

Muscle fatigue or neuromuscular disease may result in central activation failure during maximal voluntary contractions (MVCs). Superimposition of an electrically stimulated contraction during an MVC has been used to detect central activation failure. To determine the most sensitive means of quantitating central activation failure using this technique, we compared the increment in isometric force from single, double, and high-frequency trains (50 Hz, 500 or 1000 ms) of stimuli of the peroneal nerve imposed during three separate MVCs of the dorsiflexor muscles. Completeness of activation was quantitated with the central activation ratio (CAR) = MVC/(MVC + stimulated force). Comparisons were made of the CARs of three groups of subjects during the three stimulation conditions: 7 healthy subjects, 13 patients with amyotrophic lateral sclerosis, and 5 healthy subjects after fatiguing exercise. For all three groups, the CAR was significantly lower during the train of stimuli condition (means = 0.76–0.89) compared with either the single or double stimuli conditions (means = 0.96–1.00). The results suggest that a superimposed high-frequency train of stimuli is a more sensitive indicator of central activation failure during isometric MVCs compared with either the superimposed single or double stimuli methods. © 1996 John Wiley & Sons, Inc.
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QUANTITATION OF CENTRAL ACTIVATION FAILURE DURING MAXIMAL VOLUNTARY CONTRACTIONS IN HUMANS

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During investigations of human skeletal muscle function involving voluntary contractions, it is often assumed that there is complete activation of the muscle when contractions are “maximal.” However, under some conditions, there may be a failure of central motor drive which results in less than maximal activation of the muscle.^{7,9,13} This is termed central activa-

tion failure, and can result from either: (1) a failure to recruit all motor units, or (2) a reduction in maximal discharge rate. The resulting force, therefore, does not represent the muscle’s true maximum force-generating capacity. Conditions where central activation failure may occur include fatiguing exercise, decreased effort, and disease states in which there is disruption of upper motor neuron function.

The completeness of voluntary activation of a muscle may be indirectly assessed prior to or during the development of fatigue using a combination of voluntary and electrically stimulated contractions. Several methods involving superimposed electrical stimuli (single, double, or trains of stimuli) have been used to determine the adequacy of central activation during maximal voluntary contractions (MVCs) in both healthy and clinical populations. The “twitch interpolation” technique, originally applied by Merton,²⁰ involves imposing a supramaximal single³ or double⁴ stimulus during an MVC. By using supramaximal stimulation of the motor nerve, all motor units are recruited. Any increment in force from the stimulus suggests incomplete activation of the muscle under study.

Using this technique, central activation failure has been ruled out as an important mechanism of

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muscle weakness and fatigue in some studies.^{3-6,30} However, other investigations using the single or double stimulus method indicated that central activation failure may, in fact, be responsible for a portion of the muscle fatigue developed in healthy populations during certain types of exercise.^{8,18} Previously, we have used a superimposed train of stimuli (50 Hz, 240 ms) rather than a single stimulus, to investigate central activation failure.^{13,14,27-29} Using a superimposed train, we observed significant central activation failure during sustained MVCs in a group of chronic fatigue syndrome patients.¹³ In contrast, other investigators observed no failure of central activation, assessed using a single superimposed stimulus, in a study of chronic fatigue patients.¹⁶ The controversy regarding the role of central activation failure in fatigue may exist in part because the source of failure during fatigue varies with the type of exercise performed, and because the sensitivity of the twitch interpolation technique in detecting central activation failure may be insufficient in some cases. We have also used the superimposed train of stimuli technique to detect significant central activation failure in the unfatigued muscles of patients with neurologic and neuromuscular disorders, including amyotrophic lateral sclerosis²⁷ and multiple sclerosis,²⁸ both of which involve upper motor neuron dysfunction.

The results of these studies suggest that accurate quantitation of central activation failure is vital to a more complete understanding of the sources of failure both in muscle weakness resulting from disease, and in the development of muscle fatigue in healthy and clinical populations. The purpose of this study was to determine the relative sensitivity of superimposed single, double, and trains of stimuli for detecting central activation failure during maximal voluntary isometric contractions of the dorsiflexor muscles of healthy subjects and patients with amyotrophic lateral sclerosis (ALS). To further examine the relative sensitivity of each method, we made the same measurements in a group of healthy subjects at the end of fatiguing exercise. Preliminary results of this study have been published in abstract form.¹²

