at each of the different currents and each of the different currents greater than ITS were compared by Pitman-Morgan's test for identical variances.<sup>8,9</sup> In order to reduce the risk of falsely discarding the less painful submaximal stimulation mode, the level of significance was set at 0.01.

## Results

Four patients were withdrawn from the study because of unstable neuromuscular blockade during measure-

ments. The demographic data for the remaining 20 patients (mean [range]) were: age 45 yr (21–78 yr); weight 68 kg (51–99 kg); height 165 cm (155–182 cm); and wrist circumference 16.0 cm (14.5–18.0 cm).

The mean  $\pm$  one standard deviation TOF ratios at 58 mA were  $0.40 \pm 0.02$  and  $0.71 \pm 0.01$  in the two series, respectively. There were no statistical differences between the mean TOF ratios at the varying current outputs. The standard deviation increased, however, as the currents decreased, and was significantly greater at each of the currents less than 40 mA at TOF 0.40 and at each of the currents less than 45 mA at TOF 0.70 (fig. 2) ( $P < 0.01$ ).

The precision ( $\overline{\text{TOF}}_{a_{\text{curr}}} - \overline{\text{TOF}}_{b_{\text{curr}}}$ ) of TOF ratio monitoring was acceptable except at 20 and 25 mA, where the limits of precision exceeded  $\pm 0.05$ . The standard deviation of the difference between the intracurrent measurements was significantly increased ( $P < 0.01$ ) at each of the currents less than or equal to 25 mA compared to the standard deviation at 58 mA (fig. 3). The precision mean (mean difference in TOF ratio) ranged from  $-0.01$  to  $0.01$ . Precision calculated using the  $\overline{\text{TOF}}_{c_{\text{curr}}} - \overline{\text{TOF}}_{d_{\text{curr}}}$  differences gave similar results.

The accuracy ( $\overline{\text{TOF}}_{\text{curr}} - \overline{\text{TOF}}_{58}$ ), however, was unacceptable at all currents less than or equal to 40 mA. Compared to 55 mA the standard deviations were significantly increased at currents less than or equal to 45 mA ( $P < 0.01$ ). The accuracy mean (mean difference in TOF ratio) ranged from  $0.00$  to  $0.01$  (fig. 4).

ITS was mean (range) 15 mA (10–25 mA) and 16 mA (10–25 mA) at TOF ratios 0.40 and 0.70, respectively. Stimulation at 58 mA was supramaximal in all patients.

Figures 5 and 6 show the precision ( $\overline{\text{TOF}}_{a_{\text{curr}>\text{ITS}}} - \overline{\text{TOF}}_{b_{\text{curr}>\text{ITS}}}$ ) and accuracy ( $\overline{\text{TOF}}_{\text{curr}>\text{ITS}} - \overline{\text{TOF}}_{58}$ ) at each of the different currents greater than ITS. Except at ITS, the precision was acceptable and not significantly different from the precision at ITS + 35 mA. The pre-

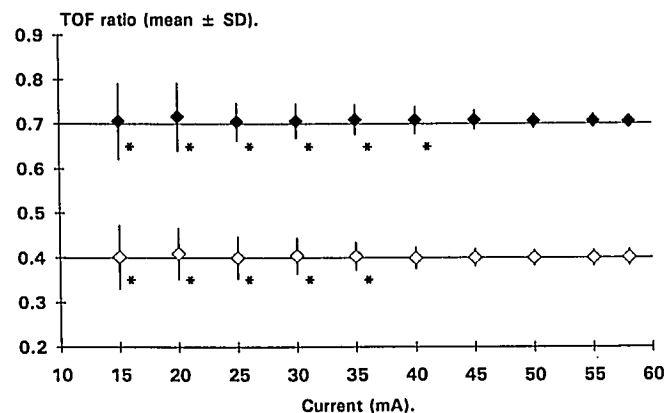


FIG. 2. TOF ratios from the two series of measurements at each of the different stimulating current outputs. Open diamonds = TOF 0.40; filled diamonds = TOF 0.70. \* $P < 0.01$  from SD at 58 mA.

