Volume 30, No. 5
May 1969

THE JOURNAL OF Anesthesiology
THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

Twitch, Tetanus and Posttetanic Potentiation as Indices of Nerve–Muscle Block in Man

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Twitch, tetanus and posttetanic potentiation are muscle responses to varying frequencies of indirect stimulation. Responses to tetanic stimulation at various frequencies are a more sensitive index of neuromuscular transmission than twitch or posttetanic potentiation. In lightly anesthetized man, tetanus is maintained at stimulus frequencies from 50 to 200 Hz, and higher. During partial neuromuscular block tetanus is not maintained at the higher frequencies of stimulation even though the magnitude of twitch may have returned to control levels. If neuromuscular transmission is marginally adequate, the tetanic response fails at higher stimulus frequencies. This study demonstrates the use of tetanus at various frequencies to diagnose neuromuscular block not apparent by twitch studies alone. It is suggested that clinical nerve stimulators be modified to provide tetanic stimulation at several fixed frequencies.

THE USE OF MUSCLE RELAXANTS during general anesthesia has been common for many years. Individual variations in the effects and durations of action of given doses of relaxant are well recognized.[1] Because of this, several workers[2, 3, 4] have advocated routine clinical use of small portable nerve stimulators to evaluate neuromuscular transmission continually. Estimation of the degree and type of neuromuscular block has been based on the pattern of the evoked muscle response with changes in stimulus frequency.[5] Because the use of these devices is becoming more popular, we decided to explore, in detail, muscle twitch, tetanus and posttetanic potentiation (PTP) in man during anesthesia. In a subsequent paper the relationship of the peripheral nerve–muscle responses to respiratory function will be reported.

Methods

Twenty patients were studied during surgical procedures. Preanesthetic medical consisted of secobarbital (Seconal) or pentobarbital (Nembutal), 50–100 mg, atropine or scopolamine, 0.3–0.5 mg and, occasionally, meperidine (Demerol), 50–100 mg, given intramuscularly one hour prior to surgery. Anesthesia was induced with intravenous thiopental (Pentothal sodium), 100–400 mg, and maintained with nitrous oxide, 4 l/min, oxygen 2 l/min, and halothane (Fluothane), 0.5–2.0 per cent. The trachea was intubated with the aid of intravenous succinylcholine, 80–100 mg. Moderate hyperventilation was maintained throughout, either manually or mechanically.

The forearm and hand were immobilized in a splint while the thumb was abducted in a yoke connected to a Grass linear displacement

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Received from the Department of Anesthesiology, Columbia University, College of Physicians and Surgeons, New York, New York 10032. Accepted for publication December 10, 1968. Supported in part by the National Institutes of General Medical Sciences, Grant GM-09069.

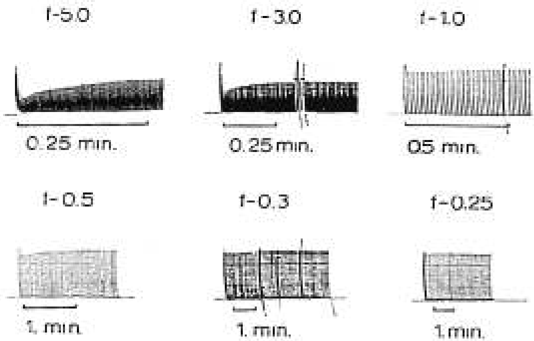

FIG. 1. Twitch response to supramaximal stimulus to ulnar nerve by subcutaneous needle electrodes at the wrist. Curare, 15 mg (iv), was given to a 60-kg patient two hours prior to these recordings. F indicates stimulation frequency per second (Hz). Bar below recording indicates time. Artifacts in second frame were caused by surgical cautery. Stimulus frequency greater than 0.5 Hz tended to elicit a smaller response.

force transducer (FT-03). The thumb was positioned carefully in full abduction so that strong tetanic contraction and the potentiated twitch following tetanus did not result in mechanical apposition of the thumb to the fingers. The ulnar nerve was stimulated at the wrist by subcutaneous needle electrodes. Stimulus currents for twitch were obtained from a Grass SC4 stimulator. An American Electronic Laboratory 104 stimulator was used for tetanic stimulation at various frequencies. Evoked responses of the adductor muscles of the thumb were recorded on a Beckman direct ink writer (Offner-Dynograph R).

