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Post-Polio Sequelae

POST-POLIO FATIGUE: A ^{31}P MAGNETIC RESONANCE SPECTROSCOPY INVESTIGATION

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ABSTRACT

Changes in high energy phosphates (HEP) and intramuscular pH during exercise were measured in 17 patients with post-polio fatigue and in 28 healthy controls using ^{31}P magnetic resonance spectroscopy (MRS). Subjects performed a dynamic hand grip exercise at low and high intensity. Mean changes in the HEP and pH showed no significant differences between the groups, although the post-polio group's response was highly variable. Six patients showed evidence of a lower lactate accumulation during the high intensity exercise when compared with controls. These data suggest that the whole body fatigue experienced by polio survivors is not related to any systemic metabolic abnormality.

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Post-polio sequelae (PPS) are symptoms that occur in persons more than 30 years after they have contracted and recovered from poliomyelitis. The clinical course of PPS has been well described,[1-4] but the mechanisms responsible for the symptoms have not yet been identified.

Since the most prominent feature of PPS is often general, whole body fatigue, systemic abnormalities in muscle metabolism (either as a primary or secondary effect) may participate in its etiology.[5] Previous work using ^{31}P magnetic resonance spectroscopy (MRS) has shown that metabolic abnormalities are associated with muscle denervation[6] and also can be observed in patients presenting with chronic fatigue.[7] The subtle metabolic changes in denervation were observed at rest in the intracellular pH and the phosphorylation potential of the cell. In some patients with chronic or persistent fatigue of unknown etiology, abnormalities have been detected on MRS, at rest, during aerobic exercise, during anaerobic exercise, and during recovery from exercise.[7] The current investigation was undertaken to determine if any metabolic abnormalities, either systemic or specific, were present in the flexor digitorum sublimis (FDS) muscles of PPS patients. Specifically, MRS was used to monitor high energy phosphate metabolism in the forearm muscles during a standardized hand grip exercise.

MATERIALS AND METHODS

The PPS group consisted of 17 patients, 6 men and 11 women, all having been diagnosed with poliomyelitis at the time of their acute illness. The subjects ranged in age from 29 to 59 years (mean: 46.4 ± 9.8) at the time of the study with a mean age at the onset of the acute paralytic illness of 9 ± 7.7 years (range: 1 to

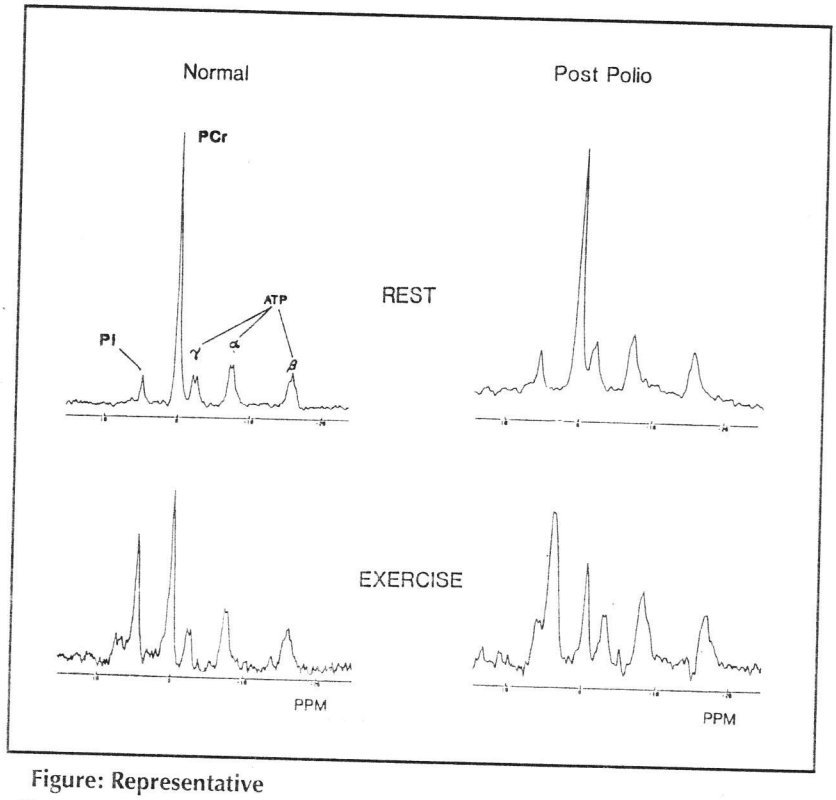

Figure: Representative ^{31}P spectra from a control (upper and lower left) and a post-polio patient (upper and lower right). The data acquisition parameters for the spectra are given in the Materials and Methods section.

