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The Relationship Between Receptor Occlusion and the Frequency Sweep Electromyogram during Competitive Neuromuscular Blockade

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The purpose of this study was to correlate the frequency sweep electromyogram (FS-EMG) responses to various levels of receptor occlusion during partial neuromuscular blockade by *d*-tubocurarine (*d*Tc). The FS-EMG represents the integrated compound muscle action potential induced by intra-muscular electrical stimulation as the stimulus frequency increases exponentially from 1 to 100 Hz. The FS-EMG response was recorded from the tibialis anterior muscles of six adult cats at different levels of neuromuscular blockade during recovery from intravenously injected *d*Tc, 0.25 mg/kg. The fraction of receptors blocked was estimated by measuring the depolarization produced by proximate intraarterial injection of graded doses of succinylcholine.

The FS-EMG became diminished for driving frequencies greater than 50 Hz when receptor occupancy was about 25–30 per cent. The responses corresponding to lower stimulus rates declined only at increasing levels of occlusion. The FS-EMG response to low-frequency stimulation did not diminish until 70 per cent of the available receptor pool was blocked. Simultaneous measurement of muscle force demonstrated a depressed response equivalent to that of the FS-EMG. These data were compared with the sensitivities reported for other tests of neuromuscular block. The frequency sweep electromyogram appears to be about as sensitive as determination of responses to sustained 5-second tetanic stimulation at 200 Hz, but more sensitive than determination of responses to tetanic stimulation at 100 Hz or twitch responses, or train-of-four measurements. (Key words: Monitoring: electromyogram. Neuromuscular junction. Neuromuscular relaxants: *d*-tubocurarine; succinylcholine. Neuromuscular transmission: receptor occlusion.)

MONITORING THE INTEGRITY of neuromuscular transmission is important when neuromuscular blocking drugs are incorporated into anesthetic management. Numerous methods for doing this have been described.[1,2] The frequency sweep electromyogram (FS-EMG) is a relatively new monitoring technique that assesses neuromuscular transmission by recording the EMG response induced by intramuscular electrical stimulation while frequency increases exponentially from 1 to 100 Hz.[3,4] In this way the FS-EMG provides a profile of the myoneural responses across a broad spectrum of driving rates.

The purpose of this study was to provide a more quantitative interpretation of the FS-EMG response and to relate it to receptor occlusion by use of the method of Paton and Waud.[5] The ability of the frequency sweep technique to detect neuromuscular blockade was also compared with sensitivities of the twitch, tetanic burst, and train-of-four methods.[6–8]

Methods

Experiments were conducted using the tibialis anterior muscle of the cat. Six adult cats weighing 2.7–3.9 kg were studied. Anesthesia was induced by intraperitoneal injection of sodium pentobarbital, 40 mg/kg. Adequate anesthesia was maintained by use of 12-mg/kg doses of pentobarbital, given intravenously as needed. A brachial artery was cannulated for blood pressure monitoring and to obtain samples for blood-gas analysis. Tracheotomy was performed. Each animal was ventilated with a positive-pressure respirator at a rate and tidal volume adjusted to maintain a blood-gas and *p*H values within normal limits (mean ± SD; *p*H 7.42 ± 0.23; P_{CO_2} 31.0 ± 2.6 torr).[9] An intravenous infusion was maintained with 5–10 $ml \cdot kg^{-1} \cdot hr^{-1}$ of 5 per cent dextrose in lactated Ringer's solution. Each cat was heparinized (initial dose 250–300 units, maintenance dose 100 units/hr) and urinary output was monitored.

The muscle tendon was transected near its insertion at the first metatarsal and a flexible cable, for force transduction, was tied to the tendon. During the surgical preparation the muscle was kept moist with physiologic saline or lactated Ringer's solution. The biceps femoris muscle was reflected to expose the popliteal artery and common peroneal nerve. The arterial end of an arteriovenous shunt, similar to that described by Waud and Waud,[10] was inserted into the sural artery to facilitate proximate arterial injection of drugs. The shunt was fixed so that the catheter tip was near (but not in) the popliteal artery. The distal sural artery and side branches of the popliteal artery were tied off. The venous end of the shunt was inserted into the dorsal saphenous vein.

