Determining central activation failure and peripheral fatigue in the course of sustained maximal voluntary contractions: a model-based approach

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Submitted 1 December 2004; accepted in final form 4 February 2005

Schillings, Maartje L., Dick F. Stegeman, and Machiel J. Zwarts. Determining central activation failure and peripheral fatigue in the course of sustained maximal voluntary contractions: a model-based approach. J Appl Physiol 98: 2292–2297, 2005. First published February 10, 2005; doi:10.1152/japplphysiol.01342.2004.—In the study of fatigue, several methods have been used to calculate the development of central activation failure (CAF) and peripheral fatigue (PF) in the course of a sustained maximal voluntary contraction (MVC). This paper presents a model that enables simultaneous determination of CAF and PF during sustained MVC by using only force registration and superimposed electrical stimulation. In the model, we explicitly use the assumption, which is virtually always made implicitly in earlier studies, that a constant relative fraction of maximal possible force is activated by the electrical stimulation. That fraction can be determined at the start and at the end of a sustained MVC. The model shows that in the course of a sustained MVC, CAF can be calculated by merely using 1) this fraction, 2) the amplitudes of the superimposed force responses to stimulation, and 3) the course of voluntary force. After CAF quantification, the development of PF during MVC becomes available as well. The present study first examines the model assumption with data of sustained MVCs of variable durations on six healthy subjects. Subsequently, it shows CAF values in a group of 27 healthy subjects determined with both the model and a method of linear interpolation for PF estimation. Model-based CAF values were significantly higher during, but not at the start and at the end of, a 2-min sustained MVC. Next to a well-justified CAF determination, the model has the advantage of simultaneously quantifying PF, which was not possible with the previous methods.  

During a sustained MVC with additional electrical stimulation (Fig. 1), CAF at time point \( t \) can be determined by

\[
CAF = \frac{F_S}{F_V} \tag{1}
\]

CAF can vary between 0 and 1. It represents the fraction of maximal possible force that is not activated voluntarily. A higher value indicates a larger failure of central activation. \( F_S \) represents the amplitude of the force added by superimposed electrical stimulation (Fig. 1). \( F_V \) is the maximally possible force response on electrical stimulation (for a review, see Ref. 4). Force responses to stimuli superimposed during sustained MVC are used as indicators of the amount of central activation failure (CAF). The amplitude of these superimposed force responses, however, is not only influenced by the amount of central activation, but also by the current amount of PF (11). Some authors neglected this disturbing factor (16, 17, 20), whereas others developed methods to avoid or handle it (2, 3, 9, 10). In earlier studies by our group (13, 14), we assumed PF to induce a linearly declining force during sustained MVC. Such assumption, however, is not based on physiological evidence.

In this paper, we deduce a model to simultaneously calculate CAF and PF during a sustained MVC. Electrical stimulation during rest usually activates only part of the muscle tissue. All studies determining CAF implicitly assume that this force response is representative for the force response that would have been obtained if the total muscle tissue were activated. Indeed, Bigland-Ritchie and coworkers (1) describe how in the unfatigued state the size of superimposed force responses to single twitches responds nearly linearly to the performed level of MVC. The contribution of PF to the force response to stimulation is thus assumed to be proportional to its contribution to total muscle force. If this assumption is recognized more explicitly, it can be used to determine the contribution of both central and peripheral factors to fatigue during a sustained MVC.

The linear approach and the newly presented method are evaluated with experimental MVCs of variable duration. In addition, CAF values determined with both methods from 2-min sustained MVCs will be compared.

MATERIALS AND METHODS

Model Development

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Fig. 1. Schematic view on sustained maximal voluntary contraction (MVC) with variable definitions. F, force produced voluntarily; Fm, maximally possible force; Fsx, force added by superimposed electrical stimulation; F0, maximally possible force response on electrical stimulation; CAP, control activation failure. Dotted line connecting F0 and Fs represents F0 estimated via the model, the dash-dot line via the method of linear interpolation.

F0 can be measured directly during the exercise, but obviously there is no possibility to directly measure Fm. The essence of CAP determination is to estimate F0 despite this inaccessibility.

