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³¹P-magnetic resonance spectroscopy of leg muscle metabolism during exercise in children and adults

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ZANCONATO, STEFANIA, STEVEN BUCHTHAL, THOMAS J. BARSTOW, AND DAN M. COOPER. ³¹P-magnetic resonance spectroscopy of leg muscle metabolism during exercise in children and adults. *J. Appl. Physiol.* 74(5): 2214–2218, 1993.—Gas exchange response to high-intensity exercise differs in children and adults. We hypothesized that these findings are related to a lower anaerobic ATP supply in children. We predicted therefore a maturation of muscle high-energy phosphate metabolism during exercise. To test this hypothesis, we measured calf muscle P_i, phosphocreatine (PCr), and pH with ³¹P-nuclear magnetic resonance spectroscopy during rest and progressive exercise in 10 children and 8 adults. No differences were found at rest in pH and P_i/PCr between children and adults. Exercise resulted in a greater increase in P_i/PCr ($P < 0.001$) and decrease in pH ($P < 0.0001$) in adults than in children. Six adults and five children exhibited a transition from a slow to a faster rate of P_i/PCr increase and pH decrease during exercise. No significant differences were found between the two groups in the initial slow-phase slopes of P_i/PCr and pH as a function of work rate. In contrast, during the fast phase, P_i/PCr increased (slope: adults 23.6 ± 9.8 , children 10.7 ± 2.5 ; $P < 0.05$) and pH decreased (slope: adults -6.0 ± 1.9 , children -3.7 ± 1.2 ; $P < 0.05$) more rapidly in adults than in children. In conclusion, high-intensity exercise results in different kinetics of P_i/PCr and pH between children and adults. These results suggest that children are less able than adults to affect ATP rephosphorylation by anaerobic metabolic pathways during high-intensity exercise.

exercise; phosphorus-31 nuclear magnetic resonance spectroscopy

THERE IS INCREASING EVIDENCE suggesting maturation of energy metabolism during growth. The oxygen cost of high-intensity exercise, normalized to the actual work done (O_2/J), is higher in children, suggesting less dependence on anaerobic metabolism (24). After vigorous exercise, blood and muscle lactate concentrations are lower and serum pH higher in children than in adults (14, 19). Finally, the increase in O_2 uptake ($\dot{V}O_2$) during constant work rate high-intensity exercise is smaller in children than in adults (1). Because the slope of $\dot{V}O_2$ during high-intensity exercise is correlated with serum lactate levels (21), the smaller slopes in children further support the idea that lactate levels in response to high-intensity exercise are truly smaller in children.

No definitive mechanism has been established for the growth-related differences in the adaptive response to high-intensity exercise. One problem has been the lack of

noninvasive methods to study muscle metabolism. The use of ³¹P-nuclear magnetic resonance spectroscopy (³¹P-MRS) now provides a safe and noninvasive way of monitoring intracellular P_i, phosphocreatine (PCr), and pH (7) that is acceptable for studies in children. These variables, in turn, allow the assessment of muscle oxidative metabolism and intramuscular glycolytic activity (7).

We hypothesized that the growth-related changes in whole body $\dot{V}O_2$ and O_2 cost of exercise observed during high-intensity exercise depend on a lower ATP supply by anaerobic metabolism in children. This could result either from changes in the mechanism of glycolysis in muscles or from a different pattern of fiber type recruitment. We therefore expected a maturation of the kinetics of high-energy phosphate metabolites in muscle tissue during exercise. This hypothesis was tested by examining P_i, PCr, β -ATP, and pH kinetics in calf muscles during progressive incremental exercise. Results obtained from children were compared with those from adults.

METHODS

Population

Ten healthy prepubertal children (8 boys and 2 girls, aged 7–10 yr, mean age 9.3 ± 1.0 yr) and eight healthy adults (5 males and 3 females, aged 20–42 yr, mean age 33.7 ± 6.9 yr) volunteered for the study. None of the subjects smoked, used medications, or was overweight. The study was approved by the Human Subjects' Internal Review Board of Harbor-UCLA Medical Center. Informed consent was obtained from each subject and/or, when appropriate, a parent.