22). The mean time from onset of the polio to participation in the study was 37.4 ± 6.1 years (range: 28 to 50). All subjects complained of new, general fatigue and believed it was a limiting factor in their daily routines. The subjects were screened to exclude those with depression based on Beck Depression Inventory scores.[8] A medical history and physical examination were completed prior to entry into the study, with emphasis on neurologic and musculoskeletal assessment. Medical Research Council (MRC)[9] grading was used to document forearm muscle strength.

The control group consisted of 28 healthy, untrained volunteers, ranging in age from 25 to 58 years (mean: 33.6 ± 6.3). Seventeen of the subjects were men and 11 were women. None of the control subjects had a previous history of polio or any other myologic or neurologic disorder. Electrodiagnostic testing was not performed on these individuals.

Electrodiagnostic Studies: The FDS muscle of the dominant arm in polio subjects was examined using electromyography (EMG)[10] to determine if there was any evidence of denervation or reinnervation. One to three other muscles in the body that were known to have been weak during the original illness or continued to be weak also were studied using EMG to ensure that all of the PPS had electrodiagnostic findings consistent with having had poliomyelitis. The EMG techniques and analysis are detailed elsewhere.[10] In all cases, the dominant arm forearm was studied by MRS prior to electrodiagnostic evaluation. Both examinations were done on the same day. Three subjects in whom electromyography indicated that there were abnormalities in the FDS of the non-dominant arm were brought back within 2 weeks for MRS of this limb.

^{31}P Magnetic Resonance Spectroscopy: A detailed description of the exercise protocol has been previously reported.[11,12] Briefly, it consisted of three successive spectra (1 × 128 scan; 2 × 32 scans) obtained at rest, followed by four acquisitions (32 scans each) while the subject squeezed a hand-held manometer bulb to 100 mm Hg at 2-second intervals (EX1). A metronome was used to help the subjects maintain the proper cadence. Then two additional spectra (32 scans each) were obtained while the subject squeezed the bulb to 300 mm Hg using the same repetition rate (EX2).

The studies were conducted using a 26 cm, horizontal bore, 1.9 Tesla superconducting magnet and an Oxford Research Systems TMR 32/20 spectrometer. Subjects inserted their forearm into the bore of the magnet where ideal placement would have the FDS over a 4 cm single turn surface coil embedded in a Plexiglas™ armrest. The magnet homogeneity was adjusted on the proton signal. Using the same doubly tuned coil, MRS was performed at 32.5 MHz. Nominal 70° pulses of 30 microsecond duration were applied at 2.256 second intervals and 2048 data points collected using a spectral width of 4000 Hz and 12 bit resolution. Before Fourier transformation, the free induction decay (FID) data were zero filled to 4096 points and multiplied by a 10 Hz exponential line broadening factor to improve the signal-to-noise ratio. After Fourier transformation and phasing, the resulting spectra were fit to the sum of 7 Lorentzian line shapes using a nonlinear, least squares computer algorithm. The relative concentrations of phosphocreatine (PCr), inorganic phosphate (Pi), and adenosine triphosphate (ATP) were determined from the areas under the fitted curves. The relative concentration of ATP was determined from the beta (β-ATP) peak as the alpha and gamma peaks of ATP could contain contributions from other metabolites. Intracellular muscle pH was calculated from the chemical shift (δ, expressed in parts per million) of Pi from PCr using the formula:

$$pH = 6.75 + \log[\delta - 3.27]/[5.69 - \delta]$$[11]

Data Analysis: To facilitate comparison with previous published reports on fatigue,[11,13,14] PCr/Pi and intracellular pH were determined at rest and at the end of EX1 and EX2. The patients and the controls were compared using an Analysis of Variance (ANOVA) with $P<.05$ as the

