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Biochemistry

Energy metabolism of the untrained muscle of elite runners as observed by ^{31}P magnetic resonance spectroscopy: Evidence suggesting a genetic endowment for endurance exercise

(exercise physiology/muscle metabolism/NMR)

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ABSTRACT **The purpose of this study was to investigate whether genetically determined properties of muscle metabolism contribute to the exceptional physical endurance of world-class distance runners. ATP, phosphocreatine, inorganic phosphate, and pH were quantitatively determined by ^{31}P nuclear magnetic resonance spectroscopy in the wrist flexor muscles of elite long-distance runners and sedentary control subjects. These muscles had not been exposed to any specific program of exercise training in either group of subjects. The "untrained" muscles were examined at rest, during two cycles of three grades of exercise, and in recovery. The flexor muscles of the athletes had higher concentrations of phosphocreatine and ATP than did those of the control subjects at rest and during exercise. The athletes' muscles possessed a higher capacity for generation of ATP by oxidative metabolism than did control subjects' muscles according to the following criteria: (*i*) high force output, 60% of maximum voluntary contraction, was more easily reached and better maintained in both exercise cycles; (*ii*) the ratio of inorganic phosphate to phosphocreatine rose less during exercise and recovered faster in the postexercise period; (*iii*) there was no loss of adenine nucleotides or total phosphate from the athletes' muscles but significant losses from the control subjects' muscles; and (*iv*) the pH decreased no more than 0.1 unit in the athletes' muscles during exercise, attesting to a relatively slow glycolysis and/or a rapid oxidation of lactate. In the muscles of the control subjects, on the other hand, the pH decreased nearly 0.4 unit early in the first exercise cycle, indicating a relatively fast glycolysis and/or slower oxidation of lactate. In the second exercise cycle, the pH returned to near normal in the control subjects' muscles, reflecting diminished lactate formation because of glycogen depletion and lactate washout by the high blood flow induced by exercise. By the end of the exercise program, the maximum voluntary contractile force for the control subjects had declined to <60% of the initial value. This decline could be explained best by exhaustion of the glycolytic contribution to muscle contraction. Therefore, the residual maximum strength provided a measure of the oxidative capacity to support contraction, as is discussed. In conclusion, we suggest that a greater oxidative capacity relative to glycolytic capacity for support of contraction in untrained muscle of world-class runners reflects a genetic endowment for physical endurance. Additional systemic effects of training cannot be completely excluded. ^{31}P magnetic resonance spectroscopy provides a noninvasive method for assessing this endowment.**

This study compares the metabolic characteristics of untrained muscles of elite long-distance runners with those of nonathletic control subjects. The wrist flexor muscles of the forearm were chosen for study because they were "untrained"; that is, no specific exercise program involving these muscles was undertaken. The muscles were examined by ^{31}P magnetic resonance spectroscopy (*in vivo* NMR) at rest, during two cycles of graded exercise, and in recovery. It seemed possible that constitutional (genetic) differences in metabolism between the athletes and the controls as distinct from effects of training might be revealed in these untrained muscles. These differences could help to explain why world-class runners can reach levels of physical endurance unattainable by all but a very few persons regardless of the training program.

There are no earlier measurements of metabolites in untrained muscle of athletes to our knowledge. However, Jansson and Kaijser (1) found an unexpectedly high percentage of oxidative [type I (slow twitch)] fibers in the relatively untrained deltoid muscle of elite orienteers¶ which led them to suggest that this could be a constitutional rather than a training attribute of endurance athletes. Most prior studies of metabolites in exercising muscle required repeated biopsies (for review, see ref. 2). The variety of metabolites that can be determined in biopsied material by chemical analysis is greater than that by ^{31}P magnetic resonance spectroscopy. However, the latter procedure is noninvasive, allows an unlimited number of *in vivo* measurements during prolonged exercise (3–5), and can be used to estimate ATP and phosphocreatine (*P*Cr) and to determine the physiologically relevant concentrations of P_i and free ADP more reliably than by chemical analyses. Magnetic resonance spectroscopy has the further advantage that a relatively large and therefore more representative mass of tissue is examined. The technique is also uniquely capable of measuring tissue pH noninvasively, a particularly valuable parameter for this investigation.