Protocol

Progressive cycle ergometer test. Each subject performed a progressive cycle ergometer test to volitional fatigue to determine the maximal O_2 uptake ($\dot{V}O_{2\max}$) (9). During the test, ventilation and gas exchange were measured breath by breath and $\dot{V}O_2$ was computed on-line as previously described (4). $\dot{V}O_{2\max}$ was taken as the peak $\dot{V}O_2$ achieved by each subject before cessation of exercise.

Calf exercise. The test took place inside a 1.5-T Spectrovision clinical imager (Picker International, Cleveland, OH). The subjects underwent a supine progressive exercise to volitional fatigue using a treadle ergometer. We designed this device based on the work of Quistorff et al. (20). The exercise consisted of full right plantar flexion

against the treadle at a frequency of 1/s. Work rate was controlled by a stepwise increase in pressure of a pneumatic device every 64 s until the limit of the subject's tolerance. The limit of tolerance was identified as the point at which the subject could no longer maintain either a plantar flexion frequency of 1/s or a full range of motion.

³¹P-MRS

A 10-cm receive-only coil was positioned on the gastrocnemius head of the right leg. The leg was inserted through a linear head coil that was tuned to phosphorus (for radio-frequency excitation) such that the surface coil was positioned in the center of the active region of the head coil. The patient was then inserted into the magnet so that the surface coil was located in the center of the magnetic field. Positioning was confirmed by obtaining ¹H scout images in both the axial and sagittal orientations. The surface coil was identified in the images by an aqueous solution of methylene diphosphonic acid located at the center of the surface coil. The homogeneity of the magnetic field was optimized by shimming on the proton signal of the tissue water. The radio frequency was then switched to ³¹P, and resting spectra were obtained with repetition times of 1 and 10 s to correct for possible spin-lattice relaxation time (T_1) differences. The subject then began the exercise test. Spectroscopy was performed continuously during 3 min of rest and throughout exercise. The spectra parameters were flip angle = 90°, spectral width = 2,000 Hz, repetition time = 1 s, and number of free induction decays per spectrum = 32. Thus, each spectrum represented the average over 32 s.

Data Analysis

³¹P-MRS. Data were analyzed adding a small exponential line broadening (3.5 Hz) before the Fourier transformation. For each data set, a computer baseline and curve-fitting routine employing a nonlinear least-squares analysis on mixed Lorentzian and Gaussian line shape (provided by Picker International) was used to calculate the areas under P_i , PCr, and β -ATP peaks. P_i /PCr and PCr/ β -ATP were then determined. The areas were corrected for possible T_1 saturation effects by calculating the ratio of each peak area to the standard area for the resting spectra at both 10 and 1 s repetition times. PCr has been reported to have a T_1 of 4.5–6.5 s, P_i a T_1 of 4–5 s, and β -ATP a T_1 of 3–4 s (6). Cellular pH was determined by comparing the chemical shift difference between the PCr and P_i signals using the following equation (23): $\text{pH} = 6.75 + \log [(\sigma - 3.27)/(5.69 - \sigma)]$, where σ is the chemical shift in parts per million between the P_i and PCr signals.

Normalization

To compare different sized subjects, $\dot{V}O_{2\text{max}}$ and work rate (measured as pressure applied to the pneumatic device, i.e., psi) were normalized to body weight as previously described (8).

Statistical Analysis

Measurements of $\dot{V}O_{2\text{max}}$ and spectroscopy resting parameters in children and adults were compared by Student's unpaired t test. Within each group paired t test was used to compare the resting and end-exercise values of P_i /PCr, pH, PCr/ β -ATP, and β -ATP. The difference between the end-exercise and resting spectroscopy parameters was calculated and compared between children and adults by unpaired t test. The relationship between pH and P_i /PCr was studied by linear regression. Some subjects exhibited a transition point between a slow and a fast phase of P_i /PCr increase and pH decrease during exercise. In these individuals, linear regression was used to fit the first and second portions of the relationship of P_i /PCr and pH to work rate. The slopes and intercepts of the best-fit lines were compared in children and adults by unpaired Student's t test. Results are presented as means \pm SD.