Table

SUMMARY OF THE MRS AND EMG DATA FOR THE PPS PATIENTS AND CONTROLS

		Rest		End EX1		End EX2					
ID	Sex	pH	PCr/Pi	pH	PCr/Pi	mm Hg	pH	PCr/Pi	PCr/Pi vs pH†	MRC Scale	EMG
1	M	7.04	7.7	6.99	3.3	250	6.67	0.9	N	5	N
2R*	M	7.02	10.7	7.02	3.1	300	6.95	1.1	N	5	A
2L	M	7.09	8.6	7.06	1.0	200	6.84	0.3	A	4	A
3	M	7.04	6.1	7.10	3.5	300	7.01	0.7	A	5	A
4	F	7.06	13.2	6.93	0.8	300	6.72	0.6	N	5	N
5R**	F	7.10	5.8	6.64	0.7	INC	INC	INC	INC	4	A
5L*	F	7.08	8.4	7.05	2.8	250	7.05	1.5	A	5	A
6	F	7.07	7.6	6.99	1.3	100	6.64	0.4	N	5	N
7	F	7.03	5.1	7.05	4.8	200	7.12	1.1	A	5	N
8	F	7.09	7.1	7.10	3.2	280	6.97	0.8	N	5	N
9‡	F	7.03	6.0	7.06	2.7	300	N/A	N/A	INC	5	N
10	F	7.12	5.7	6.97	1.6	300	6.59	0.4	N	5	N
11R*	F	7.05	6.3	6.93	1.4	150	6.68	0.8	N	5	N
11L††	F	7.01	7.7	6.96	2.6	100	6.98	2.6	INC	5	A
12	M	7.09	6.9	7.19	1.2	120	7.10	1.3	A	5	N
13	M	7.06	8.9	7.01	3.9	180	7.04	1.3	N	5	N
14	F	7.05	5.2	6.99	3.5	300	6.93	1.8	N	5	N
15	F	7.07	7.6	6.99	2.3	130	6.79	1.6	N	5	N
16	F	7.07	7.4	7.01	2.8	200	6.96	1.1	N	5	A
17	M	7.06	7.3	7.11	5.4	300	6.96	1.0	A	5	N
Mean		7.06	7.5	7.03	2.8	230	6.88	1.0			
± SD		0.03	2.0	0.07	1.3	70	0.18	0.4			
Control mean		7.06	6.9	7.02	2.8	295	6.81	0.8			
± 1SD		0.03	1.9	0.08	1.3	10	0.22	0.5			

*Indicates the dominant arm when two arms on the same subject were evaluated. R = right, L = left.

**Patient unable to perform EX2 due to fatigue.

†The PCr/Pi vs pH plot was compared with the controls: A = abnormal, N = Normal, INC = incomplete data.

‡Patient moved arm during EX2 and spectra not useable.

††Patient was too "fatigued" to exercise at a higher level and the PCr/Pi did not drop to below 2.0, the level that is necessary to unveil an abnormality in the pH response.

level of significance. The PCr/Pi vs pH response during exercise was also plotted as the presentation of the data in this manner permitted the determination of whether the change in pH was appropriate for the change in the PCr/Pi ratio (compared to the control group). The PCr/Pi ratio is an indirect estimate of the phosphorylation potential, which determines the mitochondrial activity of the muscle cells.[14] Assuming that (PCr + Pi) was a constant, the ratio of βATP/(PCr + Pi) was also calculated to determine if the exercise was severe enough to diminish the ATP stores.[15]

To correlate the MRS and EMG data, the MRS results, reflected by PCr/Pi vs pH, and the EMG results were coded as either normal or abnormal (Table). The phi coefficient was then calculated using a Yates correlation for small sample size. The EMG results and the PCr/Pi ratio were correlated using a point biserial correlation.

RESULTS

Electromyography: All the PPS subjects demonstrated EMG abnormalities consistent with previous poliomyelitis in at least one muscle in the body. Seven FDS muscles in five patients had at least one EMG abnormality: increased motor unit potential amplitude, increased recruitment frequency, decreased interference pattern, polyphasic potentials, or satellite potentials. No FDS muscle had fibrillations or sharp waves consistent with acute denervation. Only two of the arms tested were rated as having decreased strength using the MRC scale.

31P Magnetic Resonance Spectroscopy: The Table summarizes the MRS findings in the FDS muscles in the PPS and control subjects during rest, EX1, and EX2. For the control subjects, the resting intracellular pH was 7.06 ± .03, which is consistent with previously reported values in the literature.[5,12,16] The resting pH of the PPS group was not statistically different from that of the controls, at 7.06 ± .03. Rest and maximum exercise spectra for a typical control and a post-polio patient are shown in the Figure. The single Pi peak in the exercise spectrum would

indicate that the MRS signal was predominantly coming from exercising muscle.[6] During exercise, there were no striking abnormalities, but some individual differences were noted. During maximum exercise (EX2), 10 of the 17 subjects were not able to generate the 300 mm Hg pressure in the manometer bulb. These subjects were encouraged to continue to exercise at a level they were able to sustain (exercise level indicated in the Table). One subject was unable to perform EX2 with the non-dominant right arm.

In six subjects, deviations from the control group in the PCr/Pi vs pH plots were apparent. An abnormality was reported when at least three data points during EX1 and EX2 were at least one standard deviation outside the control mean. The PCr/Pi for this group of six fell to 1.0 ± 0.4 at the end of EX2 and was not significantly different from the controls. The corresponding pH of 7.01 ± 0.10 was significantly higher than the mean control value of 6.81 ± 0.22 (ANOVA: $F = 5.27$, $P<.05$).

The exercise was severe enough in three of the PPS subjects[2,5,12] to decrease (>20%) the concentration of ATP (as reflected by the βATP/(PCr + Pi) ratio) during exercise. In the remaining patients the ATP levels were maintained within 10%.