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A cuff electrode was placed around the common peroneal nerve before the incision was closed. The animal was then placed in a stereotaxic frame with the leg immobilized and the tendon of the tibialis anterior muscle attached to a strain gauge force transducer. A pool of warmed paraffin was formed around the tibialis anterior muscle. The entire hind limb was warmed by a circulating hot-water system so that the muscle temperature remained at 36°C. The temperature was monitored with a thermistor probe inserted into the fascial plane between the tibialis anterior and extensor digitorum longus muscles.

Two coiled-wire stimulating electrodes and one bifilar recording electrode were inserted into the muscle. These electrodes and the method for their insertion have been described elsewhere.[4,11] Muscle depolarization was recorded with wick electrodes from the muscle surface. The active electrode was positioned with its tip in a region of high end-plate density. The end-plate region was located by scanning the muscle surface with the active electrode until a maximum deflection (i.e., maximum voltage) was obtained following administration of succinylcholine (SCh) (10 nM; 0.003 mg). The reference electrode was placed near the aponeurosis of the muscle.

Periodically, distribution of muscle blood flow was checked by arterial injection of Evans blue dye through the shunt. When properly perfused, the muscle turned blue and returned to normal color within a few minutes. Ischemic areas failed to change color. Data from animals in which ischemia was found were deleted.

The dose–response characteristics were measured for each animal. Depolarization was recorded following intraarterial injections of succinylcholine. Doses of 20, 10, 5, 2.5 and 1.25 nM were used. Infusions of SCh were spaced 20 to 30 min apart, with the longer intervals following the larger doses. Measurements were repeated until a stable, repeatable dose–response relationship was obtained. Dosage was adjusted by changing the concentration of the injectate while maintaining a constant volume (0.25 ml) per injection.

After the control FS-EMG response and the dose response to SCh were obtained, *d*-tubocurarine (*d*Tc) (0.25 mg/kg) was given intravenously. The FS-EMG response was then measured. The muscle depolarization produced by injection of SCh was measured and compared with the response elicited prior to administration of *d*Tc. Receptor occlusion (RO) was calculated using the equation:

$$\mathrm{RO} = \frac{(\text{dose ratio} - 1)}{(\text{dose ratio})}$$

where dose ratio is the relative amount of SCh needed to evoke a response (depolarization) equivalent to that produced before administration of *d*Tc.[5,7] The level of receptor occlusion was measured at one-hour (minimum) intervals to prevent desensitization induced by repeated doses of SCh.[5] Periodically, after the neuromuscular response had returned to control levels, test doses of SCh were given to verify that the dose response was the same as that at control levels.

The FS-EMG response was recorded just prior to injection of SCh, as well as between injections of SCh during recovery from *d*Tc. The FS-EMG measurements were made at 5-min intervals. After each dose of succinylcholine an interval of at least 15 min elapsed before the next FS-EMG measurement. Scatter diagrams were constructed to show the FS-EMG responses at different points in the stimulation paradigm (corresponding to stimulation frequencies of 2, 5, 10, 20, 50, and 100 Hz) as a function of receptor occlusion during recovery from neuromuscular blockade with *d*Tc. In order to standardize the data, the absolute amplitude of the FS-EMG response during the stimulation sweep is expressed as a ratio of the amplitude of the initial (1 Hz) response, thus forming a "normalized" response curve. A ratio of close to one indicates intact neuromuscular transmission, and a low value indicates a failure in myoneural conduction. Fitting of the curve for the data points indicating the relationship between the level of receptor occlusion and the normalized FS-EMG ratio was performed on a Hewlett-Packard HP-67 programmable calculator using the Standard Pac SC03 curve-fitting program. Statistical inferences were based on Student's t test.

The "sensitivity" of the frequency sweep technique was defined as the level of receptor occlusion present when the FS-EMG response has returned to within normal limits. Sensitivity was determined by the point of intersection of the curves fitted to the data points and the mean control FS-EMG ratio for each of the corresponding stimulus rates.

