

# letters to the editor

The following is the abstract of the article discussed in the subsequent letter:

**Ng, A. V., H. T. Dao, R. G. Miller, D. F. Gelinas, and J. A. Kent-Braun.** Blunted pressor and intramuscular metabolic responses to voluntary isometric exercise in multiple sclerosis. *J. Appl. Physiol.* 88: 871–880, 2000.—To test the hypothesis that a lower mean arterial pressure (MAP) response during voluntary isometric exercise in multiple sclerosis (MS) is related to a dampened muscle metabolic signal, 9 MS and 11 control subjects performed an isometric dorsiflexor contraction at 30% maximal voluntary contraction until target failure (endurance time). We made continuous and noninvasive measurements of heart rate and MAP (Finapres) and of intramuscular pH and  $P_i$  (phosphorus magnetic resonance spectroscopy) in a subset of 6 MS and 10 control subjects. Endurance times and change in heart rate were similar in MS and control subjects. The decrease in pH and increase in  $P_i$  were less throughout exercise in MS compared with control subjects, as was the change in MAP response. Differences in muscle strength accounted for some of the difference in MAP response between groups. Cardiovascular responses during Valsalva and cold pressor tests were similar in MS and control subjects, suggesting that the blunted MAP response during exercise in MS was not due to a generalized dysautonomia. The dampened metabolic response in MS subjects was not explained by inadequate central muscle activation. These data suggest that the blunted pressor response to exercise in MS subjects may be largely appropriate to a blunted muscle metabolic response and differences in contracting muscle mass.

## *Intramuscular Metabolic Responses to Voluntary Isometric Exercise in Multiple Sclerosis are Consistent with Central Neuronal Fatigue*

*To the Editor:* In their excellent and comprehensive recent article exploring the origins of fatigue in multiple sclerosis, Dr. Ng and colleagues (1) concluded that multiple sclerosis (MS) subjects exhibit a reduced mean arterial pressure (MAP) response to exercise, consistent with decreased contracting muscle mass and inconsistent with dysautonomia. They hypothesized that “the smaller metabolic response during submaximal exercise in MS was probably due to failure within the muscle itself, at a location upstream of the energy supply.”

On further analysis of their results, I raise the alternate hypothesis that the smaller metabolic response to submaximal exercise in MS is primarily due to “central neuronal fatigue” and not to failure within the muscle itself.

The authors tested the tibialis anterior muscles of subjects at baseline and during and after 30% maximal voluntary contractions (MVC) to fatigue. The MS group had lower endurance (257 s) than the control group (305 s). The electromyographic (EMG) signal during exercise decreased to 58% baseline in the MS group and 69% baseline in the control group. Postexercise

strength (MVC) decreased to 72% baseline in the MS group and 56% baseline in the control group. Also, MAP during exercise increased by 32 mmHg in the MS group and by 59 mmHg in the control group while the  $P_i$ -to-phosphocreatine ratio increased to 1.05 in the MS group and 3.40 in the control group.

If we calculate end-exercise residual EMG (%maximum) vs. residual strength (%preexercise MVC) ratios (rEMG/rMVC), we obtain ratios of 0.8 for the MS group and 1.2 for the control group. Thus, for the MS group, EMG deteriorates quite a bit at the end of contraction, in contrast to muscle fiber capabilities, which remain relatively well preserved, as evidenced by a relatively high postexercise MVC. For the control group, EMG remains relatively well preserved at the end of contraction, in contrast to muscle fiber capabilities, which are quite “spent,” as evidenced by a relatively low postexercise MVC.

The fact that EMG deteriorated significantly more than did muscle fiber capability in the MS group points to a “neurogenic” cause of fatigue. The authors considered this in their analysis and obtained “central activation ratios”, ratios of MVC to maximum electrically evoked contraction. Both the MS and control groups had ratios of 1.0, arguing against central activation failure.

However, “central activation failure” is not the same as central neuronal fatigue. Central neuronal fatigue is a time-dependent variable and could in theory have recovered by the time postexercise MVCs and central activation ratios were obtained.

Let us say that energy-intensive sustained transmission of neuronal impulses along impaired demyelinated central pathways eventually leads to stepwise conduction failure of involved axons. The dropout of corticomotoneuronal impulses translates to a decrease in EMG signal and strength before individual muscle cells have had a chance to deplete themselves of energy substrate. This would explain why the  $P_i$ -to-phosphocreatine ratio and MAP did not increase much in the MS group. At the end of exercise, impairment of central transmission of neuronal impulses recovers quickly, say in 15–30 s. Thus, when the MS subject is asked ~1.5 min later (Ng, personal communication) to perform a postexercise MVC, a good performance (72% of preexercise MVC) ensues. Because central motoneurons have recovered, complete central activation occurs and a normal central activation ratio is obtained.