RESULTS

Cycle Ergometer Exercise Test

No statistically significant difference was found in $\dot{V}O_{2\text{max}}$ normalized to body weight between children ($45.4 \pm 5.8 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) and adults ($38.2 \pm 10.9 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$).

Exercise and ³¹P-MRS

³¹P-MRS spectra during exercise in a representative adult and child are shown in Figs. 1 and 2, respectively. No significant differences were observed at rest in pH (children 7.04 ± 0.03 , adults 7.04 ± 0.02), P_i /PCr (children 0.22 ± 0.09 , adults 0.17 ± 0.02), or PCr/ β -ATP (children 2.85 ± 0.35 , adults 3.19 ± 0.55) between children and adults. The maximal work performed, even when normalized to body weight, was significantly higher in adults ($0.12 \pm 0.02 \text{ psi/kg}$) than in children ($0.08 \pm 0.02 \text{ psi/kg}$; $P < 0.001$).

P_i /PCr Ratio

Examples of P_i /PCr and pH changes during exercise in one adult and one child are shown in Figs. 3 and 4, respectively. During exercise, P_i /PCr significantly increased in

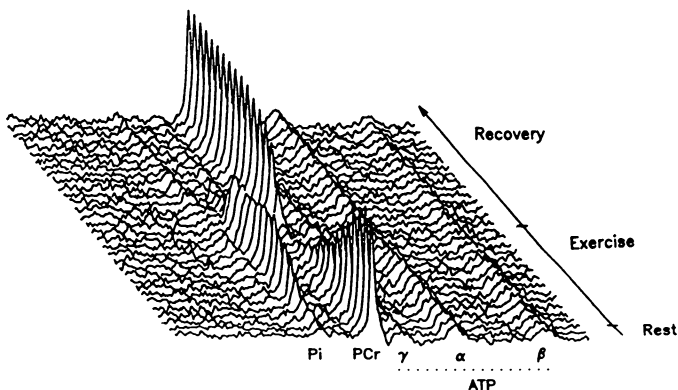


FIG. 1. ³¹P-nuclear magnetic resonance spectroscopy (³¹P-MRS) spectra from right calf of 35-yr-old man at rest, during incremental plantar flexion to exhaustion, and recovery. PCr, phosphocreatine.

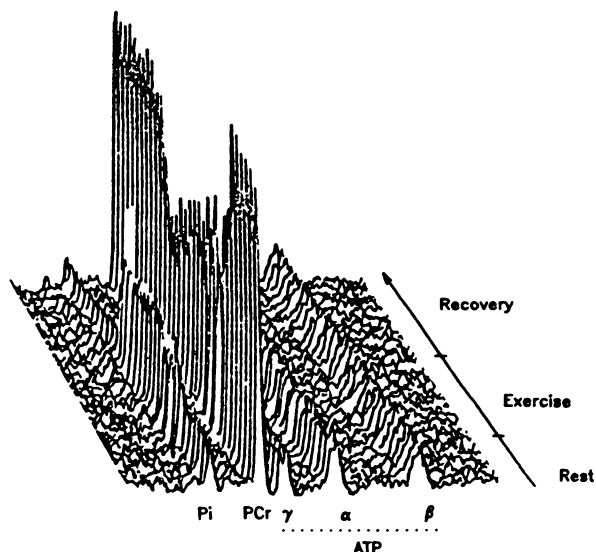


FIG. 2. ^{31}P -MRS spectra from right calf of 8-yr-old boy at rest, during incremental exercise, and recovery.