All studies into CAP implicitly assume that the relative fraction of maximally possible muscle force that can be produced with the specific stimulation parameters is constant. With β as this relative fraction, this assumption can be written as

\[ F_m = \beta' \cdot F_m \]

where \(\beta' = \beta = \text{constant} \)

\( F_m \) represents the maximally possible force, which is the voluntary force that would be produced if CAP were zero (Fig. 1).

At first sight, explicitly stating this assumption seems not to be very helpful in the estimation of \( F_m \), because neither \( \beta' \) nor \( F_m \) can be measured directly during ongoing exercise. However, the values of \( \beta' \) and \( F_m \) can be determined. Because we assume \( \beta' \) to be independent of time, determining \( \beta' \) at any time t should be sufficient.

In practice, it can be calculated at two moments in time, namely directly at the start (\( \beta^0 \)) and at the end (\( \beta^T \)) of the contraction.

At the start of contraction, \( \beta \) is defined as:

\[ \beta^0 = \frac{F^0}{F_m^0} \]  

Eq. 2

\( F^0 \) (i.e., the force response to an electrical stimulus during rest before MVC, Fig. 1) can be measured directly.

We know that:

\[ F^0 = (1 - \text{CAP}) \cdot F_m^0 \]  

Eq. 3

in which \( F^0 \) is the force voluntarily produced (Fig. 1), and therefore at the start of exercise:

\[ F_m^0 = \frac{F^0}{1 - \text{CAP}^0} \]  

Eq. 3a

Since

\[ \text{CAP}^0 = \frac{F^0}{F_m^0} \]  

Eq. 1a

Equation 3a can be rewritten as

\[ F_m^0 = \frac{F^0}{1 - F_m^0\cdot\text{CAP}} \]  

Eq. 4

\( F_m^0 \) is supposed to be equal to \( Fs^0 \) (Fig. 1). Combining Equations 2 and 4 and substituting \( F_m^0 \) for \( Fs^0 \) results in:

\[ \beta^0 = \frac{F^0}{F^0/(1 - F_m^0\cdot\text{CAP})} = \frac{F^0}{F_m^0} \cdot (1 - F_m^0\cdot\text{CAP}) = \frac{F_m^0}{F^0} \cdot F^0 \cdot (1 - F_m^0\cdot\text{CAP}) \]  

Eq. 5

This can be rewritten as

\[ \beta^0 = \frac{F_m^0}{F^0} \cdot F^0 \cdot (1 - F_m^0\cdot\text{CAP}) \]  

Eq. 6

In words: the denominator \( F^0 \) represents the maximal voluntary force, which is the maximal possible force (\( F_m^0 \)) minus the force “lost” because of the presence of central activation failure (\( \text{CAP}^0 \cdot F_m^0 \); see Fig. 1). The numerator represents the maximal possible stimulated force minus the amount of force that can be added to \( F^0 \) by electrical stimulation because of CAP. Via Eq. 6, \( \beta^0 \) can be determined using three variables that can all be measured directly.

Similarly, \( \beta^T \) can be determined (Fig. 1) via

\[ \beta^T = \frac{F^0 - F_m^0}{F^0} \]  

Eq. 6a

Now that we know how \( \beta \) can be calculated at time 0 and time T, we will derive the consequences for the CAP determination.

Combining the explicit assumption with Eq. 1 leads to

\[ \text{CAP}^t = \frac{F_m^t}{\beta \cdot F_m^t} \]  

Eq. 7

Since

\[ F_m^t = F^t + F_m^t \cdot \text{CAP}^t \]  

Eq. 1

Equation 7 can be rewritten as

\[ \text{CAP}^t = \frac{F_m^t}{\beta \cdot (F^t + F_m^t \cdot \text{CAP}^t)} \]  

Eq. 7a

Combining Eq. 7a with Eq. 1 gives

\[ \text{CAP}^t = \frac{F_m^t}{\beta \cdot (F_m^t + F_m^t \cdot \text{CAP}^t)} = \frac{F_m^t}{\beta \cdot (F_m^t + F_m^t \cdot F_m^t)} \]  

Eq. 7b

With the use of the explicit assumption \( F_m^t = \beta \cdot F_m^t \), this results in

\[ \text{CAP}^t = \frac{F_m^t}{\beta \cdot (F_m^t + F_m^t \cdot 1/\beta)} \]  

