Blunted pressor and intramuscular metabolic responses to voluntary isometric exercise in multiple sclerosis

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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 Pi (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 Pi 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.

dysautonomia; muscle activation; muscle strength; fatigue; cardiovascular autonomic regulation

MULTIPLE SCLEROSIS (MS) is a demyelinating disease of the central nervous system that can result in white matter lesions or plaques. Damage to the myelin sheath can lead to slowed or blocked motor nerve conduction, which may result in ataxia, spasticity, muscle weakness, and fatigue. MS can be of a relapsing-remitting or primary progressive nature and is highly variable among individuals. The autonomic nervous system can also be affected, and clinically significant disturbances in bowel, bladder, and sexual function are well documented (30). Although abnormalities in one or more cardiovascular reflexes (2, 8, 10, 12, 37, 40, 45, 50, 51), including a blunted exercise blood pressure (BP) response (10, 37, 40, 50, 51), have been reported in persons with MS, the significance of these findings are not clear (2, 12, 37, 51). A recent study by Pepin et al. (40) demonstrated a dampened arterial blood pressure, or pressor, response to sustained isometric handgrip exercise to exhaustion in MS compared with control subjects. Endurance time was also decreased in the MS group. Interestingly, the heart rate (HR) response to exercise was similar in the MS and control groups. These investigators (40) and others (10) have suggested that an impaired autonomically mediated pressor response may contribute to exercise intolerance and fatigue in MS.

Regulation of the exercise pressor response is both centrally and peripherally mediated (33). The central component, known as central command, is thought to be an activation of the cardiovascular centers in the brain stem, in parallel with motor unit activation, and primarily affects the increase in HR during isometric exercise (16, 28, 29, 53). The primary peripheral component is a chemo- or metaboreflex originating in the active muscle (1, 29, 31, 53). The stimuli for this reflex are the muscle metabolites produced during exercise (e.g., proton, P_i), which activate afferent type III and IV nerve fibers (7, 18, 48, 52). These afferents, in turn, feed back to the central cardiovascular centers, which results primarily in an efferent, sympathetically mediated vasoconstrictor response (29, 53). Thus a blunted pressor response could result not only from an impaired efferent autonomic response but also from a blunted afferent stimulus.

We have previously observed a reduced muscle metabolic response to voluntary exercise in persons with MS, possibly due to intramuscular activation failure (22). Specifically, the changes in intramuscular pH and the ratio of P_i to phosphocreatine (PCr) (P_i/PCr) were less in MS compared with control subjects during graded intermittent isometric exercise (22). These findings raised the possibility that the attenuated exercise pressor response previously observed in persons with MS need not be the result of a cardiovascular autonomic impairment. In fact, a smaller than expected pressor response in persons with MS may represent an appropriate pressor response to a blunted muscle metabolic production during exercise. The distinction between whether a blunted pressor response in persons with MS is the result of a cardiovascular autonomic impairment or the result of altered muscle function may have important clinical implications.

The purpose of this study was to determine whether a blunted exercise pressor response in MS was primar-
illy the result of an autonomic impairment or whether it was associated with and appropriate to a blunted muscle metabolic response. We tested the following hypothesis: during isometric exercise, persons with MS compared with control subjects will show a blunted BP response, a normal HR response, and a blunted muscle metabolic response. Testing consisted of sustained voluntary isometric ankle dorsiflexion, during which beat-to-beat arterial BP and HR were measured simultaneously, along with intramuscular Pi and pH.

To determine whether any observed differences in autonomic function were generalized or exercise specific, we also examined the BP and HR responses to a Valsalva maneuver and a cold pressor test, two nonexercise pressor stimuli. To determine whether a blunted muscle metabolic response was the result of impaired muscle activation, we assessed voluntary muscle activation by using electromyography (EMG) and electrical stimulation techniques (21, 22, 36). Finally, we examined the relationship between symptomatic fatigue and cardiovascular autonomic function, because such a relationship has been implicated in other chronic diseases in which symptomatic fatigue is a major complaint (6, 15).