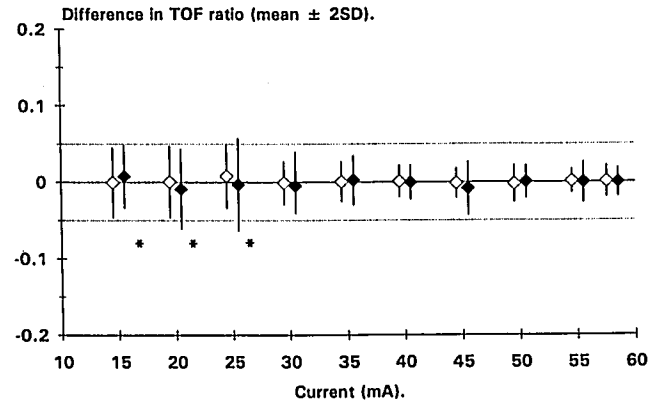


FIG. 3. Precision: intracurrent difference between repeated TOF ratio measurements ( $\overline{\text{TOF}}_{a_{\text{curr}}} - \overline{\text{TOF}}_{b_{\text{curr}}}$ ) at each of the different current outputs. Open diamonds = TOF 0.40; filled diamonds = TOF 0.70. \* $P < 0.01$  from SD at 58 mA.

cision mean ranged from  $-0.01$  to  $0.01$ . Precision calculated using the  $\overline{\text{TOF}}_{c_{\text{curr}>\text{ITS}}} - \overline{\text{TOF}}_{d_{\text{curr}>\text{ITS}}}$  differences gave similar results. The accuracy, however, was unacceptable at all currents less than or equal to ITS + 20 mA. Compared to ITS + 35 mA the standard deviations of accuracy were significantly increased at all currents less than or equal to ITS + 25 mA ( $P < 0.01$ ). The accuracy mean ranged from  $-0.00$  to  $0.01$ . The mean (range) core temperatures at the TOF ratios 0.40 and 0.70 were  $36.4^\circ\text{C}$  ( $36.0\text{--}37.0^\circ\text{C}$ ) and  $36.4^\circ\text{C}$  ( $36.0\text{--}37.0^\circ\text{C}$ ), while at the same time the peripheral temperatures were  $34.4^\circ\text{C}$  ( $33.3\text{--}35.4^\circ\text{C}$ ) and  $34.3^\circ\text{C}$  ( $32.9\text{--}35.5^\circ\text{C}$ ), respectively. The mean (range) arterial blood pressures at the TOF ratios 0.40 and 0.70 were 83 mmHg ( $67\text{--}100$  mmHg) and 79 mmHg ( $58\text{--}107$  mmHg), respectively.

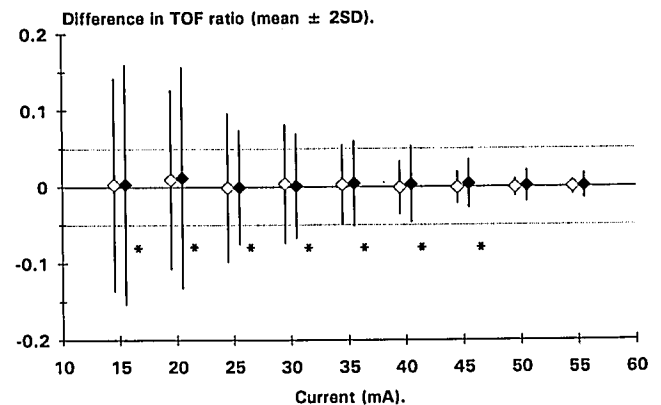


FIG. 4. Accuracy: intercurrent agreement between TOF the ratios at each of the different lower currents compared to the TOF ratio at 58 mA ( $\overline{\text{TOF}}_{\text{curr}} - \overline{\text{TOF}}_{58}$ ). Open diamonds = TOF 0.40; filled diamonds = TOF 0.70. \* $P < 0.01$  from SD at 55 mA.

