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Temporal Relation between Acoustic and Force Responses at the Adductor Pollicis during Nondepolarizing Neuromuscular Block

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Background: **Contracting muscle emits sounds. The purpose of this study was to compare the time course of muscular paralysis at the adductor pollicis muscle (AP) with use of acoustic myography and mechanomyography.**

Methods: **Thirteen elective surgery patients, American Society of Anesthesiologists physical status I, received rocuronium (0.6 mg/kg intravenously) as a bolus dose during general anesthesia. Force of AP was measured with use of a strain gauge, and sounds were recorded simultaneously with use of a small condenser microphone fixed on the palmar surface of the hand over the AP. Supramaximal stimulation was applied to the ulnar nerve at 0.1 Hz for 45–60 min. In seven patients, the response to train-of-four stimulation was also recorded during recovery.**

Results: **Force and sounds both were equally sensitive in measuring maximum block. The relation between sound and force was curvilinear, with good agreement near 0 and 100% and acoustic response exceeding mechanical response at intermediate levels of block. The acoustic signal had a slower onset and a faster recovery than the force response. The fade response of sound to train-of-four stimulation also recovered faster than that of force.**

Conclusion: **Acoustic myography is an alternative method to monitor muscular paralysis that is easy to set up and applicable to most superficial muscles. However, the time course of relaxation at AP using acoustic myography differs from the time course of force relaxation. Therefore, these two methods are not equivalent when applied to AP. (Key words: Acoustic myography; muscular paralysis; muscular sound; rocuronium.)**

MONITORING muscular responses to electrical stimulation delivered as single twitches, as train-of four (TOF) or in short bursts, is still the mainstay in the evaluation of the action of muscle relaxants.[1] Although several methods have been described that can be used for this purpose, recording force output from muscle remains the gold standard in monitoring the state of neuromuscular block (NMB). Unfortunately, recording of muscle force output is too complicated for routine clinical use. Furthermore, the application of this method is largely limited to the adductor pollicis muscle (AP), whose response to muscle relaxant is not typical of those muscles subserving respiration or maintaining airway patency. Skeletal muscles vibrate laterally during the build-up of longitudinal forces, producing sound waves or acoustic myography (AMG) that can be detected by microphones or accelerometers fixed to the skin overlying the muscle.[2–5] In normal awake volunteers, the amplitude of AMG has been shown to be proportional to force output during twitch contractions of the hypothenar muscles,[6] the AP,[7,8] and the diaphragm[9] in response to graded transcutaneous nerve stimulation and fatigue. Recent reports from this[10] and one other laboratory[11] also indicated a good relation between acoustic and force responses of small hand muscles during competitive NMB, suggesting the possibility of using AMG to monitor the time course of muscular relaxation or recovery. However, the temporal relation between the acoustic and the force responses during competitive NMB has not been investigated. Temporal relations are more relevant to the pharmacodynamics of muscle relaxants. In the current study we report substantial temporal differences between acoustic and force responses at the AP during rocuronium NMB, suggesting that these two methods, although reflecting similar mechanisms, are not equivalent.

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Materials and Methods

Patients and Techniques of Anesthesia

After obtaining approval of the institutional ethics committee and written informed consent, 13 patients with American Society of Anesthesiologists physical status I were enrolled in the study. Age varied from 25 to 55 yr (mean, 38.5 yr). Body mass index varied from 23.5 to 31.5 kg/m^2 (mean, 26.7 kg/m^2). Six subjects were women. All were undergoing short surgical procedures leaving free access to one arm and requiring only one dose of muscular relaxant. No premedication was given. General anesthesia was induced with propofol 1–2 mg/kg preceded by fentanyl 2–3.8 μg/kg or alfentanil 26–35 μg/kg. After loss of consciousness, rocuronium 0.6 mg/kg was injected as a bolus dose. Anesthesia was maintained with a propofol infusion (eight patients) or a halogenated anesthetic (sevoflurane; five patients). In all patients, blood pressure remained stable during the procedures, and no other complications were noted.