MATERIALS AND METHODS

Subjects. Twenty-one healthy subjects (8 female, 13 male) and 20 patients (3 female, 17 male) who fulfilled the diagnostic criteria for ALS²⁴ volunteered for this study. A subset of the healthy subjects (4 female, 5 male) volunteered for the fatiguing exercise protocol. The patients ranged from mild to severely affected by their disease. Clinical evaluation revealed modest weakness, Medical Research Council scale = 4.2 ± 0.2 (normal = 5.0, Ref. 19), and mild

spasticity, Ashworth Scale = 1.7 ± 0.2 (normal = 1, Ref. 25) in the dorsiflexor muscles of this patient group. All volunteers signed consent forms as approved by the human research committees of the University of California, Veterans Affairs Medical Center, and California Pacific Medical Center, San Francisco.

Experimental Arrangement. A photograph of the experimental apparatus is shown in Figure 1. Subjects were comfortably seated with both legs extended straight in front of them. The angle at the hip was approximately 125°. After placement of the surface electrodes (see below), the leg to be studied was fixed in a knee brace and inserted into a Lexan tube designed to hold it stationary during all isometric dorsiflexion contractions. The foot was held against a foot platform (25 cm × 14 cm rectangle, ankle angle 120°) with an adjustable Velcro strap (4 cm wide) tightened across the metatarsal heads, and another strap supporting the foot under the Achilles tendon. To be consistent in placement, the distal edge of the strap was aligned 1 cm proximal to the interdigit fold of the small toe in all subjects. To distribute pressure evenly across the top of the foot, a piece of neoprene and a 7 cm × 9 cm piece of thermoplastic (North Coast Medical, San Jose, CA) molded to the shape of the foot were placed under the Velcro strap before tightening. This arrangement occasionally causes some occlusion of blood flow to the toes; however, this is generally relieved once exercise begins. We have not observed any effect of this partial occlusion on the dorsiflexor muscle measurements. The subject then performed a brief MVC and, if possible, the Velcro was tightened further. The Lexan tube was then secured in place and a minimum of 10 min rest was given. All volunteers tolerated this arrangement well.

Force output was measured with a force transducer (West Coast Research, Los Angeles, CA) attached beneath the foot platform. The transducer's resolution is 0.1 N. The analog signal from the force transducer was amplified (TECA electromyograph TE-4, White Plains, NY), converted to a digital signal and displayed on a computer monitor using Labview software (National Instruments, Austin, TX). The data were then transferred to a spreadsheet template for analysis. The force transducer was calibrated before the study and excellent linearity was observed ($r^2 = 0.999$).

Electrical Stimulation. Standard surface electromyography^{13,14,21} using 10-mm nonmagnetic gold-plated electrodes and conducting gel was performed. The