METHODS

Subjects. The MS group consisted of five women and four men with definite MS (41), who were recruited from the surrounding community (Table 1). These persons were selected to be nonsmokers and had no other major disease (e.g., cardiovascular, metabolic). Health status was based on a standardized health questionnaire and complete clinical neurological examination by a neurologist. One woman was taking thyroid medication, and one woman was taking Elavil, an antidepressant. No other medications were used at the time of this study. All MS subjects were ambulatory, either without assistance or with a cane. Clinical measures included the expanded disability status scale (EDSS) and Ashworth spasticity score (3). Briefly, the EDSS is a clinical scale of disability from 1 to 10, where increasing numbers represent increasing disability (27). The Ashworth scale is a measure of spasticity from 1 to 5, where increasing numbers represent increasing spasticity. To further characterize the volunteers, foot tap speed (number in 10 s), manually assessed muscle strength (32), and Fatigue Severity Scale (26) score for all MS and control subjects were obtained. A slowing of the rate of foot taps is an indicator of upper motoneuron dysfunction (23). Manually assessed muscle strength is a subjective score from 0 to 5, where 5 is normal strength and 0 is no detectable strength (32). The Fatigue Severity Scale measures subjective symptomatic fatigue on a scale of 1–7, where an increasing score represents increased subjective fatigue (26).

The control group was composed of six men and five women, who were also recruited from the surrounding community. This group was similarly selected to be healthy, nonsmoking, nonathletic (no more than 1 exercise session/wk for the last 3 mo), and free from major chronic disease. Before their participation, all volunteers provided signed informed consent, as approved by the Committees on Human Research of the University of California at San Francisco and the California Pacific Medical Center.

Cardiovascular measurements. An automated beat-by-beat Finapres (Ohmeda, Louisville, CO) BP monitor was used to measure HR and BP (17). Finapres measurements were obtained from the right middle finger with the arm and hand outstretched and supported at heart level. For comparison, arterial BPs during an initial rest period of 5 min in a quiet room were also obtained by manual sphygmomanometry. Finapres data were recorded continuously on a polygraph recorder (model 79D, Grass, Quincy, MA) and analyzed manually. Analyses were based on mean arterial pressures (MAP). During exercise, chest wall excursions were indicated by a mercury-in-Silastic strain gauge taped to the chest wall and recorded by using a chart recorder. Blood flow occlusion was achieved automatically by rapid inflation of a large blood pressure cuff, placed just above the knee, to 25 mmHg above systolic pressure.

Valsalva maneuver. A resting baseline Finapres measurement of MAP and HR was obtained for 5 min before testing. The Valsalva maneuver consisted of blowing through a small mouthpiece, to a pressure of 40 mmHg, for 15 s. Before and during the test, a small leak was maintained in the system with a hypodermic needle to ensure an open glottis. The pressor response to the Valsalva maneuver is baroreflex mediated. The peak rise in MAP during phase IV of the Valsalva maneuver was obtained as an indication of vasomotor sympathetic function (43). The ratio of the maximal HR generated during phase II divided by the minimal HR occurring during phase IV was determined as an indication of cardiac parasympathetic function (43).

Muscle force and activation measurements. After the Valsalva maneuver, the subject was instrumented for the force, activation, and metabolism measurements. These methods have been described in detail previously (19, 22, 36). Exercise testing occurred with the subject seated and one leg extended. The leg was stabilized with a knee brace, and the foot angle was 120° plantar flexion. Dorsiflexor isometric force was measured with a force transducer mounted under a footplate. The transducer signal was amplified and coupled to personal computer. Visual feedback of force during voluntary contractions was provided by a lighted display board placed in front of the subject. Force and EMG data were collected by using Labview software (National Instruments, Austin, TX) and subsequently transferred to a spreadsheet for analysis.

As a measure of muscle activation, the surface EMG was obtained every 15 s during exercise (500 Hz, 1.5-s windows). The EMG was measured by using circular electrodes (10-mm diameter) placed on the tibialis anterior muscle. The active electrode was placed on the belly of the tibialis, the reference
electrode was placed on the medial malleolus, and a copper ground plate was placed on the calf. The EMG filter settings were 0.1 Hz and 0.3 kHz. The EMG signal was subsequently rectified, integrated, and expressed relative to the maximal level obtained during the preexercise maximal voluntary contraction (MVC). The EMG was also Fourier transformed by using MATLAB software (MathWorks, Natick, MA), and the median spectral frequency was recorded and expressed relative to that obtained during the first 3 s of exercise.

Dorsiflexor muscle MVC was the peak of three trials, each separated by 2 min of rest. Subjects were instructed during each trial to perform a maximal dorsiflexion as hard and fast as possible and were verbally encouraged during each trial.

To assess the completeness of voluntary activation during the MVC, a 0.5-s train of 50-Hz supramaximal stimulation of the peroneal nerve, at the fibular head, was superimposed during the third MVC. The central activation ratio was determined as the ratio of the force produced voluntarily (i.e., MVC) to the total force produced (19), where total force was the sum of voluntary force plus any "added force" from the superimposed stimulation [ratio = MVC/(MVC + superimposed force)]. Thus, if activation was complete and there was no superimposed evoked force, then the central activation ratio = 1.0.