Eq. 8

Having calculated values for \( \text{CAP}^t \) and \( \beta \), PF during MVC can be determined:

\[ \text{PF}^t = 1 - \frac{\beta \cdot F_m^t}{F_m^t} = 1 - \frac{\beta \cdot (1 - \text{CAP}^t)}{F_m^t} \]  

Eq. 9

After a last simplification in writing, Equations 8 and 9 result in the following equations to determine \( \text{CAP} \) and PF:

\[ \text{CAP}^t = \frac{F_m^t}{\beta \cdot (F^t + F_m^t)} \]  

Eq. 8a

and

\[ \text{PF}^t = 1 - \frac{\beta \cdot F^t}{(1 - \text{CAP}^t) \cdot F_m^t} \]  

Eq. 9a

In fact, to determine \( \text{CAP}^t \), the amplitude of \( F_m^t \) (see Eq. 1 and Fig. 1) is now estimated by \( \beta \cdot F^t + F_m^t \). When \( \beta \) has been determined as described above with Eqs. 6 and/or 6a, the manageable descriptions \( \delta t \) and \( \delta a \) can be used to calculate \( \text{CAP} \) and PF values during a sustained MVC at any moment at which electrical stimulation is applied.

**Experimental Procedures**

**Experiment 1.** The first experiment was designed to test the validity of the assumption of a constant \( \beta \) over time. In addition, it provides
the possibility to test whether PF can be assumed to develop linearly, as supposed in our former studies. This is also relevant because CAF values obtained with both methods will be compared in Experiment 2.

Six healthy subjects [age 22.4 (SD 1.5); 5 women, 1 man] were recruited for this experiment. They gave their informed consent before the first experiment. The protocol was approved by the local ethics committee “Commissie Mensgebonden Onderzoek Regio Arnhem-Nijmegen.” The experimental setup has been described in detail elsewhere (13, 14). In our former studies, subjects made a single 2-min sustained MVC of the elbow flexor muscles. In the present experiment, trials of 15, 30, 45, ..., and 105 s MVC (8 levels) were also made.

In short, subjects were instructed to make a sustained MVC of their biceps brachii muscle. Before and directly after contraction, a stimulus event (described below) was applied to the relaxed muscle at the endplate region. During MVC, stimulus events were applied every 15 s, starting directly after the start of contraction. The last stimulus event was given just before cessation of the voluntary contraction. A stimulus event consisted of five times a five-pulse 100-Hz train (duration 40 ms). Pulse duration was 100 μs. The average of the five responses to such a short train is referred to as “the force response” and is used for analysis. During voluntary contraction, the intertrain interval was 300 ms; during rest, the intertrain interval was 1,000 ms. Pilot experiments had shown that these intertrain intervals were appropriate to avoid fusion of the single force responses. Before the start of the protocol, the location of the motor points was determined.

Then the current was increased until the force did not rise anymore. This intensity was used in all stimulus events. The initial stimulus event was not preceded by a short voluntary contraction, because pilot experiments showed that potentiation did not occur with this type of stimulus event.

The subsequent trials were separated at least 2 days, and the eight trials had a random order. Subjects were not informed about the duration of the contraction, but they knew it would be between 15 s and 2 min. To keep intertrial variability as low as possible, for every subject chair height and ergometer settings were kept constant. The location of the electrodes for stimulation stayed marked on the subjects’ arms during the period of the complete set of experiments.

To test the assumption of a constant β, this variable was determined both at the start (β₀) and at the end (βₜ; t = 15, 30, ..., 120 s) of every trial. For each individual, β₀/βₜ was plotted vs. t. Least-squares linear regression analysis tested slope (≠ 0) significance. The same procedure was done on the averaged data from the six subjects.