To produce maximum twitch, the stimulus intensity was varied from 80 to 250 volts, the stimulus duration was set at 1.5 msec and frequency at 0.3 Hz (18/min). In every instance the intensity was gradually increased from 0 volts to that sufficient to evoke a perceptible twitch response (threshold). Electrode polarity was reversed to see if the response could be increased. The intensity was then set to double this threshold value. Maximum response was checked by varying the stimulus intensity around the final setting. In studies of tetanic response we used stimulus frequencies of 25, 50, 100 and 200 Hz; tetanus trains were delivered for 0.5 sec at 10-sec intervals. Posttetanic potentiation was studied by superimposing a tetanus train (30 Hz for 5 sec) on a basic stimulus frequency of 0.3 Hz.

Results

Twitch

If twitch is evoked under the conditions defined, it is stable, reproducible and will show little change in magnitude. The effect of d-tubocurarine on neurally-evoked peripheral twitch response is well documented. During such a block the magnitude of twitch in response to supramaximal stimuli is known to be frequency-dependent.[6] Figure 1 clearly demonstrates that during recovery from neuromuscular block produced by curare an interval of three to four seconds between successive stimuli is required if a steady level of twitch response is to be obtained. Also shown is that the greater the stimulus frequency, the smaller is the twitch response and the greater the variability. In general, the more frequent the stimulation the less the individual muscle response. The magnitude of twitch response cannot be increased by increasing intensity or duration of each stimulus (if set at maximum prior to block). Knowledge of the magnitude of twitch response, even with the limitations pointed out above, is useful in the conduction of anesthesia. When combined with tetanus and posttetanic potentiation, its usefulness in evaluation of the status of neuromuscular transmission is enhanced.

Tetanus

It has been observed repeatedly[6] that following administration of curare neuromuscular block is more pronounced at higher frequencies of stimulation. Also, sustained muscle tension (tetanus plateau) to tetanic stimulation becomes nonsustained (tetanus fade) at higher stimulus frequencies. For any given frequency the change from a sustained to a nonsustained state is dependent upon the degree of curare block. Figure 2 shows the muscle tension output produced by tetanic stimulation at fre-