Recordings

The basic experimental setup used in this study has been described in detail previously[8] and is schematically illustrated in figure 1. The position of the arm and hand was secured by a brace. The isometric force was measured with a strain gauge connected by a strap to the proximal phalanx of the thumb, amplified and powered by a Hewlett Packard 8805 amplifier (Palo Alto, CA). The length of the strap was adjusted in such a way as to produce a passive tension less than 1 kg.

The AMG signal was recorded by a miniature condenser microphone (Monacor, Farum, Denmark), 6 mm in diameter, embedded in a Plexiglas capsule that was fixed with an adhesive ring to the palm surface of the hand overlying the adductor pollicis. The volume of the air chamber in front of the microphone was 0.09 c^3. The AMG signal was amplified and bandpass filtered between 0.5 and 500 Hz with a multichannel signal conditioner (MP100 amplifier; Biopac Systems Inc., Santa Barbara, CA).

Muscle twitches were produced by stimulating the ulnar nerve transcutaneously at the wrist with 0.2-ms square-wave pulses generated by a constant current stimulator (Innervator; Fisher and Paykel Healthcare, Laguna Hills, CA) and a current intensity set at 60 mA.

Protocol

The neurostimulator and recordings of twitch force, AMG, and synchronizing pulses were started with the injection of rocuronium and continued for 45–50 min. In all patients, the stimulator was set at a twitch rate of 0.1 Hz. In seven patients, TOF stimulation was also used intermittently to monitor the recovery of residual block, starting at approximately 20% recovery of the single twitch.

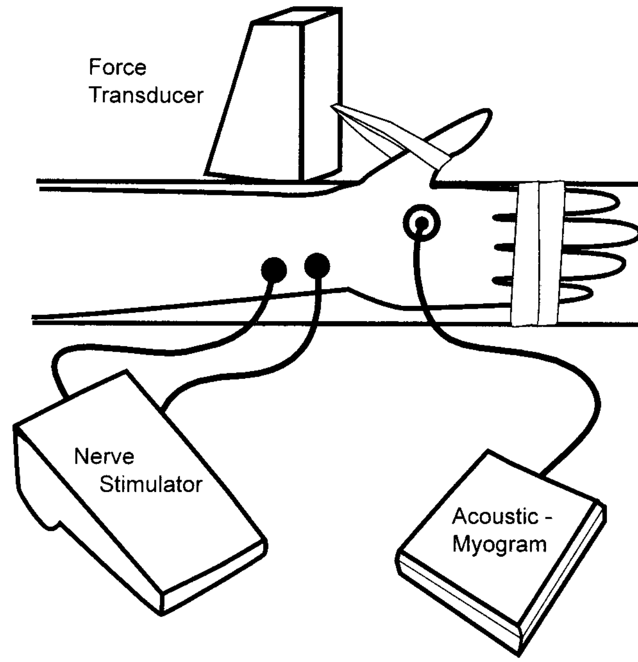

Fig. 1. Experimental setup. The hand is braced with the thumb lightly abducted and connected by an inextensible strap to a force transducer. A light microphone is fixed to the palmar surface of the hand with adhesive rings just over the adductor pollicis muscle to record the acoustic myogram. Surface electrodes are positioned over the ulnar nerve and deliver the current provided by the stimulator.

Signal Processing and Analysis

After amplification, all signals were continuously sampled at a rate of 1,000 Hz using a commercially available software and hardware system (Acknowledge; Biopac Systems Inc.) and stored online on a microcomputer.

The twitch force was measured as the peak amplitude of force above baseline (P_t). The AMG signal was measured as peak-to-peak (AMG_{pp}). The total area above and below the isoelectric line of the AMG signal over a period of 300 ms was also measured. However, both analyses provided very similar results (AMG area % = $AMG_{pp}\% \cdot 0.98 + 1.07$; $r^2 = 0.93$; n= 2,466), such that only the peak-to-peak determinations were retained in the final analysis. P_t and AMG_{pp} were each expressed as a fraction of the mean control value (average of 5–10 measurements) recorded just before the injection of rocuronium. For the responses to TOF stimulation, the amplitudes of the fourth twitch (T4) was expressed as percent of the first twitch (T1).