Results

As expected, it was found that FS-EMG amplitude decreased progressively with increasing levels of receptor occlusion. This change was not uniform for all stimulating frequencies. Based upon the changes induced in the FS-EMG and the measured receptor occlusion, the FS-EMG response curve could be divided into three separate regions corresponding to driving frequencies. During recovery from *d*Tc the FS-EMG amplitude decreased by different amounts in these three regions. At low levels of *d*Tc only the high-frequency ($f > 50$ Hz) response was depressed. With increasing levels of block a decline was detectable

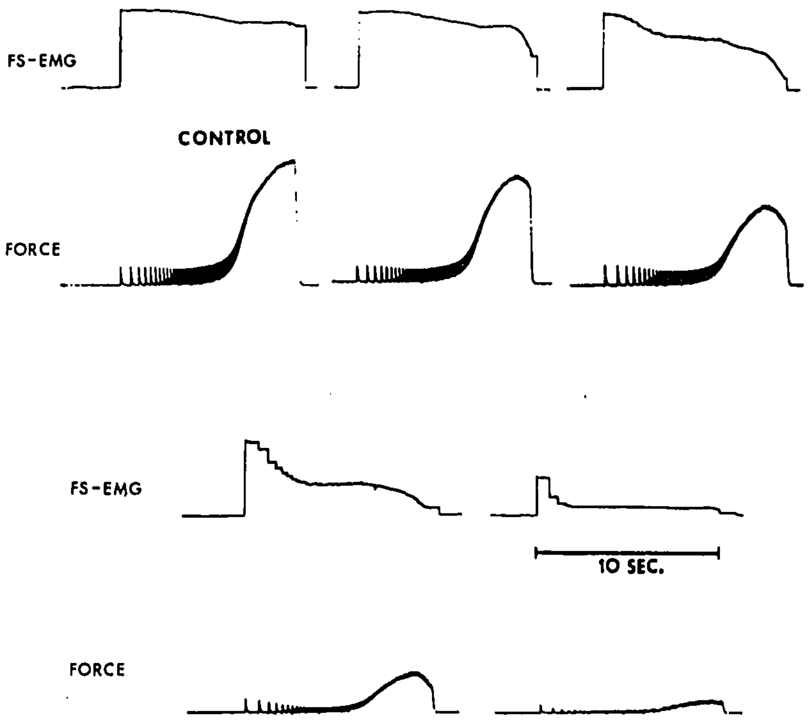

FIG. 1. Examples of the frequency sweep electromyogram (FS-EMG) response. The upper tracings in each panel show the FS-EMG during increasing neuromuscular blockade. The lower tracings show the mechanical force recorded simultaneously. In normal unblocked muscle, a slight diminution in FS-EMG amplitude occurs at high frequencies. During low levels of neuromuscular blockade, the responses at low and moderate stimulus rates do not change. The high-frequency response, however, does show a more rapid, steeper decline. As neuromuscular transmission becomes more deeply blocked, the FS-EMG response falls off slightly in the low-frequency region, reaches a plateau in the mid-frequency range, and then falls off more steeply again at higher stimulus rates. During deep levels of block the response diminishes rapidly in the low-frequency range and may be totally absent at higher frequencies.

in the low-frequency range ($f < 5$ Hz), and it reached a steady-state plateau in the mid-frequency ($5 \leq f \leq 50$) range. At the deepest planes of blockade only the initial few pulses may be normal, or near normal, after which the FS-EMG rapidly declines and may become negligible. These changes in the FS-EMG are illustrated in figure 1.