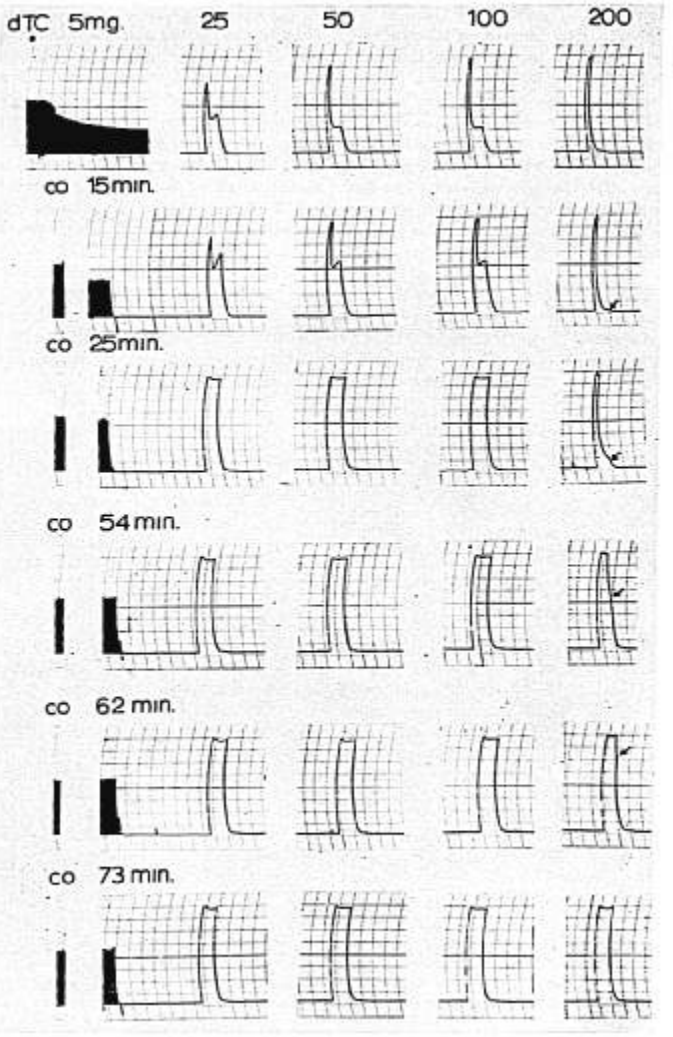

FIG. 2. Twitch and tetanus response to nerve stimulation at various times following 5 mg of *d*-tubocurarine (iv) in a 62-kg subject. Single stimuli were delivered at a frequency of 0.3 Hz. Frequencies of tetanic stimulation are indicated in the top row (duration 0.5 sec). Strips at left (CO) are control twitch responses before administration of curare. Arrows indicate tetanus plateau during stimulation. Note that the twitch response had returned to control level at 25 minutes but tetanus (200 Hz) was not sustained until 73 minutes after curare administration.

quencies of 25, 50, 100 and 200 Hz at various time intervals after intravenous injection of 5 mg of curare. As the neuromuscular block produced by curare decreases, tetanus fade becomes apparent only at the higher stimulus frequencies. The twitch response recovers to the control level far sooner than maintained muscle response to tetanus at the higher frequencies. The responses of sustained or non-sustained tetanus with increasing frequencies of stimulation are a far more sensitive index of neuromuscular block by curare than twitch alone.

This method was used to evaluate the level of neuromuscular block produced by curare at the completion of an operation. Figure 3 shows an example of the effect of neostigmine and atropine. A 76-kg male patient received 42 mg of curare; the last dose, 12 mg, was given two hours prior to the completion of surgery. The top tracing is the muscle response to single and tetanic stimulation at various frequencies immediately following the completion of surgery. Atropine, 1.0 mg, and neostigmine, 2.5 mg, were given intravenously (fig. 3, middle tracing). There is little change in the twitch magnitude but tetanus plateau is present at higher levels with increasing stimulus frequency. The bottom tracing, taken three minutes later, shows tetanus fade only at a stimulus frequency of 200 Hz. Twitch tension remains unchanged throughout. Spontaneous movement began with the bottom tracing, as shown by movement of the baseline. No additional anticholinesterase was required in the postoperative period.

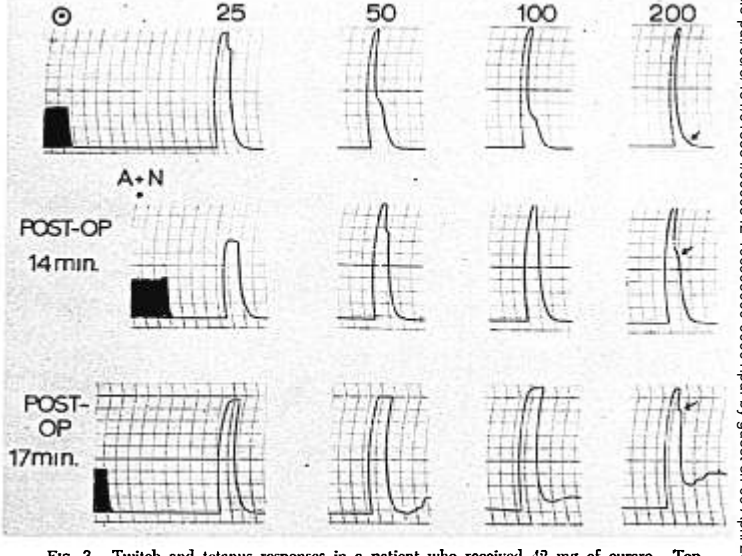

FIG. 3. Twitch and tetanus responses in a patient who received 42 mg of curare. Top tracing at completion of surgery (⊙). Second and bottom tracing following intravenous injection of atropine, 1 mg, and neostigmine, 2.5 mg. Stimulation frequencies as in figure 2. The twitch tension output was essentially unchanged. The ability to sustain tetanus at highest stimulus frequencies (100–200 Hz) was greatly improved following the medication. Baseline shift in the bottom tracing was caused by spontaneous movement.