Peak amplitude of force and AMG_{pp} were each plotted against time after a bolus injection of rocuronium and the time to 90%, 75%, 50%, and 25% blockade determined during onset and during recovery of NMB. The maximum level of block and time to maximum blockade were defined as the minimal twitch height as determined by the computer and the time at which this was found.

Statistical Analysis

The onset and recovery times were compared using a paired *t* test. Linear and curvilinear regression techniques were used to compare P_t and AMG_{pp}. For the latter relations, the data during the plateau phase of relaxation were omitted to obtain a balanced representation of the various levels of relaxation.

The average bias and limits of agreement between the two methods were determined using the method of Bland and Altman.[12] The bias was determined as the difference between AMG_{pp} and P_t and related to the mean of the two measures of muscular relaxation. The upper and lower limits of agreement between these two methods were determined as ± 2 SD of the differences between AMG_{pp} and P_t. All statistical computations were performed using commercially available software (SPSS Advanced Statistics, version 6.1; SPSS Inc., Chicago, IL).

Results

Time Course of Relaxation and Recovery with Use of Mechanomyography or Acoustic Myography

Representative tracings of the force and sound signals during the onset and recovery of muscular paralysis in one patient are illustrated in figure 2. The sound signal is a multiphasic oscillating signal. The onset and duration of these oscillations approximate those of the force change.

The average time course of muscular relaxation and recovery obtained by ensemble averaging of P_t and AMG_{pp} from 13 patients is illustrated in figure 3A. Pharmacodynamic measures of relaxation for the group are given in table 1. The maximum depression and the time to maximum depression were not found to be significantly different for these two measures of relaxation. However, AMG_{pp} showed a slower onset and a faster recovery than P_t. Indeed, the time to 50% and 75% depression were significantly longer, and the time to 25%, 50%, 75%, and 90% recovery were significantly shorter for AMG_{pp} than for P_t.

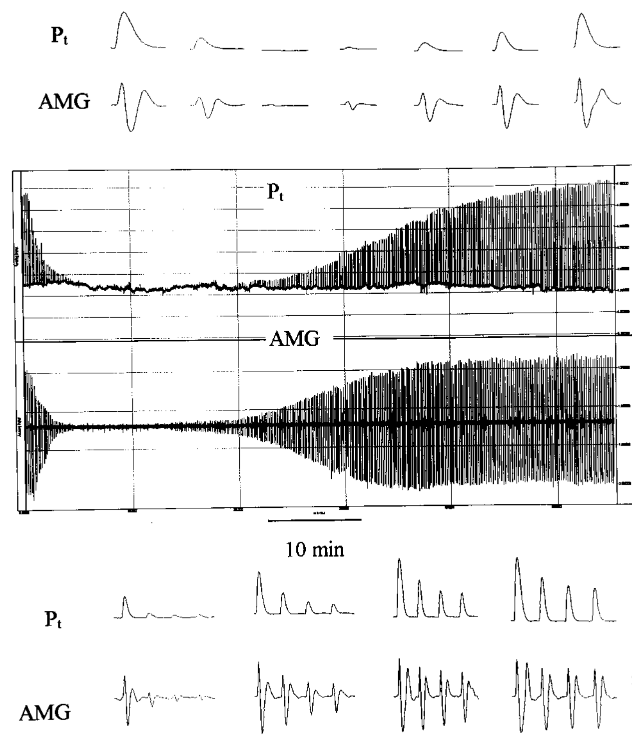

Fig. 2. Representative records of twitch force (P_t) and of the corresponding acoustic signal (AMG) in one patient during onset and recovery from muscular paralysis. The compressed 55-min record is shown in the middle. Representative tracings of P_t and AMG during single twitches (*top*) and during train-of-four stimulation (*bottom*) are shown on a shorter time base.