Muscle metabolic measurements. We obtained magnetic resonance spectroscopy measurements of intramuscular pH and Pi, continuously and noninvasively in a subset of 10 control and 6 MS subjects before and during exercise. These methods have been described previously (20, 22). A 2.0-T, 30-cm-bore Oxford Systems superconducting magnet and GE-CSI unit with a Nicolet 1280 computer (Fremont, CA) were used for the collection and processing of the metabolic data. A single-tuned 3 × 5-cm oblong magnetic resonance surface coil was situated over the belly of the tibialis anterior, proximal to the EMG electrode. The leg was placed horizontally into the bore of the magnet, and the magnet was then shimmed to obtain a water peak width at half height of <40 Hz.

A baseline phosphorus spectrum was obtained at rest (4-min average), and spectra consisting of 30-s averages were obtained during exercise and occlusion. The block size was 4,000 for the rest spectra and 2,000 for the exercise and occlusion spectra. For all spectra, the repetition rate was 750 ms, pulse length was 12 μs (nominal angle of 50°), and sweep width was 4,000 Hz.

After acquisition, the magnetic resonance data were transferred to a SUN workstation and analyzed by using NMR1 software (New Methods Research, East Syracuse, NY). The peaks corresponding to phosphomonoesters, phosphodiesters, PCr, P1, and adenosine triphosphate were fit for all spectra. All peaks were fit to avoid inaccurate estimation of peak areas in regions of overlapping peaks (e.g., phosphomonoesters and P1). Because P1 and pH are considered to be important stimulators of the exercise chemoreflex (17, 48, 52), the data concerning these metabolites are presented. Calculations of pH were based on the chemical shift of P1 from PCr, and P1 was expressed in millimoles per liter. To further characterize muscle energetics we also report P1/PCr at rest and the end of exercise (9).

Isometric endurance test. After the left leg and probe was fitted into the bore of the magnet, and before shimming, MVC and central activation ratio measurements were obtained. All subjects then practiced attaining and maintaining the target force level of 30% MVC for ~5 s. Subjects were familiarized with the inflation cuff with one brief suprasystolic inflation of 10 s.

After these baseline force measurements were obtained, the Finapres cuff was attached to the right middle finger with the arm and hand outstretched at heart level and resting on a padded surface. The Finapres servo unit and hand were fixed to a board in such a way that the distance from the magnet to the servo unit was maximized. The magnet was then shimmed, and resting phosphorus data were acquired with the subject sitting quietly (~15 min).

For the endurance test, subjects were instructed to maintain ankle dorsiflexion at a constant 30% MVC until force dropped to below 90% target force (i.e., 27% MVC) for 2 s. This end point was determined by the same investigator for all studies. Subjects received visual feedback from the force monitor, as well as verbal encouragement. BP, HR, and metabolic measurements were obtained continuously during the endurance test. Because Valsalva or other breath-holding maneuvers can affect cardiovascular measurements independently of exercise (55), chest wall excursions were monitored continuously. To determine whether there were differences in effort sense between control and MS groups, ratings of perceived exertion using the Borg 10-point scale (5) were obtained at 20-s intervals.

To further examine the central and peripheral mechanisms of BP regulation, we occluded blood flow at the end of exercise. When the subjects were no longer able to maintain the required force, the thigh cuff was inflated, and the subjects were then told to relax the contraction. The cuff remained inflated for 1.5 min. During this time, BP, HR, and muscle metabolites were measured continuously. A measure of chemoreflex sensitivity was obtained as the ratio of the change in MAP to both P1 and pH during occlusion. To determine whether discomfort or pain could have affected cardiovascular measurements during occlusion, we obtained ratings of perceived pain (24) every 30 s during occlusion. The perceived pain scale (24) was based on a modified Borg rating of perceived exertion scale. Immediately after the cuff was deflated, subjects were instructed to perform a postexercise MVC. For the fatigue analysis, MVC was expressed relative to preexercise values.

Cold pressor test. After recovery from the endurance test (~15 min) and with the leg still in the magnet, new baseline BP and HR measurements were obtained. The cold pressor test was then performed. This test consisted of immersing the left hand, up to the wrist, in an insulated bucket of ice water (1–3°C) for 2.5 min (24). The pressor response to cold is determined in large part by cutaneous sensation (24). To determine whether there was any difference in cold or pain perception in control and MS subjects during this test, we measured perceived pain (24) every 30 s during the test.