Some of the methodology in this work was developed in our earlier studies in which steady-state exercise was quantified and the recruitment of oxidative fibers [mostly types I and IIA (intermediate fast twitch)] was differentiated from recruitment of glycolytic fibers [type IIB (fast twitch)] by ^{31}P magnetic resonance spectroscopy during exercise in certain cases (4, 6). An approach to quantitating by this technique the relative maximum oxidative and glycolytic capacities to support muscle contraction is proposed here.

METHODS

Subjects. The athletes were screened by an expert track coach (R.L.B.). They were world-class long-distance runners, three males and one female, ages 26, 28, 28, and 35

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Abbreviations: MVC, maximum voluntary contraction; *P*Cr, phosphocreatine.

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¶Orienteering is a sport that demands a high level of endurance running.

years. One was a recent world champion in the 1500-m race; another was an Olympic alternate for the United States in the marathon, and the others were close to these individuals in performance. They were all in training programs consisting essentially of running from 55 to 100 miles per week (1 mile = 1.609 km).

The control subjects were 4 men and 1 woman, age range 20–23 years. All were sedentary but healthy and nonobese. Only one subject engaged in any routine exercise. This consisted of walking 2 miles per day and playing 1.5 hr of tennis per week.

Instrumentation. The forearm of the seated subject was held by Velcro straps on a platform in the 27.6-cm bore of a 1.9-Tesla superconducting magnet. Spectra were acquired with a Fourier-transform magnetic resonance spectrometer [TMR 32 (Oxford Research Systems, Oxford) or PE 280 (Phosphoenergetics, Philadelphia)]. The wrist flexor muscles of the upper forearm were held firmly by Velcro straps against an inductively driven coil, 4 cm in diameter (7, 8), in the homogeneous region of the magnet. The subject depressed an exercise bar by flexion of his wrist, and the force was recorded by a Cybex ergometer (Lumex, Ronkonkoma, NY) (3, 7). For all subjects, data from both dominant and nondominant arms have been averaged in the presentation of results.

Exercise Protocol. To determine the initial maximum voluntary contractile force (MVC), the subject exerted his maximum effort to depress the exercise bar. This effort was repeated three times at 1-min intervals, and the highest force was noted. After a rest period of 5–8 min, the subject began the first cycle of exercise (1–18 min). He depressed the bar by flexing his wrist once every 5 s for a 6-min interval, adjusting the force to 20% of his initial MVC. Without intervening rest, the subject continued for two further 6-min intervals, increasing his force output to 40% and then 60% of initial MVC, respectively. Exceptions will be noted. Without interruption, a second 18-min cycle (19–36 min) of 20%, 40%, and 60% MVC was executed, giving a total exercise time of 36 min. The subject then rested for a recovery period of 3 min.

Magnetic Resonance Spectroscopy Measurements. At the outset of each exercise trial, the magnetic field was adjusted for maximal proton resolution (≈0.4 ppm). The proton spectrum obtained at 80.3 MHz was used to calculate the percent lipid content from the total water and lipid protons in the tissue examined. Spectra of ^{31}P metabolites were acquired at 32.5 MHz, with a pulse of 45 μs and a repetition time of 5 s. The pulse was timed to occur 4 s after each contraction. First, a spectrum was acquired during 3 min with the muscles at rest. Subsequent spectra were accumulated during each minute of exercise, but only the summation of the last 3 min of each 6-min interval has been plotted in the figures. The spectra accumulated during the last 2 min of the post-exercise recovery period were normalized to 3 min. The resonance areas of P_i, *P*Cr, and ATP were determined by a nonlinear least-squares curve-fitting program and/or by triangulation (4, 6). The proportionality factor to convert all resonance areas to concentrations of P-containing metabolites for all subjects was derived by assuming that the area of the β-P peak of ATP for the control subjects at rest was 5.5 mmol of ATP per kg (wet weight) of muscle, as determined in biopsy samples from comparable subjects by Harris *et al.* (9). Concentrations of P_i and *P*Cr were corrected by factors of 1.18 and 1.29, respectively, to account for saturation effects. The chemical shift of P_i, with *P*Cr set at zero, was used to estimate pH (5). An example of the spectra obtained at rest and during the first exercise cycle (1–18 min) is shown in Fig. 1.

Statistical comparisons of the runners and control subjects at a specified time interval were performed by using the two-tailed Student *t* test.

