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Ischemic exercise and the muscle metaboreflex

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Cornett, Jacob A., Michael D. Herr, Kristen S. Gray, Michael B. Smith, Qing X. Yang, and Lawrence I. Sinoway. Ischemic exercise and the muscle metaboreflex. *J Appl Physiol* 89: 1432–1436, 2000.—In exercising muscle, interstitial metabolites accumulate and stimulate muscle afferents. This evokes the muscle metaboreflex and raises arterial blood pressure (BP). In this report, we examined the effects of tension generation on muscle metabolites and BP during ischemic forearm exercise in humans. Heart rate (HR), BP, P_i, $H_2PO_4^-$, and pH (^{31}P-NMR spectroscopy) data were collected in 10 normal healthy men (age 23 ± 1 yr) during rhythmic handgrip exercise. After baseline measurements, the subjects performed rhythmic handgrip for 2 min. At 2 min, a 250-mmHg occlusion cuff was inflated, and ischemic handgrip exercise was continued until near fatigue (Borg 19). Measurements were continued for an additional 30 s of ischemia. This protocol was performed at 15, 30, 45, and 60% of the subjects' maximum voluntary contraction (MVC) in random order. As tension increased, the time to fatigue decreased. In addition, mean arterial pressure and HR were higher at 60% MVC than at any of the other lower tensions. The NMR data showed significantly greater increases in $H_2PO_4^-$, P_i, and H^+ at 60% than at 15 and 30% MVC. Therefore, despite the subjects working to the same perceived effort level, a greater reflex response (represented by BP and HR data) was elicited at 60% MVC than at any of the other ischemic tensions. These data are consistent with the hypothesis that, as tension increases, factors aside from insufficient blood flow contribute to the work effect on muscle metabolites and the magnitude of the reflex response.

autonomic nervous system; exercise pressor reflex; blood pressure; nuclear magnetic resonance; handgrip

CLASSIC EXPERIMENTS by Alam and Smirk (1) suggested that metabolites within exercising muscle stimulate sensory nerves, thus evoking an exercise pressor response. The magnitude of the reflex is highly dependent on the level of tension developed. Specifically, at low tensions the reflex response is small, whereas at higher tensions the reflex pressor response is far greater. It has generally been thought that this tension effect is due to differences in the adequacy of blood flow at the different tensions (14). In other words, at higher tensions the reflex is engaged because flow delivery is insufficient to satisfy the greatly enhanced metabolic needs of the contracting skeletal muscle. However, other mechanisms may also contribute to this effect. At low tensions the predominant muscle fibers recruited are characterized as "slow twitch" and "fatigue resistant" (5, 6). At higher tensions "fast-twitch," "fatigue-sensitive" fibers are also recruited (5, 6, 19). For a given amount of developed tension, the slow-twitch fibers produce less metabolic products (20). Therefore, we speculate that work which engages fast-twitch as well as slow-twitch fibers would be more likely to produce metabolic by-products and to engage the muscle reflex.

Previous animal studies have examined the effect of muscle fiber type on the exercise pressor reflex (13, 15, 24). In this paper we evaluated the effects of tension on the exercise pressor reflex and muscle metabolites (^{31}P-NMR spectroscopy) during ischemic conditions. We reasoned that, if factors other than flow adequacy contributed to the workload effect, then ischemic fatiguing exercise at low tensions should evoke a smaller pressor response than ischemic fatiguing exercise at higher tensions. Moreover, if differences in muscle fiber recruitment at high and low tensions contributed to the differences in the pressor response, then we would anticipate that contraction at the higher tensions would evoke a greater fall in cellular pH than would be seen when contraction was performed at a lower tension. The results of this study support these hypotheses.

METHODS

Subjects. Ten normal male volunteers were studied (mean age 23 ± 1 yr, range 20–24 yr). All were in good health, right handed, and on no medications. All subjects gave informed written consent to participate in the study. Subject demographic data are presented in Table 1.

We measured mean arterial blood pressure (BP; in mmHg) using an automated device that employs the volume-clamp method (Finapres; Ohmeda, Madison, WI).