both groups ($P < 0.01$), reaching a mean end-exercise value of 0.54 ± 0.12 in children and 2.00 ± 0.79 in adults. The increase in P_i/PCr from rest to end exercise was significantly higher in adults than in children ($P < 0.001$). A slow phase (first slope) and a fast phase (second slope) of P_i/PCr increase during exercise were found by visual inspection in six adults, and the transition occurred at a mean work rate of 0.05 ± 0.01 psi/kg ($40 \pm 5\%$ of the maximal work rate). Similarly, a transition was observed in five children at 0.05 ± 0.01 psi/kg ($62 \pm 16\%$ of the maximal work rate). This transition corresponded to a P_i/PCr value of 0.45 ± 0.08 in children and 0.60 ± 0.17 in adults. No significant difference was found in the first slope of P_i/PCr to work rate between children (5.9 ± 1.9) and adults (7.4 ± 4.0). However, the second slope was significantly steeper in adults (23.6 ± 9.8) than in children (10.7 ± 2.5 ; $P < 0.05$).

pH

There was a significant decrease in pH with exercise in both children and adults ($P < 0.001$). The decrease observed from rest to end exercise was significantly greater in adults (0.36 ± 0.11) than in children (0.11 ± 0.05 ; $P <$

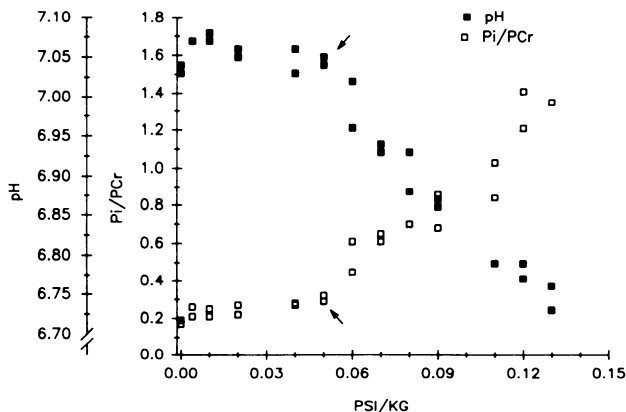


FIG. 3. P_i/PCr and pH at rest and during incremental exercise in 33-yr-old man. Arrows, transition points between slow and fast phases of P_i/PCr increase and pH reduction.

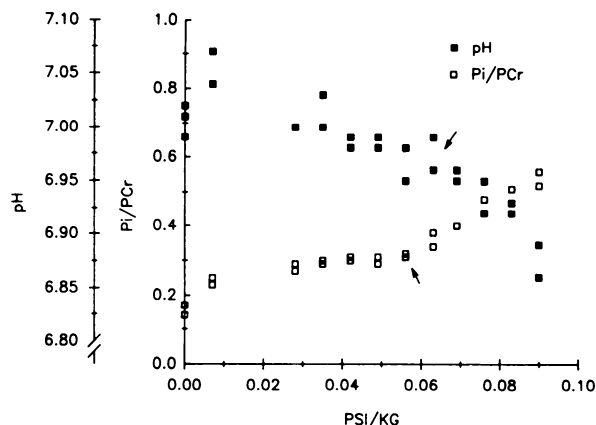


FIG. 4. P_i/PCr and pH at rest and during incremental exercise in 9-yr-old girl. Arrows, transition points between slow and fast phases of P_i/PCr and pH changes.

0.001). A slow phase (first slope) and a fast phase (second slope) of pH decrease were identified by visual inspection in six adults and five children, and the transition occurred at the same time as did the transition for P_i/PCr data. The first slope of pH to work rate was not different between children (-0.45 ± 1.42) and adults (-0.35 ± 1.04). In contrast, during the fast phase, pH declined more rapidly in adults (-6.02 ± 1.89) than in children (-3.74 ± 1.17 ; $P < 0.05$).

Relationship Between pH and P_i/Pcr

Negative linear relationships were found between pH and P_i/PCr in both children and adults. However, no significant differences were found between children and adults for the slope (children -0.23 ± 0.13 , adults -0.22 ± 0.08) or the intercept (children 7.14 ± 0.08 , adults 7.09 ± 0.08) (Fig. 5).

