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Criteria of Adequate Clinical Recovery from Neuromuscular Block

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Twitch, Tetanus and Train-of-Four as Indices of Recovery from Nondepolarizing Neuromuscular Blockade. By Hassan H. Ali, John J. Savarese, Philip W. Lebowitz, Frederic M. Ramsey. ANESTHESIOLOGY 1981; 54:294–7. Reprinted with permission.

This study was undertaken to compare the sensitivities of the train-of-four response (2 Hz for 2 s), the single twitch (0.15 Hz), and the tetanic response (50 Hz for 5 s) as indices of residual nondepolarizing block. Spontaneous or induced recovery of evoked thumb adduction in response to ulnar nerve stimulation was studied. One hundred and seven adult surgical patients were divided according to the relaxant used, into six groups. We found that when the single twitch recovered to control height, the train-of-four ratio was well below 1.0. This ratio was significantly lower during spontaneous recovery than following neostigmine antagonism of the block ($P < 0.01$). The tetanic response was fully sustained when the train-of-four ratio was above 0.7. When the ratio was less than 0.7, variable degrees of fade of tetanus were evident. Analysis of variance indicated similar train-of-four ratios among the six groups at complete recovery of the single twitch irrespective of the relaxant technique used ($P < 0.1$). It is concluded that a train-of-four ratio of 0.7 or higher reliably indicates the recovery of the single twitch to control height and a sustained response to tetanic stimulation at 50 Hz for 5 s. The clinical significance of this study is as follows: the train-of-four response provides the same indication of clinical recovery from nondepolarizing block as obtained from tetanic stimulation at a physiological frequency; and reliance on the recovery of the single twitch to control height as a criterion of spontaneous return to normal clinical neuromuscular function may be misleading. (Key words: Antagonists, neuromuscular relaxants: neostigmine. Measurement techniques: neuromuscular blockade. Monitoring: stimulator, nerve. Neuromuscular relaxants: *d*-tubocurarine; metocurine; pancuronium. Neuromuscular transmission.)

I HEREIN revisit our article[1] published two decades ago in ANESTHESIOLOGY. The revisitation in this journal fulfills our dream of witnessing an idea become an established landmark for monitoring the response to an important class of drugs (muscle relaxants) in our day-to-day practice of anesthesia and in assessing criteria of adequate clinical recovery that ensure patient safety in the perioperative period (see Web Enhancement for photograph on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org).

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Prior to 1970, neuromuscular blocks in humans were sporadically measured as either the response to single, repeated, motor nerve stimuli or to brief tetanic stimulation.[2,3] Neither method was satisfactory. On the one hand, the return of the single twitch to a control response does not indicate complete recovery, assuming a control response has even been established. On the other hand, tetanic stimulation is painful in conscious patients or those recovering from anesthesia. Moreover, frequencies higher than 50 Hz are nonphysiologic.[4]

To improve patient monitoring, Utting, Gray, and I[5–7] examined the evoked muscle response to various frequencies of single, repeated neural stimulation at (0.1–10 Hz) and to a train-of-four (TOF) ratio at 2 Hz for 2 s. The latter was repeated once every 10 s. As we reported in three consecutive articles, we confirmed that the TOF ratio (the height of the fourth evoked response as a fraction of the first response in the same train) is an objective index that does not need a control response to indicate recovery from a nondepolarizing neuromuscular block. We found that, at a TOF ratio of

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Readers interested in this topic should also see the article presented on page 1042 of this same issue (Debaene B, Plaud B, Dily M-P, Donati F. Residual Paralysis in the PACU after a Single Intubating Dose of Nondepolarizing Muscle Relaxant with an Intermediate Duration of Action. ANESTHESIOLOGY 2003; 98:1042–8).

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0.6, the conscious, nonmedicated volunteers could achieve head lift for approximately 3 s.

These investigations laid the foundation for further studies to evaluate this new concept of monitoring neuromuscular function. In addition, the new method attracted the attention of many clinical investigators and others that designed studies to scrutinize the clinical applications of the TOF in the perioperative period. Furthermore, several biomedical engineering firms adopted the new concept and started to design and build peripheral nerve stimulators to deliver the TOF pattern as well as monitors to measure the response both mechanically and electromyographically. These monitors were made available to many anesthesia departments nationally and internationally.