Statistical analyses. For the isometric endurance test, occlusion, cardiovascular, ratings of perceived exertion, and metabolic variables were analyzed with repeated-measures ANOVA. Because of individual variations in endurance time during the isometric exercise, these variables were normalized to 100% endurance time. Regression models were also used to examine relationships between selected variables, and unpaired t-tests were used to test for the equality of slopes between groups. The relationship of the pressor response to strength was also determined by analysis of covariance (ANCOVA) because active muscle mass, which is reflected by strength, may affect the magnitude of the pressor response to isometric exercise (34, 44). Because of the “ceiling” of the central activation ratio at 1.0, nonparametric Mann-Whitney and Wilcoxon signed-rank test comparisons were used to compare the central activation ratio data between groups, and median (range) data are reported. For
all remaining data, pairwise comparisons between groups were performed with unpaired t-tests. Except for central activation ratio and clinical measures, data are presented as means ± SE.

RESULTS

Subjects. Subject characteristics are summarized in Table 1. There were no differences between control and MS subjects in age, height, or weight. The MS group was weaker than the control group, whether measured manually or by force transducer (MVC). The median EDSS for the MS group was 2 (range 1.5–4.5). The median Ashworth spasticity score was 1 (range 1–2). The median fatigue score in MS subjects was 3.9 (range 2.3–7.0); therefore, about one-half of the MS subjects could be characterized as having “severe” fatigue. Greater symptomatic fatigue (Fatigue Severity Scale) could be characterized as having “severe” fatigue. Endurance and fatigue. Endurance times at 30% MVC were similar between control and MS groups (control: 305 ± 54, MS: 257 ± 57 s; P = 0.55). After exercise, MVC had decreased significantly from baseline in both groups (P = 0.02), and there was no statistical difference between groups in the degree of muscle fatigue (control: 56 ± 6, MS: 72 ± 9% preexercise MVC; P = 0.15). We were not able to obtain a postexercise MVC from one control subject.

Relative integrated EMG levels at the end of exercise, just before thigh-cuff inflation, were not different between groups (control: 69 ± 9, MS: 58 ± 6% maximum; P = 0.32). There was no difference in median spectral frequency at the initiation of exercise between groups (control: 34 ± 2, MS 40 ± 9 Hz; P = 0.46). However, at end exercise, the median spectral frequency of the EMG had decreased to a significantly lower level in control compared with MS subjects (control: 59 ± 3, MS: 79 ± 7% initial; P < 0.01).

The median preexercise central activation ratio was 1.0 for both the control (range 0.96–1.0) and MS groups (range 0.88–1.0). The median postexercise central activation ratio was 1.0 for the control (range 0.56–1.0) and 0.93 for the MS subjects (range 0.78–1.0). There was no difference in central activation between groups either pre- or postexercise or within groups pre- vs. postexercise. These data suggest that there was no difference in the completeness of voluntary activation between groups before or during the exercise.

Cardiovascular responses to exercise. Starting from similar baseline rest values, MAP increased linearly with exercise time in both groups (Fig 1A; time main effect, P < 0.001). However, despite similar endurance times, the MAP change from baseline was less in MS compared with control subjects (main effect P < 0.01, interaction P < 0.01) at all relative exercise intensities except 30 and 70% (P = 0.06). The difference between groups increased with increasing endurance time (end exercise, control = 59 ± 7; MS = 32.0 ± 4 mmHg).

There was no indication of breath-holding-type maneuvers in either group.

To determine whether differences in the MAP responses were influenced by differences in strength, an ANCOVA was performed for the MAP at end exercise, with MVC as the covariate. The ANCOVA indicated that ~33% of the difference in MAP between groups at the end of exercise could be accounted for by differences in strength. However, the change in MAP from baseline to 100% endurance time still tended to be different between groups after accounting for strength (adjusted means, control: 55 ± 6, MS: 37 ± 6 mmHg; P = 0.07). The 95% confidence interval for the difference in means of the MAP response at 100% endurance time was −0.2 to 35.1 mmHg. Thus 0 (i.e., no difference) was included in this interval. These results suggest that a blunted pressor response may still be likely even after accounting for differences in strength.

HR also increased linearly from similar rest values in both groups (P < 0.01, Fig 1B). However, unlike the MAP response, there were no significant differences between control and MS groups in the magnitude of the HR response.

Ratings of perceived exertion increased in a linear fashion in both groups during exercise, and there were no differences between groups at any relative endurance time (Fig 1C).
The MAP and HR responses to the isometric exercise of the subset of subjects studied with magnetic resonance spectroscopy (10 control, 6 MS) were similar to those of the entire group. That is, the pressor response was blunted in the MS group (main effect, $P = 0.01$), and there was no difference in the HR response (main effect, $P = 0.25$; data not shown).