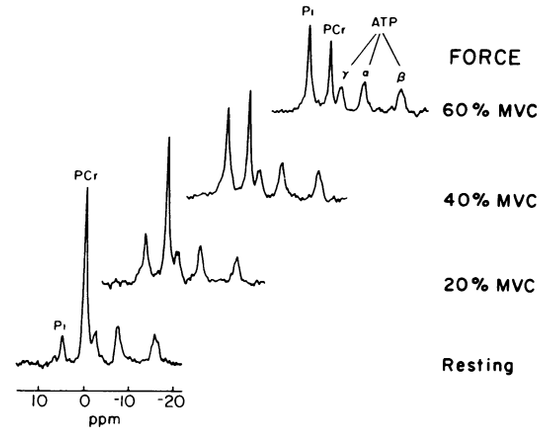

FIG. 1. ^{31}P magnetic resonance spectra and force measurements (% MVC) of wrist flexor muscles of a championship long-distance runner at rest and during contraction at three levels of exercise during the first cycle of the protocol (1–18 min). Ergometer measurements (% MVC) were obtained as described. Spectra were acquired during the last 3 min of each 6-min interval and plotted with 10-Hz line broadening. The times of force measurements and spectral data collection were: 20% MVC, 4–6 min; 40% MVC, 10–12 min; and 60% MVC, 16–18 min.

RESULTS

Contractile Force Exerted During Exercise. The elite runners could maintain without difficulty the highest level of contractile force (60% of the initial MVC) in the final interval of both the first and second cycles of the exercise protocol (13–18 min and 31–36 min, respectively). The control subjects, on the other hand, maintained the level of 60% MVC with some difficulty in the first cycle (13–18 min) as shown by the relatively large standard error (±3.1%) of the force measurement as compared with that (±0.9%) for runners. In the second cycle, half of the trials by control subjects did not reach the 60% MVC level (31–36 min), presumably because of exhaustion of the glycolytic component of muscle contraction (average MVC, 51% ± 4.4%). The performance of one subject who could not achieve 60% MVC is plotted in Fig. 2. After the sharp decline of force output from 55% MVC, a new steady state appeared to be established at 38% MVC.

Concentrations of P Metabolites During the Exercise Protocol. The concentration of *P*Cr in the resting untrained muscles of the athletes was 25% higher than that in the muscles of control subjects (Fig. 3 *Upper*), and it remained higher throughout the protocol (P = <0.02 to <0.01). These

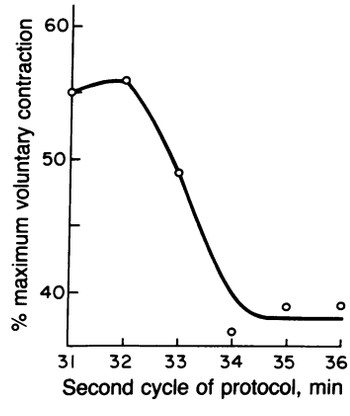

FIG. 2. Decline of contractile force in the wrist flexor muscles of a control subject unable to achieve 60% MVC during the last 6-min interval (31–36 min) of the exercise protocol.

differences were not explained by a difference in lipid content that was 11 ± 5% in the forearm of the athletes and 14 ± 5% in the control subjects. *P*Cr levels decreased about 60% in the first exercise cycle (1–18 min) in both groups. During the first interval of the second cycle (19–24 min), when the force output was decreased from 60% to 20% MVC, the *P*Cr level increased twice as rapidly in the athletes as in the control subjects. Similarly, in the postexercise recovery period, *P*Cr was regenerated 1.5 times faster in the athletes, indicative of a higher oxidative metabolism in their muscles.

The average P_i concentration in resting flexor muscles of the runners was significantly higher than in the control subjects ($P = <0.02$). However, concentrations of P_i during the first cycle of exercise (1–18 min) were the same in both groups of subjects (Fig. 3 *Lower*). In the second exercise cycle (19–36 min), the increase in P_i in the athletes duplicated that seen in the first cycle—evidence of the remarkable uniformity of metabolism that characterized this group. For the control subjects, however, the increase of P_i in their second exercise cycle was significantly less than in the first cycle, indicating a change in metabolism as exercise proceeded. This lower concentration of P_i at the end of the second cycle (31–36 min) correlated with a lower level of total P (see Fig. 5) and a lower percent MVC (53%) in the control subjects (Fig. 3). In the postexercise recovery period, P_i decreased rapidly to the resting level in the athletes' muscles, but remained slightly elevated in the control subjects' tissues.