Figures 2 and 3 depict the relationship between the FS-EMG response and receptor occupancy measured during recovery from *d*Tc. The response in the mid-frequency range is exemplified by those of four different frequencies chosen from within this range (fig. 2). It was found that these data could be best described by linear curves. The slopes and intercepts of the fitted curves were nearly identical for stimulation rates of 5 to 50 Hz. Using the criteria defined in the methods for estimating sensitivity, the sensitivities (mean ± SD) at the frequencies shown in figure 2 were calculated to be 0.18 ± 0.1; 0.20 ± .06; 0.27 ± 0.8 and 0.26 ± .04 at 5, 10, 20, and 50 Hz, respectively. The mean (±SD) of the sensitivities within this mid-frequency region was calculated to be 0.28 ± .03. Therefore, occlusion of 35 per cent (0.28 + 2 SD) or more of the available receptor pool will result in a detectable reduction in the FS-EMG response.

The data from the low- (<5 Hz) and high-frequency (>50 Hz) regions of the FS-EMG spectrum could not be fitted to linear curves. The normalized responses in the low-frequency region, characterized by the 2-Hz response (fig. 3) remained nearly constant until occlusion of about 70–75 per cent of the receptors. After this point the FS-EMG response declined rapidly with increasing levels of neuromuscular block. The 100-Hz response, on the other hand, declined at a much lower level of occlusion. In most animals the 100-Hz response began to diminish rapidly for receptor occupancies of more than 20–25 per cent. The data from the 2- and 100-Hz responses were best described by exponential functions. The curves fitted to these data are shown in figure 3. Intersection of these curves and the mean control levels produced estimates for sensitivity of 70 per cent at 2 Hz and 27 per cent for the 100-Hz response.

It was also found that the relationship between receptor occupancy and the FS-EMG response was the same whether the FS-EMG response was normalized to the 1-Hz value or expressed as fraction of the control level. The data for the 2- and 100-Hz levels are shown in figure 3 for both processing techniques. These results demonstrate that by normalizing the FS-EMG responses at higher frequencies to the 1-Hz level, each response curve can serve as its own control, eliminating the need for pre-*d*Tc control measurements.

Muscle force and FS-EMG responses were found to be well correlated. Figure 4 shows the relationship between force and fraction of receptors occluded in the mid-frequency region of the FS-EMG spectrum. The data points represent force measured coincident with the FS-EMG data of figure 2. The slopes and