During occlusion, MAP decreased significantly ($P < 0.001$) from end-exercise levels to a stable level in both control and MS groups (Fig. 2A). Compared with control, MAP was less in MS subjects at the beginning and throughout the occlusion period (main effect, $P = 0.003$). This difference matched the difference in MAP during exercise. The interaction term was not significant ($P = 0.88$). Thus, although starting from different end-exercise levels, the MAP response was similar in both groups during occlusion.

The HR response also decreased during occlusion to stable levels in both groups (Fig. 2B). There was no difference in HR response between control and MS subjects at end exercise or during occlusion (main effect, $P = 0.24$). Lack of a significant interaction ($P = 0.79$) again suggests a similar HR response to occlusion in control and MS subjects. Subjects found the occlusion uncomfortable, but there was no difference in ratings of perceived pain between control (5 ± 1 units, “painful”) and MS (4 ± 1 units, “moderately painful”) subjects ($P = 0.38$).

Metabolic responses to exercise. Because of the individual variation in endurance times, common metabolite measures for all subjects were obtained at 33, 66, and 100% of endurance time (Fig. 3). Before exercise, $P_i$ and pH were similar in control and MS groups. The $P_i/PCr$ was also similar in control and MS groups (control: $0.11 ± 0.01$, MS: $0.13 ± 0.02$; $P = 0.29$). During exercise, the increase in $P_i$ was less in MS compared with control subjects at all relative endurance times (main effect, $P < 0.01$; interaction, $P < 0.01$, Fig. 3). Similarly, the decrease in pH was less in the MS groups compared with control subjects at all relative endurance times (main effect, $P < 0.01$; interaction, $P < 0.01$, Fig. 3). At the end of exercise, $P_i/PCr$ tended to be higher in control compared with MS subjects (control: $3.40 ± 0.70$, MS: $1.05 ± 0.91$, $P = 0.06$). Together, the smaller changes in $P_i$, pH, and $P_i/PCr$ during exercise were less in MS compared with control subjects, indicating a dampened muscle metabolic response in MS. Values are mean ± SE. *$P < 0.05$, MS vs. control subjects.
Table 2. Individual and group slopes and Pearson correlations for MAP and metabolite relationships during isometric exercise in MS and control subjects

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>MAP vs. P&lt;sub&gt;i&lt;/sub&gt;</th>
<th>MAP vs. pH</th>
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<tr>
<td></td>
<td>Slope</td>
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<td>MS</td>
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<tr>
<td>1</td>
<td>0.3</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
<td>0.7</td>
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<tr>
<td>4</td>
<td>1.4</td>
<td>0.86</td>
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<tr>
<td>5</td>
<td>1.5</td>
<td>0.59</td>
</tr>
<tr>
<td>6</td>
<td>0.0</td>
<td>0.02</td>
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<tr>
<td>Mean ± SE</td>
<td>0.9 ± 0.3*</td>
<td>0.57 ± 0.12*</td>
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Control

|             | Slope    | r        | Slope    | r        |
|-------------|----------------------|-----------|
| 1           | 1.4      | 0.92     | -97.3    | -0.94    |
| 2           | 2.4      | 0.87     | -170.2   | -0.83    |
| 3           | 1.4      | 0.99     | -84.1    | -0.72    |
| 4           | 2.9      | 0.98     | -97.4    | -0.70    |
| 5           | 0.8      | 0.60     | -54.1    | -0.65    |
| 6           | 2.4      | 0.78     | -66.9    | -0.37    |
| 7           | 1.3      | 0.93     | -70.4    | -0.84    |
| 8           | 1.4      | 0.90     | -45.8    | -0.59    |
| 9           | 1.3      | 0.88     | -52.0    | -0.75    |
| 10          | 1.4      | 0.85     | -185.0   | -0.99    |
| Mean ± SE   | 1.7 ± 0.2 | 0.87 ± 0.04 | -92.4 ± 15.7 | -0.74 ± 0.06 |

r, Pearson correlation coefficient. For both MAP vs. P<sub>i</sub>, and MAP vs. pH, slopes were steeper in MS compared with control subjects, as were strengths of relationships. *P < 0.05, MS compared with control subjects.

different between control and MS only at the end of exercise.

Relationships between BP and metabolites. Individual slopes and correlations for the MAP and metabolite regressions are presented in Table 2 and illustrated in Fig. 4. The slopes were steeper in control compared with MS both for MAP vs. P<sub>i</sub> and for MAP vs. pH. Furthermore, as indicated by the correlation coefficients, the strengths of the MAP and metabolite relationships were stronger in control than MS.

As an overall indication of “chemoreflex sensitivity,” we calculated the ratio of the change in MAP from baseline vs. both P<sub>i</sub> and pH during occlusion. The MAP/P<sub>i</sub> was different between groups (control: 20.1 ± 1.2, MS: 15.1 ± 1.1 units; P = 0.02), but the MAP/P<sub>H</sub> was not (control: 7.6 ± 1.5, MS: 5.0 ± 1.0 units; P = 0.20).