A lower P_i/PCr ratio was seen in the athletes than in control subjects at all levels of exertion except the last 60% MVC (Fig. 4). The lower ratio was indicative of a greater

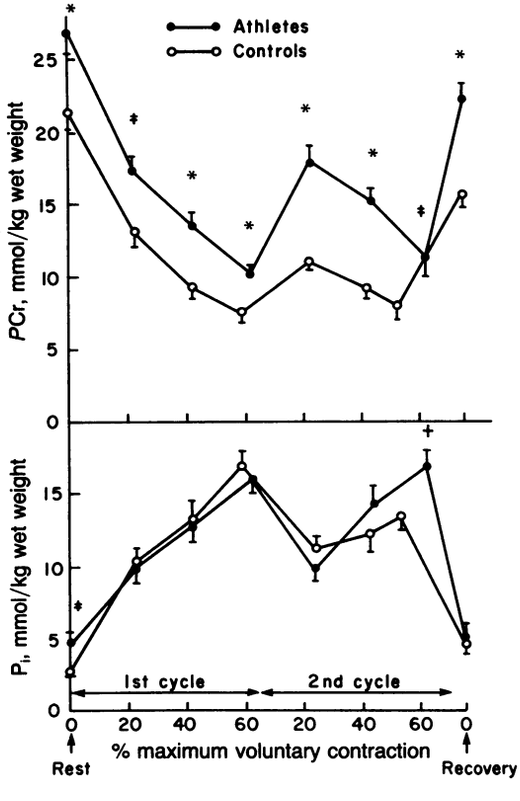

FIG. 3. Mean concentrations of *P*Cr and P_i in the wrist flexor muscles of elite long-distance runners and control subjects at different levels of contractile work during the exercise protocol. *P*Cr and P_i concentrations were determined from the resonance areas as described. The spectral data and force measurements (% MVC) in the figure represent the average values for the last 3 min of each 6-min interval during two exercise cycles. Significant differences between the two groups of subjects are indicated as follows: †, $P = <0.05$; ‡, $P = <0.02$; *, $P = <0.01$. Vertical bars = 1 SEM.

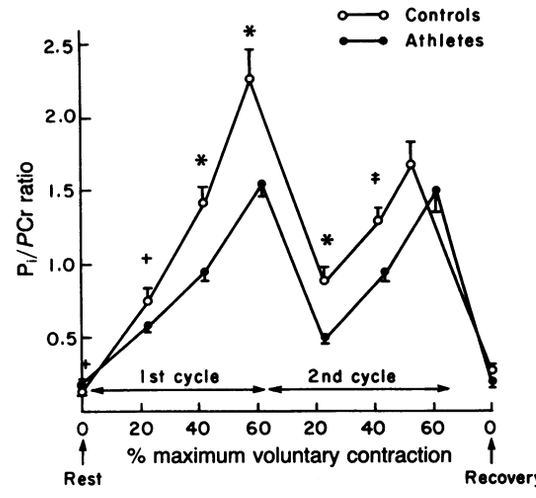

FIG. 4. P_i/PCr ratios in the wrist flexor muscles of athletes and control subjects at different levels of contractile work during the exercise program. The P_i/PCr ratios were calculated from the values in Fig. 3. Significant differences between the two groups of subjects are indicated as follows: †, $P = <0.05$; ‡, $P = <0.02$; *, $P = <0.01$. Vertical bars = 1 SEM.

capacity of the athletes to maintain energy-rich phosphate. For the runners, the changes in the P_i/PCr ratio with time were identical in the first (1–18 min) and second (19–36 min) exercise cycles, a further evidence of their uniform metabolism. At their highest MVC (62%), the P_i/PCr ratio was 1.5. In the case of the control subjects, the P_i/PCr ratio was very high (2.3) at the end of the first cycle (16–18 min). It rose less, however, during the second cycle (19–36 min) possibly because of P loss (Fig. 5) and a decline in the force output to 51% MVC.