^{31}P-NMR experiments. The ^{31}P-NMR spectra were obtained by using a 1.9-T, 26-cm bore superconducting magnet

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Table 1. *Subject demographic data*

Subject	Height, in.	Height, cm	Weight, lbs.	Weight, kg	Resting MAP, mmHg	Resting HR, beats/min
1	68	172.7	150	68.2	76	47
2	72	182.9	165	75.0	81	66
3	72	182.9	173	78.6	83	58
4	70	177.8	140	63.6	93	76
5	68	172.7	165	75.0	88	66
6	74	188.0	165	75.0	87	56
7	73	185.4	185	84.1	86	69
8	70	177.8	218	99.1	98	61
9	70	177.8	170	77.3	80	60
10	68	172.7	150	68.2	82	74
Mean	70.5	179.07	168.1	76.4	85.4	63.3
SE	0.7	1.7	6.9	3.1	2.1	2.8

MAP, mean arterial pressure; HR, heart rate.

(Oxford Instruments, Abbington, UK) interfaced to a radio-frequency transmitter-receiver (Nicolet Instrument, Madison, WI). The flexor digitorum superficialis muscle was located in the nondominant arm by using low-voltage muscle stimulation. The field homogeneity was adjusted to give a line width in phosphocreatine (PCr) of ~20 Hz at one-half peak height. The 2.5-cm circular coil was positioned over the flexor digitorum superficialis and held in place by a piston and cylinder coil mount. The ^{31}P spectra were collected at 32.5 MHz with a 1.9-s delay between the radio-frequency pulses by using a 6-kHz bandwidth sampled with 2,048 data points. The radio-frequency power was adjusted to give a maximum signal by using the inhomogeneous radio-frequency field of this coil. Each spectrum was produced by a Fourier transformation of 16 transients averaged over 30 s with the use of 7-Hz exponential filtering. During baseline, P_i levels are of low intensity; thus baseline spectra were taken in 1-min intervals to maximize the signal-to-noise ratio. During exercise, P_i peaks are much larger, and 30-s spectra were taken. The signal-to-noise ratio for the 30-s PCr spectra was, on average, ~10. The areas under the respective spectral curves were used to determine the concentrations of P_i and PCr. A Lorentzian peak-fitting program on the spectrometer's Tecmag software was used to determine both peak area and frequency. Forearm intracellular pH was calculated from the chemical shift of the P_i peak relative to the fixed PCr peak (12). The ^{31}P-NMR parameters presented in this study are P_i, H^+, $H_2PO_4^-$, and P_i ratio (P_i/PCr + P_i). The total value of PCr + P_i remained constant during the use and resynthesis of PCr.

Protocol. All of the data were collected at The Milton S. Hershey Medical Center's NMR facility. Subjects were placed supine with their nondominant arm abducted 90° and placed in the bore of the magnet. A specially designed nonmagnetic handgrip dynamometer was then placed in the subject's nondominant hand within the magnet. The maximum voluntary contraction (MVC) was then obtained, and, from this, fixed percentages of MVC (15, 30, 45, and 60%) were calculated to serve as the tensions for the four separate trials performed by each volunteer. The workload sequence was randomized for each subject (Fig. 1).

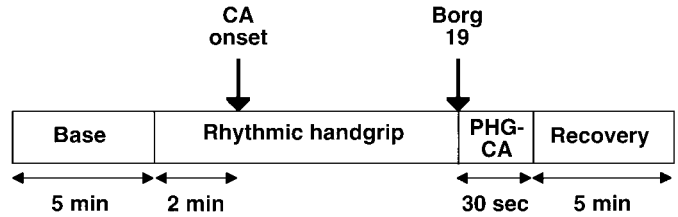

Fig. 1. Schematic representation of experimental protocol. Base, baseline; CA onset, start of forearm circulatory arrest (CA); PHG-CA, posthandgrip-CA.

A BP cuff was placed on the dominant, nonexercising arm, and baseline BP measurements were taken with an automated BP device utilizing the oscillometric method (Dinamap; Critikon, Tampa, FL). This data served as a check for the BP measurement obtained from the volume-clamp BP device. After 2 min of baseline measurements, the BP cuff was removed and replaced with the volume-clamp BP device (Finapres, Ohmeda). A forearm occlusion cuff was positioned on the nondominant arm proximal to the anticubital fossa.