To test the validity of the assumption of a linear increase of PF, we tested whether Fₛ/ₜ declined linearly with time (t = 15, 30, ..., 120 s) during MVC. To reduce intertrial variability, relative values (Fₛ/ₜ/Fₛ/₀) were calculated from data within each trial. For each individual, a linear (Fₛ/ₜ/Fₛ/₀ = q + r·t), a second-order polynomial (Fₛ/ₜ/Fₛ/₀ = q + r·t + s·t²), an exponential (Fₛ/ₜ/Fₛ/₀ = q + r·e⁻ᵗ), and a power function (Fₛ/ₜ/Fₛ/₀ = q + r·tᵃ) were fit via the least-squares technique. F tests were used to determine whether one or more of the three-parameter functions (exponential, second-order polynomial, and
power) were better than the two-parameter function (linear). The same analysis was done on the averaged data of all subjects. $R^2$ of the linear fit was also determined.

**Experiment 2.** Both the linear interpolation method and the newly presented method were applied on data of a 2-min sustained MVC with electrical stimulation. Therefore, data of 27 healthy subjects [age: 39.8 (SD 14.3), 15 women, 12 men] were used. The data from some of these subjects were presented in our earlier studies (13, 14). The protocol was the same as described for experiment 1.

Both $\beta^0$ and $\beta^T$ were determined via Eqs. 6 and 6a, respectively. Values were compared with a paired-samples $t$-test. Least-squares linear regression determined the relation between $\beta^0$ and $\beta^T$.

For computing CAF and PF via the model, for each subject the mean of $\beta^0$ and $\beta^T$ was used in Eqs. 8a and 9a. Possible differences between CAF values determined with the model and the method of linear interpolation were tested with multiple paired-samples $t$-tests. The model provided PF values at any moment during the contraction at which a stimulus event was given. The linear interpolation method only uses information about peripheral fatigue after finishing the 2-min sustained contractions. Obviously, the linear interpolation also gives an estimate for PF at any moment during contraction. PF values obtained by both methods during sustained 2-min MVC were compared with multiple paired $t$-tests.

**Statistics**

Differences were regarded significant if $P < 0.05$. Regression analyses and paired-samples $t$-tests were performed with the Statistical Package for the Social Sciences 12.0.1; $F$ tests were done with Matlab 6.5 (The MathWorks).

**RESULTS**

**Experiment 1**

Data of each individual collected from the eight trials of MVC of variable duration are presented in Figs. 2 and 3.

Figure 2 shows the course of $\beta^T/\beta^0$. In all but one subject, the slope of the linear fit was not significantly different from zero. In subject 5, the slope was negative ($P = 0.027$). Mean $r^2$ of the linear fit was 0.25 (SD 0.18), also indicating the lack of a linear trend with time. When all subjects were averaged, $\beta^T/\beta^0 = q + r \cdot t$ fitted best, with $q = 1.09$ and $r = -0.068$. If $\beta^T/\beta^0$ had been perfectly constant, $q$ and $r$ would be 1 and 0, respectively. The 95% confidence interval of $q$ was 0.98–1.20; the 95% confidence interval of $r$ was $-0.22$ to $+0.085$. Thus $\beta^T/\beta^0 = 1 + 0 \cdot t$ did not describe the relation significantly worse than the best fit.

With respect to PF, in five of the six individual subjects, neither a second-order polynomial nor an exponential or power function described its course significantly better than the linear function (Fig. 3). Mean $r^2$ of the linear fit was 0.75 (SD 0.18). In one subject (subject 5) both a second-order polynomial and an exponential fit were significantly better than a linear fit ($P = \ldots$).

**Innovative Methodology**

2295

**Figs. 2 and 3. Relative amplitudes of $F_s$ (Fig. 1) measured at the end of sustained MVCs of variable durations.** Amplitudes of the final force responses during rest after the MVCs as a fraction of the amplitudes of the initial force responses. Each panel presents an individual subject. Solid lines represent linear fits; dotted lines, second-order polynomial fits; dash-dot lines, exponential fits; dashed lines, power fits. In all subjects but subject 5, the 3-parameter functions were not significantly better than the linear one. In that subject, both a second-order polynomial and an exponential fit did significantly better than a linear fit.
Innovative Methodology

DISCUSSION

In this paper, we proposed a model to determine CAF during sustained MVC. It enables a simultaneous unbiased calculation of CAF and PF from force recordings at any moment during the contraction, provided that superimposed electrical stimulation is given just after the start of, just before the end of, and at the moments of interest during sustained MVC.