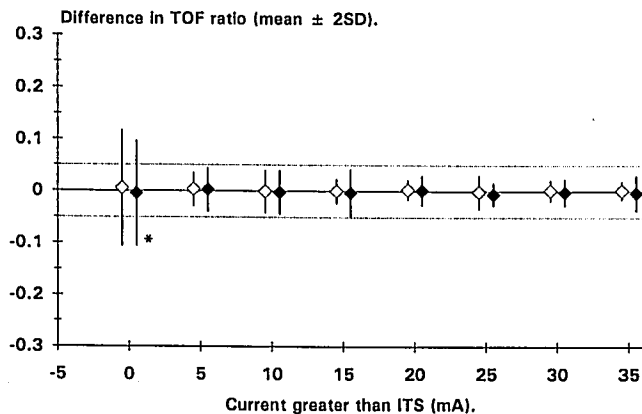


FIG. 5. Precision with ITS used as elevated current zero point: intracurrent difference between repeated TOF ratio measurements at each of the different current outputs greater than ITS ( $\text{TOF}_{a_{\text{curr}>\text{ITS}}} - \text{TOF}_{b_{\text{curr}>\text{ITS}}}$ ). Open diamonds = TOF 0.40; filled diamonds = TOF 0.70. \* $P < 0.01$  from SD at 40 mA greater than ITS.

### Discussion

The results of the present study showed that the accuracy of TOF ratio monitoring was poor at low stimulating currents close to ITS. The studied population required a stimulating current of at least 45 mA or at least ITS + 25 mA, provided that the acceptable limits (acceptable difference in TOF ratio) for precision and accuracy were  $\pm 0.05$  and that the TOF ratio at 58 mA was regarded as the "reference standard." Precision and accuracy both were calculated at different currents (true zero point) and at different currents above ITS (ITS used as elevated zero point). The latter may be preferred because ITS is easy to determine in clinical practice, overcoming the problem of differences in the patients' sensitivity to stimulation.

Ideally the TOF ratios at the different currents should have been determined at the very same time. However, this is practically impossible. A central presumption in our study, therefore, was that we were able to keep the neuromuscular blockade stable during the entire period of measurements. As a consequence, all series of measurements in which the TOF ratio at 58 mA drifted more than 0.04 during the period were discarded. This criterion was set after a pilot study, in which the absolute difference between replicated TOF ratio measurements ranged from 0.00 to 0.04. It was later justified by the results of the present study, in which the precision at 58 mA was  $0.00 \pm 0.02$ . Because the level of neuromuscular blockade could change within these limits without being noticed, we compensated for an eventual linear drift by using a special stimulation sequence design and interpolation, imitating a situation where all the TOF ratios at the different currents had been measured at the same time in the middle of each period of measurements.

Brull *et al.*<sup>4</sup> have addressed the same question of TOF

monitoring at varying currents in a recent study, which, however, differs in some respects from the present study. They examined a wide range of TOF ratios, whereas we examined two very narrow ranges at the TOF ratios 0.40 and 0.70, representing the limit for manually detectable fade<sup>10</sup> and the limit for clinically satisfactory neuromuscular recovery,<sup>11,12</sup> respectively. The present study presents the conditions at more current outputs, and it overcomes the problem of differences in patient sensitivity by also presenting the results at the different currents greater than ITS. Both studies show that the mean TOF ratio is consistent at varying currents, while the variability, as illustrated by the standard deviation, increases with decreasing currents. Brull *et al.* also calculated the differences between pairs of TOF ratios at different currents, *i.e.* the accuracy. Compared to 50 mA, accuracy was  $0.01 \pm 0.16$  and  $0.00 \pm 0.10$  (mean  $\pm$  two standard deviations) at 20 and 30 mA, respectively. This is very similar to our results, where the accuracy at TOF ratio 0.70 was  $0.01 \pm 0.14$  and  $0.00 \pm 0.07$  (mean  $\pm$  two standard deviations) at 20 and 30 mA respectively. The smaller standard deviations found in present study may be explained by the use of the mean of four TOF ratios when calculating the accuracy.