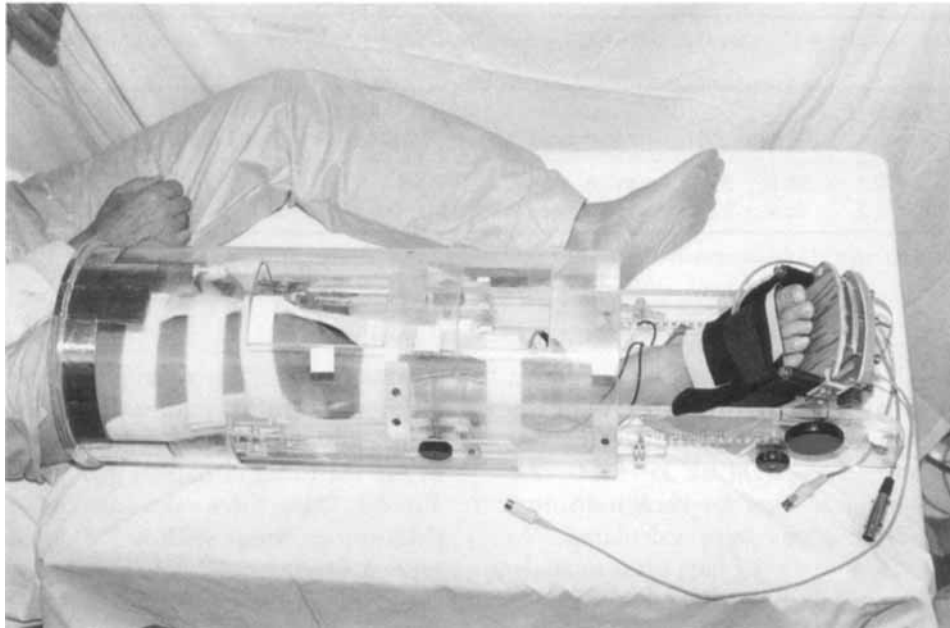


FIGURE 1. Photograph of the experimental apparatus. The subject is seated comfortably with the legs extended in front. The electrodes are attached to the leg to be studied, and the leg is secured in the knee brace, which has been inserted into the circular Lexan tube. The thermoplastic and neoprene are placed under the Velcro strap, and the foot is then strapped tightly to the foot plate. The force transducer is mounted on the bottom of the foot plate. The circular Lexan tube is strapped securely to the cart, so that no movement occurs (not shown). Isometric dorsiflexion is performed by pulling the foot against the strap. See text for more detail.

stimulating electrodes (10 mm diameter, mounted 2.5 cm apart on a piece of lexan) were placed longitudinally over the peroneal nerve approximately 1 cm distal to the fibular head. For each subject, precise placement of the stimulating electrodes was established by palpation of the nerve and by the observation of dorsiflexion of the unrestricted foot upon stimulation. The active recording electrode was placed on the belly of the tibialis anterior. The reference electrode was placed on the medial malleolus. A copper grounding plate (8 cm \times 9 cm rectangle) was placed over the lateral aspect of the calf midway between the stimulating and recording electrodes. All electrodes were secured with tape on the leg of the subject prior to positioning the leg in the knee brace and Lexan tube.

The stimulation voltage was set 25 V above that necessary to produce a maximal compound muscle action potential (observed during a 0.1-ms single stimulus). This supramaximal voltage was then used for all subsequent stimuli (single, double, train). The interpulse interval of the double stimulus was 20 ms.³⁰ The train stimulus was 50 Hz and lasted 1.0 s for all subjects except the exercise group, who received a 50-Hz, 500-ms train. Our pilot studies in healthy subjects ($n = 12$) showed that the time to maximal force during the 50-Hz, 500-ms stimulation was 458 ± 22 ms, and that 90% of maximal force was reached

within 300 ms. These results indicated that a 50-Hz, 500-ms stimulus was sufficient to obtain maximal tetanic force in the dorsiflexor muscles of healthy subjects.

Procedure. Prior to any voluntary contractions, each subject was given a series of single, double, and train stimuli, with 1 min rest between each stimulus. Generally, 2–3 stimuli of each type were elicited. The subjects then performed a “practice” MVC and three successive 3–4-s MVCs during which the single, double, and train stimuli were imposed, in that order. This progression biased any potential learning effect in favor of the single stimulus in that voluntary force might become progressively higher with practice. During each MVC, the stimulus was triggered manually after force plateaued. Again, a minimum of 1 min rest was provided between contractions. To ensure maximal effort, subjects were exhorted to “pull fast and hard” and to “pull through the stimulation.” In the healthy subjects who volunteered for the exercise protocol (a sustained 4-min isometric MVC), the superimposed stimuli were given before and during the final 30 s of exercise, at which time “extra effort” was demanded of the subjects. This high-intensity protocol was chosen because it produces central activation failure.¹³ During this fatigue protocol, force fell to $24.0 \pm 3.8\%$ of initial MVC.

Table 1. Twitch, twitch-pair (TP), tetanic, and MVC forces in the unfatigued dorsiflexor muscles of control and ALS groups (mean \pm SE).*

Group (n)	Twitch force (N)	TP force (N)	Tetanic force (N)	MVC (N)	Twitch/MVC	TP/MVC	Tetanus/MVC
Controls (21)	9.0 \pm 2.2	29.3 \pm 5.8	114.6 \pm 17.4	151.8 \pm 17.4	0.05 \pm 0.01	0.14 \pm 0.02	0.75 \pm 0.07
ALS (20)	7.8 \pm 1.2	15.2 \pm 2.3	106.2 \pm 13.9	114.4 \pm 16.1	0.07 \pm 0.01	0.14 \pm 0.02	1.06 \pm 0.11

*The mean of the individual ratios of stimulated/voluntary forces for both groups are also given.