Several studies have determined CAF at the start and at the end of a sustained contraction by comparing the decline in voluntary force with the decline in tetanic force during rest (e.g., Refs. 2, 8, 20). Other studies have compared the superimposed muscle force development during rest just after finishing exercise (3). To enable CAF determination at intermediate points in time during a sustained contraction, in our earlier studies we assumed a linear force response during rest before starting exercise, while the superimposed force response at the end of contraction was compared with a force response during rest just after finishing exercise (3). To enable CAF determination at intermediate points in time during a sustained contraction, in our earlier studies we assumed a linear PF increase during sustained MVC (13, 14). In this way, the force response of the muscle in rest, $F_s$, was assumed to be known at any moment in time, facilitating CAF estimation. However, other measures for PF, such as muscle fiber conduction velocity and pH values, appeared to indicate a nonlinear increase of PF (8, 13, 21). The present study shows that in the particular case of a 2-min sustained MVC of the elbow flexor muscles, linearity cannot be rejected; a linear function did not describe the data significantly worse than more complex functions in five of six subjects. However, in one individual and also when data of all subjects were averaged, a second-order polynomial was more accurate. We expect this kind of nonlinearity to be more prominent if sustained contractions of longer durations or at lower force levels are made.

An earlier method related the size of the superimposed force responses to the actual MVC (5, 10, 15). In this case, to
determine CAF, the implicit assumption was made that the decline of MVC is fully caused by peripheral factors. The decline of MVC caused by central fatigue, the variable to be estimated, was neglected, which is principally inconsistent and disturbs the calculation of CAF when it is significantly different from zero. A better method was introduced by Kent-Braun (7, 8) and Kent-Braun and Le Blanc (9) and also used by Nybo and Nielsen (12) and Stackhouse et al. (19). They calculated central activation as MVC divided by the total muscle force, where the total muscle force is the sum of MVC plus force from superimposed electrical stimulation. In general, however, the value of the added force and thus the total force depends on the stimulus given (duration, frequency, amplitude), and higher CAF values will be obtained when the stimulus is able to activate a larger part of the muscle more strongly (6, 18). This is actually illustrated by Stackhouse and coworkers (19). They determined a so-called central activation ratio during nonfatiguing contractions at defined percentages of maximum voluntary effort using different stimulus trains. The results reported higher ratios than anticipated based on the effort level, an effect that was stronger when the stimulus train resulted in a lower electrically elicited force during rest (19).

In the mathematical model, the actual value of $\beta$ theoretically does not influence the determined value of CAF. To obtain a reproducible result, stimulation should be preferentially supramaximal, although activation of antagonists should be avoided (18). If the stimulus event is such that a preceding MVC potentiates the force response, care must be taken that the initial rest twitch is also potentiated (4). Shield and Zhou (18) discuss the advantages and disadvantages of different types of stimulus events.

Our results showed that the assumption of a constant relative fraction ($\beta$) of maximally possible force ($F_m$) being activated by electrical stimulation, was reasonable in five of six individual subjects and in the averaged data of these subjects. Likewise, data of 27 healthy subjects showed no significant change of $\beta$ over 2-min sustained MVC. We do not expect that this relation will change when MVC is being sustained for a longer period.

On the basis of the presented results, both the linear PF development assumption and the new model appear to be defendable on the data of individual subjects in the case of a 2-min sustained MVC of the elbow flexors. On the averaged data, the linear development of PF can already be rejected for this short exercise. So we advise to use the newly presented method in future studies determining the course of CAF during sustained MVCs. First of all, it has the advantage of determining PF simultaneously, which previously was not possible without the use of additional techniques. It can also be argued to be the safer choice because of absence of any assumptions in CAF determination, except for the assumption of a constant $\beta$ that is implicitly present in almost all methods. Finally, it should be noted that application of the model is not restricted to sustained maximal efforts. Theoretically, it can also be used in protocols using lower force levels or for interrupted contractions.

ACKNOWLEDGMENTS

We thank N. Hoogenboom and H. Jansen for roles in acquiring experimental data, H. van Dijk for development of the required experimental software, and R. Oostenveld for contribution to the data analysis. We greatly appreciate the subjects’ voluntary participation.

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