In contrast, for normal subjects, there is relatively little or no central neuronal fatigue and the EMG signal remains relatively well preserved until the end of exercise; however, as it starts to fall, we see a decline in EMG spectral frequency, not seen in MS patients, indicating that muscle cells are becoming depleted of energy substrate. Thus, in normal subjects, the fall in EMG signal

appears to stem from conduction failure of energy-depleted individual muscle cells (muscle cell fatigue) and not from central conduction failure or neuronal fatigue. In reality, because MS patients range along a spectrum from near normal to significantly involved, the fall in EMG signal and decreased endurance seen in these subjects could stem from various combinations of central neuronal fatigue and muscle cell fatigue.

In conclusion, the comprehensive study of Dr. Ng and colleagues reveals new insights into the mechanisms of fatigue in normal and MS subjects and is consistent with a central neuronal fatigue hypothesis for MS. Sustained energy-intensive neuronal transmission along impaired demyelinated central pathways could result in temporary conduction failures and subjective sensations and objective manifestations of fatigue. This hypothesis is consistent with the results of Dr. Ng and colleagues, which show decreased utilization of energy substrate in MS subjects with appropriately reduced MAP responses to exercise.

#### REFERENCES

1. **Ng AV, Dao HT, Miller RG, Gelinias DF, and Kent-Braun JA.** Blunted pressor and intramuscular metabolic responses to voluntary isometric exercise in multiple sclerosis. *J Appl Physiol* 88: 871–880, 2000.

Marko Bodor  
980 Trancas St., Suite 5  
Napa, California 94558  
E-mail: mbodor@post.harvard.edu

#### REPLY

*To the Editor:* We thank Dr. Bodor for his comments regarding our recent observations (2) of a blunted pressor and muscle metabolic response to exercise in persons with multiple sclerosis (MS). Dr. Bodor proposes “that the smaller metabolic response to submaximal exercise in MS is primarily due to central neuronal fatigue and not to failure within the muscle itself.” Dr. Bodor likens central neuronal fatigue to central nerve conduction block. This is an interesting suggestion, which is consistent with the central nervous system deficits that could result from MS. Dr. Bodor bases this suggestion mainly on indirect evidence provided by the change in the surface-rectified integrated electromyogram (EMG) during exercise. In this study, we did not measure central nerve conduction velocity and did not attempt to determine whether central conduction block occurred, as might be expected with MS. However, as reported originally (2), there was no difference between MS and control in the residual EMG level reached at end exercise ( $P = 0.32$ ). These results are not consistent with central conduction block in the MS compared with the control group. If central conduction block occurred to a significant degree in the MS group, then one might expect the EMG level reached at end exercise in the MS group to be less than that of the control group.

Dr. Bodor has calculated ratios of end-exercise residual EMG to postexercise residual MVC from the group means and bases much of his argument on the different ratios obtained between MS and control. Such an EMG-to-force ratio can give insight into central (3) and periph-

eral (1) mechanisms of muscle fatigue. As was described in our paper, postexercise MVC measurements did not occur until the end of postexercise blood flow occlusion, which lasted 1.5 min (2). In contrast, the relative end-exercise EMG levels were obtained before the thigh-cuff inflation, at the end of exercise (sustained 30% MVC). Thus the end-exercise EMG measurement did not correspond to the postexercise MVC measurement. We performed additional analyses on the individual EMG-to-force ratios of the MS and control groups at the beginning of exercise (30% MVC) and at end exercise (failure to maintain 30% MVC) just before thigh-cuff inflation. At the initiation of exercise, the MS group had a tendency toward a greater EMG-to-force ratio [MS =  $1.53 \pm 0.74$ , (SD), control =  $1.03 \pm 0.23$ ;  $P = 0.06$ ]. This greater EMG-to-force ratio is consistent with our previous observations (3) and is indicative of a greater central neural drive in the MS group necessary to generate the same relative force as the control group. By end exercise, the EMG-to-force ratio had increased threefold in both groups, probably due to reduced contractile efficiency of the fatigued muscle. At end exercise, these ratios were similar in the MS and control groups [MS =  $4.7 \pm 3.6$  (SD), control =  $3.2 \pm 1.9$ ;  $P = 0.26$ ], another point against the hypothesis that conduction block underlies this type of fatigue in MS.

We would like to emphasize that our study was designed to investigate the previously reported blunted exercise pressor response to exercise in MS (4); therefore, we accepted some design limitations related to our ability to examine the mechanisms of muscle fatigue in this study. As a result, care should be taken not to overinterpret our results, particularly where there were no significant differences between groups in endurance time ( $P = 0.56$ ) or residual EMG ( $P = 0.32$ ). Although the data from this study do not support Dr. Bodor’s suggestion, the idea of central neuronal fatigue in MS is a potentially important one that could be more fully investigated using cortical stimulation techniques and a protocol specifically designed to examine central fatigue in MS.

#### REFERENCES

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2. **Ng AV, Dao HT, Miller RG, Gelinias DF, and Kent-Braun JA.** Blunted pressor and intramuscular metabolic responses to voluntary isometric exercise in multiple sclerosis. *J Appl Physiol* 88: 871–880, 2000.
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Alexander V. Ng  
Robert G. Miller  
Jane A. Kent-Braun  
Magnetic Resonance Unit  
Veterans Affairs Medical Center  
University of California  
San Francisco, California 94121  
E-mail: alexander.ng@marquette.edu