Data Analysis. Peak force (Newtons) for all single (twitch), double (twitch-pair, TP), trains (tetanus), and MVCs were calculated and the highest value obtained for each measurement for each individual was used. The ratios of the twitch/MVC, TP/MVC, and tetanus/MVC were determined for each individual and then the group means were calculated. No smoothing was performed on the data prior to analysis. To quantitate central activation failure during each MVC, we calculated the central activation ratio (CAR) according to the following equation:

$$\text{CAR} = \frac{\text{MVC}}{\text{total force}}$$

where total force = stimulated + voluntary forces. Thus, CAR = 1.0 indicates complete voluntary activation of the muscle. Because the data can be amplified in post processing, it was possible to detect increases in force of 1–2% during the superimposed stimuli.

Comparisons of the CAR from the superimposed single, double, and train stimulation conditions were made using repeated measures analysis of variance (ANOVA) for the healthy control, ALS, and fatigue subjects. For the purpose of comparing the sensitivity of these methods, only the data from subjects who demonstrated CAR < 1.0 during any one of these measurements were included in the analysis (henceforth referred to as the “subgroups”). To determine whether differences in CAR under each condition were caused by differences in the voluntary force achieved before the superimposed stimulation, peak forces for each of the three MVCs were compared using repeated measures ANOVA for each subgroup. The intrasubject variability of the three MVCs (SD/mean of the three trials for each individual) was also calculated and expressed as the mean coefficient of variation for each subgroup. Post hoc comparisons of the CAR during the tetanus condition were made between the healthy controls ($n = 21$) and ALS ($n = 20$) groups using an unpaired *t*-test. Significance level for all statistical analyses was $P < 0.05$. All group data are presented as mean \pm SE.

RESULTS

Muscle Force. The mean peak forces from the single, double, trains, and maximal voluntary isometric contractions in the unfatigued dorsiflexor muscles of the control and patient groups are presented in Table 1. These force values are consistent with those from our previous studies,^{13,14,28} as well as from the reports of others.^{3,4,31} Also presented in Table 1 are the ratios of the twitch, twitch-pair, and tetanus vs. MVC force for the individual data from both groups. As expected, the twitch/MVC and TP/MVC ratios were small, indicating that in both patients and controls a single or double stimulus produces only a fraction of the total force that the dorsiflexor muscles are capable of generating. These ratios were similar to those from our previous studies,^{13,14,28} and consistent with those reported by other investigators studying the same^{3,4,31} and different² muscles. In contrast to the twitch/MVC and TP/MVC ratios, the tetanus/MVC ratio was 0.75 in controls and 1.06 in ALS ($P = 0.02$), indicating that tetanic force production was a large fraction of the MVC. In several muscle groups, including the dorsiflexors, the ratio of tetanus/MVC is typically less than 1.0.^{5,13,29} This is probably due to coactivation of the antagonist muscles during stimulation of the peripheral nerve. The higher tetanus/MVC ratio in the ALS group compared with controls suggests that the patients were unable to fully activate the dorsiflexor muscles during voluntary contractions, which is consistent with upper motor neuron dysfunction in this disease.^{8,24,27}

Central Activation Failure. The CAR (mean \pm SE) for each of the three groups, as well as the percentage of subjects in each group who demonstrated CAR < 1.0 for each condition are presented in Table 2. In the unfatigued dorsiflexors, 7 (2 female, 5 male; 48 \pm 6 years of age) of 21 healthy control subjects and 13 (2 female, 11 male; 51 \pm 3 years) of 20 ALS patients had a CAR < 1.0 during at least one of the three superimposed stimuli. Five (2 female, 3 male; 30 \pm 2 years) of the 9 volunteers who performed the fatiguing exercise protocol also demonstrated CAR

Table 2. Central activation ratio (CAR) assessed by superimposed single, double, and high-frequency trains of stimuli for each group (mean \pm SE).*

Group (n)	CAR: single (%)	CAR: double (%)	CAR: train (%)
Control (21)	1.00 \pm 0.00 (0%)	1.00 \pm 0.00 (4.8%)	0.96 \pm 0.02 (33.3%)
ALS (20)	0.98 \pm 0.00 (35%)	0.98 \pm 0.01 (30.0%)	0.85 \pm 0.04 (65.0%)
Fatigue (9)	0.98 \pm 0.01 (44.4%)	0.99 \pm 0.00 (33.3%)	0.89 \pm 0.05 (44.4%)

*Also included is the percentage of subjects in each group who demonstrated a CAR < 1.0 by each method.