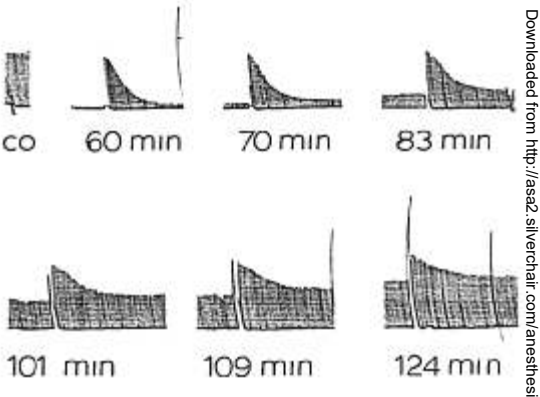

FIG. 4. Posttetanic potentiation following a total dose of 42 mg of *d*-tubocurarine in one hour. Upper left tracing (CO) is control twitch response before curare. Time after the last dose of curare is indicated. Twitch stimulus frequency was 0.3 Hz, tetanus stimulus frequency, 30 Hz for 5 sec. Note that the PTP ratio decreases from about 13/1 at 60 minutes to 18/12 at 124 minutes.

POSTTETANIC POTENTIATION (PTP)

The block produced by curare is antagonized for a short period following tetanic stimulation.[7] Neuromuscular block by curarizing drugs has been differentiated from that caused by depolarizing drugs by this response.[5] The presence of PTP has also been considered indicative of continued neuromuscular blockade by curare. Figure 4 shows PTP following complete neuromuscular block induced by curare. At 124 minutes twitch approximates control levels although PTP is still present. In an attempt to quantitate this measurement some workers[8] have used the PTP ratio. This correlates the magnitude of the posttetanic twitch with that immediately preceding the tetanus. The smaller the ratio, the less the neuromuscular block. In figure 4 the PTP ratio varies from 13/1 (at 60 min) to 18/12 (at 24 min). It should be noted that because of the evanescent effect of PTP this ratio is markedly affected by the frequency of single-twitch stimulation before and after tetanus.

Figure 5, an idealized diagram summarizing the findings in the entire group of 20 patients, shows the evoked muscle responses to stimulation at 0.3 Hz; tetanus at 25, 50, 100 and 200 Hz; and PTP following a complete neuromuscular block induced by curare. Line 1 represents complete block of twitch response although PTP is present. Lines 2, 3 and 4 represent progressive recovery of twitch response to that of control level in line 5; however, tetanus fade at 200 Hz is still present. Line 6 represents return to the normal state of neuromuscular transmission.

Discussion

Variations of twitch, tetanus and posttetanic potentiation are determined by the factors controlling release of acetylcholine stores (the neurotransmitter) from the motor nerve terminal. Recent reviews which have discussed these factors in detail[9,10,11] should be consulted for further information. Briefly, of the acetylcholine chemically recoverable from the terminal nerve filaments, only a relatively small quantity is directly involved in the process of neuromuscular transmission. Acetylcholine stores in the terminal nerve filaments are divided into: 1) a relatively small quantity, "the readily releasable store of acetylcholine," released from the motor nerve by the nerve action potential; 2) a larger quantity, "the depot stores of acetylcholine," mobilized to maintain the readily releasable store of acetylcholine; 3) a "surplus store of acetylcholine" that probably represents the precursor for 1 and 2 but cannot be released by continued nerve stimulation.[9,12] At rest the quantity of acetylcholine in the readily releasable store is probably a fixed amount. The percentage of this

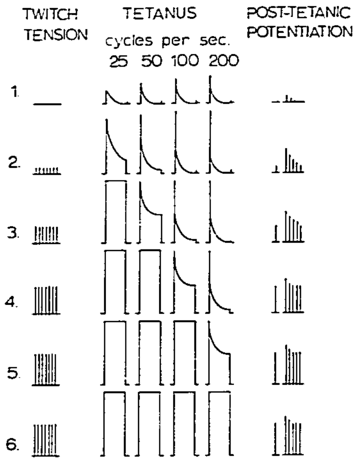

FIG. 5. Neurally evoked muscle tension. Idealized diagram of twitch, tetanus at 25, 50, 100 and 200 Hz, and posttetanic potentiation following neuromuscular block. Row 6 indicates normal response without neuromuscular block. See text for further explanation.

amount released by any one stimulus depends upon the total present in the readily releasable store. During repetitive tetanic stimulation early stimuli (with a large "readily releasable store of acetylcholine") release larger amounts of acetylcholine per stimulus than later stimuli (with the store partially depleted). The quantity of acetylcholine released decreases with time until a level is reached that is a balance between the release of acetylcholine and the mobilization of acetylcholine from the depot stores of acetylcholine; synthesis of acetylcholine is also accelerated. The level of acetylcholine release finally reached depends upon frequency of stimulation, duration of stimulation, mobilization and synthesis of acetylcholine.