Five minutes of baseline BP, heart rate (HR), and ^{31}P-NMR data were then recorded. After baseline data were recorded, the subjects then performed 2 min of rhythmic handgrip at 30 contractions/min at one of the four tensions. Subjects used visual feedback provided by a calibrated analog meter to adjust contraction force during handgrip exercise. It should be emphasized that the number of contractions was the same at the different tensions. After 2 min, the BP cuff was inflated to suprasystolic levels as the subject continued handgrip at the same tension. The subjects were instructed to continue contractions until an almost maximal level of perceived exertion (i.e., level of 19 on the Borg scale) (2). After handgrip was completed, the forearm remained ischemic for an additional 30 s. The cuff was then released, and recovery data were collected. The subjects then rested for 15 min. The same protocol was then repeated at each of the three remaining tensions.

Statistical analysis. The NMR ($H_2PO_4^-$, H^+, and P_i ratio), BP, and HR values for each of the four tensions were determined at four points in the protocol: baseline, the end of nonischemic handgrip, the end of ischemic handgrip (at Borg 19), and during posthandgrip ischemia. The mean values were examined by using a two-way repeated-measures analysis of variance. Post hoc comparisons were made by using Tukey's test. For all analysis, $P < 0.05$ was considered statistically significant.

Table 2. *Values at the end of perfused handgrip*

Handgrip Tension, %	HR, beats/min	MAP, mmHg	pH	P_i Ratio
15	63.2 ± 2.4	100.5 ± 5.6	6.987 ± 0.040	0.248 ± 0.017
30	69.0 ± 2.9	101.1 ± 3.7	6.951 ± 0.058	0.412 ± 0.025*
45	75.2 ± 3.3*	103.1 ± 4.7	6.852 ± 0.075	0.510 ± 0.030*
60	87.8 ± 4.9*†‡	120.6 ± 5.0*†‡	6.649 ± 0.093*†‡	0.597 ± 0.027*†‡

Values are means ± SE. Data are from the 2nd min of freely perfused rhythmic handgrip. P_i ratio, P_i/P_i + phosphocreatine. Statistically different from *15% tension, †30% tension, and ‡45% tension ($P < 0.05$).

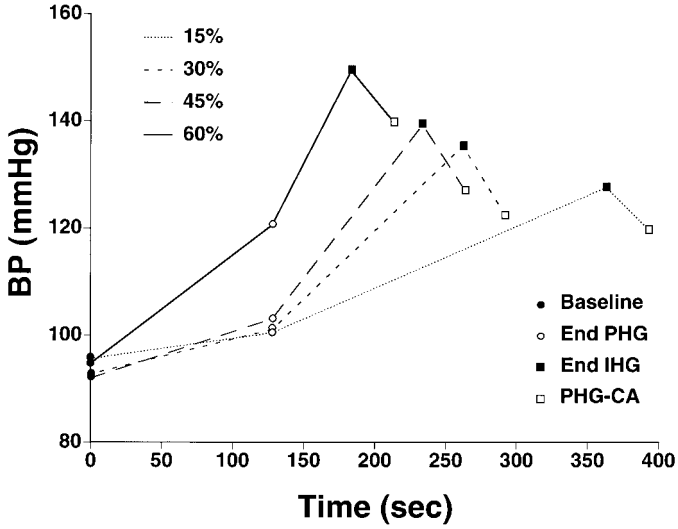

Fig. 2. Effects of the 4 different generated tensions [15, 30, 45, and 60% maximum voluntary contraction (MVC)] on blood pressure (BP). Note decrease in time to fatigue as tension increased. Also of note is that the end PHG and PHG-CA values increased with increasing muscle tension. End IHG, end of ischemic handgrip.