< 1.0 during one of the three superimposed stimuli at the end of exercise. An example of the increase in force elicited in an individual with ALS during a superimposed train of stimuli is presented in Figure 2. While a plateau in force had been attained, a 1-s train resulted in a further increase in isometric force, suggesting incomplete voluntary activation of the dorsiflexor muscles in this patient (CAR = 0.74). In this subject, the superimposed single and double stimuli elicited no increase in muscular force above that of the voluntary contraction. Thus, the CAR under both of these conditions was 1.0.

To compare the relative sensitivity of the three superimposed stimuli in detecting central activation failure, only the CARs from the subgroups of individuals with CAR < 1.0 under any one of the three stimulation conditions were compared. The individual MVC and total force (MVC + stimulated force) data for each subgroup under all three conditions

are presented in Figure 3. In all three subgroups, the largest increase in total force above the MVC occurred during the superimposed train of stimuli. The mean CAR data for each subgroup are presented in Table 3. In the subgroup of control subjects, incomplete central activation was detected only during the train trial. In all three subgroups, the CAR was significantly lower under the train of stimuli condition compared with either the single or double stimuli conditions, $P < 0.01$. There was no significant difference in CAR during the single compared with double stimuli conditions in any subgroup. These results suggest that a superimposed train of stimuli is more sensitive in detecting central activation failure than either a superimposed single or double stimulus, and that there is no difference in sensitivity between the single and double conditions.

To determine whether the differences in CAR observed during the train compared with single and double stimuli conditions were due to differences in the force produced during each MVC, we compared the MVCs for the three conditions. The average forces for each MVC are presented in Figure 4. There were no differences in MVC force before the three superimposed stimuli in any of the three subgroups. This result suggests that there was no effect of variable maximum voluntary force on the CAR measurements. The intrasubject variability of the three MVCs were: $7.0 \pm 1.2\%$ in the control subgroup, $6.8 \pm 1.2\%$ in the ALS subgroup, and $6.8 \pm 2.3\%$ at the end of exercise in the fatigue subgroup.

DISCUSSION

The major finding of this study was that a superimposed train of stimuli is more sensitive than either a

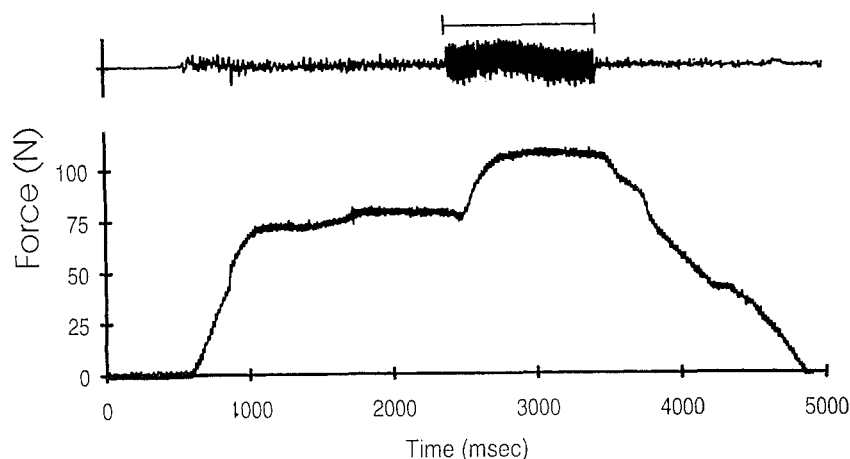


FIGURE 2. A representative example of the interference electromyography (arbitrary units) and force (Newtons) responses from a high-frequency train of stimuli imposed during an MVC in a 50-year-old male with ALS. The horizontal bar indicates 1.0 s. The central activation ratio in this case was 0.74. There was an increase in force only from the superimposed train of stimuli. The CARs for the single and double stimuli for this patient were both 1.0.