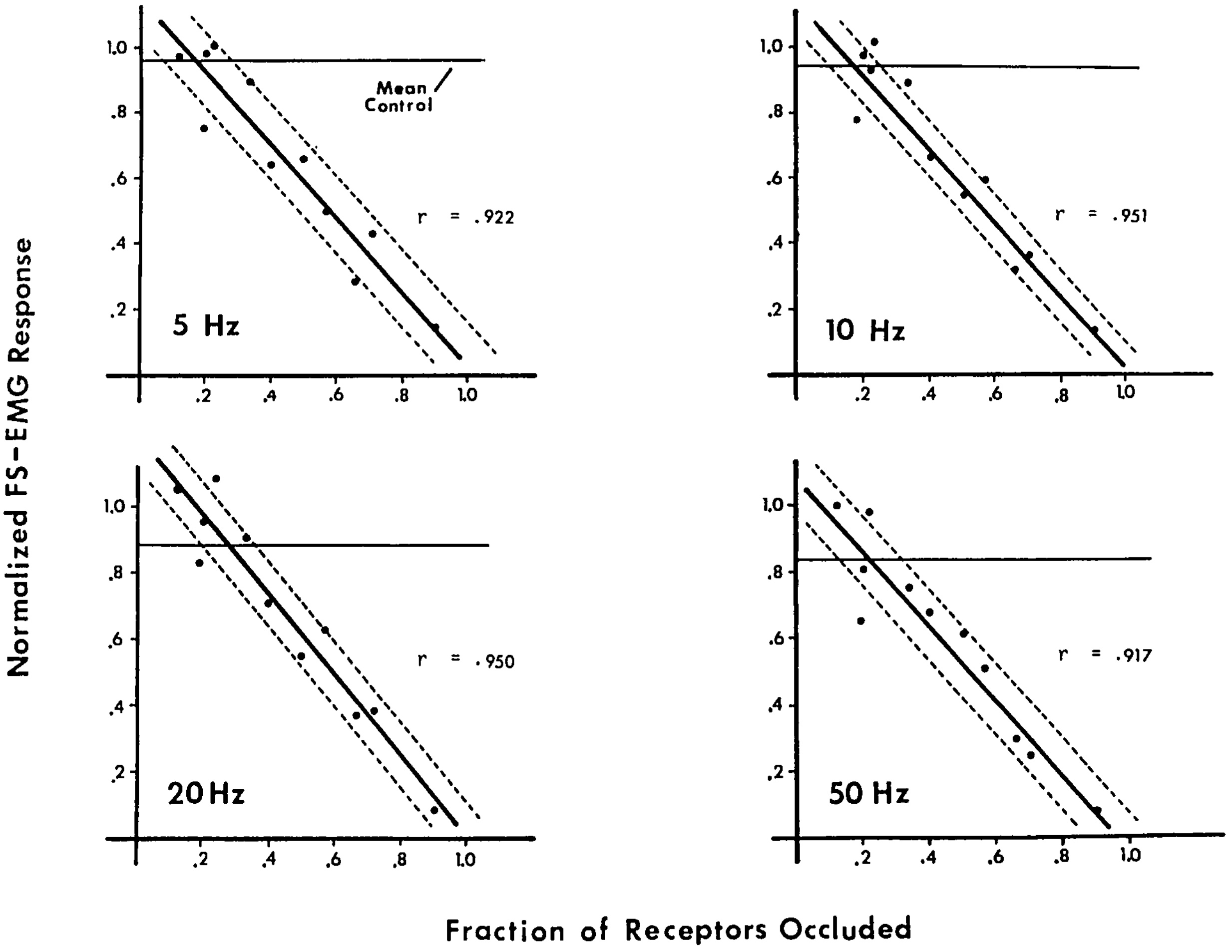

FIG. 2. Scatter diagrams showing the relationship between the frequency sweep response in the mid-frequency region and levels of receptor occlusion. The frequency sweep electromyogram (FS-EMG) amplitudes at points within the response curve corresponding to stimulation frequencies of 5, 10, 20, and 50 Hz are plotted versus the fractions of receptors occluded by *d*-tubocurarine. The solid heavy lines represent a linear regression curve fitted to the data points. The dashed lines show the standard error boundaries for the fitted curves. The solid horizontal lines indicate the mean normalized FS-EMG ratios of the control responses at the individual frequencies.

