Exertional Rhabdomyolysis during a 246-km Continuous Running Race

KATERINA P. SKENDERI, STAVROS A. KAVOURAS, COSTAS A. ANASTASIOU, NIKOS YIANNAKOURIS, and ANTONIA-LEDA MATALAS

Laboratory of Nutrition and Clinical Dietetics, Department of Nutrition and Dietetics, Harokopio University, Athens, GREECE

ABSTRACT

SKENDERI, K. P., S. A. KAVOURAS, C. A. ANASTASIOU, N. YIANNAKOURIS and A. MATALAS. Exertional Rhabdomyolysis during a 246-km Continuous Running Race. Med. Sci. Sports Exerc., Vol. 38, No. 6, pp. 1054–1057, 2006. Background: To evaluate the effect of continuous, moderate-intensity ultraendurance running exercise on skeletal muscle and hepatic damage, as indicated by serum enzyme activity measured immediately following the race. Methods: Thirty-nine runners of the Spartathlon race (246-km continuous race from Athens to Sparta, Greece) who managed to complete the race within the 36-h limit participated in this study. Mean finishing time of the study participants was 33.3 ± 0.5 h and their average age, height, and body mass were 41 ± 1 yr, 174 ± 1 cm, and 67.5 ± 1.1 kg, respectively. Blood samples, taken a day before and immediately after completion of the race, were assayed for the following variables: creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (γ-GT). Results: A dramatic increase in most of muscle and liver damage indicators was observed. The mean values for CK, LDH, AST, and ALT after the race were 43,763 ± 6,764, 2,300 ± 285, 1,182 ± 165, and 264 ± 37 IU/L⁻¹, respectively. These values were 29,384 ± 4,327, 585 ± 89, 5,615 ± 902, and 1,606 ± 331% higher than the corresponding values before the race (P < 0.001) for CK, LDH, AST, and ALT, respectively. However, there was not a significant increase in γ-GT levels. Conclusion: Muscle and liver damage indicators were elevated at the highest level ever reported as a result of prolonged exercise, although no severe symptoms that required hospitalization were observed in any of the participants. The data suggest that even moderate-intensity exercise of prolonged duration can induce asymptomatic exertional rhabdomyolysis. Key Words: CREATINE KINASE, LACTATE DEHYDROGENASE, SPARTATHLON, ULTRAENDURANCE EXERCISE

As a response to strenuous exercise with repetitive eccentric muscle contraction, especially in unacclimated individuals, muscle damage characterized by myocellular morphological alterations and protein leakage can occur (2,25). It has been shown that prolonged and intense exercise like marathon running causes muscle damage, as measured by elevated serum enzymes like creatine kinase (CK). It is also suggested that both intensity and duration are related to muscle damage in a dose– response manner (2,13,14,22).

The foot race of Spartathlon is an annual ultramarathon race (246 km of continuous running) that takes place in Greece every September. It is based on the historic run of Pheidippides, who ran from Athens to Sparta (Herodotus, The Persian Wars, VI, 106). Spartathlon is one of the world’s toughest and longest continuous running races, where athletes run in dirt roads, muddy paths, and climb 1200 m in altitude without being allowed to rest or sleep, even during the night. The goal of the participants is to complete the race within the 36-h time limit. No previous study has ever examined the muscle responses to such a prolonged and continuous running race.

The purpose of this study was to evaluate the degree of muscle damage induced by this kind of exercise, which is characterized by very prolonged duration but moderate intensity. We also tested the hypothesis that the fastest runners would have more profound alterations in the markers of muscle damage examined.

MATERIALS AND METHODS

Subjects and exercise protocol. A total of 104 runners gave their consent to participate in the study. Of those, 39 managed to complete the race, whereas the remaining 65 either dropped out or did not managed to finish within the 36-h time limit and were eliminated from the study. The race consisted of a 246-km distance, during which runners attempt to cover the distance from Athens to Sparta, in ambient temperatures between 5 and 36°C. The race started at 7:00 a.m. in Athens, and successful competitors had to reach the finish line in Sparta by 7:00 p.m. the following day (within 36 h). The subjects consumed fluids (water, beverages, and sports drinks) and carbohydrate-rich foods (bread, cookies, fruits, pasta) available at the 75 checkpoints throughout the race where they could eat and drink ad libitum. The study was approved by the
TABLE 1. Demographic characteristics of the study participants.

| Age (yr) | 41 ± 1 |
| Body mass (kg) | 67.5 ± 1.1 |
| Height (m) | 1.74 ± 1 |
| BMI (kg m\(^{-2}\)) | 22.3 ± 0.3 |
| W/H | 0.84 ± 0.01 |

Values are means ± SE. BMI, body mass index; WH, waist to hip ratio.

institutional review board of Harokopio University. All subjects were informed of all procedures and purposes of the study and gave their written consent prior to participation in the study.