Ten years after the introduction of the TOF concept, just about the time we were embarking on studies to develop new short-acting, nondepolarizing relaxants, my colleagues, Savarese, Lebowitz, Ramsey, and I[1] recognized the need to define the optimal criteria for adequate clinical recovery from neuromuscular block. We realized that the assessment of clinical criteria (such as the ability to open the eyes widely, cough effectively, and sustain tongue protrusion, hand grip, head lift, and leg raising) is most reliable when the patient is conscious and cooperative. Other respiratory variables, such as vital capacity, tidal volume, and inspiratory force, would also be helpful. The latter two can be reasonably measured in unconscious, but spontaneously breathing, patients. Criteria that do not require patient cooperation include measurement of the evoked responses to peripheral motor nerve stimulation, *i.e.*, twitch, tetanus, and TOF.

In 1969, Gissen and Katz[3] suggested that 100–200 Hz tetanic stimulation is a more sensitive index of recovery than the single twitch. A few years later, Epstein and Epstein[8] recommended a tetanic frequency of 30–50 Hz as adequate for monitoring residual curarization. Waud and Waud[9] had previously determined receptor occupancy in an animal model, which does not apply to the clinical setting, and concluded that the TOF ratio is slightly more sensitive than the single twitch at 0.1 Hz and far less sensitive than a 5.0-s 100-Hz tetanus.

However, we were convinced that the TOF ratio is more sensitive than the single twitch at 0.15 Hz and at least as sensitive as the response to a 5.0-s 50-Hz tetanus. In addition to the fact that the latter frequency is more physiologic than 100-Hz tetanus, Stanec *et al.*[10] showed that 5.0-s tetanic stimulation at a frequency higher than 70 Hz was not sustained in the absence of neuromuscular blocking drugs. We, therefore, compared the TOF ratio with fade of tetanic tension at 50 Hz at the times when the response to the single twitch at 0.15 Hz recovered to the control height.[1] In this revisited article, we reported that, irrespective of the muscle relaxant used, patients who were allowed to recover spontaneously until the single twitch reached control height showed significantly greater fade of the TOF response (TOF ratio = 44 ± 5%) than did patients following reversal with neostigmine (TOF ratio = 68 ± 4%, $P < 0.01$). In 18 of 28 patients where tetanic response followed TOF, tetanus was fully sustained at a TOF ratio of 73 ± 2%, $P < 0.01$. In the remaining 10 patients, both TOF and tetanic responses showed variable degrees of fade. The TOF ratio was 64 ± 3%, while tetanic response ratio was 76 ± 4%, $P < 0.05$.

Engback *et al.*[11] advocated another pattern of nerve stimulation that used two short bursts of three stimuli at a frequency of 50 Hz separated by 750 ms. This pattern was described as "double burst stimulation." Engback *et al.* claimed that they could manually discern a degree of fade to double burst stimulation when the TOF response appears to show no fade, but they were uncertain about the degree of manual or visual fade of the tetanic response at 50 Hz for 5 s. My personal experience was that it was very hard to discern the difference between the two bursts because, with the arrival of the first burst, the patient moves the hand vigorously enough to make comparison with the second burst of stimulation very difficult.

The question always arises, which TOF ratio would correlate with adequate clinical recovery? A ratio greater than 0.75 was found to correlate with signs of adequate recovery from nitrous oxide–oxygen–opioid balanced anesthesia as well as with recovery during the perioperative-period.[12,13] Other clinical investigators suggested that a TOF ratio of at least 0.9 would ensure that the patient could be discharged safely from the ambulatory care facility.[14]

It should be emphasized that, irrespective of the method used in assessing adequacy of clinical recovery, one has to consider as many criteria as possible to ascertain the return of muscle strength to a level compatible with adequate pulmonary ventilation and protection of the upper airway. These include the responses to tetanic stimulation, TOF, double burst stimulation, and an inspiratory force of at least 30–40 cm H_20 negative pressure. Further criteria include the ability of the responsive patient to sustain as many voluntary activities as possible: head lifting, leg raising, hand gripping, eye opening, tongue protrusion, adequate swallowing, and, last but not least, adequate coughing.

In conclusion, John Norman, in a 1998 commentary[15] on our first article,[5] stated that the introduction of TOF monitoring was a noteworthy achievement. After its introduction, neuromuscular block was monitored more often and better assessed.

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