The conclusions of the two studies differ despite the good agreement found in the results. Brull *et al.*<sup>4</sup> concluded that TOF testing can be reliably used intraoperatively as well as postoperatively using 20- or 30-mA stimuli administered *via* surface electrodes, provided, of course, that four evoked twitches are registered. Correlation analysis and comparison of means, however, are insufficient for making decisions on the acceptability of performance.<sup>13</sup> These decisions should be made following definition of the tolerable error and calculation of precision and accuracy.<sup>6,7</sup>

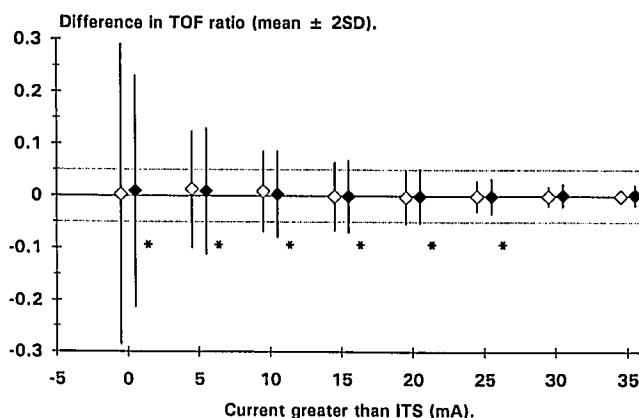


FIG. 6. Accuracy with ITS used as elevated current zero point: intercurrent agreement between TOF ratios at each of the different current outputs greater than ITS compared to the TOF ratio at 58 mA ( $\text{TOF}_{\text{curr}>\text{ITS}} - \text{TOF}_{58}$ ). Open diamonds = TOF 0.40; filled diamonds = TOF 0.70. \* $P < 0.01$  from SD at 40 mA greater than ITS.

In the present study, 0.05 was chosen as the acceptable difference for both precision and accuracy. It is evident that the chosen error must be greater than the limits of precision of the reference standard method, but it is difficult categorically to define the upper limit where the error becomes clinically significant. It depends on how the TOF ratio is measured. When the TOF ratio is evaluated manually, residual paralysis can not be ruled out, because it is not always possible to feel fade even at TOF ratios of 0.40–0.50.<sup>14</sup> Until recently, a TOF ratio of 0.70 has been regarded as an indicator of clinically satisfactory neuromuscular recovery; however, this has now been challenged,<sup>15–17</sup> and an even greater TOF ratio may be necessary. The risk of further lowering the fade detection point of 0.40 should therefore be minimized. Regarding 0.05 as the tolerable error implies that TOF ratio monitoring is unacceptable at currents less than ITS + 25 mA. When TOF ratio is evaluated electromyographically or mechanically or by measuring acceleration, a greater error might be acceptable, but still, most often, the response is evaluated manually in the awake patient.

Identification of ITS has also been recommended for prediction of the current necessary for supramaximal stimulation of the ulnar nerve at the wrist.<sup>18</sup> Provided that a minimum of 20 mA is delivered, then supramaximal stimulation can be assured if the current is equal to 2.75 times ITS.<sup>18</sup> When comparing this recommendation with the results of the present study, it appears that the current demand for TOF monitoring is less than it is for supramaximal stimulation when ITS is greater than or equal to 15 mA. Consequently, TOF monitoring may be performed at some degree of submaximal stimulation. However, the relation between the current demand for TOF monitoring and the exact point at which the stimulating current becomes supramaximal remains to be evaluated.

In summary, we recommend that ITS be identified for each patient, and that TOF monitoring in awake patients be performed at currents 25 mA greater than ITS.

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