**Anthropometric assessment.** A digital scale with an accuracy of ±100 g was used to measure body mass. All subjects were weighed without shoes in shorts and T-shirts. Subjects were also weighed at the end of the race to assess hydration status. Height was measured without shoes to the nearest 0.5 cm using a stadiometer, with the shoulders in relaxed position and arms hanging freely. Body mass index (BMI) was calculated as body mass (kg) divided by height (m) squared. Waist and hip circumferences were measured to the nearest 0.5 cm, and their ratio was calculated.

**Blood sampling.** A 10-mL blood sample was drawn from an antecubital vein without stasis the day before and within 15 min after the end of the race. Of the sample, 7 mL was immediately transferred to nonadditive tubes for serum and allowed to clot at room temperature for 30 min. The rest (3 mL) of the sample was immediately put into an EDTA-treated tube for whole-blood hematological analysis. Serum was separated from whole blood by centrifugation at 1500 × g for 10 min at 4°C. The samples were then stored frozen at −80°C until assayed.

**Blood analysis.** Whole blood was analyzed for white blood cells (WBC), red blood cells (RBC), hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC) by an automated analyzer (Sysmex F-820, Japan).

Serum samples were analyzed for the following rhabdomyolysis and hepatic injury markers: creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (γ-GT). All markers were measured by commercially available assays (Alfa Wassermann Diagnostics) using an automated analyzer (Schiparelli Biosystems, Inc.).

**Statistical analysis.** Values are presented as means ± standard error of the mean. Pre- and postrace values were compared by paired t-tests. The relationship of finishing time with liver and muscle damage markers was tested by performing single regression analysis. Significance was set at P < 0.05. All analyses were performed using the SPSS software (SPSS for Windows, version 10.0).

**RESULTS**

The anthropometric characteristics of the study participants are presented in Table 1. The mean finishing time for the runners participating in our study was 33.3 ± 0.5 h (range: 23.3–36.0 h). Body mass of the runners decreased −1.9 ± 0.3 kg or −2.8 ± 0.5%. None of the subjects experienced an adverse medical event requiring medical attention during or after the race. Mean values of hematological variables of the study participants before and after the race are presented in Table 2. White blood cell count was significantly increased after the race. Significant increases were also observed in hematocrit, hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin, indicating hemococoncentration. Red blood cell count and platelet count significantly decreased after the race. The mean values of serum activity of CK, LDH, AST, ALT, and γ-GT, pre- and postrace, are presented in Table 3. Prerace values were within the normal reference range for all participants. Postrace values for CK, LDH, AST, and ALT were, respectively, 29,384 ± 4,327, 585 ± 89, 5,615 ± 902, and 1,606 ± 331% higher than the corresponding values before the race (P < 0.001). No statistically significant difference was observed between pre- and postrace values for γ-GT (Table 3). Finishing time was not significantly correlated with CK activity after the race (Fig. 1) or with the activities of the other enzymes examined (not shown).

**DISCUSSION**

The influence of prolonged exercise in hematological and biochemical variables was first reported in 1903 by Blake et al. (3). Several studies have examined the influence of marathon running on cardiac, hemostatic, and inflammatory markers (10,19–21). Serum enzymes like CK, LDH, AST, and ALT are related to membrane permeability and have been used as biochemical indicators of tissue damage (16). Our study is the first to investigate the influence of continuous, moderate-intensity, ultraendurance exercise on the status of skeletal muscle and hepatic enzymes. In our subjects the activities of CK, LDH, AST, and ALT were dramatically increased, ranging from 585 ± 89% for LDH to 29,384 ± 4,327% for CK. Our group (39 runners) was one of the largest group reported in the literature. Our observations are in agreement with other investigations concerning races like marathons (10,21); however, the magnitude of responses has never been reported for athletes that were not hospitalized.

Increases in hemoglobin, hematocrit, and WBC count immediately after a marathon race have been reported in previous studies (5,8,9,11,27). In our athletes, statistically
significant differences were observed in white blood cell count after the race. We hypothesized that the continuous low-intensity exercise triggers a temporary inflammatory response by activating the white blood cell populations, like many clinical situations (e.g., trauma, burn, surgery, or sepsis). The hemocconcentration seen by increases in hematocrit and hemoglobin was probably induced by dehydration. Red blood cell count decreased, despite the small but statistically significant increase in hematocrit and hemoglobin, possibly due to red cell damage. Hemolysis is a well-documented side effect of endurance exercise, especially in runners, attributed mainly to the mechanical damage associated with running, a phenomenon that has been described as “foot strike hemolysis” (18).