$\text{PCr}/\beta\text{-ATP}$ and $\beta\text{-ATP}$

Neither group showed a significant change in the area of the $\beta\text{-ATP}$ peak during exercise. $\text{PCr}/\beta\text{-ATP}$ fell progressively with exercise in both children (end-exercise value 1.9) and adults (end-exercise value 1.4). Adults showed a greater drop in $\text{PCr}/\beta\text{-ATP}$ than did children ($P < 0.01$).

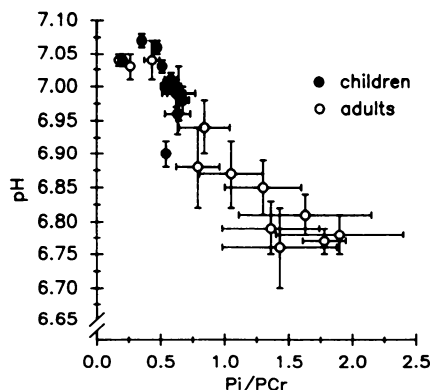


FIG. 5. Relationship of pH to P_i/PCr at rest and during incremental exercise in children and adults. Data are means \pm SE.

DISCUSSION

This study shows that during high-intensity exercise, muscle P_i/PCr increases to a smaller extent in children than in adults even when the data are scaled appropriately for body size. In addition, children show a smaller drop in intramuscular pH. A slow phase and a fast phase of P_i/PCr increase and pH decrease were noted in 75% of the adults and 50% of the children.

As leg muscle work rate increases, ADP and P_i are released from the breakdown of ATP and PCr. Current theory holds that ADP and P_i regulate the rate of oxidative phosphorylation precisely so that homeostasis of the ATP concentration is obtained (7). As the rate of ATP hydrolysis approaches the maximal rate of tissue oxidative phosphorylation, glycolysis (similarly activated by ADP and P_i) assumes an increasing proportion of the metabolic burden (7). In adult healthy subjects, the relationship between P_i/PCr and work rate is characterized by an initial linear portion. The slope of P_i/PCr to work rate is directly proportional to the rate of mitochondrial oxidative metabolism. This is followed by a second steeper slope that is associated with disproportionate activation of glycolytic processes (8), resulting in net production of lactic acid and increased $[H^+]$. Therefore, ^{31}P -MRS can indirectly monitor glycolytic activity by measuring intracellular pH.

The initial linear slope was the same in children and adults, suggesting a similar rate of mitochondrial oxidative metabolism during low-intensity exercise. However, the different responses in P_i/PCr and pH during high-intensity exercise indicate growth-related differences in energy metabolism in the high-intensity exercise range.

Our data might suggest that children have a higher rate of muscle oxidative phosphorylation during heavy exercise than adults. A greater O_2 utilization could result from factors that influence mitochondrial oxidative ATP resynthesis: delivery of O_2 from the capillary blood, delivery of substrates, or greater density of mitochondrial population. Each of these factors might be responsible for a greater O_2 -dependent ATP generation, lower P_i/PCr , and higher pH during exercise in children.

However, a more efficient oxidative metabolism in children alone should not inhibit the glycolytic capability. As work rate increases, the children, like the adults, would eventually require glycolysis and its accompanying lactate production as an additional mechanism of ATP rephosphorylation. This phenomenon is observed after training; although anaerobic metabolism occurs at higher work rates than pretraining, lactate levels ultimately achieved are significantly higher (15).

Alternatively, there could be less functional glycolytic capability in children so that the rate of glycolysis may not be sufficient to meet muscle energy requirements and would result in early muscle exhaustion. The minimal drop in pH seen in children with heavy exercise demonstrates that even after the transition point, i.e., when further energy sources appear to be required, the glycolytic processes play less of a role. Moreover, the children achieved an end-exercise P_i/PCr of 0.54 ± 0.12 (only 27% of adult values). This indicates that soon after the threshold, when the oxidative rate has presumably reached its

maximum, children can no longer sustain muscular contraction.