Resting levels of adenine nucleotide phosphate (sum of α-, β-, and γ-P peaks) and ATP alone (β-P peak) in the untrained flexor muscles of the athletes were 20% higher than in control subjects ($P = <0.02$) (Fig. 5 *Middle* and *Bottom*). In the athletes' first exercise interval (1–6 min), the total adenine nucleotides decreased ≈20% in concentration. The nucleotide levels then stabilized and tended to increase in the second cycle (19–36 min). Likewise, the ATP level in the runners decreased significantly with the onset of exercise ($P = <0.02$) but had regained the initial value by the postexercise recovery period. By contrast, in the controls the adenine nucleotides drifted downward with continued exercise, leading to significant differences in concentrations between athletes and controls during the second exercise cycle and postexercise recovery ($P = <0.02$ to <0.01). For the control subjects, the overall losses of adenine nucleotide P and ATP during exercise were significant ($P = <0.02$).

The sum of phosphate in adenine nucleotides, *P*Cr, and P_i, termed "total P," for athletes and control subjects is shown at the top of Fig. 5. The initial level of total P was 25% higher in the resting muscle of athletes ($P = <0.01$). The value for the runners decreased 15% with the onset of exercise (1–6 min) and thereafter essentially stabilized. In the control subjects, there was an initial decrease in total P of about 8%. A further significant decrease occurred during the second exercise cycle (19–36 min) and the postexercise recovery period ($P = <0.01$). During that time, the concentrations of these metabolites became significantly different between the athlete and control groups ($P = <0.01$).

pH Changes During the Exercise Protocol. The initial pH at rest was 7.04 ± 0.01 in the flexor muscles of the athletes, and it decreased no more than 0.1 pH unit at any time during exercise (Fig. 6). In the controls, the initial pH was 7.03 ± 0.02, but it decreased 0.35 ± 0.07 unit during the first exercise

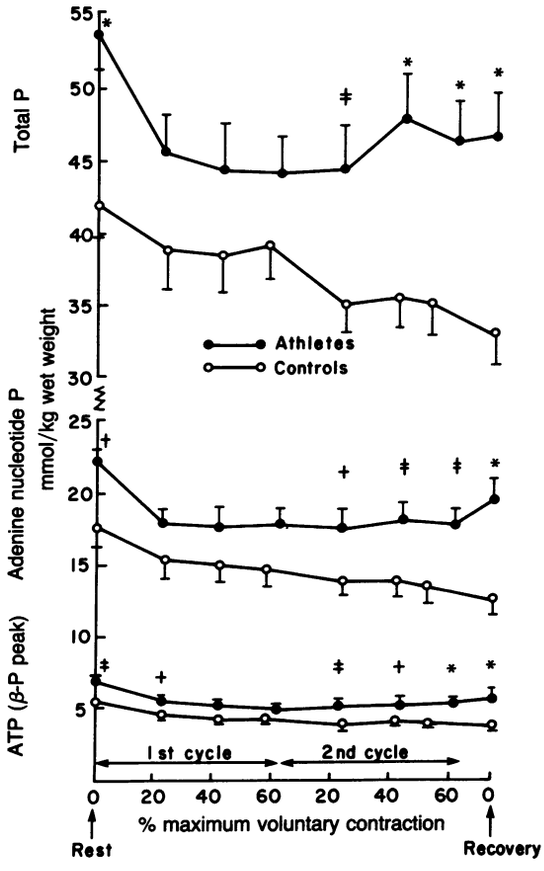

FIG. 5. Concentrations of adenine nucleotide P, ATP, and total P in the wrist flexor muscles of long-distance runners and control subjects at different levels of contractile force during two exercise cycles. Concentrations of total P, adenine nucleotide P (sum of α-, β-, and γ-P peaks, which include ATP, ADP, and NAD), and ATP alone were calculated as described. The data are plotted as in Fig. 3. †, $P = <0.05$; ‡, $P = <0.02$; *, $P = <0.01$. Vertical bars = 1 SEM.

cycle ($P = <0.001$) (Fig. 6). It then increased sharply by about 0.2 unit to pH 6.87 at the start of the second cycle at 20% MVC (19–24 min) and continued to increase thereafter despite the rise in work output to 40% and 51% MVC (25–36 min). These pH changes in the control group suggested a marked dependence on glycolytic metabolism during the first