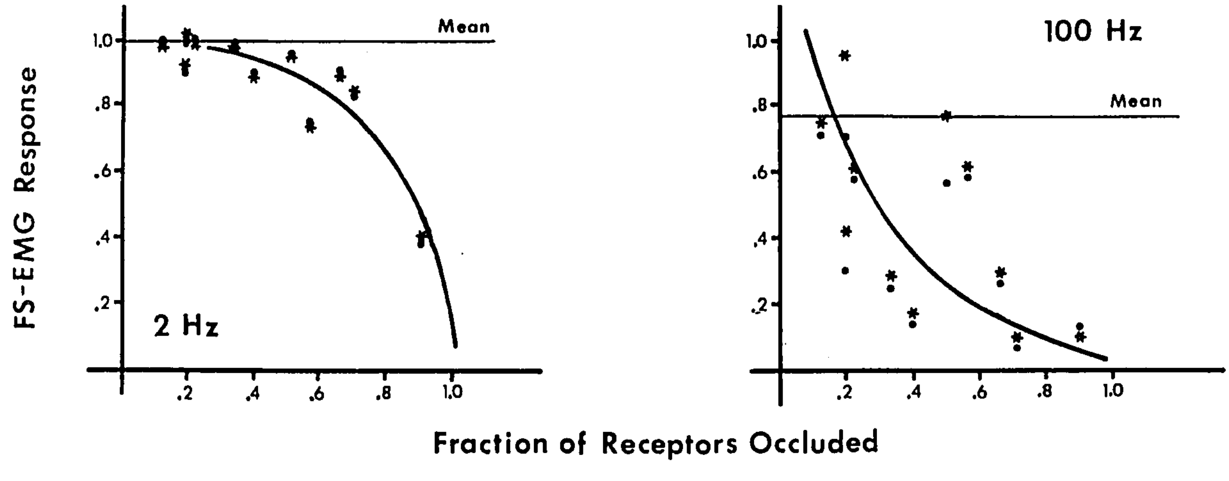

FIG. 3. Plot of the normalized frequency sweep electromyogram (FS-EMG) responses versus receptor occlusion at stimulus rates corresponding to 2 and 100 Hz. The data points were fitted to exponential curves shown by the solid heavy curved lines. The solid circles indicate the amplitudes of the FS-EMG normalized to the 1-Hz amplitude (as in figure 2). The asterisks show the same data expressed as a ratio of each animals' own control amplitude at 2 and 100 Hz, respectively.