A potential limitation of the present study relates to the surface coil size. Our coil allows examination of a hemisphere of tissue with a radius of ~ 5 cm. Because of the different sizes of the subjects, there undoubtedly were some differences in the relationship of the surface coil to active muscle. However, within each group, our results were independent of the subjects' size. In addition, weight and height for the smallest adults were comparable to those of the biggest children.

It could also be argued that the children did not reach their real maximal work rate. Objective criteria for maximal effort are not easy to define even for cycle ergometry, let alone single-leg treadle exercise. The children were told that they would be doing a hard exercise and were actively encouraged throughout the test. In addition, a transition in the P_i/PCr to work rate slope, i.e., a critical point in the cellular energy metabolism, was observed in 50% of the children at 62% of the maximal work rate. The same value (62%) was reported for the ratio of anaerobic threshold to $\dot{V}O_{2\max}$ in children of comparable age during maximal cycle ergometer exercise (9).

The results of this study are consistent with previous studies that reported growth-related differences in gas exchange response to high-intensity exercise. A higher CO_2/O_2 cost ratio (i.e., higher acidosis) for 1 min of heavy exercise was observed in adults compared with children (2). For constant work rate heavy exercise, $\dot{V}O_2$ approaches a steady state by the 3rd min in children, whereas in adults it constantly increases (1) [as noted, $\dot{V}O_2$ slope has been suggested to be related to blood lactate (21)]. Bar-Or (3) reported a lower anaerobic capacity (measured by a supramaximal 30-s cycle ergometer test-Wingate anaerobic test) in young children compared with adolescents and adults. In addition, in the few invasive studies that have been done in children, blood and muscle lactate concentrations at high-intensity exercise are lower in children than in adults (14, 19).

Our results cannot be explained by a faster lactate removal or subsequent metabolism in children. Because we measured P_i/PCr , we could determine changes in glycolysis independent of changes in pH. If glycolysis had increased with a simultaneous increase in lactate removal, then we ought to have found a more rapid increase in P_i without a parallel drop in pH in children. This was not the case, as seen in the relationship between P_i/PCr and pH, which was the same in children and adults.

Both phosphofructokinase (PFK) and glycogen phosphorylase are key regulatory enzymes of glycolysis, but little attention has been paid to a possible maturational pattern of their activity. Eriksson et al. (13) reported a lower muscle concentration of PFK in 11- to 13-yr-old children compared with adults. In addition, studies in rats showed a 17-fold increase in total PFK activity occurring during the first 2 mo of age (equivalent to birth to puberty in humans). This was accompanied by a dramatic decrease in C-type PFK subunit and an increase in M-type subunit, the isozyme best suited for glycolysis (12). Finally, low levels of C-type PFK subunit have been shown to promote increased affinity for fructose 6-phosphate and diminished susceptibility to ATP inhibition

(10, 11). Maturation of the muscle metabolic response to exercise might be related to the hormonal changes (increase in testosterone, estradiol, growth hormone, and insulin-like growth factor I) that occur during puberty (18). To date, little is known about the effect of these hormones on functional and structural muscle growth. Testosterone has been shown to increase sarcotubular and mitochondrial enzymes in mature male subjects (22). In addition, Kelly et al. (17) demonstrated that testosterone administration stimulated the transition from type IIa (fast oxidative glycolytic) to type IIb (fast glycolytic) fibers in guinea pig temporalis muscles.

A maturation of skeletal muscle fiber type pattern might also account for growth-related differences in the metabolic response to high-intensity exercise. In particular, the children studied may have had a higher proportion of slow fibers. However, to date a few small studies examining biopsies of human diaphragm (16) and hind-limb muscles (5) demonstrated that fiber type differentiation occurs relatively early in life and that by 6 yr of age the skeletal muscle histochemical profile is similar to that of a young adult.

In conclusion, muscle high-energy phosphate kinetics during high-intensity exercise are different in children and adults. In this range of work children seem to rely less on anaerobic glycolytic metabolism than do adults. Our results suggest that ^{31}P -MRS spectroscopy during exercise may prove useful in identifying abnormal muscle metabolism and in assessing the value of therapeutic approaches designed to improve exercise tolerance in children with a variety of disease.

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