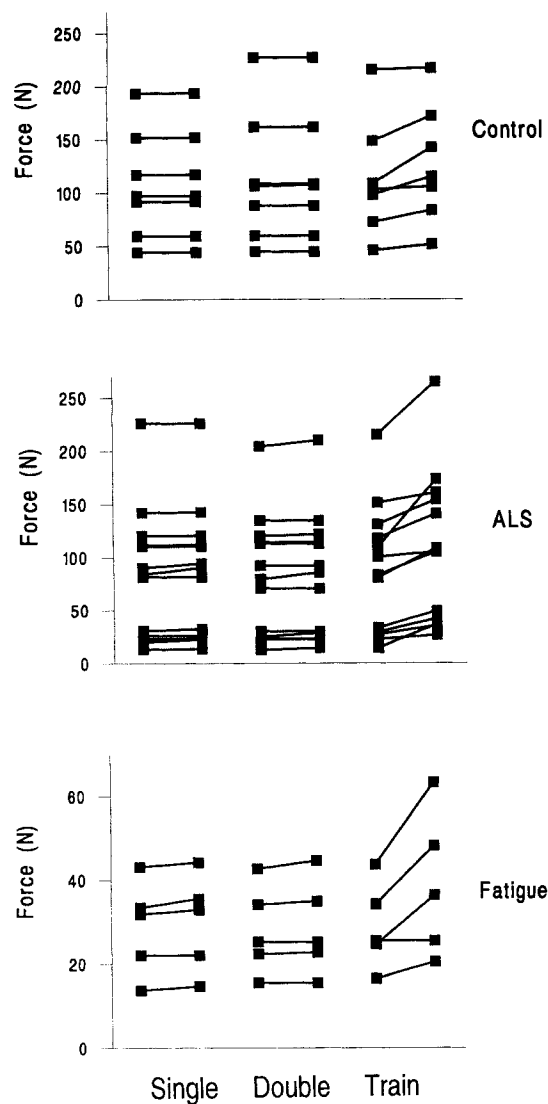


FIGURE 3. Individual plots of the peak MVC (left square in each column) and total force (right square in each column) for the control (top), ALS (middle), and fatigue (bottom) subgroups during the superimposed single, double, and train of stimuli conditions. Total force = peak MVC force + any increased force due to stimulation. A line with a positive slope indicates an increase in force with stimulation. For all three subgroups, the largest increase in force was observed during the superimposed train of stimuli.

superimposed single or double stimulus in detecting central activation failure during maximal voluntary isometric contractions in the human dorsiflexor muscles. This finding is based on the observation that the central activation ratio (CAR = MVC/total force) was significantly lower in all three subgroups during the train compared with single and double conditions. This result could not be attributed to differences in the amount of voluntary force produced under the different conditions (Fig. 4), and is instead ascribed to the greater force-generating capacity of a train of stimuli. Superimposing a supramaximal

Table 3. Central activation ratio (CAR) assessed by superimposed single, double, and trains of stimuli in healthy control, ALS, and fatigue subgroups (mean \pm SE).

Subgroup (n)	CAR: single	CAR: double	CAR: train
Control (7)	1.00 \pm 0.00	1.00 \pm 0.00	0.89 \pm 0.03
ALS (13)	0.97 \pm 0.01	0.97 \pm 0.01	0.76 \pm 0.04
Fatigue (5)	0.96 \pm 0.01	0.98 \pm 0.01	0.78 \pm 0.06

Individuals from each group who demonstrated CAR < 1.0 under any of the three conditions were included in the respective subgroup. The CAR was significantly reduced in the train compared with single and double conditions in all three subgroups ($P < 0.01$).

train of stimuli during an MVC provides a better measure of the total force a muscle is capable of producing, and thus quantitation of the completeness of voluntary activation is more accurate using this method.

Force Modulation. During a voluntary contraction, muscular force is modulated by the central nervous system via changes in motor unit recruitment and discharge rate (or firing frequency). As the amount of force produced increases from submaximal to maximal, the increment in force is achieved by increasing both recruitment and discharge rate.^{22,23} During a single supramaximal stimulus of the motor nerve, all motor units are recruited. However, because there is only a single stimulus there is no opportunity for the summation of force that occurs with repeated stimuli. As a result, twitch force is only a small fraction (5–15%) of tetanic and maximal voluntary force.^{2–4,13,28,31} This was demonstrated in the present study by the small twitch/MVC and TP/MVC ratios. Thus, it is reasonable to expect that a single superimposed stimulus will be insufficient to detect