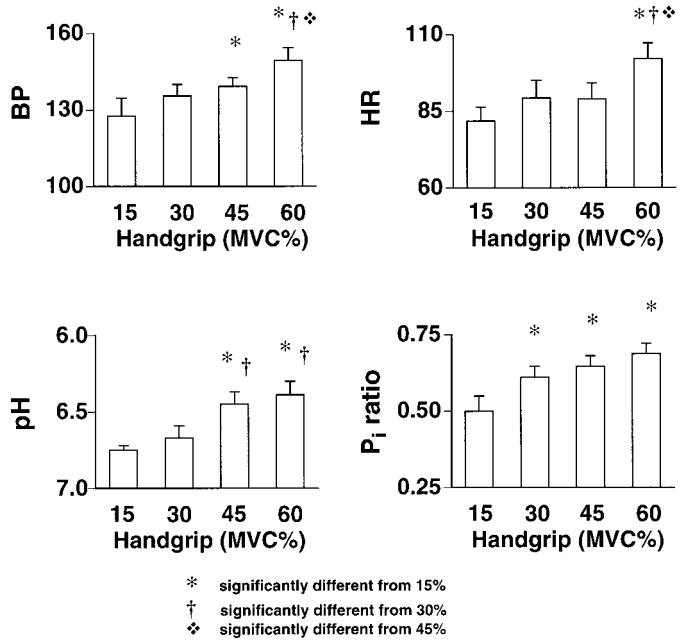

Fig. 3. BP, heart rate (HR), pH, and P_i ratio [P_i/P_i + phosphocreatine (PCr)] values at the end of ischemic exercise. Note the increase in all parameters with increasing tension.

RESULTS

No significant difference in $H_2PO_4^-$, H^+, the P_i ratio, HR, or BP were seen during the baseline periods that preceded each tension. After 2 min of perfused handgrip, 60% MVC caused much greater changes in HR, BP, pH, and the P_i ratio than were observed during the 15% tension (Table 2).

The time to fatigue decreased as a function of tension (Fig. 2). Of note, the BP responses at the end of ischemic exercise were graded, with 15% response being less than the 45 and 60% responses and the 30 and 45% responses being less than the 60% responses (Figs. 2 and 3). pH responses also were affected by tension, with the 15% pH being higher than the 45 and 60% responses (Fig. 3). A similar trend was noted for the P_i ratio (Fig. 3). The effects of tension on the various parameters were, in general, still present during postexercise ischemia (Figs. 2 and 4).

DISCUSSION

Study findings. In the present study, we demonstrated that work intensity had a profound effect on the magnitude of the ischemic muscle reflex because greater BP responses were seen at the higher tensions than at the lower ones. This effect was independent of blood flow and the perceived level of effort because all bouts of contraction were ischemic and all were performed to the same level on the Borg scale. NMR analysis of the working muscle demonstrated that tension also affected the development of cellular acidosis and the P_i ratio.

It is generally acknowledged that the muscle reflex is engaged at high tensions near the point of fatigue (18, 22). Additionally, it has been suggested that this reflex is engaged more at high tensions than at lower ones (21); an effect that has, in part, been thought to be due to a greater flow and/or metabolite mismatch at higher tensions (4, 21). The present report expands on these prior ones by suggesting that the effects of muscle tension generation on the sympathetic response are not solely due to a greater muscle compressive effect on the feeding arteries at the higher tensions. If this were the case, then the BP response should not have been influenced by percent MVC.