Nonexercise pressor responses. Before the Valsalva maneuver, there was no difference between groups in rest MAP (control: 93 ± 3, MS: 97 ± 5 mmHg; P = 0.53). The peak increase in MAP from rest during phase IV of the Valsalva maneuver was similar in control (24 ± 3.8 mmHg) and MS (28 ± 6.6 mmHg; P = 0.59) groups. Similarly, there was no difference in resting HR (control: 73 ± 2, MS: 73 ± 4 beats/min; P = 1.00) or in the ratio of maximal HR during phase II to minimal HR during phase IV of the Valsalva maneuver (control: 1.56 ± 0.07, MS: 1.68 ± 0.12; P = 0.38). These data suggest a normal sympathetic and parasympathetic cardiovascular autonomic response in the MS group to the Valsalva maneuver, a nonexercise pressor stimulus.

Cold pressor test. These results are based on 11 control and 8 MS subjects because of excessive discomfort in 1 MS volunteer. MAP was the same in both groups during rest (control: 96 ± 3, MS: 96 ± 3 mmHg; P = 1.00). The peak increase in MAP from rest was also similar for each group (control: 27 ± 4, MS: 25 ± 4 mmHg; P = 0.74). There was no difference between groups in resting HR (control: 72 ± 3, MS: 70 ± 4 beats/min; P = 0.69) or in the peak change in HR from rest levels (control: 12 ± 3, MS: 12 ± 4 beats/min; P = 1.00). During the cold pressor test, maximal perceived pain was the same in both groups (control: 27 ± 3, MS: 26 ± 2, P = 0.12), indicating that the cold pressor test was perceived in a similar fashion by each group. These results provide further support that the autonomic cardiovascular responses to the cold pressor test, another nonexercise pressor stimulus, were intact in this MS group.

Symptomatic fatigue and autonomic function in MS. Because the slopes of MAP and metabolites were different between MS and control subjects, we sought to explore the relationship between symptomatic fatigue and altered BP regulation in the MS group. We considered the individual correlation coefficients (n = 6) of MAP and P<sub>i</sub>, and of MAP and pH, to be indexes of the degree to which the chemoreflex was intact in this group, where poor correlations between MAP and metabolite indicated a poor chemoreflex. On the basis of their fatigue scores, the MS subjects fell into two groups: those with high levels of symptomatic fatigue and those with low (normal) levels (high = 6.5 ± 0.4, low = 3.1 ± 0.4 units; P < 0.01). The average MAP and pH correlation coefficients were also different between these two groups (high = -0.31 ± 0.06, low = -0.61 ± 0.04; P = 0.01). There was no difference between groups in the MAP and P<sub>i</sub> correlation coefficients (high = 0.41 ± 0.1, low = 73 ± 0.1; P = 0.21). Thus those MS subjects...
who showed the weakest relationship between MAP and pH also reported the greatest symptomatic fatigue.

**DISCUSSION**

By simultaneously measuring the cardiovascular and muscle metabolic responses to sustained submaximal isometric exercise, we have shown that both the exercise pressor response and the muscle metabolic response are blunted in MS compared with control subjects. These results support the hypothesis that the blunted exercise pressor response in MS may be appropriate to a decreased muscle metabolism and not necessarily arise from a generalized cardiovascular dysautonomia in MS.

Cardiovascular regulation. Previous studies have demonstrated that the exercise pressor response, as well as other cardiovascular autonomic reflex responses, can be diminished in MS (10, 37, 40, 50, 51). In these studies, the blunted exercise pressor response was taken as evidence of a cardiovascular autonomic impairment. However, most prior exercise studies did not account for differences in strength, endurance time, or exercise intensity between MS and control groups. In one exception, Pepin et al. (40) recently showed that the blunted pressor response was coincident with a decreased exercise endurance time during isometric hand-grip contractions sustained to the endurance limit at 30% MVC. On the basis of these and other results (10), it was suggested that an autonomic impairment may limit exercise capacity in persons with MS (10, 40).

Our observation of a blunted exercise pressor response in a group of mild to moderately impaired persons with MS is consistent with earlier studies (10, 37, 40, 50, 51) and suggests that this response is a characteristic finding in MS. However, unlike in the study of Pepin et al. (40), endurance times were similar in our MS and control groups, which implies that the blunted pressor response did not limit isometric endurance in the MS group studied. Our observation of normal MAP and HR responses to the Valsalva maneuver and the cold pressor test suggest that any autonomic impairment was not of a general nature but was specific to exercise.