During tetanic stimulation the final level of acetylcholine release is always lower than the initial level. If this final level of acetylcholine release is not sufficient to depolarize the muscle membrane to threshold levels, neuromuscular transmission will fail, resulting in tetanic fade. Mobilization and synthesis of acetylcholine continues for a period of time even after stimulation stops, so that following the tetanic stimulation an enhanced response will follow another single stimulus. The above represents a simplification of many factors affecting acetylcholine release from the motor nerve terminal by nerve stimulation.

Usually there is a large safety reserve factor involved in transmission. The amount of neurotransmitter released per impulse exceeds by several times the minimum quantity needed to evoke a muscle response. Therefore, the decline in the level of acetylcholine output with repetitive stimulation is not manifested during normal neuromuscular transmission. If, however, neuromuscular transmission is partially blocked (as with curare), any further reduction in acetylcholine release will result in transmission failure. And, since acetylcholine release decreases proportionately to the increasing frequency of stimulation, transmission failure (tetanic fade) becomes more pronounced as stimulating frequency is increased. PTP appears because tetanus results in increased mobilization and synthesis of acetylcholine. This continues for a period of time after cessation of stimulation, so that a single stimulus after tetanus results in an enhanced muscle response.

It appears that evaluation of neuromuscular block by tetanus response is more sensitive than evaluation by twitch alone. Presently available portable stimulators [2,3,4] produce tetanus at single fixed frequencies (18–50/sec). A simple circuit modification would make it possible to test muscle responses at several stimulus frequencies. This would mean greater accuracy in diagnosing the level of neuromuscular block. However, clinical judgment must always recognize the fallability of any one monitoring method. This method is proposed only as an added source of information in guiding the overall conduction of anesthesia. We believe that the practicing anesthesiologist should have available a method of evaluating neuromuscular transmission, such as one of the various portable nerve stimulators. The modifications we propose should make this method more valuable, although by no means is this

a quantitative guide as to the actual state of neuromuscular transmission.

In summary, we have examined in detail neurally-evoked muscle responses as exemplified by twitch, tetanus and posttetanic potentiation. The response to repetitive stimulation is a more accurate index of the level of block than twitch or PTP. A neurophysiologic explanation for the clinical phenomena of twitch, tetanus and PTP has been proposed. It is suggested that clinical twitch monitors be altered to furnish tetanus at several stimulation rates. The response to tetanus may also be used as a measure of adequate dosage of anticholinesterases in the reversal of curare block.

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Obstetrical Anesthesia

SPINAL LEVEL IN PREGNANCY The pregnant patient requires less anesthetic agent for induction of spinal anesthesia than the nonpregnant patient. The authors review the postulate that compression of the inferior vena cava (IVC) by the pregnant uterus causes engorgement of the vertebral system, which in turn decreases the capacity of the subarachnoid space for spinal fluid and decreases the amount of drug necessary to produce spinal anesthesia. IVC pressure in pregnant patients at term was elevated, compared with nonpregnant controls, but CSF pressures were similar in both groups. Since elevating IVC pressure produced only a transient rise in CSF pressure, it was assumed that the return to normal of CSF pressure was the result of a decrease in CSF volume. When the IVC pressure of nonpregnant women was increased by abdominal compression to the level found in women at term, the spinal anesthetic dermatome level produced was similar to that of pregnant women and was significantly higher than the level produced when IVC pressure was not elevated. (*Barclay, D. L., Renegar, O. J., and Nelson, E. W.: The Influence of Inferior Vena Cava Compression on the Level of Spinal Anesthesia, Amer. J. Obstet. Gynec. 101: 792 (July) 1968.*)