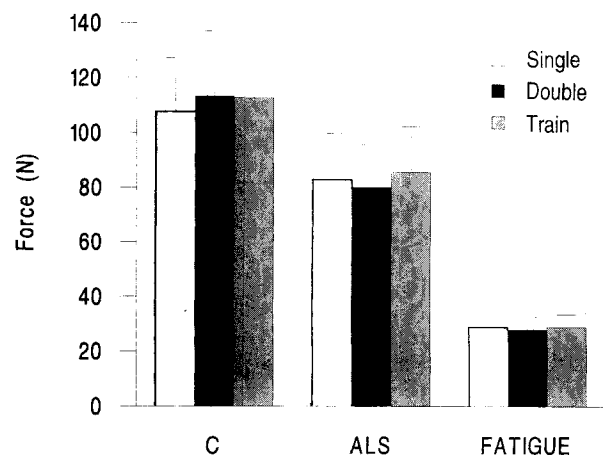


FIGURE 4. Mean MVC force during the superimposed single, double, and train of stimuli conditions for each of the three subgroups. Within each group, there was no difference in the MVC force produced during any of the three conditions.

central activation failure, particularly as voluntary force approaches maximal. As indicated by previous investigators, this problem may be particularly manifest during studies of muscle fatigue in which twitch force falls to very low levels.³⁰ Therefore, as demonstrated in the present study, the use of a superimposed train of stimuli is most appropriate for investigations of the extent to which maximal voluntary force represents the total force-producing capacity of a muscle.

Central Motor Drive. The causes of reduced central motor drive are not clear, although they could include decreased volition, altered reflex inputs,⁸ reduced maximal discharge frequencies,¹¹ or central disease processes.²⁶ The observation of central activation failure in both the unfatigued (7 of 21 subjects) and fatigued (5 of 9) muscles of our healthy subjects is similar to the recent reports of Gandevia and co-workers, who used the twitch interpolation technique to examine the completeness of voluntary muscle activation.^{1,8,18} In contrast, earlier investigations using the twitch interpolation technique suggested no impairment of central activation in healthy subjects.^{5,6} In the present study, we detected no central activation failure in the dorsiflexor muscles of our healthy subjects using single or double stimuli; a superimposed train of stimuli was necessary to make this observation (Tables 2 and 3.) Thus, we attribute at least a portion of the previous discrepancies in the literature to the use of the relatively insensitive twitch interpolation technique. In addition, it is likely that in cases where central activation failure was observed using twitch interpolation, the full magnitude of that failure may have been underestimated. In the future, the use of the superimposed stimulation technique for the investigation of central activation failure in both unfatigued and fatigued human skeletal muscle should involve a train of stimuli for accurate quantitation of reduced central motor drive. The optimal parameters for this train have yet to be determined.

Previously, no impairment of central motor drive to the dorsiflexor muscles was observed in healthy elderly subjects using twitch interpolation.³¹ However, our own observations using a superimposed train of stimuli suggest that there may be increased central activation failure in healthy elderly adults compared with young subjects. In the present study, 4 of 5 subjects aged >60 years had CARs <1.0. It is apparent that this question needs further investigation. We observed no obvious differences between men and women in the completeness of central activation, although this was not studied systematically.

In clinical populations, the issue of impaired central motor drive is important to the understanding

of the source of weakness and excessive fatigue often observed in patients with chronic disease. In the present study, ALS patients had a significantly lower CAR using the superimposed train of stimuli compared with healthy subjects of the same age (Table 3). In addition, the tetanus/MVC ratio was significantly higher in the ALS group (Table 1). Both of these results suggest an inability on the part of the patients to fully activate their dorsiflexor muscles voluntarily, which is consistent with upper motor neuron dysfunction in this group.

Multiple sclerosis (MS) is a disease of the central nervous system in which upper motor neuron function is likely to be impaired. Previously, Rice et al. observed both reduced maximal firing frequencies and incomplete activation using the twitch interpolation technique in subjects with MS.²⁶ Likewise, we observed central activation failure in a group of moderate to severely impaired MS patients using a superimposed train of stimuli.²⁸ In patients with chronic fatigue syndrome, Lloyd et al. observed no excessive central activation failure using the double stimuli technique prior to and immediately after fatiguing submaximal exercise.¹⁶ In contrast, using a superimposed train stimulus, we observed significant activation failure in a group of chronic fatigue syndrome patients both before and immediately after a 4-min sustained MVC.¹³ The discrepancy between these studies may be due to differences in the superimposed stimulus, patient selection, exercise protocol, or muscle studied (biceps brachii vs. tibialis anterior). Reduced central activation has also been reported in post-polio-syndrome patients using both the twitch interpolation² and superimposed train²⁹ methods. In summary, these studies indicate that impaired central motor drive may occur in the unfatigued and fatigued muscles of patients with various neurologic and chronic diseases. Weakness and fatigability in these populations may therefore partly arise from impaired central activation. Thus, accurate quantitation of the completeness of central activation is imperative in studies of altered muscle function in disease. The results of the present investigation indicate this can best be accomplished using the superimposed train method.