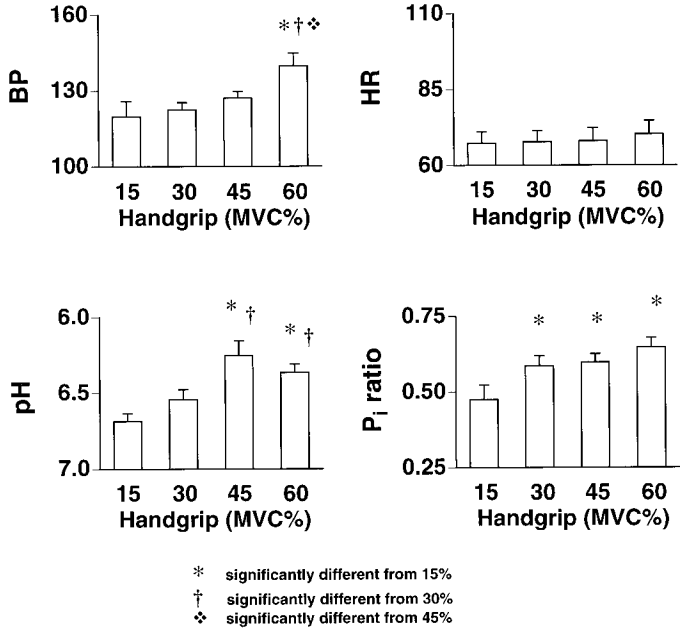

Fig. 4. BP, HR, pH, and P_i ratio (P_i/P_i + PCr) values at the end of PHG-CA. Note the increase in BP, pH, and P_i ratio with increasing tension.

What is the explanation for this flow-independent, tension-dependent difference in muscle metabolism and reflex engagement? We believe our findings may be explained by an effect of tension on muscle fiber type recruitment.

Prior work by Gollnick and colleagues (5, 6) suggests that exercise at low tensions engages predominantly slow-twitch, high-oxidative muscle fibers, whereas exercise at higher tensions leads to the recruitment of both oxidative slow-twitch and the more glycolytic fast-twitch fibers. Oxidative fibers by definition are less dependent on anaerobic glycolyses and generate less metabolic by-products (3, 20). We speculate that, during the 15% MVC, the recruited oxidative fibers release only small amounts of muscle metabolites, which, in turn, evoked minimal muscle afferent stimulation and a smaller pressor response. At higher tensions, we believe the greater activation of glycolytic fibers leads to greater muscle afferent stimulation and greater muscle reflex engagement. This line of reasoning is consistent with the work of Henneman and Mendell (8), who described the orderly characteristics of α-motoneuron recruitment. These studies suggested that the "neural energy" necessary to discharge an α-motoneuron, the α-motoneuron firing rate, and the tension generated by the innervated muscle cell correlate with the size of the fiber. This has been termed the "size principle" (8–10). Moreover, our results are consistent with prior studies that suggest that slow oxidative muscle fibers engage the muscle reflex far less effective than do more glycolytic fibers (16, 24).

Limitations and other considerations. We should emphasize that the above line of reasoning does not take into consideration other important factors (aside from the recruitment pattern) that can contribute to the amount of tension generated during the different bouts of static contraction. For example, it is known that, in addition to recruitment, muscle tension can be altered by changes in the firing rate of individual α-motoneurons. Indeed, it has been shown that any increase in muscle tension will lead to an increase in firing rate as well as fiber recruitment (8).

In the present studies, we used NMR to provide an index of cellular work done, as well as an index of cellular pH. We did not utilize this method to draw any conclusions regarding which substance or substances produced by muscle cells are responsible for engaging the muscle reflex.

It is also possible that the results presented are explained by the nonlinear engagement of the muscle mechanoreflex. It is known that mechanoreceptors can be sensitized by the metabolic by-products of exercise (7, 11, 17, 23). However, we observed that the pressor responses seen during the periods of postexercise ischemia (when mechanoreflexes are not engaged) followed the same general trends as those seen at the end of ischemic exercise. In other words, in the absence of any mechanical deformation of the afferent's receptive field, we observed similar BP-tension relationships. We believe this observation is most consistent with the effects of contraction on metabolite-sensitive muscle afferents.

We cannot exclude that the reflex effects we observed were not due simply to the use of more muscle mass with the engagement of a larger pool of muscle afferents. Clearly, additional work will be necessary to exclude this possibility.

In conclusion, fatiguing ischemic handgrip at a low tension caused less impressive changes in cellular metabolism then that seen during handgrip performed at higher workloads. The degree of cellular metabolic changes paralleled the magnitude of the evoked pressor reflex. These metabolic and reflex effects were not due to an influence of tension on the muscle oxygen supply-to-demand ratio because the work was performed under ischemic conditions. We believe these findings are most consistent with the hypothesis that low tensions engage predominantly oxidative muscle, whereas higher tensions lead to the engagement of more glycolytic fibers, which more vigorously engage the muscle reflex.

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