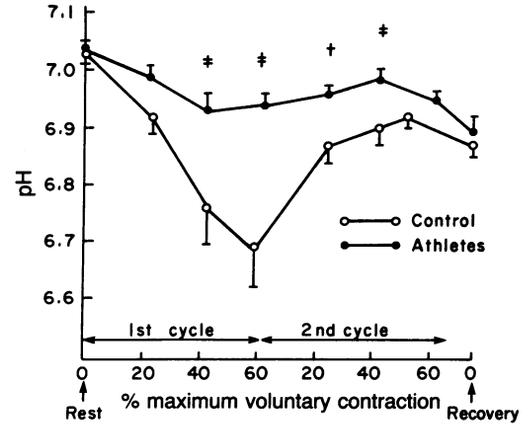

FIG. 6. The pH of the wrist flexor muscles of the runners and control subjects at different levels of contractile force during the exercise program. The pH was determined by the chemical shift of P_i as described. †, $P = <0.05$; ‡, $P = <0.02$; *, $P = <0.01$. Vertical bars = 1 SEM.

cycle of exercise and on oxidative metabolism in the second cycle. In the postexercise recovery period, the pH decreased 0.05 unit in both groups of subjects, consistent with a rapid *P*Cr resynthesis.

DISCUSSION

Concentrations of P Metabolites in Muscles at Rest. The higher concentrations of *P*Cr, adenine nucleotides, and P_i (25%, 22%, and 54%, respectively) in the resting forearms of the athletes as compared with those of the control subjects (Figs. 3 and 5) reflected greater concentrations in the muscle tissue itself since the correction for the greater adipose content of the control tissue was only about 3%. The content of these metabolites in adipose tissue is relatively low. Biopsy determinations in trained muscles of athletes have shown higher (10) or no (11) differences in ATP and *P*Cr concentrations compared to controls, but no measurements have been reported for untrained muscle in athletes. The higher concentrations of ATP and *P*Cr would contribute little to endurance performance because they do not constitute quantitatively significant energy reservoirs. However, higher concentrations may manifest a greater potential for synthesis of high-energy phosphate (3, 4).

Alterations in ATP and Adenine Nucleotide P Levels During Exercise. The initial decreases in the total adenine nucleotide P and ATP concentrations (Fig. 5), which occurred with the onset of exercise at 20% MVC (1–6 min), did not appear to be due to loss of magnetic resonance spectroscopic visibility since they have been noted earlier in biopsy studies of exercise (10, 12). There are several possible explanations for this altered "initial state" biochemistry. The onset of exercise establishes a major, continuing drain on ATP, which induces a lower steady-state concentration of the nucleotide despite ATP resynthesis via creatine kinase, mitochondrial phosphorylation, and/or glycolysis. Furthermore, there may be a lag between the drop of ATP in the myofibrils and activation of mitochondrial ATP synthesis via the creatine shuttle (13); the "Ca^{2+} burst," postulated to occur at the initiation of exercise (14), could preempt ATP for restoration of Ca^{2+} to the threshold concentration. Finally, the microcirculation may not have increased fast enough to keep pace with the O_2 requirement in the mitochondria.

After the initial decrease in ATP concentration, the stabilization of adenine nucleotides in the untrained muscles of athletes, even at high levels of exercise (7–36 min), is evidence for superior oxidative metabolism. The progressive decrease in nucleotide concentrations in the muscles of the control subjects involved equivalent losses in the α-, β-, and γ-P components, indicating that ATP was degraded beyond ADP. These losses could be best explained by a slower oxidative regeneration of ATP, thereby causing accumulation of AMP, which would promote its degradation to adenosine and inosine. The latter compounds pass out readily through the sarcolemma (15). Calculated values for ADP concentrations (3) at 20%, 40%, and 60% MVC in the first exercise cycle were 37, 51, and 82 μM, respectively, in the control subjects' muscles as compared with 20, 38, and 59 μM in the runners' muscles. The lower concentrations are consistent with a larger V_{max} for mitochondrial oxidative metabolism in the runners, assuming $K_{m(ADP)}$ to be 20 μM in all cases (16).

Alterations in Total P and P_i During Exercise. It appeared that total P was lost from the muscle in the first 6 min of exercise (Fig. 5) because there were no compensatory increases in phosphate mono- or diesters as observed by ^{31}P magnetic resonance spectroscopy (data not shown). The loss may have been due in part to the efflux of adenosine and inosine already noted and associated P_i. The continued loss in the control subjects during the second exercise cycle and postexercise recovery period presumably resulted from rel-

atively inadequate ATP resynthesis and accelerated ADP degradation. It was observed (Fig. 3) that P_i was the only parameter that did not differ in value between the two groups during the first 30 min of the protocol. This suggests that there may be physiological constraints on P_i concentration which, in turn, may be related to the partial metabolic control of contraction by P_i (17). However, in the last 6 min of the protocol (30–36 min), the P_i increased significantly less in the control group as compared with the runners, possibly because of excessive loss of P_i and the beginning of the failure of force output by control subjects.