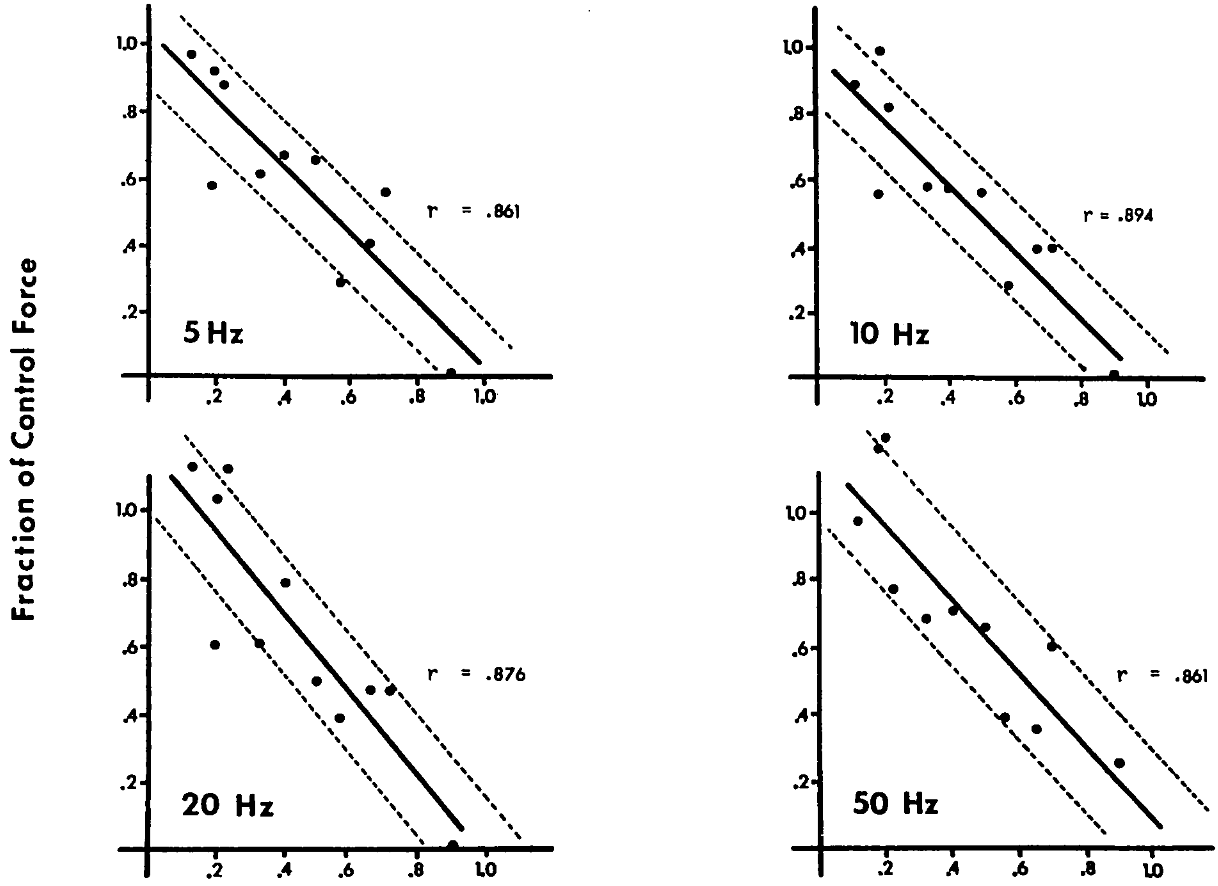

FIG. 4. Scatter diagrams showing the relationship between the muscle force produced during frequency sweep stimulation and the fraction of receptors blocked by *d*-tubocurarine. These data were obtained simultaneously with the frequency sweep electromyogram (FS-EMG) data of figure 2. The abscissa represents the muscle force as a fraction of the control response at each of the frequencies listed. The heavy solid line shows the linear curve fitted to these points, and the dashed lines represent the standard error bounds. There was no statistically significant difference in the slopes and/or intercept points of the curves fitted to the FS-EMG and force data.

intercepts of the regression lines fitted to the force data were found not to be significantly different from those of the FS-EMG data. However, the force data were slightly more variable than were the electrical responses.

Discussion

It is well known that variations in stimulation frequencies markedly affect the dose responses of nondepolarizing muscle relaxants.[12,13] The fractions of free receptors necessary to produce normal responses are less at lower stimulation frequencies than at higher rates. The results of this study are consistent with available information describing the abilities of various patterns of stimulation to detect nondepolarizing neuromuscular blockade. Comparison of our results with those of Waud and Waud[6–8] indicates that in the mid- and high-frequency regions of the response curve the "sensitivity" of the sweep frequency technique is greater than that of the train-of-four technique or the twitch response (table 1). The response from the low-frequency region, characterized by the 2-Hz response, is in excellent agree-

TABLE 1. Comparison of Indices of Neuromuscular Blockade

	Stimulus Rate (Hz)	Per Cent Receptors Needed for a Normal Response*
Twitch response†	0.1	20–25
Train-of-four‡	2	25–30
Tetanic fade ratio‡	30	20–25
	100	50
	200	70
Frequency sweep (exponential increase)		
Low-frequency range	1 < 5	25–30
Mid-frequency range	5 ≤ 50	35
High-frequency range	50 ≤ 100	70–75

* The more receptors needed, the greater the sensitivity.
† Waud and Waud.[7]
‡ Waud and Waud.[8]

ment with that reported for the train-of-four method.[8] Waud and Waud[6] showed that fade in the response to 100-Hz tetanic stimulation was detectable at a receptor occupancy of about 50 per cent and, at 200 Hz, 30 percent. The estimated sensitivity of the FS-EMG response with 100-Hz stimulation was 27 per cent. Even though sensitivity equal to or greater than that of the FS-EMG response can be attained by use of fixed-frequency tetanic stimulation, the rate necessary is much higher (approximately 200 Hz) than that used for the FS-EMG (100 Hz maximally).

Most investigators have used muscle force rather than the FS-EMG as an index of neuromuscular function. The difference between our results for sensitivity in the high-frequency region and those reported for fixed-frequency stimulation at high rates cannot be attributed to measurement of different muscle parameters (EMG *vs.* force), since simultaneous measurement of force during frequency sweep stimulation gave results consistent with those of the FS-EMG.

The advantage of the frequency sweep technique is that it provides a measure of neuromuscular function that would otherwise be obtainable only by use of several fixed-frequency paradigms. The high-frequency region of the frequency sweep response is most sensitive to small changes in myoneural function or low levels of neuromuscular blockade, while the low-frequency response provides assessment during deep levels of blockade comparable to that obtainable by use of the train-of-four technique. As in the train-of-four technique, each FS-EMG test run acts as its own control, eliminating the need to establish preanesthetic control levels. Furthermore, the sensitivity attainable with frequency sweep stimulation is comparable to that obtainable by use of trains of high-frequency tetanic stimuli, which are very painful. The gradual increase in stimulation rate and the use of intramuscular stimulation minimize the pain perceived during frequency sweep stimulation. Consequently, this technique is suitable for monitoring both anesthetized and conscious individuals.

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