Relation between P_t and AMG_{pp}

The relation between AMG_{pp} and P_t was best fitted by a second-order polynomial function. The average relation for the group is shown in figure 3B. For the 13 patients studied, the average regression coefficient (r^2) for the polynomial function was 0.93 ± 0.07. By comparison, linear and power functions yielded r^2 values for the group of 0.84 ± 0.09 and 0.87 ± 0.07, respectively. The linear (1.82 ± 0.56) and the quadratic terms (−0.0078 ± 0.0056) of these polynomials for the group were significantly different from zero, but the intercept (−5.8 ± 12.0) was not.

Residual Block

Representative tracings of P_t and AMG_{pp} during TOF stimulation are shown in figure 2. The relation between

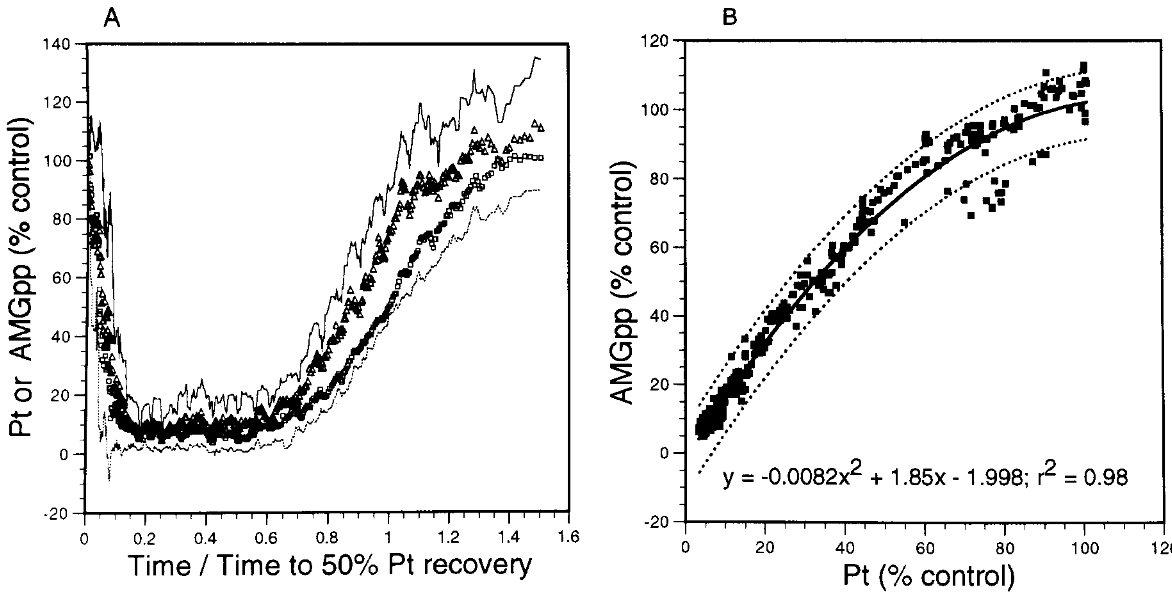

Fig. 3. (*A*) Time course of twitch force (P_t; squares) and of acoustic response (AMG_{pp}; triangles) of adductor pollicis muscle during rocuronium neuromuscular blockade. Data are time ensemble averages for 13 patients after time for each patient had been normalized to 50% recovery time of P_t. Continuous and dotted lines show ± 1 SD for AMG_{pp} and P_t, respectively. (*B*) Relation for the group between AMG_{pp} and P_t. Data points taken from (*A*). The data points are fitted with the indicated second-order polynomial function (solid line). The dotted lines represent the 95% confidence interval about the predicted mean. In both (*A*) and (*B*), AMG_{pp} and P_t are each expressed in percent of their respective control value.

the fade response of AMG_{pp} and of P_t during TOF stimulation is shown in figure 4 and was best fitted by a curvilinear function.