Single stimuli are much more tolerable to the subject than are trains of stimuli, which makes the use of superimposed single or double stimuli attractive. However, the results of this study provide strong evidence that the use of single or double stimuli may result in significant underestimation of central activation failure. We found that progressing the stimulation from single to double to trains made the train of stimuli easier to tolerate.

Methodology. Since Merton's report²⁰ of the use of the superimposed stimulus technique for evaluating central activation, several methods of expressing the data have been developed. Beginning with Belanger and McComas,³ some investigators have expressed the increment in force during the single superimposed stimulus as a percentage of the force from a single stimulus obtained immediately after the MVC.^{1,5,9,16,30} In the past, we have expressed the increment in force during the superimposed train of stimuli as a percentage of the MVC force developed immediately prior to the stimulus (the "added force" measure).^{13,14,27-29} However, there are some disadvantages to both these methods of expressing this type of data. In the former case, an additional stimulus is required in order to perform the normalization, and the resulting percentage is not immediately intuitive. In the latter case, there is no "ceiling" for the measurement. For example, in a very weak patient with a large increment in force during the superimposed stimulus, the "added force" value might reach several hundred percent. In the current study, we have suggested an approach to overcome the disadvantages of the previous methods. By expressing the voluntary force as a fraction of the total force produced [$MVC/(MVC + \text{superimposed train})$], a relatively intuitive answer to the question "to what extent is the subject capable of full voluntary activation of the muscle?" is obtained. Thus, a value of 1.0 equals full voluntary activation. Any value less than 1.0 provides the fraction of full activation that the subject can achieve.

Recently, several new techniques have been introduced for assessing central motor activation. These include transcranial magnetic stimulation of the motor cortex (e.g., Ref. 10), magnetic resonance functional imaging (e.g., Ref. 17), and positron emission tomography (PET) measurements of cerebral blood flow (e.g., Ref. 15). In combination with peripheral nerve stimulation, magnetic stimulation of the motor cortex can provide information regarding, for example, central conduction velocities. The imaging techniques (functional imaging, PET) provide spatial information regarding motor cortex activation. However, quantitation of the extent of activation failure in muscle weakness or fatigue using these new techniques is currently not possible. It may be possible that combining the technique described in the present study with a measure of motor cortex activation (e.g., localized signal intensity changes in functional imaging) will eventually provide a more complete understanding of central activation during voluntary exercise in humans. Currently, we are able to *quantify*

the central activation deficit using the superimposed stimulation technique.

Limitations. To measure the CAR, it is necessary that the superimposed stimulus excite all motor units in the muscle. This is best accomplished by supramaximal stimulation of the motor nerve. Thus, while some muscles such as the dorsiflexors are suitable for this analysis, other such as the plantarflexors may be more difficult to assess. An additional limitation involves the fact that there may be excitation of antagonist muscles during stimulation. Although this does not occur in some muscles (e.g., adductor pollicis, Ref. 20), the fact that in our preparation tetanic force is lower than MVC force suggests some antagonist activity. A possible limitation of superimposing a train of stimuli during an MVC may be related to the duration and frequency of stimulation. It might be expected that a prolonged 50-Hz stimulus would result in a decrease of voluntary force as a result of the "silent period" that follows supramaximal stimulation. However, any decrease in voluntary force due to an extended silent period would, if anything, result in an underestimation of the extent of central activation failure, as "total force" would fall.

Finally, although central activation failure can be quantitated using the CAR, the cause(s) of this failure cannot be determined with certainty. It is clear that volitional factors may have an effect on this measurement, although the high reproducibility of the MVC in the present study suggests that maximal effort was elicited from the subjects. In addition, we are currently unable to separate losses in MVC force due to poor discharge rate modulation from losses in MVC force due to an inability to recruit some motor units. Future studies will focus on developing methods to enable us to make this distinction.

Conclusion. The data indicate that, in human dorsiflexor muscles, the use of a superimposed train of stimuli provides a relatively sensitive measure of the completeness of voluntary activation during maximal voluntary isometric contractions. The use of a superimposed single or double stimulus may result in significant underestimation of the extent of central activation failure in studies of muscle strength and fatigue in both healthy and clinical populations.

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