Our observation of a normal HR response to isometric exercise in MS is also consistent with the findings of Pepin et al. (40). Whereas the exercise pressor response is, in large part, a function of the peripheral chemoreflex (29, 53), the HR response to voluntary isometric exercise is, primarily, a function of central command (1, 29, 53). Thus the finding of similar HR responses between groups suggests that the central command pathways were intact in the MS group we studied. A similar HR response in MS and control subjects further argues against a generalized central autonomic impairment in the MS group and implicates the chemoreflex pathway in the blunted exercise pressor response we observed. Caution must be applied to this interpretation of central command because there is some evidence that HR may also be under chemoreflex control (38). Thus we cannot completely exclude the possibility that HR during voluntary exercise was partially under chemoreflex control.

During postexercise occlusion of blood flow, the central command component of the pressor response is removed, resulting in a rapid recovery of HR and a partial recovery of MAP (Fig. 2). Occlusion prevents washout of metabolites and therefore maintains the chemoreflex component of the pressor response, resulting in a sympathetically mediated elevation of MAP (1, 29, 52). Thus the use of postexercise blood flow occlusion can help dissociate central command from the peripheral chemoreflex, which allows the chemoreflex to be studied in isolation. Occlusion was confirmed in the present study by the unchanged Pi and pH during cuff inflation. Although the behavior of MAP and HR was similar between groups during occlusion, we had expected HR to return more closely to baseline levels in both groups (29). The slightly elevated HRs in both groups during occlusion may have been explained by the discomfort of the procedure, because perceived pain was 4–5 for both MS and control.

Influence of muscle mass or strength. Active muscle mass can influence the magnitude of the pressor response (34, 44) during isometric exercise. The mechanisms for an increased pressor response with a larger muscle mass have been hypothesized to be the result of an increased number of chemosensitive neural afferents activated or the recruitment of more or larger motor units via central command (44). Relative force is not thought to be related to the magnitude of the exercise pressor response (35). However, because maximal force or strength is proportional to muscle mass (i.e., cross-sectional area), it is not surprising that differences in strength accounted for about one-third of the difference in the MAP response to exercise between groups, as indicated by the ANCOVA. That is, the greater active muscle mass, implied by the greater absolute force produced at 30% MVC by controls, resulted in a greater MAP response.

Overall, these cardiovascular data suggest that the mechanism for the blunted pressor response was not an impaired autonomic reflex but was rather a smaller afferent signal from the muscle. This possibility is consistent with our finding of a blunted muscle metabolic response during exercise in the MS subjects.

Muscle metabolism. Our observation of a diminished muscle metabolic response to voluntary isometric exercise confirms our previous observation made during intermittent graded isometric exercise in a different group of MS volunteers (22). This blunted metabolic response suggests that factors limiting endurance are different in MS compared with control subjects and that muscle metabolism did not limit endurance in MS. It is very unlikely that the difference in the metabolic response was because of a higher metabolic capacity in the MS group, because oxidative capacity is markedly reduced in the dorsiflexor muscles in MS (20, 21). It could be hypothesized that central muscle activation was impaired in MS, leading to incomplete muscle activation and therefore a reduced metabolic demand in the muscle. However, our activation measures argue
against this possibility. Central activation, measured by the central activation ratio, was not different between MS and control subjects before or at the end of exercise. Similarly, the integrated EMG increased to similar levels at end exercise in both groups, suggesting that neural drive (4) was similar between groups. The EMG median spectral frequency decreased by end exercise in the control compared with MS subjects. However, changes in EMG spectral frequency are thought to reflect, in large part, the accumulation of metabolic by-products (e.g., $H^+$), which may result in a slowing of sarcolemmal action potential conduction velocity and a decrease in EMG median spectral frequency (11). Thus, the difference in median spectral frequency is likely a reflection of the differences in Pi concentration and pH during exercise in the two groups. Overall, these activation data suggest 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.

The observation of a diminished muscle metabolic response lessens the possibility of a primary, exercise-specific autonomic efferent abnormality. Such an abnormality, which might limit muscle perfusion pressure, would be expected to result in an increased muscle metabolic response during exercise, because a limitation in oxygen delivery results in a greater reliance on anaerobic energy sources. Thus, as observed previously in a different group of subjects (22), the diminished muscle metabolic response to voluntary exercise in the MS group is puzzling.

An alternative explanation for the smaller metabolic response in MS might be that, because of the weakness and lower absolute force produced in the MS group, there was less intramuscular pressure and therefore relatively better perfusion in MS compared with control during exercise. This might allow for better $O_2$ delivery with the result that the energy needs of the muscle were met more fully by oxidative metabolism in the MS group. This interpretation is supported by the smaller change in $Pi$, $Pi/PiCr$, and pH in MS compared with control subjects. Elucidation of the mechanisms of this response in MS awaits further investigation.