Bias and Limits of Agreement

The bias and limits of agreement between AMG_{pp} and P_t were calculated for 3,311 paired observations during single twitches and for 237 paired observations during TOF stimulation. Group results during twitches and during TOF stimulation are illustrated in figures 5A and 5B, respectively. For single twitches and for TOF stimulation, there was a significant positive bias of 9.68 ± 13.67% and 17.56 ± 13.42%, respectively, indicating that the AMG tends to underestimate the level of neuromuscular blockade as measured by P_t. For these calculations, the mean of P_t and AMG_{pp} averaged 52% for single twitches and 67.5% for TOF stimulation. The lower and upper limits of agreement were, respectively, −17.7% and 37.1% for single twitches and −9.3% and 44.4% for TOF stimulation. For single twitches as well as for TOF stimulation, the bias was greatest at intermediate and low levels of block but virtually nil at high levels of block (*i.e.*, at a mean of P_t and AMG_{pp} < 10%).

Discussion

As these results show, the onset of NMB was associated with a progressive attenuation of the muscular sound that was progressively restored during recovery. During the recovery period, the muscular sound also displayed a characteristic fade response to TOF stimulation. These findings are in accordance with earlier reports from this[10] and another laboratory,[11] suggesting that acoustic signals from muscles can be used to monitor the onset and recovery from NMB. The maximum level of depression was also comparable for these two methods. However, the acoustic response showed a slower onset and a faster recovery than the twitch force. Thus, although these two methods clearly reflect the onset and the recovery of muscular paralysis at AP, they are not interchangeable.

The curvilinear relation between AMG_{pp} and P_t explains the different time course of AMG_{pp} and of P_t that we observed. This relation was best described by a second-order polynomial function. A recent study by Dascalu *et al.*[11] reported a linear relation between the acoustic response recorded over the thenar muscle group and the adduction force at the thumb during NMB achieved with various agents. No definite explanation

Table 1. Pharmacodynamics of Rocuronium Using P_t and AMG_{pp}

	Force	Sound	*P*
% Block (time [min])			
10	0.87 ± 0.09	0.95 ± 0.15	0.558
25	1.04 ± 0.1	1.34 ± 0.16	0.022
50	1.39 ± 0.15	1.75 ± 0.19	0.007
75	2.16 ± 0.26	2.92 ± 0.45	0.072
Maximum	7.46 ± 0.86	7.46 ± 1.01	0.999
% Recovery (time [min])			
25	26.79 ± 2.45	24.01 ± 2.79	0.012
50	32.32 ± 2.95	28.68 ± 2.91	0.000
75	37.51 ± 3.54	32.94 ± 3.41	0.000
90	41.66 ± 3.59	37.25 ± 3.67	0.028
Maximum depression (% control)	3.4 ± 1.3	6.8 ± 2.1	0.098

Time in minutes after the injection of rocuronium for twitch force and for the sound intensity to reach the indicated levels of neuromuscular block during onset (% block) and during recovery (% recovery).

Maximum depression-minimum value of P_t and AMG_{pp} recorded during onset and expressed in percent of the control value.

Values are mean ± 1 SEM for 13 patients.

P = statistical level of significance for the difference between P_t and AMG_{pp} (paired *t* test).

can be offered for these different results. Their data showed considerably more scatter, and their recording technique differed markedly from ours. They used a large microphone positioned over the thenar muscle, and twitch force appears to have been recorded from the distal phalanx of the thumb. Whether these technical differences can account for the different results cannot be determined from the current study. In our preliminary report, we suggested that a linear relation could provide a reasonably good fit to the acoustic *versus* P_t relation.[10] However, this suggestion was based on a limited data set obtained mostly during onset and early recovery. Over the range of NMB investigated then, a linear relation indeed provided a reasonably good fit. Similarly, in the current study, a linear fit accounted for 84% of the variance. However, when the full range of NMB is considered, the relation clearly becomes curvilinear. The cause of this curvilinearity is unclear.