EMG/MRS Data Correlations: The variance in the MRC score for the FDS was insufficient to allow rational correlational analysis with the other variables. The calculated phi coefficient indicated that there was no significant association between the MRS and the EMG data. The point biserial correlational analysis revealed that there was no significant relationship between the EMG results and the PCr/Pi ratio. There was also no correlation found between the exercise level (mm Hg) sustained during EX2 and the final pH, PCr/Pi, or MRC score.

DISCUSSION

The PPS group showed no unique metabolic abnormalities that could be used to characterize their fatigue. The mean values for PCr/Pi and intracellular pH were within normal limits during rest, EX1, and EX2; however, there were large individual variations in these parameters. The results of previous research relying on muscle biopsy data[17-19] (fiber typing and enzyme concentrations) and EMG[20] have demonstrated considerable heterogeneity in the PPS population. Therefore, the heterogeneity of the MRS results should not be all that surprising.

It has been shown in patients with partial denervation of the forearm muscle that the rest values for pH and PCr/Pi differed from a control group.[6] Zochodne et al[9] found that, at rest, patients with partial denervation had a pl 7.09 ± 0.03 with a corresponding PCr/Pi of 4.6 ± 1.5. Only five of the PPS pati (seven FDS muscles) had EMG docume evidence of chronic denervation/reinnerva in the forearm muscle studied, and none of tl had resting PCr/Pi ratios under 5.8. It app that the denervation in the patients may not l been severe enough to alter the mitochond phosphorylation potential or that the FDS m cle has been reinnervated adequately by sec dary sprouting.

The forearm muscles in six patients did acidify significantly during exercise, e though the task was performed at a level t reduced the PCr/Pi ratio substantially fr resting values. The PCr/Pi changes were sim to the control group during EX2, but the lack significant accumulation of lactic acid co indicate either a relative decrease in glycoly activity compared to the controls, or a m efficient handling of the lactate load in these patients. Reduced acidification during high tensity exercise also has been noted in patie with mitochondrial myopathies.[14] Argov et a hypothesized that these patients may handle t lactate load more efficiently. At rest, the patier with mitochondrial myopathies exhibited a gre reduced PCr/Pi ratio. This was not the case the PPS patients in whom the PCr/Pi ratio at re was the same as the control group.

Increased lactate handling efficiency could achieved by a greater than expected increase blood flow during exercise. This would enab the lactic acid to be removed more quickly fro the exercising muscle. We are not aware of an direct measurements of muscle blood flow PPS subjects, but cutaneous blood flow ha been measured[21] and was found to be lower i the affected limb. In addition, Grimby et al found a lower capillary density in muscles o PPS subjects when compared to controls, whic could also impede lactate removal by the blood Thus, it is unlikely that blood flow could b responsible for the lack of acidification durin exercise.

Functional decompensation is characteristic of PPS. After a long period of functiona stability there may be an atrophy of moto neurons that are extended beyond their limit and are unable to keep up to the metabolic demands of their enlarged motor units. This results in the dropping out of individual collat eral sprouts and muscle fibers.[18] This loss would lead to reduced strength in the affected limb,[22] which was evident during EX2, when some of the PPS subjects were unable to reach the 300 mm Hg level. These PPS subjects exercised at their maximum maintainable handgrip strength.

This should have resulted in a greater acidification than the controls, who were exercising below their maximum. Since the opposite trend was observed, the lack of acidification during EX2 becomes even more significant.

Additionally, considering the fiber dropout, it may be hypothesized that the remaining fibers undergo a "conditioning" due to the increased demands. This would cause an increase in the oxidative capacity of the muscle[23] which would decrease anaerobic metabolism. However, it has been shown that the concentration of the oxidative enzyme, citrate synthase, is substantially lower than normal[17,23] in polio survivors, which could limit exercise endurance. Indeed, in the exercise protocol employed here, with a work to rest ratio of 1, endurance becomes an important component. Recently, it has been demonstrated that modest increases in citrate synthase activity with a resulting increase in endurance can be achieved in polio survivors by a high-intensity resistance exercise program.[23]

A similar pH response to exercise has been noted in patients with McArdle's disease.[24] In the McArdle's patients, it is the absence of the glycogen converting enzyme phosphorylase that limits the glycolytic production of lactate. Such an explanation in the PPS patients is unlikely, because the glycolytic enzymes of PPS affected muscle have been shown to be within normal limits.[17] A lower glycolytic activity would be consistent with a change in the fiber composition of the affected muscle, such as the hypothesized transition from type II (phasic, glycolytic) to type I (tonic, oxidative) fibers that occurs following acute poliomyelitis.[17,25]

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