In control and MS subjects, the stronger correlation of MAP and $Pi$, compared with MAP and pH, suggests that $Pi$ was more important than pH in the generation of the exercise pressor response in these volunteers. The exercise pressor response is mediated by the reflex increase in muscle sympathetic vasoconstrictor activity that accompanies the increase in certain intramuscular metabolites (7, 48, 52). Previous work has shown that $Pi$ or diprotonated phosphate (H$_2$PO$_4^-$) are more important than pH in evoking the exercise-induced increases in muscle sympathetic vasoconstrictor activity and MAP (48), although the role of H$_2$PO$_4^-$ is not unequivocal (54). In addition, $H^+$ was found to be an important mediator of muscle sympathetic vasoconstrictor activity in some (42, 47, 52), but not all (48, 54), studies. Thus, the role of specific metabolites in the activation of the exercise pressor reflex remains controversial. For the purpose of this study, the observation of a dampened metabolic response in MS provides a new potential mechanism for the blunted pressor response observed in this group.

A difference was noted in the individual regression slopes of MAP to metabolite concentrations between control and MS subjects (Table 2). This difference suggests that the relationship between intramuscular metabolites and the pressor response may be different in some persons with MS compared with controls. In addition, although chemoreflex “sensitivity” to pH was different between groups, there was no difference in $Pi$ sensitivity. The importance of these observations is unclear at this time.

MS is a highly variable disease. Perhaps the variable nature of MS is best illustrated by our finding of a significant difference in the correlation coefficients for MAP and pH in MS subjects who reported high compared with low symptomatic fatigue. Those persons with MS who may have had an altered chemoreflex response to isometric exercise (i.e., low correlation between MAP and metabolites) were also those most likely to report increased symptomatic fatigue. Interestingly, the correlation coefficient of MAP and pH in MS subjects who reported low (normal) fatigue was similar to control, consistent with an intact chemoreflex in those MS subjects. These findings may have important clinical significance because symptomatic fatigue or lassitude is a dominant complaint in MS (13, 14, 25, 39) and can interfere with activities of daily living (13, 14, 25). Previous studies have found that symptomatic fatigue does not correlate with disability level (13, 14, 25) or with muscle fatigue (46). We emphasize that these findings were observed in only a small number of volunteers. However, to our knowledge, the observation of a possible relationship between cardiovascular autonomic dysfunction and symptomatic fatigue in persons with MS is unique and awaits further study in a larger number of subjects.

Limitations. Much of our interpretation of chemoreflex function is based on magnetic resonance spectroscopy measurements of muscle metabolites. There are several limitations to this approach: 1) only intramuscular metabolites are measured and afferent stimulation by extracellular metabolites is inferred from these measurements; 2) only the area under the surface coil can be measured and these measurements are assumed to approximate the rest of the muscle; and 3) we measured proton and high-energy phosphate metabolites and not others that may have a role in the stimulation of chemosensitive nerve fiber endings, such as bradykinin or prostaglandins (33, 49).

We have emphasized the chemoreflex as a pressor mechanism in this study, but mechanoreflexes originating from pressure-sensitive nerve fiber endings also contribute to the exercise pressor reflex (18). However, mechanoreceptors are likely to be important primarily during the initiation of the contraction. Thus, even if mechanoreflexes were affected by MS, it would not alter our overall interpretations, which are based on the entire exercise response and occlusion.
It is possible that cognitive or sensory deficits may have been confounding factors in the MS group. However, no significant cognitive or sensory impairments were noted in the clinical evaluations. Furthermore, sensory perception was similar in both groups during exercise, occlusion, and the cold pressor test, as indicated by the perceived exertion and pain scales. Thus, although cognitive and sensory abilities can be important considerations in MS, they did not appear to be factors affecting outcomes in this group of MS subjects.

In summary, we have observed a normal HR but blunted exercise pressor and muscle metabolic responses in a group of mild to moderately impaired MS subjects compared with controls. The blunted pressor response may be largely appropriate to a blunted muscle metabolic response and differences in contracting muscle mass. Similarly, the normal responses to the Valsalva maneuver and cold pressor test argue against a generalized cardiovascular autonomic impairment in persons with MS. However, the regression and correlation analyses of MAP vs. metabolites suggest that some individuals with MS may have impairment of the autonomically mediated muscle chomoreflex during isometric exercise and that this may be related to symptomatic fatigue. These latter findings may have significant clinical relevance in this population.

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