Based on current acoustic models for vibrating muscles,[4,5] the amplitude of the lateral vibrations for a given active axial tension should be determined by the length of the muscle fibers, the elastic modulus of the muscle, and its mass. When these factors are controlled or kept constant, as in the current study, the amplitude of the lateral vibrations (and of the acoustic signal) should be directly related to the active tension. In line with these predictions, previous studies in awake volunteers using the hypothenar muscle group,[6] the AP,[7,8] or the diaphragm[9] as models, all reported linear relations between the acoustic and the force responses during twitch contractions over a wide range of force. In these studies, twitch force was varied by fatiguing the muscle[6–9] or by varying the intensity of nerve stimulation.[8,9] By contrast, in the current study twitch force was manipulated pharmacologically. This opens the possibility that the curvilinear relation observed here could be related to the pharmacologic properties of muscle relaxants.

Several hand muscles other than the AP are activated by ulnar stimulation. Furthermore, there is evidence in the literature suggesting that the relative sensitivity of different hand muscles to muscle relaxants differ. The first dorsal interosseous muscle, which contributes significantly to the adduction force of the thumb, has been shown in electromyography studies to be more sensitive than AP to nondepolarizing muscle relaxants.[13] Conceivably, the AMG recorded over the palmar surface of the hand may be less affected by the cocontraction of first dorsal interosseous muscle than P_t. This would cause P_t to decline more rapidly during onset and to recover more slowly during recovery than AMG. It is of interest that comparable differences have been noted previously when comparing muscular relaxation measured by electromyography and mechanomyography.[14,15] The underlying mechanism may also be comparable. Alternatively,

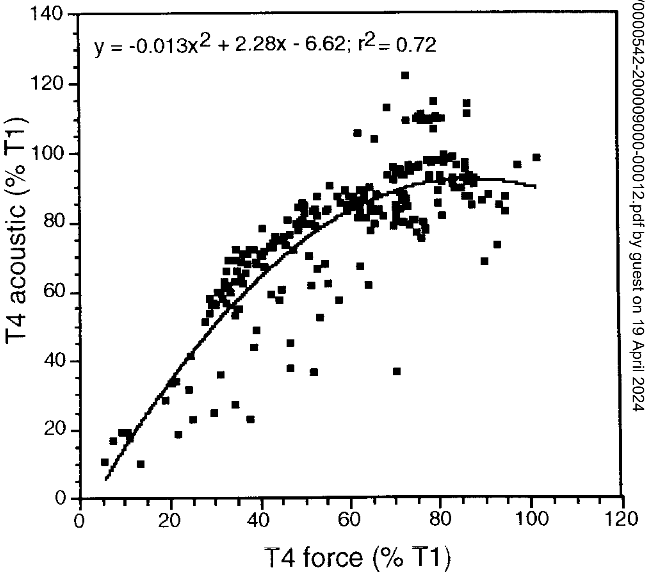

Fig. 4. Relation between acoustic and force responses during train-of-four stimulation. The amplitude of the fourth twitch of each train was expressed as a percentage of the first twitch (T4/T1). The data from seven patients is shown. The solid line is the best fit second-order polynomial function.