pH Changes During Exercise. The pattern of pH change provided the clearest indication of the greater oxidative capacity of the runners' muscles (Fig. 6). The relatively small pH change in the runners' forearms is consistent with a major participation of oxidative fibers as compared with glycolytic fibers at all levels of exercise. The marked decrease in pH seen with the control subjects in the first cycle of exercise (1–18 min) was doubtless due to greater glycolytic activity, leading to lactate accumulation, and to relatively less oxidative capacity. There is much evidence (1, 18–20) to indicate that glycolysis is activated as oxidative metabolism fails to meet energy needs. In the second cycle of exercise (19–36 min), the return of the pH to near the resting value in the control muscles is best explained by a sharp decrease in glycolysis as a consequence of glycogen depletion (1, 19, 20). The previously accumulated lactate was metabolized to some extent and, more importantly, was washed out by the increase in blood flow engendered by exercise. With little residual glycolysis and substantial *P*Cr and ATP depletion in the fast-twitch fibers (4, 20), oxidative metabolism now provided virtually all of the energy for contraction. It was insufficient in several control subjects to achieve the 60% MVC level. In the runners, however, 60% MVC was not sufficiently high to activate glycolysis, at least to the point of lowering the pH.

The Oxidative V_{max}. Chance *et al.* (3) developed a simple procedure to quantify the fraction of maximal oxidative metabolism (V/V_{max}) that is used at any time during work that employs only oxidative fibers. This condition occurs with exercise at very low work loads, a condition that was most nearly approximated here at the 20% MVC level. Calculations of V/V_{max} based upon the ADP values as calculated above gave values of 50% and 65% for runners and control subjects, respectively (3, 7). Consequently, at a work load of 20% MVC, the runners were able to work at a 15% lower V/V_{max} than the nonrunners. The superior oxidative capacity of the runners compared to nonrunners is thus quantified.

The results in this paper suggest an experimental method for determining the oxidative V_{max} and the glycolytic V_{max} by measurements made at the highest work loads. The oxidative V_{max} can be evaluated in those cases in which the glycolytic capacity has been exhausted and only oxidative capacity remains effective as was suggested for a single subject as shown in Fig. 2. In the control group as a whole, the 60% of initial MVC in the second exercise cycle could not be reached in 4 of 10 trials. The average value reached with maximal exertion (41% MVC) by this subgroup was now a measure of their average oxidative V_{max}. Based on those observations, a more generally applicable protocol could be designed that first would exhaust the glycolytic capacity by a progressive increase in the contractile force to a high level. Immediately thereafter, the force output should be reduced to a level low enough to allow the pH to return to normal but high enough to prevent resynthesis of glycogen. At that point, a MVC measurement would indicate the oxidative V_{max}. The difference between the initial MVC and this oxidative V_{max} would yield the glycolytic V_{max}.

Genetic Endowment for Endurance Exercise. There are two major differences between this investigation and earlier studies of muscle metabolism in athletes. First, the tissue was examined by ^{31}P magnetic resonance spectroscopy rather than by biopsy. Some advantages of magnetic resonance spectroscopy were noted in the introduction, and this study demonstrates particularly its value for P_i and pH determinations. Second, the muscles studied were not those involved in athletic performance and training. The flexor muscles of the wrist remain flaccid during running,[‖] and the subjects engaged in no program that would train them. We have postulated that examination of metabolism during exercise of untrained muscles could reveal some of the constitutional properties that underlie the high performance of elite athletes. The possibility that athletic training could affect untrained muscle cannot be rigorously excluded. It is well known that the endurance athlete increases his cardiac output by training, but the exercise used in our study would put only a very small demand on the circulatory capacity even of the sedentary subjects. The pulse rate, for example, rose only about six to eight points. We are unaware of any evidence that humoral or neuromuscular factors are generated in exercising muscle that increase oxidative capacity in resting muscle. Therefore, evidence from the present study suggests that a superior oxidative capacity for energy production in muscle is an important genetic attribute. Multiple genes determining muscle fiber composition, enzyme makeup, and neuromuscular elements may contribute to increase this capacity.

[‖]This statement is based on observations by one of the authors, R.L.B., who has many years of experience as a professional coach of elite runners.

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