Determination of CK is the most common marker to assess skeletal muscle damage. In studies of high-force eccentric exercise, a common variable used to estimate the degree of muscle cell injury is the enzyme creatine kinase (CK), which is released from the damaged cells and accumulated in the blood (17). However, measurements of other postrace enzyme levels (LDH, AST, and ALT) are also indicative markers of skeletal muscle injury. Other investigators suggest that the elevation in myoglobin, total CK, creatine kinase-MB (CK-MB), and AST after the marathon indicate exertional rhabdomyolysis and leakage from skeletal muscle, whereas ALT, as a more specific marker for hepatic injury, show little change (23). In our study, although ALT increased significantly, this observation was not as dramatic as the other examined variables (CK, LDH, and AST), indicating greater damage in skeletal muscle than in liver. γ-GT, which is considered a specific indicator for liver damage (12), showed no significant change after the race, suggesting that the increases in the other variables should be mainly attributed to leakage from muscle cells but not the liver.

To our knowledge, no study has ever examined the muscle damage induced by ultraendurance exercise at the cellular level. However, some data do exist on the morphological alterations in muscle tissue in marathon running. Hikida et al. (6) have demonstrated that marathon running induces inflammation, as evidenced by the presence of leucocytes and other phagocytic cells in the extracellular and the extravascular space, disorientation and degeneration of myofibrils, and even disruption of the sarcolemma, release of mitochondria in the extracellular space, and muscle fiber necrosis.

Physical exercise increases metabolic demand, which in turn generates reactive oxygen species (ROS). One major source of ROS during exercise is thought to be the mitochondria of active muscles (15). Hence, there is a possibility for a direct link between the overall oxidative stress of exercise and muscle/liver injury. However, such a direct or indirect impact of ROS production on the cell function of other organs (i.e., the liver) needs further clarification. Additionally, the exercise-induced inflammatory response can also trigger reactive oxygen species production, which in turn can damage the cell membrane and lead to a leakage of enzymes into the blood stream or to a total disruption of muscle membranes (6,26). Although oxidative markers were not evaluated in the present study, it can be hypothesized, based on previously published data (4), that cell injury was also related to oxidative stress.

Another hypothesis of the present study was that runners who finished the race faster would have a greater increase in blood CK compared with runners who had a slower pace, due to the greater exercise intensity. Hunter and Critz (7) and Stansbie et al. (24) found that the exercise-induced increase in CK activity is intensity dependent. However, we did not find such a relationship. On the contrary, we found that CK activity in serum increased dramatically to all runners and was not related to the finishing time (Fig. 1). It should be noted that in the aforementioned studies the exercise intensities used were not matched to the total work produced. Our data provide evidence that even moderate-intensity (approximately 8 METs) (1) prolonged exercise may cause substantial muscle damage equal to that observed in higher-intensity exercise of the same total workload.

Given the continued popularity of ultraendurance running, athletes may increasingly exhibit symptoms of exhaustion or circulatory collapse during ultraendurance events. Such runners may have concentrations of serum CK, LDH, AST, and ALT similar to levels in patients undergoing acute myocardial infarction or severe hepatic injury. Postrace CK, LDH, ALT, and AST levels were dramatically elevated in our study population, indicating a significant skeletal muscle and minor hepatic damage. These values are the highest reported as a result of prolonged exercise. Our results provide information about trends in laboratory values in ultramarathon

| Table 3. Serum enzyme activities of the study participants before and after the race. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Before          | After           | P value         |
|                                | Cr-kinase (U/L) |                 |                 |
|                                | 178.1 ± 17.9    | 43.762 ± 6.763  |
|                                | Lactate dehydrogenase (U/L) | 373.9 ± 26.9 | 2.299 ± 284.5 |
|                                | Aspartate aminotransferase (U/L) | 24.5 ± 1.9 | 11.182 ± 165.1 |
|                                | Alanine aminotransferase (U/L) | 20.3 ± 1.6 | 246 ± 36.5 |
|                                | Gamma-glutamyltransferase (U/L) | 32.2 ± 3.0 | 34.5 ± 4.4 |

Values are means ± SE.
| Statistically significant difference compared with prerace values (P < 0.001). |
runners that physicians will find useful in the treatment of such individuals. It is postulated that very prolonged moderate-intensity exercise does induce exertional rhabdo-

myolysis, which remains asymptomatic and possibly not related to clinical symptoms often observed in ultra-endurance athletes.

REFERENCES