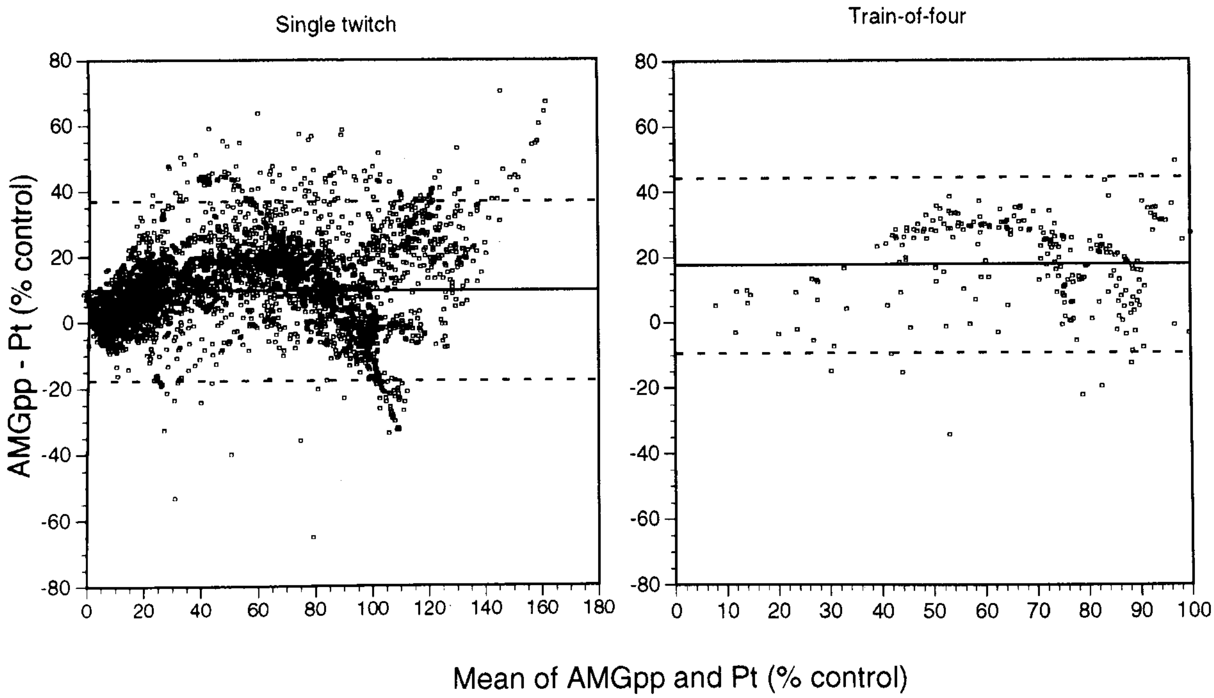

Fig. 5. The differences between acoustic (AMG_{pp}) and force (P_t) responses during single twitch (*A*) and train-of-four stimulation (*B*) are plotted against the mean of the two measurements. (*A*) AMG_{pp} and P_t are each expressed as percent of their respective control value. (*B*) AMG_{pp} and P_t are each expressed as percent of the value of the first twitch of each train. In both (*A*) and (*B*) the solid line shows the average difference and the dotted lines show ± 2 SD about the mean difference.

the AMG recorded over AP could be contaminated by the activity of other surrounding muscles having a greater resistance to NMB, causing a slower decay and a faster recovery of AMG. Additional studies will be required to test these possibilities.

Whatever the exact mechanism(s) involved, the curvilinearity of the AMG *versus* force relation in our study had significant effects on the parameters usually used to describe the pharmacodynamic properties of muscle relaxants. According to this relation, P_t would be more sensitive than AMG_{pp} at low levels of NMB but less sensitive at high levels of NMB. The curvilinearity also explains the significant positive bias in favor of AMG. However, the bias was not distributed uniformly across all levels of NMB. At intermediate and low levels of blockade, both methods differed significantly, but at high levels of NMB, both methods were equivalent. Thus, both methods would appear to be equally valid when assessing conditions that require maximum blockade, such as when assessing intubation conditions, but both would differ when evaluating submaximal blockade or residual block. Indeed, as predicted by the curvilinear relation, the fade response of the AMG_{pp} recovered faster than the fade response of P_t. A force TOF fade ratio of 0.7 corresponded an AMG_{pp} TOF fade ratio of 0.9. In view of the now-recommended recovery of the TOF ratio to values as high as 0.9 at AP,[16] these differences between AMG_{pp} and P_t are likely to be of clinical significance. It will thus be important in future studies to determine whether this difference is inherent to the methods of measurement or whether it is a reflection of a differential sensitivity of hand muscles to competitive muscle relaxants.

In summary, the current study has shown that AMG, although showing an equivalent depression as mechanomyography during maximum blockade at AP, has a lower sensitivity than mechanomyography at intermediate and low levels of blockade. As a result of this difference, AMG displayed a slower onset and a faster recovery than mechanomyography. The two methods, therefore, are not interchangeable at submaximal levels of NMB.

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